Original research

AEROTOXIC SYNDROME: A NEW OCCUPATIONAL DISEASE?

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ABSTRACT

Background: Concerns related to adverse health effects experienced by aircrew exposed to aircraft contaminated air have been ongoing for over 6 decades. Unfiltered breathing air is supplied to the cabin via the engine compressor. The likelihood that oil leaking over the engine oil seals may enter the cabin air supply has prompted continuing debate about the hazards associated with exposure to neurotoxic substances and to the thermally degraded or pyrolysed mixture. In this study, we undertook an in-depth investigation of aircrew involved in suspected aircraft contaminated air events.

Methods: Two studies were conducted to review the circumstances and symptoms of a cohort of aircrew working in the pressurized air environment of aircraft. A table of effects was then used for categorizing symptoms and reviewing other sources of data related to aircraft fluids and selected other conditions.

Results: Both acute and chronic exposures to neurotoxic and a wide range of thermally degraded substances were confirmed, along with a clear pattern of acute and chronic adverse effects. The latter were supported by medical findings and diagnoses, notably involving the neurological, neurobehavioural and respiratory systems.

Conclusion: A clear cause and effect relationship has been identified linking the symptoms, diagnoses and findings to the occupational environment. Recognition of this new occupational disorder and a clear medical investigation protocol are urgently needed.

Keywords: AEROTOXIC SYNDROME, AEROTOXICITY, CABIN AIR CONTAMINATION, CABIN AIR QUALITY, JET ENGINE OILS, OIL FUMES, TCP

INTRODUCTION

In 1955, the first civilian aircraft adopted the military practice of bleeding unfiltered air (so-called bleed air) from engine compressors to supply the cabin ventilation system. Adverse effects on crew exposed to low levels of synthetic jet engine oil leaking over the oil seals were soon observed *(1)*. It was promptly recognized that air bled from the engine compressors was contaminated via internal engine oil leakage into the compressor air *(2)*. Hydraulic and de-icing fluids may also contaminate incoming engine air. Military studies found that the base stock of engine oils produce a wide variety of toxic substances as temperatures increase (i.e. when pyrolysed) *(3)*.

Turbine engines utilize synthetic lubricants that generally include an ester base stock (95%), a wide variety of triaryl phosphates (TAPs), organophosphate (OP) anti-wear additives (around 3%), amine antioxidants and proprietary ingredients (1–2%). The commercial formulation of the OP additive is generally cited as tricresyl phosphate (TCP). Exposure of such substances to extreme temperatures generates a large number of pyrolysed compounds and hydrocarbons. Hydraulic fluids are made up primarily of tributyl phosphates (TBPs) and triphenyl phosphates, while de-icing fluids consist of ethylene and propyl glycols.

Over the last 2 decades, many ad hoc air-monitoring studies have been performed during normal engine operations. These have focused on TCP, which is

routinely found in 25–100% of air samples taken during flights *(4)*. TBP was identified in 73% of flights, while low levels of TBP and triphenyl phosphate metabolites have been found in 100% of urine samples.

While increasing numbers of reports and case studies have been published over the years, there has been much debate about the contamination sources and components, toxicity, consistency of signs and symptoms, and lack of causal mechanism *(5–7)*. The lack of an accepted international protocol for the medical investigation of crew and passengers after an air quality incident means that consistent data has been difficult to obtain. This is further complicated by the fact that, at the levels encountered, the toxicants tend to cause a diffuse set of neurological and other symptoms currently classified as nonspecific.

The aim of this study was to undertake an in-depth investigation of aircrew involved in suspected aircraft contaminated air events to determine whether the reported symptoms and diagnoses are consistent with exposure to pyrolysed jet engine oil and engine/aircraft fluids or to other factors.

METHODS

Two independent studies were conducted to review the circumstances and symptoms of a cohort of aircrew working in the pressurized air environment of aircraft in which bleed air contamination was recognized to occur. A table of effects was then used to categorize symptoms and review other sources of data related to aircraft fluids and selected other conditions.

First, in a BAe 146 aircraft pilot health survey PhD research project (study A) *(8)*, United Kingdom pilot unions were requested to supply a list of all known United Kingdom certified BAe 146/146 Avro RJ aircraft (BAe 146) pilots. In all, 274 BAe 146 pilots (14% of the known total; 7% women) responded to a telephone interview or written questionnaire regarding their contaminated air exposure history, health effects and medical diagnoses. Data were collected (by SM) from 2005 to 2009 on demographics, flying history, flight deck air quality history, health effects and other comments. Of these, 142 of the pilots reported specific symptoms and diagnoses, 30 reported adverse health effects, but provided no detail, while 77 reported no health effects and 25 failed to advise either way.

The second study was a case study analysis of 15 potential cabin air quality incidents (study B). The incidents were selected because they were reported to be consistent with acute hyperventilation and hypoxia *(9)* and extensive data was available. Data sources included: airline, crew and maintenance reports; incident investigation and regulator reports; health effects and medical records; and media, union and legal reports. The incidents took place in Australia, Germany, the United Kingdom and the United States of America. Extensive data on the aircraft flight history, acute and long-term effects on crew, medical diagnoses and findings, and maintenance findings were collated.

A table was then developed to categorize acute and chronic symptoms. Study A included 142 pilots reporting specific symptoms, while study B included specific symptoms reported per incident, rather than per person. Substances utilized in the oils and hydraulic and de-icing fluids were then assessed against the European Regulation EC No. 1272/2008 on classification, labelling and packaging of substances (CLP), hazard classifications *(10)* and hazard databases. Symptoms were compared with published literature on cabin air, hyperventilation and hypoxia. Study A reviewed the workplace environment and general health of the group of pilots, whereas study B reviewed the various associated health and operational factors of the 15 suspected contaminated air events.

Authors of this paper include a qualified respiratory physician (JB) and medical pathologist (CVH), who are competent to analyse and interpret the health effects outlined in the studies. The first author (SM) is a commercial pilot with a PhD and MSc in this research area, and is thus uniquely qualified to perform the data assessment.

RESULTS

STUDY A

Study A included the 219 pilots who reported either specific (n = