Aerotoxic syndrome: A new occupational disease caused by contaminated cabin air?

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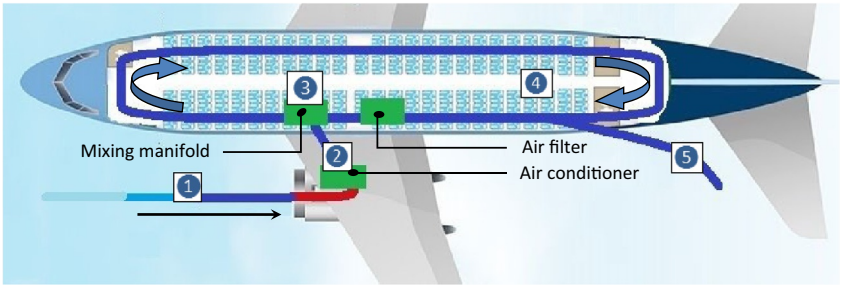
1. Introduction

The term "aerotoxic syndrome" was proposed in 1999 by Balouet and Winder to describe a constellation of symptoms reported by pilots and cabin crew following exposure to hydraulic fluids, engine oil and pyrolysis products during flight (Balouet and Winder, 1999). Cabin air on most commercial aircraft is supplied from the engines or auxiliary power unit. Air is drawn from outside and then circulated around the engine where it is heated and pressurized to a breathable level before being "bled off" and pumped into the aircraft (see Fig. 1).

Cabin air can be contaminated by a large number of toxic substances such as ingestion of exhaust from other aircraft, engine oil and hydraulic fluid leaks, combusted and pyrolised materials (e.g., carbon monoxide) and application of de-icing fluids and insecticides. Contamination can occur in two ways: (1) chronic repeated low-level exposure due to jet aircraft design which allows continuous leaking of lubrication oil past wet seals, occurring



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.

Fig. 1 Bleed air.

without a detectable fume event, (2) acute high-level exposure associated with odors and sometimes a visible haze, due to changes of engine power or air supply configuration. Less frequently due to general system failure such as seal bearing leakage, worn seals, overfilling of oil and of hydraulic reservoirs (Howard et al., 2017; Michaelis et al., 2021).

Over the last two decades several case studies and health surveys have been published describing adverse health effects reported by aircrew and passengers, thought to be related to exposure to contaminated air. Symptoms frequently reported by aircrew following a fume event include eye-, nose-, throat- and airway-irritation, nausea, headaches, dizziness, cognitive impairment and fatigue. Occasionally aircrew, including pilots, have been completely incapacitated by fumes and were forced to perform emergency landings. Once exposure stops often resolution of symptoms is reported. In case of repeated exposure, it takes longer for aircrew to recover after each episode. Once a threshold is passed in number of repeated episodes, symptoms may persist and become chronic (Mackenzie Ross, 2008).

Although the aviation industry recognizes that some people experience acute symptoms following fume events—with transient discomfort—debate continues as to whether exposure to contaminated air can cause long-term health effects (UK Civil Aviation Authority Guidance for passengers and healthcare professionals, 2015). Air quality monitoring studies, undertaken over the last decade, have examined a small number of chemicals and gasses and concluded levels were too low to cause adverse effects (Crump et al., 2011; de Ree et al., 2014; Wolkoff et al., 2016). However, these on-board studies have a number of methodological weaknesses, the most important being that most studies did not capture a fume event and only a limited number of chemicals were studied, without due consideration of the synergistic effects of chemical mixtures. Also, these studies did not explore the possibility that cumulative low-level exposure may be as harmful as a single episode of high level exposure. Finally individual differences in rate or even ability to metabolize certain compounds, were not taken into consideration. This means the health risks may be higher than assessed hitherto.

Nonetheless many researchers continue to argue that the health risks of exposure to contaminated cabin air are negligible and they suggest chronic ill health is more likely to be caused by factors, unrelated to toxic gasses such as psychological factors (including mass hysteria, nocebo effects, psychosomatic conditions). In addition, it is argued that specific work-related factors have to be taken into consideration, such as shift work, jet lag, relative

hypoxia, exposure to cosmic radiation and pressure changes (Cable, 2003; COT report, 2007; van Drongelen et al., 2015; Wolkoff et al., 2016). The symptoms reported by aircrew following a contaminated air event are diverse, occurring in many other medical conditions and common even in the general population. Similar symptoms have been reported by aircrew who were not exposed to contaminated air (McNeely et al., 2018).

Furthermore, many researchers object to the term 'aerotoxic' because it implies causation when this is yet to be established beyond any degree of certainty. Diagnostic tests like brain imaging and investigations of peripheral nerve conduction and the autonomic nervous system often fail to reveal abnormalities in many individuals (de Graaf et al., 2014). Considerable scientific uncertainty still surrounds this issue and given the limited number of high-quality research studies undertaken over the last two decades, we consider further research is warranted. In this chapter we review the possibility that:

1) Aerotoxic syndrome is the result of long-term, low-level exposure to a mixture of toxic compounds, including various organophosphates, solvents and carbonmonoxide.
2) These toxic compounds are attached to ultrafine particles in bleed air, crossing oil seals, and entering cabin air, and are absorbed by the human body via inhalation.
3) Symptoms develop in pilots and cabin crew, especially in those with a reduced capacity to metabolize toxic compounds as a result of genetic polymorphisms.

2. Incidence of fume events

Fume events are defined as any incident associated with smells, smoke or mist inside an airplane with impairment to the health of occupants (Anderson, 2021). Events reported range from hazy smoke entering the cabin to the smell of dirty socks or burned rubber. This definition may include a fog of ultrafine (<100 nm) droplets in bleed air, which can occur under standard operating conditions (Amiri et al., 2017; Michaelis et al., 2021). Fume events can occur at any time during operation of the aircraft, although most likely (80%) during take-offs and landings. In 2013, the International Air Transport Association published on its analysis of safety reports from more than 150 airlines, covering 31 million flights during the period 2008–2012 (IATA, 2013). Of these, 3444 reports were categorized as "smoke, fumes and odor", which is equivalent to about one event

per 10.000 flights. Engine-related fumes were the most commonly reported source. Smell events do not necessarily indicate the presence of toxic contaminants, often the source of a smell event cannot be identified (Anderson, 2021; Rosenberger, 2018; Schuchardt et al., 2019). The incidence of fume events has been difficult to determine because cabin air is not routinely monitored for the presence of chemical contaminants. In addition, underreporting of symptoms is common among aircrew. Nevertheless, the aviation industry accepts that fume events occur on commercial aircraft; some aircraft types (BAe 146, Airbus 320 and Boeing 757) report more events than others. In a study of 33 aircraft models in the period 2007–2012, the highest fume event frequency for one aircraft model (Boeing 757) was 7.8 per 10.000 flights (Shehadi et al., 2016). The reported frequency of fume events varies widely, see Table 1. Regulatory authorities estimate fume events happen on 0.2–0.5% of flights. If only those events are counted cabin crew judged worthwhile to report, one event occurs in every 460 flights (Cannon, 2016).

Table 1 Frequency of reported fume events and reported complaints.

Author, year	Period	Aircraft type	Frequency	Remarks
National Research council, 2002	One year, 2002	Boeing 737, BAe 146	0,09 (B737)-3,88 (BAe 146) per 1000 flights	
Michaelis, 2003	Questionnaire October 2001: 106 respondents; 93 of 106 after fume event	B757 (102 of 106) B737 A320	1674 fume events; most reported complaints: ENT irritation, headache, dizziness, impaired concentration, fatigue, nausea, vomiting, diarrhoea	Only 61 of 1674 incidents reported
Singh, 2004	1998–2003	Australian airforce	0,5 incidents per 1000 flight hours	
Murawski, 2008	January 2006-June 2007	US commercial aircraft	0,86 events per day	470 incident reports; 51 % caused flight delay or cancellation

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Table 1 Frequency of reported fume events and reported complaints.—cont'd

Author, year	Period	Aircraft type	Frequency	Remarks
IATA, 2013	2008–2012	150 airlines, 31 million flights	1 event per 1000 flights	3444 incident reports, smoke, fumes and odor
German Federal Bureau of Aircraft Accidents Investigation, 2014	2006–2013	Transport aircraft, Airbus 319–330, Boeing 737–757, Antonov	663 fume events, (460 smell-, 188 smoke) in 6 years	In 15 cases health impairment
Heutelbeck et al., 2016	2015	Not reported	11 flight crew, admitted < 5 days after fume event: headache, fatigue, respiratory distress, cogn. impairment, salivation, gastro-intestinal symptoms	Low NTE activity (3,1-6,3 nmol, normal values 3-24) in 10 of 11 flightcrew
Shehadi, 2016	2007–2012	33 aircraft models Airbus, Boeing, Douglas, Mc Donnell-Douglas	Mean: 2,1 incidents per 10.000 flights; Boeing 757: 7,8 per 10.000 flights	Events widely distributed across all commercial aircraft models
Klerlein and Loizeau, 2019	Questionnaire after fume event, March 2017-March 2018. Of 610 aircrew involved, 376 responded, 354 were included	81 flights Air France	185 of 354: no complaints 169 of 354 (48 %): ENT irritation, headache, dyspnea, lightheadedness	Only 53 of 169: medical investigation by health care provider
Anderson, 2021	2002–2011	US airlines	1–2 events per 10.000 flights, max 8 per 10.000 flights	12.417 fumes-smoke incident reports

Aircrew complain of ill health in around 30% of fume event reports (Michaelis, 2016). In a one-year survey of Air France from March 2017 to 2018, 81 flights with an onboard fume event were noted, involving 610 aircrew; of these 376 (61.6%) answered an online questionnaire. The mean delay between fume event and response was 11 days. Symptoms reported included eye, nose and throat irritation, headache, lightheadedness and dyspnea. Only 14% of aircrew attended the airport medical service or occupational health service (Klerlein and Loizeau, 2019). More severe symptoms were reported in another survey of fume related health problems, involving 106 pilots who were members of the British Airline Pilots Association (Michaelis, 2003). These symptoms were fatigue, decrease in performance, confusion, impaired concentration and short term memory, muscle weakness and diarrhea. In this study the duration of fume events lasted seconds to hours. Similar symptoms were reported in a German study of 11 flight crew members, investigated within 5 days after a fume event. The main symptoms were fatigue, headache, impaired concentration and memory, gastrointestinal symptoms, paresthesias, chestpain or dyspnea, vertigo, disorientation, sweating, sensation of thirst and dry mouth but also increased salivation (Heutelbeck et al., 2016). Another German study reported fume events in the cabin of transport aircraft. A total of 648 fume events occurred between 2006 and 2013, 460 smell and 188 smoke events, with health impairment in 15 cases (German Federal Bureau of Aircraft Accident investigation, 2014).

3. Bleed air contaminants

Hydraulic fuels and engine oils contain a large number of potentially toxic chemicals. A recent cabin air quality study, carried out on 177 flights involving 61 bleed air aircraft and eight bleed air free aircraft B787, quantified 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 (see Tables 2 and 3). Measurements include various organophosphate compounds (tricresylphosphate (TCP), triphenylphosphate (TPhP), dibutylphenylphosphate (DBPP) and tri-n-butyl phosphate) and volatile organic compounds (toluene, benzene, formaldehyde, acetic acid, acetone, ethanol) (Solbu et al., 2011; Winder and Balouet, 2002). Cabin air may be polluted by pyrolytic degradation products of engine oil, or due to thermal decomposition of hydraulic fluids. Other causes of contamination arise from

Table 2 In-flight measurements conducted since 2011.

Author, year	Target compound	Number of flights/ samples	Aircraft type	Findings	Remarks
Crump et al., 2011	VOC, CO, TCP, ToCP, TnBP, toluene, xylene	100 flights	B757 cargo, B757, A319, A320/1, BAe 146,	In >95% of cabin air samples no total TCP or ToCP detected. Highest ToCP level of 22.8 μg/m^3 during climb of a B757. Mean total TCP 0.14 μg/m$^{3.}$ Maximum 28.5 μg/m^3. Highest TnBP level 21.8 μg/m^3. Low concentrations of toluene, xylene	(1) The suitability of the sampling and analysis method applied for TCP determination were questioned. (2) No fume events recorded
Denola et al., 2011	TCP and other organo-phosphates	46 flights, 78 samples	Three types from Australian Defense force: fighter trainer, cargo transporter and fighter bomber, 46 different aircraft	In 11 of 78 samples TCP levels detected from 0.12–4.99 μg/m^3. In 2 samples high TCP levels of 21.7 and 51.3 μg/m^3. Other peaks were TiBP, TnBP and TPhP.	During the flight with TCP level 51.3 μg/m^3 smoke in the cabin was reported.
Solbu et al., 2011	Organo-phosphates	95 Samples from 47 flights	40 Aircraft (jet engine and propellor airplanes, helicopters)	TCP detected in 4% of air samples, only in propellor airplanes and helicopters; levels ranging from <75 ng/m^3 to 290 ng/m^3. TnBP in all jet engine and propellor airplanes and in 58% of helicopters: 24–4100 ng/m^3. DBPP in the jet and propellor airplanes: <75 to 310 ng/m^3. TPhP in one propellor airplane: 110 ng/m^3	TCP detected in 39% of the wipe samples and in all 6 HEPA filters from the jet engine airplanes, 1.1–4.3 ng/g per hour. No ToCP detected in air and wipe samples.

Spengler et al., 2012	TCP, VOC, CO, ozone, carbon-dioxide	83 Commercial flights	6 Aircraft models (2 Airbus, 4 Boeing, from 3 US airlines	TCP was detected in 1 of 71 samples. Acetaldehyde was found in 81% of 70 samples, acetone in 79%, acrolein in 71%, formaldehyde in 49%, propionaldehyde in 17%	ToCP not detected
Houtzager et al., 2013	TCP	80 Air sampes	4 B737–700s, 3 B737–800s, 3B737–900s, and from 2 B737–700s and 800s while running the APU.	In 37 of 80 samples TCP; 0.5 to 155 ng/m^3, average 6.9 ng/m^3. Highest TCP levels during climb and descent.	TCP levels in wipes 0.01 to 0.06 ng/cm^2
Guan et al., 2014	VOC	107 Flights, 76 China domestic and 31 inter-national flights	A320, A321, B737, A330, B747, B777	Benzene, toluene, xylene, ketones, aldehydes (acetone), esters, alcohols, alkanes and alkenes were detected	Concentrations varied in the three different flight phases, peaking before take-off or during cruise
Wang et al. (2014a,b)	VOC	84 Air samples, in 5 flight-phases, in 14 flights	B737–800, China domestic flights	19 VOCs were detected. Highest levels for D-limonene, decanal, nonanal, toluene, xylene, acetic acid, benzene and 6-methyl-5-hepten-2-one	Only one third of VOC emission attributed to fuels, oil, combustion, 29% to (drink)services, 10% to perfumes, cosmetics, cleaning agents

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Table 2 In-flight measurements conducted since 2011.—cont'd

Author, year	Target compound	Number of flights/ samples	Aircraft type	Findings	Remarks
Rosenberger et al., 2016	Aldehydes	353 Samples, 108 flights	26 Aircraft, 11 A380, 15 A321	Formaldehyde 0.4–44 μg/m^3 (median 4.9) and acetaldehyde 0.3–90 μg/m^3 (median 4.6) were detected	15 Smell events were reported, measurements in these phases did not differ from phases without smell events
Schuchardt et al., 2019	Aldehydes,VOC, CO, carbon-dioxide, organophosphates, including TCP	840 Samples, in 5 flight phases, in 177 flights	A320, A321, A340, A380, B747, B767, B787	Mean total VOC concentration: 122–370 μg/m^3; low formaldehyde and acetaldehyde. Organophosphates: 0.74–5.36 μg/m^3. Highest: TnBP, and in A321 TCiPP, low TCP	Increased levels of propylene glycol in winters due to de-icing. TCP also detected in B787. (non-bleed-air)

TnBP = tri-n-butyl phosphate, TiBP = tro-isobutylphosphate, TPhP = triphenylphosphate, DBPP = dibutylphenylphosphate, TCiPP = trichloroisopropylphosphate, VOC = volatile organic compounds, CO = carbonmonoxide.

Table 3 Summary of exposure data from in-flight measurement studies conducted since 2011 (in μg/m^3).

Contaminent of concern	Mean/range	Maximum concentration value	References
Organophosphates	0.74–5.36	7.45	Crump et al. (2011); Rosenberger et al. (2016); Rosenberger (2018); Denola et al. (2011); Schuchardt et al. (2019); Solbu et al. (2011)
Tricresylphosphate (TCP)	0.14	51.3	
Tri-ortho-cresylphosphate (ToCP)	0.07	22.8	
Tri-n-butylphosphate (TnBP)		21.8	
Diphenylphosphate (DPP)		0.3	
Trichloro-isopropylphosphate (TCiPP)	0.429		
Total Volatile Organic Compounds (T-VOCs)	122–370	7230	Rosenberger (2018)
Aldehydes	21.6 (13–35)	429	Rosenberger (2018); Rosenberger et al. (2016); Chen et al. (2021)
Formaldehyde	0.4–44; median 4.9	134	
Acetaldehyde	0.3–90; median 4.6	234	
Solvents			Wang et al. (2014a,b); Guan et al. (2014); Chen et al. (2021)
Benzene	14.78	77.9	
Ethylbenzene	7.04	45.1	
Toluene	29.84	209.3	
Xylene	4.55	62.9	
Acetone	14	384	
Ozone	0–117	302	Rosenberger et al. (2016); Bekö et al. (2015)
Flame retardants			
Polybrominated phenylesters	0.04–20 ng/m^3	2100 ng/m^3	Allen et al. (2013)
Carbonmonoxide	0–3 ppm	> 5 ppm	Rosenberger, 2018; Rosenberger et al., 2016
Insecticides: Permethrin, d-Phenothrin	120–300 μg pyrethrins/person	830 μg pyrethrins/person	Pang et al. (2020),
Ultrafine particles	417–100.000 particles/cm^3	500.000 particles/cm^3	Li et al. (2014); Zhai et al. (2014); Michaelis et al. (2021)

kerosene fumes ingested during taxiing or (waiting for) take-off, and the application of de-icing products or insecticides in the cabin. Cold air drawn from outside is heated to aircraft engine temperatures of more than 500 °C This may alter the composition of the original oil and hydraulic fluids and create other toxic semivolatile compounds such as alkylated TCP, trimethylolpropane phosphate (TMPP) and tri-butyl phosphate (Chen et al., 2021; de Boer et al., 2015). Products of incomplete combustion, such as carbon monoxide are also present in engine oil fumes and potentially neurotoxic. The synergistic effects of these compounds is as yet unknown.

All published air quality studies report detection of small amounts of contaminants in cabin air under normal operating conditions. Yet to date none revealed a fume event of sufficient severity to trigger formal reporting procedures (Harrison and Mackenzie Ross, 2016). Interestingly, mean concentrations of volatile organic compounds and aldehydes are reported to be lower in the B787 aircraft than in the bleed air aircraft.

4. T(*O*)CP and other organophosphates

With proven neurotoxicity TCP is the most comprehensively studied chemical substance in air quality studies. TCP/ToCP was used as an adulterant in Jamaica ginger, a medicinal alcohol extract used for stomach problems, commonly abused as an illicit source of alcohol. In the 1930's in the United States it led to "ginger jake paralysis" in 20.000–50.000 people. Other major toxic outbreaks involving more than 10.000 victims were described in Morocco and China (Wang et al., 1995).

In the aviation industry, this compound is used as an anti-wear, extreme pressure additive in lubricants and hydraulic fluids. In gasoline it is used as a flame retardant and lead scavenger. TCP is a potentially neurotoxic organophosphate (OP) compound which inhibits human butyrylcholinesterase (BChE) as well as acetylcholinesterase (AChE), thus disrupting neuronal function. Although TCP is an organophosphate, it has no application as a pesticide, though the neurotoxic mechanisms are considered to be similar (Costa, 2006). TCP is a mixture of various cresyl isomers, i.e. ortho-, meta- and para-TCP. Tri-ortho-cresylphosphate (ToCP) is more toxic than the meta- and para-forms. Isomers containing mono-ortho-cresyl phosphate are considered to be most toxic, followed by the di-ortho and tri-ortho compounds.

The inhibition of red cell AChE and of plasma BChE by the metabolite of ToCP, 2-(2-cresyl)-4H-1,3,2-benzodioxaphosphorin-2-oxide, (or cresyl

saligenic phosphate, CBDP) is probably the most important underlying mechanism for ToCP neurotoxicity. ToCP and especially CBDP are known to affect Neuropathy Target Esterase (NTE) and cause a delayed neuropathy called OPIDN. Non-cholinergic toxicity has been proven in animal experiments with very low concentrations of ToCP. One possible mechanism being impairment of glutamate signaling (Hausherr et al., 2014). The recommended safe exposure limit is considered to be breathing 0.1 mg/m^3 of ToCP for 30 min by a 70 kg individual (Schopfer et al., 2010). The maximum total-TCP concentrations in flight deck air reported in various studies are lower, 50–100 ng/m^3, with exceptions as high as 290 ng/m^3 (Crump et al., 2011; de Boer et al., 2015).

The Dutch Organization for applied scientific research TNO measured concentrations of TCP isomers inside the cockpit during 20 flights of nine different Boeing 737-type aircraft. In addition, wipe samples were taken from the glare shield before and after the flight (de Ree et al., 2014). In 10 out of 20 flights TCP isomers could be detected, with a maximum of 155 ng/m^3 during climb. The wipe samples demonstrated small amounts of TCP, at levels below 0.1 ng/cm^2. ToCP levels were below the limit of detection. In an UK-study cabin air samples were measured in 100 flights of several types of aircraft: Boeing 757 cargo and passenger, BAe146, Airbus A319 and A320. TCP levels could be detected in the range of 0–28.5 μg/m^3, ToCP levels in the range of 1–23 μg/m^3 (Crump et al., 2011). In a few studies data are presented of TCP concentrations during a probable fume event (Rosenberger et al., 2016; Schuchardt et al., 2019). However these maximum TCP concentrations are lower, compared to the Crump data: TCP concentrations of 1.67 μg/m^{3}were measured, especially in the takeoff phase (Schuchardt et al., 2019).

T(*o*)CP is not detectable in human blood due to rapid metabolism, but there is an assay for TCP based on the active-site serine of butyrylcholinesterase reacting with the active metabolite of TCP, cresyl saligenic phosphate (Liyasova et al., 2011). Similarly new methods have been developed for the quantitation of ortho-cresyl phosphate adducts to BChE in human serum. The metabolite CBDP undergoes hydrolysis to form orthocresylphosphoserine, providing a biomarker of CBDP exposure (Johnson et al., 2015). To quantify the exposure to OP's, including T(*o*)CP, specific metabolites in urine can be measured. In a total of 332 urine samples taken from pilots and cabincrew, who reported fume events during their previous flight, ToCP was under the limit of detection (Schindler et al., 2013). Only one sample contained a low-level of TCP-metabolites.

Metabolite levels of tributylphosphate, tris-(2-chloroethyl) phosphate and triphenylphosphate were found to be significantly higher. This was confirmed in a recent air quality study, in which tri-n-butylphosphate, which originates from the hydraulic system, was the most prominent OP-contaminant (Schuchardt et al., 2019). OP-mean concentrations were in the range of 0.74–5.36 $\mu g/m^3$.

The above mentioned concentrations are inconsistent with T(*o*)CP being the sole neurotoxic agent of concern and suggest other OP compounds and other chemical substances or gasses may be to blame.

5. Mechanisms of long-term, low-dose organophosphate neurotoxicity

Three mechanism associated with central and peripheral neurotoxicity of OP's can be differentiated based on symptomatology and time of occurrence.

1) **AChE inhibition** may be involved if OP's account for ill health reported by aircrew following a contaminated air event. This results in accumulation of acetylcholine and overstimulation of the nicotinic and muscarinic ACh receptors leading to cholinergic effects: salivation, miosis, abdominal cramps and in case of high exposure reduced consciousness and flaccid paralysis. OP's deactivate cholinesterases by attaching an alkylphosphate group to the hydroxyl group of a serine residue at the enzyme's active site. Recovery from such inhibition generally takes 10–14 days (Davies et al., 2000).
2) **Non-cholinergic mechanisms.** However OP's can damage the nervous system as a result of non-cholinergic mechanisms. This most often occurs after repetitive exposure but can even result from a single intoxication. For example inhibition of NTE can cause OP-induced delayed neurotoxicity (OPIDN). The pathological substrate is a Wallerian type (or dying back) axonal degeneration accompanied by secondary demyelinisation. The most distal portion of the longest nerve tracts are affected in both the central and peripheral nervous system (Abou-Donia, 2003). The clinical picture consists of mild sensory disturbances, ataxia, muscle fatigue and twitching. Improvement is inconsistent and may require months or years. The earliest cases of tri-o-cresyl phosphate induced OPIDN have been documented in 1899, attributed to the use of creosote oil for treatment of tuberculosis (Abou-Donia, 1981).

3) "**OP-induced chronic neurotoxicity**" **(OPICN)**. OP's are also known to cause neuropsychiatric symptoms in OPICN. It may result from excessive cholinergic activity, or non-cholinergic mechanisms as OPs are known to affect other neurotransmitters, including those involved in mood regulation. OP's also affect other physiological processes such as axonal transport and mitochondrial function and may initiate a neuro-inflammatory response by release of cytokines from activated microglia and astrocytes, with apoptotic neuronal cell death (Banks and Lein, 2012; El Rahman et al., 2018). This leads to slow neurodegeneration in various brain areas—cortex, cerebellum, (hypo)thalamus, amygdala—resulting in chronic neuropsychiatric, neurologic and behavioral problems (Abou-Donia, 2003). Clinically, OPICN is manifested by fatigue, apathy, confusion, memory deficits, insomnia, and personality changes. Mood disorders may pose a diagnostic challenge, ranging from anxiety and mild depression to suicidal attempt in severe cases (El Rahman et al., 2018). However most cases present with subtle long-term neuropsychological symptoms following a history of cumulative low level exposure without previous signs of acute toxicity (Brown and Brix, 1998; Mackenzie Ross et al., 2007, 2010). Indeed studies by Terry et al., found OP's can cause adverse health effects at exposure levels below those required to cause cholinesterase inhibition (Terry, 2012).

6. Solvents

There are several other potential contaminants in jet oil which may play an aetiological role in aerotoxic syndrome. In-flight measurements of volatile organic compounds have been reported regularly, see Table 1 and 2. In a review of 47 papers, with measurements taken from 2251 flights the most frequently measured compounds were solvents and aldehydes: toluene, benzene, ethylbenzene and formaldehyde (Chen et al., 2021). Average concentrations of benzene at 5.9 $\mu g/m^3$ were higher than the permissible levels of air quality standards. In 107 randomly selected commercial flights, on average 59 different compounds in each flight were detected, with a total of 346 compounds (Guan et al., 2014). The compounds found in highest abundace on all flights were benzene series (e.g. toluene) and acetone. Other volatile compounds such as tetrachloroethene arise from the dry cleaning of fabrics in the cabin, and 1.4 dichlorobenzene evaporates as component of disinfectant for lavatories (Guan et al., 2014). Finally, de-icing

fluids—consisting of ethylene- and propylglycols—may contaminate incoming engine-air (Solbu et al., 2011).

Exposure to organic solvents occurs in a wide range of circumstances. In industrialized countries, the prevalence of occupational exposure to solvents is around 8% (Dick, 2006). A small subsample of workers who are exposed to organic solvents for a long time, e.g., daily exposure for 5 years or more (housepainters, car sprayers, shoe manufacturers), have been found to develop Chronic Solvent induced Encephalopathy (CSE). CSE is characterized by symptoms of cognitive impairment (reduced information processing speed, memory and concentration difficulties, fatigue, irritability, and mood changes (van Valen et al., 2012, 2018). In a next paragraph we elaborate on "painter's disease", compared to aerotoxic syndrome.

7. OZONE

Following Federal Aviation Regulations cabin ozone levels should not exceed 250 parts per billion by volume (ppbv) when the aircraft is above 32,000 ft. A time-weighted average ozone concentration should not exceed 100 ppbv for any 3-h period when the aircraft is above 27,000 ft. (Spengler et al., 2012). Although many planes are equipped with "converters", that promote the decomposition of ozone in the cabin air, high levels of ozone are occasionally reported, reaching 256–275 ppbv (Bekö et al., 2015; Bhangar et al., 2008; Spengler et al., 2012). Ozone concentrations are significantly higher for flights on higher latitude routes, versus flights that follow lower latitudes (Spengler et al., 2012). This is due to ozone production from solar ultraviolet radiation that is highest in the tropics, and on the other hand the result of the large-scale air circulation in the stratosphere that transports tropical ozone towards the poles. Exposure to high ozone concentrations is associated with adverse respiratory effects, especially in infants or adults with cardiopulmonary conditions (Bhangar et al., 2008). Most commonly reported symptoms are dry mouth, lips and eye symptoms, fatigue, headache, breathing discomfort and asthma-exacerbation (Bekö et al., 2015).

8. Flame retardants

Brominated flame retardants are added in seats, carpets, plastics and electronics of aircraft to prevent or slow down the outbreak of fire. High concentrations of polybrominated diphenylesters have been reported in dust samples, collected from airplanes (Allen et al., 2013; Strid et al., 2014).

9. Carbon monoxide

Another potential contaminant in cabin air is carbonmonoxide (Solbu et al., 2011). Pilots exposed to fume events, with reductions in acetyl- or butyl cholinesterases and NTE activity (Heutelbeck et al., 2016; Michaelis et al., 2017), also had carboxyhemoglobin levels above the normal range (Michaelis et al., 2017). Carbonmonoxide exposure is well known in aircraft fueling vehicles, or due to exhaust fumes from the combustion engines, and was reported by pilots of small airplanes (Cessna, Piper) in civil aviation. The most common physical symptoms of chronic low-level carbon-monoxide toxicity are headache, dizziness, breathing difficulties, nausea, and flu-like symptoms. These symptoms are non-specific and often dismissed as having a viral cause (Clarke et al., 2012). Carbon monoxide is a neurotoxin that can cause immediate or delayed cognitive impairment (Sykes and Walker, 2016).

10. Insecticides

The recent severe outbreaks of Corona and Zika virus disease showed the important role of airtravel in the rapid spread of newly emerging infections, resulting in pandemics (Eldin et al., 2020; Mangili and Gendreau, 2005). Of major concern are vectors (mosquitos) of malaria, dengue, chikungunya, Zika and yellow fever. Airlines are obligated to spray pesticides inside the aircraft cabin to kill insects that may be on board. Disinsection is undertaken as a public health measure to address the potential threat posed by insects to the health of humans, animals, plants and agriculture and to comply with quarantaine regulations of various countries. The insecticides used are Permethrin and d-Phenothrin, belonging to the synthetic pyrethroids type 1. Disinsection can be applied at several moments of the flight: (1) spraying of the entire internal surfaces of the passenger cabin and cargo at least once in 2 months. This is done shortly before passengers embark the aircraft, using Permethrin 0.2 and 0.5 g/m^2 on floors (excluded are food preparation areas), (2) pre-flight spraying, using Permethrin 2% aerosol, 35 $g/100\,m^3$ (aircrew on board), (3) before the flight takes off, using d-Phenothrin 2% aerosol, 35 $g/100\,m^3$ (passengers and aircrew on board), (4) while the aircraft starts its descent to its destination (passengers and aircrew on board). Of the countries that require disinsection, about half require the insecticides to be applied while passengers are on board, the other half

permits the use of an aerosolized spray before passengers are boarded (Sutton et al., 2007). Concerns have been expressed about the efficacy of disinsection for preventing the international spread of vectors via air travel, apart from the possible toxicity for flight crew. However, a systematic review showed that disinsection with the recommended permethrin or d-Phenothrin concentrations was highly effective against a broad range of arthropods (Pang et al., 2020). Only three papers reported symptoms in passengers or crew possibly associated with insecticide spraying in cabins. Two papers concern occupational related symptoms of 12 and 33 aircrew members, respectively (Kilburn, 2003; Sutton et al., 2007). The other paper describes a case-report of a single passenger, who developed anaphylaxis symptoms immediately after application of d-Phenothrin (van den Driessche et al., 2010). Most common symptoms in the case series of 12 flight attendants were respiratory problems, headache, irritability, tingling of hands or feet. In the other case series, 33 self selected flight attendants, who were regularly exposed to synthetic pyrethroids during flight, were compared with 202 non-exposed persons. Using questionnaires and a test battery an association was observed between exposure to pyrethroid insecticides and changes in mood and balance.

The application in aircraft of Permethrin and d-Phenothrin is not considered to pose undue risk to human (World Health Organization, 2019). The evidence linking exposure to insecticide spraying with negative health impact is limited. However, flight attendants working on international flights connected to Australia (where disinsection is mandatory) had significant higher urinary permethrin metabolite levels than those on domestic flights. In pre-flight spraying, exposure by inhalation was the main route (almost 90%) versus oral and dermal exposure. It is stated that disinsection leads to exposure at levels comparable to agricultural pesticide applicators (Wei et al., 2012, 2013).

To reduce on-board transmission of SARS-CoV-2 aircraft manufacturers recommend the use of 70% isopropylalcohol as a disinfectant for surfaces in the cockpit, cabin (tray tables, armrests, seat covers, lavatories) and cargo holds, as well as alcohol-based hand sanitizer dispensers for frequent hand disinfection, near the boarding door.

11. Nanoparticles

Air quality monitoring studies near the Amsterdam Schiphol airport and the Frankfurt International airport have demonstrated that airports are major sources of ultrafine particles (UFPs), due to aircraft exhaust

(Keuken et al., 2015; Ungeheuer et al., 2021). Particulate samples collected near a runway of an international airport in Japan showed that organic compounds in the ambient nanoparticles were dominated by nearly intact forms of jet engine oil (Fushimi et al., 2019). Using liquid chromatography for compound separation, pentaerythritol- and trimethylolpropane esters were detected—base stocks of lubrication oil—as well as jet oil additives, including TCP and trimethylolpropane phosphate (Ungeheuer et al., 2021).

These particles are also present in cabin air. High concentrations of UFPs are to be expected because of the high temperatures up to 1700 °C attained in aircraft jet engines leading to pyrolysis of engine oil (Amiri et al., 2017). Oil contamination in the compressor will result in an aerosol, i.e., a fog of ultrafine (<100 nm) droplets in bleed air, under most operating conditions (Amiri et al., 2017). Oil leaks permit UFPs to cross oil seals used in turbine engines (Howard et al., 2018). Inflight cabin events were associated with ingress of external particles. Major events were defined as 15-min averages of >10.000 particles/cc; minor events as 15-min averages between 500 and 10.000 particles/cc (Spengler et al., 2012). Aerosol composition data showed non-exhaust, non-airport sources, especially contaminated oil.

There are several studies reporting UFP measures in cabin air (Li et al., 2014; Michaelis et al., 2021). In a recent study UFPs were counted on four short-haul flights on Airbus A320 and A319 (Michaelis et al., 2021). It was explored whether particles number was associated with the age of the aircraft engines, ranging from 7 months to 14 years, and with engine or APU power changes in air supply. UFP concentrations ranged from as low as 35 to as high as 97.800 particles/cm^3. Maximum concentrations in the four flights ranged from 31.300–97.800 particles/cm^3. These peak concentrations were reached after a full-power take-off, or when APU bleed air was selected on. Two of these peak concentrations were linked by aircrew to a noticeable oil smell. Following maximum concentrations frequently rapid decreases of UFPs were recorded, as a result of the high air exchange rate in aircraft. The lowest level of UFPs was identified during steady state engine operation, during the cruise phase of flight. Although seal leakage is expected to increase with sealing wear, particle numbers were not associated with the age of the engine of these aircraft. It was concluded that counting UFPs may have potential as a rapid means to identify bleed air contamination (Michaelis et al., 2021). In a systematic review of five studies sampling 148 flights, the number of ultrafine particles showed a wide variation, counting 417–100.000/cm^3 (Hayes et al., 2021). Peaks of particle concentrations were found in climbing, descending and cruising phases in several flights (Spengler et al., 2012). At elevated power levels, median particle size is in

the range of 50–70 nm, incidentally particles larger than 2000 nm are identified (Zhai et al., 2014). So the bulk of particles form at less than 100 nm. These fine particles have a low deposition rate. At very low contamination rates, ultrafine particles can be generated even in the size of 10 nm (Amiri et al., 2017).

The above findings confirm the presence of UFP aerosols in cabin air. More studies presenting chemical analysis of these particles are urgently needed. UFPs bind with organophosphates and other toxic compounds. After inhalation these particles are preferentially deposited in the alveolar part of the lungs. They cross the air-blood barrier by pinocytosis and are able to transport the chemicals across the blood-brain barrier (Howard et al., 2018). In addition the olfactory pathway may provide a direct access of particles to the brain. Continual presence with superimposed peaks of particles in cabin air may be responsible for chronic respiratory and neurological problems. Cumulative toxicity is a probable explanation, considering a working life time of aircrew up to 20.000 flying hours (He et al., 2021; Howard et al., 2018). Hydraulic fluid fumes may be more toxic per unit mass than engine oil fumes, due to a higher concentration of organophosphates (2800 μg/m^3) and smaller particle size (He et al., 2021). So, the presence of an aerosol of ultrafine particles in bleed air may be an additional causal mechanism, with cumulative (toxic) exposure leading to aerotoxic syndrome (Howard et al., 2018).

12. Symptoms of aerotoxic syndrome (see Tables 4A, 4B, and 4C)

We previously described a case series of three patients (two pilots, one flight attendant) with probable aerotoxic syndrome (Hageman et al., 2020a,b).

The most frequently reported symptoms were headache, balance problems, fatigue, gastro-intestinal complaints and cognitive impairment. These symptoms appeared to onset during the flying career. A temporal relationship was noted between time spent on board aircraft and symptom onset or exacerbation, and symptoms reduced or resolved during holidays and days off. All three patients reported smell events during their flying career, but none reported distinct fume events. In one of these patients reduced levels of butyrylcholinesterase were measured after a flight indicating possible exposure to organophosphate compounds. All three aircrew were found to have elevated neuronal and glial auto-antibodies, compared to sera of

Table 4A Health surveys and questionnaires on symptoms of pilots and cabin crew, 2000–2020.

Nr	Author, year	Study population	Aircraft type	Remarks
1	Winder and Balouet (2000)	10 cases: pilots, first officers, pursers, flight attendants, involved in a fume event	3 models of airplanes of 5 airlines	Both immediate and long-term/ residual symptoms
2	Winder and Balouet (2001)	7 cases, pilots and flight attendants, exposed to cabin contamination	3 models of airplanes	
3	Cox and Michaelis (2002)	21 cases, 19 pilots, 2 flight attendants	BAe 146	Increase of symptoms while on duty: 84%; improvement on holidays or days off: 90%
4	Winder et al. (2002)	50 cases, 16 pilots, 34 cabin crew	BAe 146 and Airbus 320 aircraft	Onset of symptoms immediately while flying (96%), in 74% persisting complaints for 6 months
5	Michaelis (2003)	106 cases, all pilots, 93 of 106 involved in a fume event	Boeing 757	
6	Harper (2005)	60 cases, 39 pilots, 19 flight attendants, 2 not specified, after exposure to contaminated cabin air	BAe 146, Boeing 757 and Airbus	
7	Somers (2005)	39 cases, flight crew	BAe 146	Temporal relationship between onset of symptoms and exposure history
8	Mackenzie Ross (2008)	27 cases, all pilots	BAe 146 and Boeing 757	
9	Abou-Donia et al. (2013)	34 cases, pilots and flight attendants, after exposure to bleed air contamination; 4000–16.500 flying hours	n.a.	Symptoms 2–4 weeks after exposure
10	Michaelis et al. (2017)	219 cases, 77: no health problems, 142: symptoms	BAe 146	88%: aware of exposure to contaminated air, 7% visible smoke or mist; 32% median to chronic symptoms
11	Hageman et al. (2020a,b)	3 cases, 2 pilots, 1 flight attendant	Boeing 737,747 and Airbus A 330	

n.a. = not available.

Table 4B Most often reported symptoms.

Symptoms	1[a]	2	3	4	5	6	7	8	9	10	11
Irritation of eyes, nose, throat	x	x	x	x	x	x	x	x			x
Salivation	x			x							
Nausea, vomiting	x	x	x	x	x		x	x	x	x	
Flu-like symptoms								x			
Headache	x	x	x	x	x	x	x	x	x	x	x
Fatigue	x	x	x		x	x		x	x	x	x
Lethargy							x				
Disorientation	x	x									
Dizziness	x	x	x	x	x	x	x	x		x	
Cognitive impairment			x		x	x	x	x		x	x
Memory impairment	x	x	x	x					x	x	
Confusion		x			x					x	
Balance/coordination loss	x	x	x	x	x		x		x		x
Tremor	x										
Irritability		x									
Blurred vision	x	x		x	x					x	
Breathing difficulties	x	x	x	x		x	x	x	x	x	x
Chemical hypersensitivity		x		x			x				
Chest pain	x										
Palpitations	x			x					x		x
GI-complaints, cramps			x	x		x	x	x			x
Diarrhea	x			x	x		x				
Loss of sensation, tingling		x	x		x		x		x		

[a]Study number see Table 3 A.

healthy controls, consistent with central nervous system injury. All three had genetic polymorphisms of paraoxonase (PON-1), and two of cytochrome P450, leading to reduced ability to metabolize toxic compounds (Hageman et al., 2020a,b).

The symptoms reported have much in common with those reported in other case-series and surveys of aircrew, thought to have been exposed to

Table 4C Acute and chronic symptoms of pilots and cabin crew (Michaelis et al., 2017; Winder and Balouet, 2001).

Acute signs and symptoms	Chronic symptoms
Irritation of eyes, nose, throat	Irritation of eyes, nose, throat
Neurology: Headache, dizziness, confusion, balance problems, blurred vision, nystagmus, tremor, impaired memory and concentration, paresthesias	Headache, dizziness, slowed mental processing, impaired memory and concentration, difficulty multi-tasking, balance problems, paresthesias, numbness
Gastrointestinal: Nausea, vomiting, diarrhea	diarrhea
Respiratory: Breathing difficulties, shortness of breath, tightness in chest	Breathing difficulties, cough, tightness in chest
Cardiological: Increased heart rate, palpitations	Increased heart rate, palpitations
General: fatigue	Fatigue, multiple chemical hypersensitivity, muscle pain

contaminated air. The earliest report in the literature of effects of contaminated air on board aircraft already dates back to 1977 (Montgomery et al., 1977). The authors described a military navigator who was incapacitated due to neurological and gastro-intestinal distress, after synthetic lubricating oil fumes had entered the air supply. Routine medical investigations did not reveal any abnormalities, no treatment was instigated, and he recovered within 24 h.

12.1 Questionnaire surveys

Prior to the 1980s, contaminated cabin air was masked by the impact of tobacco smoke. It was not until the enactment of smoking bans on aircraft in the early 1990s that attention turned to other potential contaminants. Since then, a number of case-series and surveys of aircrew have appeared in the literature. In a survey of 50 Australian aircrew, participants were asked to identify health symptoms experienced while flying, and factors which may have caused them. Most respondents reported that their symptoms occurred after exposure to fumes in the cabin (Winder et al., 2002). Some recovered once they vacated the plane, but symptoms persisted for 1–6 months in 82%; and 16% required hospitalization. The most frequently reported symptoms included eye and skin irritation, breathing difficulties, nausea and vomiting, headache, dizziness, balance problems, fatigue and cognitive impairment. The authors coined the term ‘aerotoxic

syndrome' for the association of symptoms with exposure to hydraulic fluids and to engine oil fumes mixing with cabin air.

Cox and Michaelis (2002) undertook a small-scale survey of Australian aircrew who reported an increase in health complaints (most notably headaches, respiratory difficulties, eye and skin irritation, fatigue and cognitive impairment) since flying the BAe-146 aircraft type. Almost half of the respondents mentioned an association with exposure to engine oil fumes. In a comparable British survey of 106 Boeing-757 pilots, a deterioration in health during their flying career was reported linked to a similar constellation of symptoms (Michaelis, 2003). Remarkably, 88% reported at least one fume event during their flying career and the total number of incidents reported amounted to 1674. Yet only 61 events (17% of the total) were officially reported to regulatory authorities. A large health survey among 4011 flight attendants, conducted by the Occupational Health Research Consortium in Aviation (OHRCA) in 2014, showed that almost 50% of flight attendants reported one or more symptoms, in which respiratory and neurological symptoms accounted for 23% and 17%, respectively (OHRCA, 2014). More recently Michaelis et al. published the findings from a survey of 219 British BAe-146 pilots, of whom 34% reported frequent exposure to contaminated air and 63% reported "adverse effects, ranging from acute to long-term symptoms". In the same paper a forensic analysis discloses 15 cabin air quality incidents in which aircrew reported symptoms leading to impairment or even complete in-flight incapacitation (Michaelis et al., 2017).

12.2 Case series

Over the last two decades a number of case-series have been published describing the health status of aircrew with a history of exposure to contaminated air on commercial aircraft. All describe a constellation of physical health complaints comparable to those reported in the surveys by Winder in 2002 or Michaelis in 2003 (Burdon and Glanville, 2005; Harper, 2005; Mackenzie Ross, 2008; Mackenzie Ross et al., 2011; Somers, 2005).

13. Evidence of central nervous system injury

13.1 Neuropsychological studies

Several neuropsychological studies have been undertaken in different countries across the globe over the last two decades, exploring the nature and severity of cognitive complaints reported by many aircrews in questionnaire surveys, see Table 5.

Table 5 Neuropsychological findings in aircrew with probable aerotoxic syndrome.

Author, year	Description of cases	Study design	Findings	Remarks
Coxon (2002)	2 pilots, 6 flight attendants, all female, age 24–56 years, (mean 36.1). Flying career: 2–12 years. Complaints after oil emissions from the BAe 146	Battery of neuro-psychological tests	Impaired: reaction time, information processing speed, fine motor skills, grip strength and auditory verbal and working memory.	No statistical analysis, no control group
Heuser et al. (2005)	26 flight attendants with complaints after "neurotoxic injury", 3 male, 23 female. (of whom) 8 had impaired smell	Occupational clinic, neuropsychological tests ($n = 26$), and PET scan ($n = 12$)	Memory/learning disability in 18/26, 2 with reading disorder, 4 had depression. All 12 PET scans abnormal: decreased frontal brain function (consistent with toxic encephalopathy).	4 abnormal PET without neuropsychological abnormalities
Mackenzie Ross et al. (2006)	1 pilot, "middle aged", with chronic complaints following contaminated air events: skin, gastrointestinal, fatigue, light headed, coordination ↓, cognitive performance ↓	Case report, clinical, laboratory and neurophysiological data	Normal scores, but submaximal on information processing speed, working memory span, verbal learning and mental flexibility. No mood disorder, somatisation or conversion disorder.	Also mild sensory neuropathy, autonomous dysfunction and increased autoantibodies against brain specific proteins
Mackenzie Ross (2008)	18 pilots, 16 male, 2 female; mean age 48.4 years (36–62), symptoms after fume events on a Boeing 757 or BAe 146 aircraft. Working: 9. Sick leave: 4. Retired: 5 Mean lifetime flying hours: 11.642, range 3000–25,000 Mean lifetime flying years: 22, range 5,5–40	Cohort study, clinical interview and detailed neuropsychological assessment	Mean full scale IQ: 119 Tests of psychomotor speed, attention, executive function and working and verbal memory below expected level. Significant correlation between exposure indices (total number of flying years) and scores on tests of verbal memory and executive function	Self selected cohort, crude indices of exposure. None of the pilots failed the malingering test

Continued

Table 5 Neuropsychological findings in aircrew with probable aerotoxic syndrome.—cont'd

Author, year	Description of cases	Study design	Findings	Remarks
Mackenzie Ross et al. (2011)	29 UK pilots, 15: BAe 146 or B 757, 14: B 737; one or more fume events in their career; mean age 50,4 years, mean years of flying 20 years	Case series, neuropsychological investigation	Reduced performance on tests of attention, psychomotor speed and visual sequencing	A random sample of 29 of 70 pilots, who returned a questionnaire, was asked to undergo neuropsychological assessment
Coxon (2014)	3 pilots: 1: 20 years flying, Fokker 27,50,70 and 100, BAe 146; fatigue, deterioration of memory 2: 30 years flying, Boeing 747, 777, headache, "brain fog" 3: 30 years flying, no further data	Case series, neuro-psychological investigation	Impaired: processing speed (in 2 pilots),executive function (3 pilots), new learning skills (3 pilots). Poor: reaction time to stimuli (2 pilots), visual memory (1 pilot)	No controls
Reneman et al. (2016)	12 aircrew (pilots average flying hours: 8130), 10 male, 2 female. Average age: 44,4 years (29–55). 11 matched controls (racing car drivers)	Questionnaire, MRI (DTI-MRI, fMRI) and detailed psychometric neuropsychological tests	More self reported cognitive complaints and depressive symptoms in aircrew. Significant group differences on reaction speed measures and interference. Neurocognitive impairment in only 3/12 aircrew.	DTI-MRI: small regions of affected white matter microstructure.

PET: positron emission tomography.
DTI-MRI: diffusion tensor imaging- magnetic resonance imaging.
fMRI: functional magnetic resonance imaging.

In 2002 Coxon published findings from a case series of eight Australian aircrew who reported mental confusion, concentration difficulties, and memory problems following alleged exposure to oil emissions on BAe 146 aircraft. All were female, age range 24–56 years and they had worked on this aircraft type for between 2 and 12 years. Psychometric assessment revealed evidence of reduced choice and sequential reaction time, psychomotor speed, grip strength and auditory verbal memory, compared to normative data, in all but one; reduced auditory working, memory span, concentration and recall of visual information in 4, and 5 aircrew showed impairment on a sequencing task (Picture Arrangement). Although this was a case series in which no control group was available for comparison and no statistical analyses were undertaken, Coxon concluded that there were sufficient grounds to warrant further investigation. She recommended a wider-scale study of BAe 146 aircrew was undertaken.

In 2005 Heuser et al. reported findings from an evaluation of 26 North American flight attendants with complaints after probable exposure to cabin fumes on one or multiple occasions. In most cases fume events resulted in flight interruption, emergency room visits or sick leave. All underwent a neurological examination and neuropsychological assessment and 12 underwent PET brain imaging. The interval between fume event and PET scan was not reported. Unfortunately, the authors did not specify the psychometric tests used or test scores but reported that all flight attendants exhibited neuropsychological deficits (particularly memory impairment) and all were diagnosed with toxic encephalopathy. Neurological examination was abnormal in 9, and mildly abnormal in 6 flight attendants showed a bilateral postural tremor, had impaired balance, coordination, smell and taste. PET imaging showed imbalance of function between cortical and subcortical areas and frontal and occipital areas. The authors recommend further research and that a protocol be created, outlining the evaluations flight personnel should undergo, following exposure to cabin fumes.

In 2006 Mackenzie Ross published a single case study involving a UK airline pilot who developed chronic ill health over an 11-year period of flying, during which he often smelt oily fumes. Routine medical investigations failed to identify the cause of his symptoms. The pilot subsequently suffered a marked deterioration in cognitive function after experiencing a contaminated air event of sufficient severity to provoke light headedness, eye and throat irritation in both the pilot and co-pilot. They filed an Air Safety Report on landing. The pilot resumed flying within a few days but developed insomnia, fatigue, coordination problems, joint weakness, excessive

sweating and poor memory and concentration and he was referred to medical specialists. Neurological examination found evidence of coordination problems, positive Romberg sign, mild sensory neuropathy, and autonomic nervous system dysfunction. Serum autoantibody tests showed increased autoantibodies against nervous system proteins. Neuropsychological assessment did not find evidence of global intellectual decline; however, performance on tests of information processing speed, auditory working memory span, auditory verbal memory and mental flexibility was below expected levels compared to premorbid estimates. The pilot passed a test of malingering, was not suffering from mood or anxiety disorder and had no history of disease, injury or substance abuse which might otherwise account for his symptoms. His neuropsychological profile was similar to that reported by Coxon in Australian aircrew. The relevant aviation authority withdrew the pilot's license on psychiatric grounds despite the fact he was not suffering from a psychological disorder and had never been examined by a psychiatrist.

In 2008 Mackenzie Ross published findings from a case series of 27 UK pilots who underwent neuropsychological and adult mental health assessment undertaken by 12 different examiners, blind to the exposure status of the pilots. Seven were referred by medical specialists and 20 referred themselves. All described distinctive oily chemical smells, the intensity of which would vary depending on phase of flight. Ten pilots had not formally reported these incidents because they assumed the smell was part of the normal working environment and not something to be concerned about. Two pilots reported being threatened by colleagues when they suggested to report fume events, and seventeen reported fume events at some point in their career. Pilots reported alarming failures at work such as being unable to retain or confusing numerical information from Air Traffic Control, forgetting whether they had lowered the undercarriage, completing tasks in the wrong sequence, concentration and decision-making difficulties. Mackenzie Ross excluded nine pilots with a medical or psychiatric history which might otherwise explain these complaints. In the remaining 18 pilots, language, perceptual skills, and general intellectual ability were relatively well preserved, but performance on tests of auditory verbal memory, processing speed, auditory working memory, and executive functioning was below expected levels in 14/11/10/9 pilots, respectively. This was consistent with their subjective complaints of attentional problems and mental slowing in everyday life. Nine were still flying, 4 were on sick leave and 5 had retired on ill health grounds. The neuropsychological profile seen in

pilots was different from that seen in a control sample and significant correlations were noted between exposure indices (e.g., total number of years or hours flying) and scores on tests of verbal memory and executive function. The deficits identified in this study could not be attributed to malingering or mood disorder. Firm conclusions regarding a causal link with contaminated air could not be determined because only crude indices of exposure were available (i.e., self-report) and the sample was small and self-selected. The author concluded further research was warranted which should include consideration of other aspects of flying which could have an adverse effect on health and cognitive function.

In 2011 Mackenzie Ross et al. reported findings from a neuropsychological study of 29 randomly selected UK pilots. The study was completed in two phases. In phase one 1500 pilots on a union database were contacted and asked to complete questionnaires on work history, exposure history and physical health. In the second phase, 29 pilots were randomy selected. Twenty-two pilots reported experiencing at least one fume event at some point in their career, with most reporting multiple exposures. This sub-sample was asked to undergo a neuropsychological assessment. Performance on psychometric tests was compared to national norms based on over 2000 adults. Pilots overall IQ was higher than the UK average, which is not surprising given their occupation. However, the pilots neuropsychological profile deviated from that seen in the standardization sample and mirrored that seen in other neurotoxic conditions and in the previously reported case series of 27 pilots. In particular they showed reduced performance on tests of attention, psychomotor speed and visual sequencing. The authors concluded this has implications for flight safety and that further research is warranted.

In 2014 Coxon described three case studies involving pilots repeatedly exposed to fume events over very long careers (17–30 years) who reported a variety of physical symptoms (fatigue, skin rashes, eye irritation, headaches, sinusitis) and a gradual decline in cognitive function. Neuropsychological assessment found evidence of impaired processing speed, executive functioning and new learning/memory. All three pilots eventually ceased flying due to ill health. They had complained of ill health and cognitive problems many times beforehand, but their symptoms were usually dismissed as 'temporary problems'. These cases highlight how neurotoxic effects can take time to fully evolve. Coxon concludes it is of utmost importance that every worker exposed to neurotoxic chemicals, who complains of cognitive impairment, is thoroughly investigated and has follow up evaluations at

regular intervals. Slowed processing speed and executive dysfunction would impair a pilot's ability to handle aircraft in an emergency situation.

In 2016 Reneman et al. published findings from a case series of 12 aircrew, 10 male, 2 female, who complained of cognitive impairment, who underwent neuropsychological assessment and MRI brain imaging including Diffuse Tensor Imaging, Spectroscopy and Functional MRI. Results were compared with those obtained from 11 healthy volunteers, matched for gender age and IQ. Only 3 of the 12 aircrew showed lower scores on only 2 (reaction time and susceptibility to interference) out of 20 psychometric tests. On MRI white matter macrostructure did not differ between the groups, but small differences were noted in microstructure in specific brain regions in the corpus callosum. Higher cerebral blood flow was noted in left occipital cortex; and hypoactivation in the right prefrontal cortex when performing an executive task. Extent of cognitive impairment correlated with subjective reports and white matter integrity; but none of these variables correlated with flight hours. No significant differences in brain metabolites or volume were observed between the groups. Given the obvious aviation safety implications, the authors conclude further research is warranted in which alternative explanations should be considered such as irregular work schedules and dysregulation of biological clocks.

Neuropsychological studies undertaken to date have documented cognitive deficits in aircrew (primarily involving reduced reactions times/processing speed, memory impairment and executive dysfunction), associated with repeated exposure to engine oil emissions in aircraft. Every study has methodological limitations in terms of sample size, lack of comparison groups and objective indices of exposure, making it difficult to establish causation. Most studies are cross-sectional. Nevertheless, these initial findings highlight the need for further research because any form of central nervous system dysfunction is dangerous in a safety critical environment and constitutes a flight safety risk. Unfortunately, industry, regulatory authorities and government departments appear reluctant to fund or commission a large-scale epidemiological study to determine whether exposure to oil and hydraulic fluid causes ill health and cognitive impairment. This despite numerous advices of researchers and even government scientific advisory committees, across the globe (COT report, 2007).

13.2 Brain imaging

DTI-MRI of 12 aircrew with cognitive complaints, revealed minor abnormalities of the white matter microstructure (Reneman et al., 2016).

These were not as prominent as imaging abnormalities recognized in other chronic toxic encephalopathies, like painters' disease (Visser et al., 2008). Using MRI-spectroscopy no significant differences between aircrew and controls were observed, in brain (choline-)metabolites nor in brain volume (Reneman et al., 2016). In another toxicology study, 12 flight attendants were analyzed for of ill health and cognitive complaints following a history of exposure to contaminated air. Positron Emission Tomography (PET) showed abnormal results in all subjects, with decreased activity in the frontal regions and increased function in occipital areas and of the limbic system (Heuser et al., 2005). Such a pattern is often seen in other neurotoxic conditions, ascribed to an imbalance in function between cortical (decrease) and subcortical (increase) areas, and imbalance of frontal (decrease) versus occipital (increase) functions.

13.3 Autoantibodies to nervous system proteins

The blood-brain barrier (BBB) protects the brain from auto-immune reactions and generally prevents developing B-cells from being exposed to unique brain antigens. In case of degraded integrity of the BBB an immune response may be provoked. Neuronal and glial proteins, which are normally present in the central nervous system, may leak into the bloodstream. Once in the systemic circulation, these antigens activate a variety of cells, culminating in B-cell activation, rendering autoantibodies production to the targeted proteins (Abou-Donia and Brahmajothi, 2020). In a wide variety of neurological diseases and syndromes serum autoantibodies have been implicated as biomarkers of specific neuronal degeneration in the central nervous system (CNS) (Diamond et al., 2009). For example, autoantibodies have been identified as reliable biomarkers for neuronal damage in dementia and traumatic brain injury (Kim et al., 2018). The last few years the accent has been on a large spectrum of paraneoplastic and other antineuronal auto-antibodies with associated diseases (Lancaster and Dalmau, 2012). The concentration of some individual autoantibodies may be disease-specific (Levin et al., 2010). The presence of serum autoantibodies may have more diagnostic utility than the brain derived protein biomarkers themselves. They are particularly useful in the chronic stage because they remain in the body for a relatively long period.

Higher levels of circulating autoantibodies compared to matched controls were found in flight crew who complained of ill health following exposure to contaminated air (Abou-Donia et al., 2013; Abou-Donia and Brahmajothi, 2020). From our own studies a pilot was tested after a set of

flights spending 45 h in the cockpit during 10 days. Significant increases in autoantibodies were noted after exposure to polluted air and correlated with the onset of symptoms. After cessation of flying for a year, this pilot's clinical condition improved and levels of serum autoantibodies normalized. Thus, a temporal relationship between exposure to air emissions, clinical condition, and levels of serum autoantibodies to nervous system specific proteins was found in this case. This suggests that autoantibody testing may be a valuable marker of nervous system injury in aerotoxic syndrome. In our cases MBP, MAP-2 and GFAP were most abnormal (Abou-Donia et al., 2013; Hageman et al., 2020a,b).

14. Involvement of the peripheral nervous system

In surveys of health symptoms in pilots and cabin crew with probable aerotoxic syndrome sensory complaints, such as paresthesia, tingling and numbness are reported in 20–70% of cases (Cox and Michaelis, 2002; Michaelis, 2003; Michaelis et al., 2017; Somers, 2005; Winder et al., 2002). These typical sensory symptoms contrast with the predominantly motor symptoms of the delayed type OP-polyneuropathy. This supports the existence of a distinct toxic sensory polyneuropathy in patients with suspected aerotoxic syndrome, probably not related to OP toxicity. In most of these patients with a corresponding pattern of complaints, nerve conduction studies were unremarkable (de Graaf et al., 2014; Heutelbeck, 2019). In a few (neurographic) studies however a mild sensory polyneuropathy was found (Mackenzie Ross et al., 2006; Michaelis et al., 2017; Winder et al., 2002).

Solvents in cabin air may be responsible for this sensory type polyneuropathy. Solvents, such as ethylene oxide and n-hexane produce a peripheral neuropathy with characteristic pathological features. These agents are known to cause cross linking of neurofilaments, focal axonal swelling, slow axonal transport, segmental demyelination and secondary axonal swelling. Most reports on solvents-induced polyneuropathy concern n-hexane, used as industrial solvent and degreasing agent (Pan et al., 2017; Puri et al., 2007).

Over the last 20 years peripheral nerve impairment has been investigated in a few studies of patients with probable aerotoxic syndrome. In one study various complaints such as restless legs, muscular jerking and tingling sensations were correlated with fume events (Heutelbeck, 2019). In some cases, balance problems, muscle fasciculations and reduced sensation were noted. Paresthesia of the hands were reported in about 30% of flight crew

members (Abou-Donia et al., 2013; Somers, 2005). One frequently used test is vibration sensitivity, which evaluates peripheral somatosensory function. In chronic low-dose OP-exposure a decreased sensitivity is described in farmers and sheep dippers (Pilkington et al., 2001). However gross neurological status (balance, motor and sensory function, reflexes) is normal in most suspected cases of aerotoxic syndrome (de Graaf et al., 2014).

Characteristic symptoms of *small fiber neuropathy*, a subtype of polyneuropathy of thin myelinated and unmyelinated nerve fibers, are unfrequently reported by pilots and cabin crew. These symptoms are painful burning paresthesia, hypersensitivity to touch and temperature-changes and autonomic complaints (Sommer et al., 2018). There is one study on the prevalence of small fiber neuropathy in patients with probable aerotoxic syndrome. In nearly all patients in this studygroup skin biopsy showed that the intra-epidermal nerve fiber density was significantly decreased. Therefore this sensory, typically painful disease may well be responsible for both sensory and autonomic complaints in pilots and cabin crew (Heutelbeck, 2019).

A skin biopsy with quantification of intraepidermal nerve fiber density is the most reliable tool to confirm the diagnosis of small fiber neuropathy (Devigili et al., 2019; Lauria et al., 2010). Both solvents and ToCP exposure may lead to a reduced density of epidermal nerve fibers (Sommer et al., 2018).

15. Respiratory symptoms

Respiratory symptoms are common among aircrew and have been reported in various studies (Burdon, 2012; Burdon and Glanville, 2005; Cox and Michaelis, 2002; Mackenzie Ross et al., 2006; Michaelis et al., 2017; Winder et al., 2002; Winder and Balouet, 2001). These symptoms include nasal or throat irritation, sinus problems, tightness of chest, cough, wheezing, influenza-like symptoms during flight, and dyspnea. In some cases, a hypersensitivity for chemical substances is evoked; for instance a cough triggered by odors or irritants (Burdon and Glanville, 2005; Roig et al., 2021). In case series spirometry is often normal or may show mild upper airway obstruction and a positive bronchodilator test. In a retrospective case series in BAe-146 flight crew, pulmonary diffusing capacity was abnormal in six of 14 pilots and flight-attendants (Burdon and Glanville, 2005). Decreased vital capacity and forced expiratory volume (FEV1) were found in cabin crew after a fume event (Heutelbeck, 2017). In the latter study most of the about 350 patients showed normal results on routine

spirometry, but more subtle abnormalities were detected using additional pulmonary testing. Small airway obstruction, a reduced alveolar-arterial gradient, and mild abnormalities of diffusion capacity and oxygenation during exercise (ergo-spirometry) are described (Heutelbeck, 2017). In most cases with respiratory symptoms after a fume event a bronchial hyperreactivity, irritant-induced asthma or reactive airways dysfunction syndrome (RADS) is diagnosed. These symptoms subside within a few months in most cases, although in some cases complaints may persist for years (Roig et al., 2021).

16. Cardiological symptoms

Cardiological symptoms and signs mentioned in aircrew are increased heart rate, palpitations and dysrhythmias (Winder and Balouet, 2000). There are no systematic studies on cardiotoxicity in aircrew after fume events. A cross-sectional study did not show an increased prevalence of cardiac events outcomes in flight attendants (McNeely et al., 2018). However, in a post-mortem study of a 43-year old airline pilot, a T-lymfocyte infiltration appeared in heart muscle tissue, consistent with lymfocytic myocarditis (Abou-Donia et al., 2014). Remarkably a similar infiltration was found in peripheral nerves, concurrent with axonal degeneration and demyelination of the brain and spinal cord.

In animal models a variation of cardiovascular complications has been reported: electrocardiografic abnormalities, myocardial infarction, cardiac failure with hemodynamic instability, and histopathological changes (apoptosis, degeneration) (Georgiadis et al., 2018). Experimental animal studies suggest that chronic low level OP exposure upregulates inflammatory mediators, leading to neurotoxicity as well as cardiotoxicity in the form of "catecholamine mediated myocarditis" (Banks and Lein, 2012). This underlying mechanism is confirmed in human studies. An examination of hearts from 13 patients who died as a result of organophosphate poisoning revealed myocarditis, pericarditis and interstitial inflammation (Anand et al., 2009).

17. Gastro-intestinal symptoms

Nausea has been reported very commonly by aircrew during or shortly after fume events. Other gastrointestinal complaints include salivation, vomiting, diarrhea, abdominal cramps and pain (Cox and Michaelis, 2002; Mackenzie Ross et al., 2006; Michaelis et al., 2017; Winder et al., 2002; Winder and Balouet, 2001). These symptoms may be regarded

as muscarinic, and are also seen in chronic occupational OP exposure, particularly in farmers and sheep dippers (Lee et al., 2003). Sheep farmers with chronic ill health present with a syndrome known as dipper's flu, with headache and gastrointestinal symptoms (Cherry et al., 2011).

18. A genetic susceptibility to organophosphates

A genetic susceptibility to OP's may explain why not all aircrew are equally affected. Over the last decade studies on chronic, low-level OP neurotoxicity revealed inter-individual differences in the ability to metabolize OP's and other organic substances as a result of genetic polymorphisms (Kaur et al., 2017; Khattab et al., 2016; Sunay et al., 2015). This may explain the difference in individual reports of ill health following exposure to contaminated air. A genetic susceptibility to OP's has been reported too in other occupational groups, with focus on the Paraoxonase (PON)-1 enzyme, involved in the detoxification of OP's (Albers et al., 2010; Cherry et al., 2011). As such, people differ in terms of PON-1 activity.

In addition, genetically based diverging levels of cytochrome-P450 activity account for differences in hepatic metabolic capacity up to 50–100 fold (Polimanti et al., 2012). Individuals expressing a very high P450 activity and a very low PON-1 activity may have a summative 4000 fold increase in threshold for toxicity.

18.1 PON-1

Human paraoxonase (PON)-1 is an essential enzyme that is synthesized mostly in the liver and secreted into the blood. PON-1 plays a major role in metabolism and deactivation of OP's. The PON-1 enzyme is characterized as an organophosphate hydrolase and it has a structural resemblance to ToCP. The PON-1 status (paraoxonase levels across PON-1 genotypes) is a predictor for OP-sensitivity, indicating if persons are more susceptible to the adverse effects of organophosphates (Furlong et al., 2006). The importance of plasma PON-1 activity level in protecting against OP exposure has been clearly demonstrated in animal experiments (Li et al., 1993; Shih et al., 1998). PON contains three isoforms (PON-1, PON-2 and PON-3) and is encoded by a cluster of genes. The gene is located on chromosome locus 7q21.3, in a region near the locus of the gene for AChE (Sunay et al., 2015). The plasma paraoxonase activity in human populations exhibit a polymorphic distribution, and individuals with high, intermediate or low paraoxonase activity can be identified (Costa et al., 2005). So far more than

400 single-nucleotide polymorphisms have been detected in human PON-1 gene. However, most of the studies focus on two amino acid polymorphisms in PON-1. One of these is the alteration of glutamine to arginine at the codon 192 (PON 192Q). The other is a single-nucleotide transversion from methionine to leucine at codon 55. Distribution of PON 192Q and 55 M/L polymorphism frequencies vary greatly across populations. The 192Q and 55 M alleles are more frequent and have low Paraoxonase-activities (Josse et al., 2001). These two polymorphisms were present in all three patients with probable aerotoxic syndrome, in a recent case series (Hageman et al., 2020a,b). Serum paraoxonase status may be a major factor in determining resistance to organophosphates in medical protocols.

18.2 CYP-450

Cytochrome-P450 enzymes mediates the hepatic metabolization of OP's. In the human genome so far 57 genes encoding for CYP-450 enzymes have been identified. Which of these 57 cytochrome P450 enzymes is involved in the metabolism of contaminants in engine oil is largely unknown (Furlong, 2011), however various studies have made some progress in characterization of specific CYP-450 enzymes (Khattab et al., 2016; Reinen et al., 2015). The genes can be classified into different families, according to the amino acid similarities of the encoding proteins. In particular, CYP-450 genes in families 1–3 encode for 22 different isoforms, mainly involved in the metabolism of drugs and toxins (Polimanti et al., 2012). More specifically CYP-1A and 1B, CYP-2D and 2E1, and CYP-3A are involved in neurotoxin breakdown (Ferguson and Tyndale, 2011). There is evidence that variations in the subtype CYP-2D6 play an important role in susceptibility to chronic OP intoxication, but so do CYP-1A2, CYP-2C19, and CYP-3A4 (Khattab et al., 2016, Mutch and Williams, 2006). In the metabolism of ToCP CYP 450-1A2 and 3A4 were found to be responsible (Reinen et al., 2015) Variation in alleles may lead to four phenotypes: poor, intermediate, rapid and ultra-rapid metabolizers. In a recent case study two of the three patients had CYP-polymorphisms, probably consistent with overexpression of enzymes mediating the conversion of OP's to its reactive metabolites (Hageman et al., 2020a,b).

19. Establishing a link with exposure

In 2000 a committee of the National Research Council (NRC) of the United States convened to study sources of cabin air contamination in aircraft and advise on control systems. Their report confirmed the occurrence

of contamination and the committee proposed a series of recommendations, including improved air quality measurement (National Research council committee on air quality in passenger cabins of commercial aircraft, board on environmental studies and toxicology, 2002). Inspired by this report the US congress instructed the Federal Aviation Administration to fund research for the improvement of cabin air quality. On carrying out this project researchers could not come to a mutual agreement with airline companies to apply air sampling devices. Most aircraft still have not been equipped with air monitoring devices. Large scale implementation of this equipment is essential to increase the likelihood of capturing a fume event. Besides objective and reliable measures such as biomarkers of both exposure and nervous system injury would be useful. These measures are indispensable to link chemical exposure to health outcomes. Researchers need to explore the possible effects of both cumulative low-level exposure to contaminants, as well as the effect of fume events. Comparable to other occupational groups, particularly those involving work with pesticides, both acute poisoning events and cumulative low-level exposure may be harmful (e.g., Farahat et al., 2003; Kamel and Hoppin, 2004; Mackenzie Ross et al., 2013; Pilkington et al., 2001; Zhang et al., 2016) (Fig. 2).

It should be considered that more than one chemical contaminant is involved in the etiology of ill health. To date the primary focus in this area has been on TCP; this OP comprises about 3% of engine oil (Michaelis, 2011). Concern is raised in view of the fact that OP's – used as chemical weapons or in pesticides—are known to be neurotoxic (Mackenzie Ross et al., 2013; White et al., 2016). Only a small number of air quality monitoring studies have been undertaken over the last decade. The conclusion is that levels of contaminants detected in cabin air fall within safe exposure standards and are *unlikely* to be responsible for alleged aerotoxic syndrome (de Ree et al., 2014). Furthermore, Schindler et al. (2013) analyzed levels of T(*o*)CP metabolites in the urine of 332 aircrew who had reported fume or smell events on their last flight; ToCP was not detected, and TCP in only a single sample. TCP was unlikely to account for their health complaints. The continued focus to date on TCP has led to the neglect of other contaminants; many other potentially toxic substances are contained in jet engine oil.

Beyond variant OP's (triphenylphosphate (TPP), dibutylphenylphosphate (DBPP), chloorisopropyl phosphate and tri-n-butyl phosphate (Solbu et al., 2011; Winder and Balouet, 2002), one should consider solvents like toluene, xylenes, and formaldehyde. Chronic solvent-induced encephalopathy (CSE) is a syndrome similar to aerotoxic syndrome in many aspects (see Table 6). CSE is recognized as an occupational disease by the International Labour

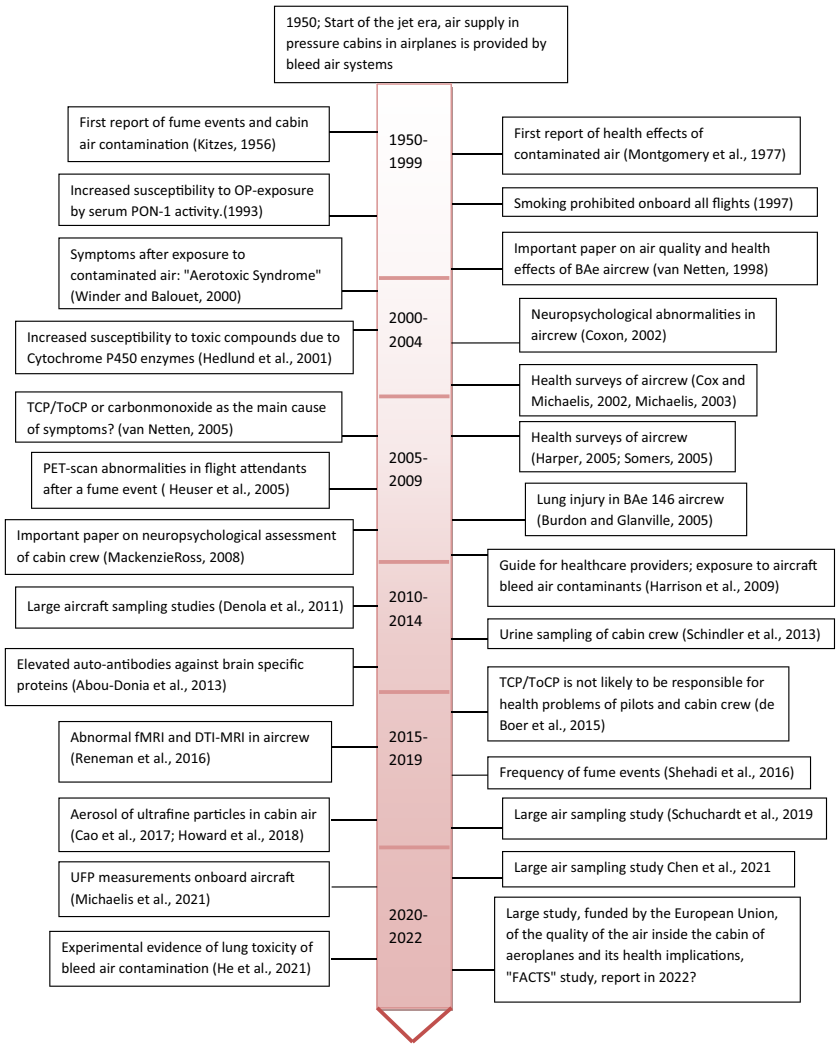

Fig. 2 Timeline, studies of cabin air contamination and health effects.

Organization (ILO, 2010), based on a landmark paper in the Lancet on the effects of solvents on the nervous system (White and Proctor, 1997) and the diagnosis is supported by later neuro-imaging findings in patients suspected of "painter's disease" (Alkan et al., 2004; Tang et al., 2011; Visser et al., 2008).

Furthermore, pilots exposed to fume events have been found to have raised carboxyhemoglobin levels, reflecting exposure to carbon monoxide

Table 6 Recognition as an occupational disease of aerotoxic syndrome, compared to solvent induced chronic toxic encephalopathy.

	Aerotoxic syndrome	Solvent-induced chronic toxic encephalopathy	References
Exposure to	Organophosphates, solvents, CO	Solvents	Harrison and MackenzieRoss (2016); Meyer-Baron et al. (2008)
Population involved	Pilots, cabin crew	Painters, carsprayers, furniture manufacturers, printers	Michaelis (2016); van Valen et al. (2018)
Duration of exposure	No data, >5000 flying hours?	>5 years of daily occupational exposure	van Valen et al. (2012)
Incidents of high exposure	Fume events	Working with solvents in an enclosed space	Shehadi et al. (2016); Lee et al. (2019)
Complaints, symptoms	Headache, fatigue, memory and concentration problems, nasal or throat irritation, sinusproblems, tightness of chest, gastrointestinal and muscle complaints, palpitations	Headache, fatigue, impaired memory and concentration, irritability, mood changes.	Michaelis (2011), Hageman et al. (2020a,b), van Valen et al. (2018).
Diagnostic criteria	Criteria of probable aerotoxic syndrome described in 2020	WHO criteria 1985, European expert group: consensus paper on neuropsychological criteria, 2012	Hageman et al. (2020a,b); van der Hoek et al. (2000); van Valen et al. (2012).
Clinical neurological examination	Occasionally balance problems, muscle fasciculations and reduced sensation.	In some cases optic atrophy (methanol), decreased smell, impaired balance, or signs of sensory neuropathy; in rare cases parkinsonism	Heutelbeck (2019); Dick (2006)

Continued

Table 6 Recognition as an occupational disease of aerotoxic syndrome, compared to solvent induced chronic toxic encephalopathy.—cont'd

	Aerotoxic syndrome	Solvent-induced chronic toxic encephalopathy	References
Neuropsychological testing	Reduced performance on tests of working memory, processing speed / reaction time and mental flexibility.	Impaired speed of information processing, memory and learning; correlation between exposure duration and cognitive complaints	Coxon (2002); Heuser et al. (2005); Mackenzie Ross (2008, Mackenzie Ross et al., 2006); van Hout et al. (2006)
Neurophysiological abnormalities	EMG: Nerve conduction unremarkable in most cases. In a few studies a mild sensory polyneuropathy. Skin biopsy: intra-epidermal nerve fiber density significantly decreased.	Increased latencies and reduced amplitudes of visual evoked responses. EMG: reduction in nerve conduction velocity, prolongation of distal latencies, mildly positive sharp waves and polyphasic potential in n-hexane exposure.	Winder et al. (2002); Mackenzie Ross et al. (2006); Michaelis et al. (2017); Heutelbeck (2019); Verberk et al. (2004); Pan et al. (2017)
MRI	DTI-MRI: slight abnormalities of the white matter microstructure (reduced FA values) in the CC, corona radiata, superior longitudinal fasciculus and thalamic radiation. fMRI: reduced brain activation (precuneus and prefrontal cortex) on a executive function task. MR spectroscopy: no significant metabolite changes	MRI: decreased volume of the genu of the corpus callosum. DTI-MRI: fractional anisotropy reduced in thalamus, caudate nucleus, correlating with attention and psychomotor speed abnormalities. Functional MRI (fMRI) during a working memory test: lower activation of anterior cingulate, prefrontal and parietal cortices MR spectroscopy: metabolite changes of basal ganglia, thalamus and parietal white matter	Reneman et al. (2016); Visser et al. (2008); Tang et al. (2011; Haut et al. (2006), Alkan et al. (2004)

SPECT/PET	PET: decreased activity in the frontal regions and increased function of occipital areas and the limbic system, especially the extended amygdala region	IBZM-SPECT: reduced striatal dopamine binding	Heuser et al. (2005); Visser et al. (2008)
Auto-antibodies against brain specific proteins	Increased auto-antibodies against central nervous system proteins	No data	Abou-Donia et al. (2013), Abou-Donia and Brahmajothi (2020)
Genetic susceptibility	High CYP P450 and low PON-1 activity	CYP2E1 polymorphism and glutathion S-transferase M1–0 genotype	Furlong (2011); Kezic et al. (2006)
Recognition as an occupational disease	No recognition in aviation medicine	Fully recognized	Wolkoff et al. (2016); Cannon (2016); ILO, (2010); White and Proctor (1997)

EMG: electromyography, DTI-MRI: diffusion tensor magnetic resonance imaging, FA: fractional anisotropy, PET: Positron Emission Tomography. IBZM-SPECT: single photon emission tomography with a highly specific dopamine D2 ligand, CYP 450: cytochrome P450, PON-1: Human paraoxonase-1.

(Michaelis et al., 2017). The most common symptoms of chronic low-level carbon-monoxide toxicity are similar to complaints reported by aircrew; headache, dizziness and nausea, however there may be a broader spectrum of symptoms, complaints, either temporary or persistent (Clarke et al., 2012; Solbu et al., 2011; Sykes and Walker, 2016).

Hydraulic and de-icing fluids can contaminate incoming engine-air (Solbu et al., 2011). Hydraulic fluids are made up of tributyl phosphates and triphenyl phosphates, while de-icing fluids consist of ethylene- and propylglycols. Finally, high concentrations of polybrominated diphenylesters, a component of flame retardants have been reported in dust samples, collected in aircraft (Allen et al., 2013).

Therefore, air quality studies must take into consideration a wide spectrum of potential toxic chemical compounds, which might combine at high temperatures to form even more toxic compounds. Researchers also need to consider that individual susceptibility leads to different expressions of illness. Increased risk is influenced by age, previous health status or genetic variability to detoxify chemicals.

20. A probable diagnosis of aerotoxic syndrome?

In this chapter we have reviewed research on various physical and neurological complaints in aircrew who report deterioration in health throughout their flying career. Causation from cabin air contamination has yet to be established. In 1965 Hill published a paper to identify necessary steps to pass from an observed association between an environmental feature and a health problem to causation (Hill, 1965). He listed the following research criteria to establish causation between exposure and disease:

1) a temporal relationship must exist between exposure and the onset of symptoms,
2) a dose-response relationship should be apparent
3) removal from exposure should modify the effect,
4) sound epidemiological studies must exist which demonstrate a strong association between exposure and disease outcome,
5) consistent findings should be documented in different populations, in different study designs, and at different times,
6) the cause-effect relationship must be biologically plausible, consistent with laboratory findings, and relatively specific,
7) in agreement with current knowledge and
8) evidence of analogous disorders, caused by similar agents should be obtained.

These criteria are discussed in detail for aerotoxic syndrome by Howard et al. (2017); Ramsden (2012). The first paper was focussed on TCP, the latter on a mixture of toxic compounds. Aerotoxic syndrome was never reported prior to the introduction of engine bleed air pressurization systems, though it was detected soon afterwards (Howard et al., 2017). In addition to temporality, consistency of the pattern of symptoms exists and epidemiological studies and animal experimental data supports a causal link. However, aerotoxic syndrome does not meet all of these criteria (Verbeek, 2012). As mentioned previously, the symptoms reported by aircrew are non-specific and common in the general population (Wolkoff, 2013). As far as we are aware, no studies have been undertaken to date, which explore the sensitivity and specificity of the symptoms which are thought to reflect aerotoxic syndrome.

The role of specific other work-related factors in aviation which might account for ill health (including cognitive impairment) have yet to be considered, such as shift work, jet lag, low ambient pressure, sleep deprivation, temperature, low humidity, noise, vibration, work/life stress and separation from family (Bor et al., 2017a,b; Lindgren et al., 2007; Mackenzie Ross, 2017; McGuire et al., 2013). What is needed is an epidemiological study comparing exposed and unexposed populations of aircrew to tease apart the aetiological role of general work factors vs toxic exposure in causing ill health.

21. Proposal of diagnostic criteria for aerotoxic syndrome

Given the continuing scientific uncertainty of the impact on health of exposure to contaminated air on commercial aircraft, further research is warranted. There is an urgent need for a clearly defined, internationally accepted medical protocol for the evaluation of health complaints among aircrew. Internationally agreed diagnostic criteria must be developed, to facilitate disease recognition and allow prospective, prognostic and treatment studies to be undertaken. We recommend multicentre and multidisciplinairy research programs for this purpose.

We proposed the following criteria for the diagnosis of probable aerotoxic syndrome (Hageman et al., 2020a,b):

1) Aircrew report symptoms, such as headache, fatigue, loss of balance, gastro-intestinal complaints, palpitations and cognitive complaints;
2) Symptoms should show a temporal relationship with flying hours and onset shortly after a fume event or directly after flying, and improve after cessation of flying.

3) The same symptoms should occur repeatedly after flying and not under other circumstances (Ramsden, 2012).
4) Objective evidence of exposure should be sought such as flight log data (flying hours), air incident reports, engineering records, on-board air monitoring or swipe measurements of chemical contaminants. Biomarkers of exposure should be taken such as reductions in acetyl- or butylcholinesterases activity or increases in carboxyhaemaglobin levels in blood serum. Other supportive findings are present such as a high P450 activity or low PON-1 activity.
5) Objective evidence of nervous system injury is available following medical tests, neuropsychological assessment, brain imaging or serum neuronal and glial autoantibody-tests (Abou-Donia et al., 2013).
6) Other causes of ill health should be excluded by medical history, physical and neurological examination, laboratory investigation and brain imaging. Neuropsychological assessment should exclude a depressive disorder, somatisation disorder, and malingering.

We propose the following medical evaluation protocol, see Fig. 3:

In cases of probable aerotoxic syndrome a stepwise diagnostic procedure should be performed in which the first step is a comprehensive medical history taking, including a thorough occupational history (flying hours, aircraft types, fume events), and a physical neurological examination (Heutelbeck, 2019; Harrison et al., 2009; Burdon and Glanville, 2005; Michaelis et al., 2017; Mackenzie Ross et al., 2006; Liyasova et al., 2011; Schindler et al., 2014; Hageman et al., 2020a,b).

The second step includes a bloodtest and chest X-ray.

In a probable case, the third step, depends on the presented symptoms, but may include respiratory function tests, electrocardiography (ECG), echocardiography, neuropsychological assessment, autonomic nervous system tests (with a tilt table test), electromyo- and -neurography, and brain MRI.

Finally genetic testing for PON-1 polymorphisms and overexpression of Cytochrome P450 enzymes may demonstrate genetic susceptibility.

22. Discussion-future study directions

Although the studies cited above document ill health among aircrew, causation continues to be debated. A number of weaknesses limit the conclusions that can be drawn, such as sample bias, inadequate measurements and potential response bias, non-specificity of symptoms and lack

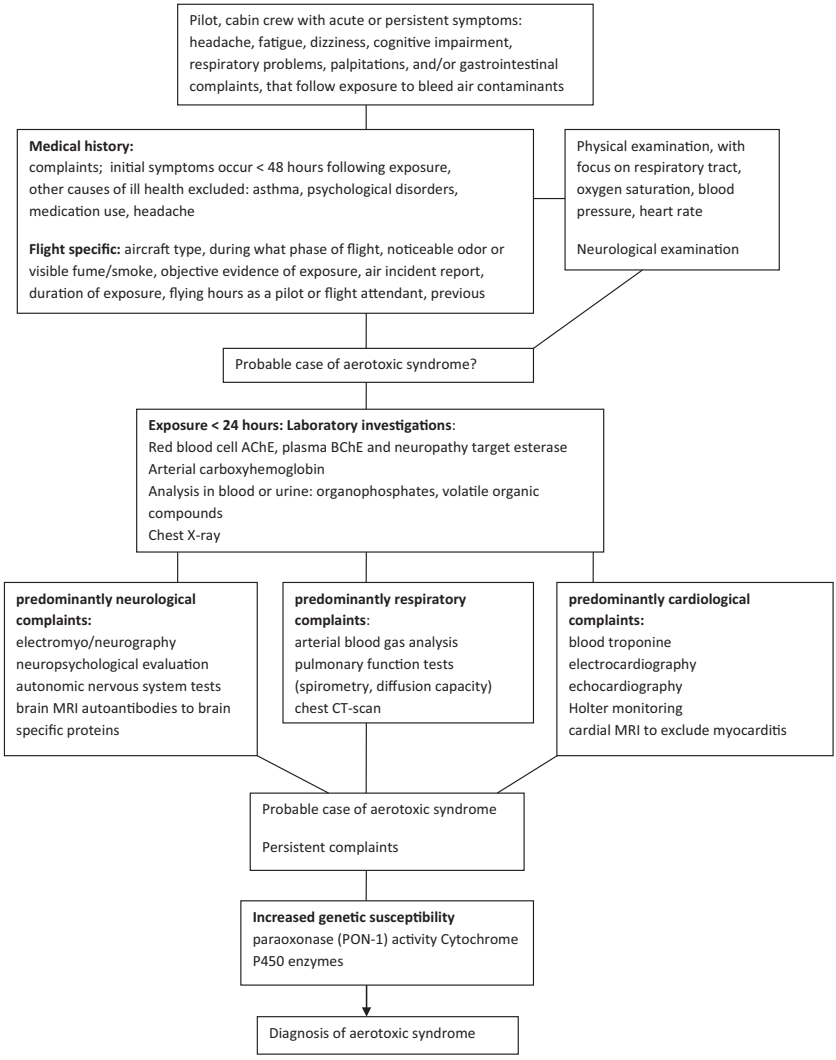

Fig. 3 Flow-chart, assessment of cases with probable aerotoxic syndrome.

of objective evidence of exposure. To date, all previous studies involve small, self-selected samples of aircrew. Researchers have undertaken questionnaire surveys of aircrew using unvalidated measures and response rates have been low (5–50%). Selection bias is involved as aircrew present themselves to physicians with symptoms they attribute to exposure to contaminated air. As a result, it remains unclear how representative these populations are of aircrew in general. The symptoms reported are diverse (involving

several organ systems) and non-specific and are highly prevalent in other clinical populations and even in the general population. Few studies include any comparison or control groups to enable researchers to determine the specificity of symptoms and association with exposure. Objective evidence of exposure is frequently lacking as cabin air is not routinely monitored for the presence of chemical contaminants. On the other hand, underreporting of health complaints is common among aircrew.

Signs and symptoms in aircrew are probably related to repeated low dose exposure to a mixture of toxic compounds. Chronic pre-exposure to repeated low dose OP's may lead to increased vulnerability to subsequent higher (fume-event) dose of organophosphate exposure (Howard et al., 2017). This may explain why a high proportion of aircrew frequently attends a hospital after a fume event, while passengers do not appear to be affected. It has been pointed out that the pattern of symptoms in aerotoxic syndrome cannot be explained by inhibition of AChE or BChE alone (Costa, 2018). When effects are seen at organophosphate doses that cause minimal or no inhibition of esterases, possible neurotoxic effects of long-term, low-dose exposure should be studied. The assumption that symptoms of aerotoxic syndrome are based on OP-induced delayed neuropathy is a failure of hazard characterization (Howard, 2020). OPIDN is not seen in aircrew. It is more likely that symptoms of aircrew are the result of OP induced chronic neurotoxicity (OPICN) (Abou-Donia, 2003). OPICN induced by low-level inhalation of organophosphates present in jet engine lubricating oils and the hydraulic fluids of aircraft could explain the long-term neurologic deficits, and the neuropsychiatric and behavioral problems (Abou-Donia, 2003). In addition to OP's, exposure to other toxic compounds, such as solvents and carbonmonoxide in cabin air, may generate synergistic effects.

What is needed is a prospective epidemiological survey of a large and representative randomly enrolled sample of aircrew, in which symptoms are described and qualified in exposed and unexposed groups and compared to rates in other clinical and general populations. Such an exposure-health outcome study will require airline participation and facilitation. Clinically sensitive and meaningful measures with circumscript sensitivity and specificity should be used to establish whether the profile of symptoms seen in aircrew who have been exposed to contaminated air, differs from that observed in other cohorts. To the best of our knowledge only one paper has been published to date which has attempted to do so. Mackenzie Ross et al. (2011) compared the profile of neuropsychological deficits observed in

aircrew with a history of exposure to contaminated air, with that of farm workers exposed to organophosphate pesticides, and plotted this against the cognitive profiles of healthy population. They found a specific profile of abnormal cognitive performance in pilots mirroring that of exposed farmers. Although these results hint at an association between exposure to neurotoxic chemicals and cognitive impairment, they do not provide incontrovertible evidence of causation in the case of ill aircrew. Scientific progress demands objective and reliable measures of exposure. Consequently the "aircraft cabin of the future" should have (1) improved engine seal designs to minimize oilleakage, (2) continuous air quality monitoring, with in-situ real time and delayed analysis, (3) bleed air sensors, distributed across the cabin, and (4) new cabin air filter technology to improve cabin air quality (Kos et al., 2018; OHRCA, 2014; Rosenberger, 2018). The new generation airplanes, like the Boeing 787 Dreamliner has a bleedless air distribution system. The air in the Dreamliner is funneled into electrical compressors near the wing, rather than through the engines. Airline-companies should invest in the development of bleedless aircraft as part of safety in aviation.

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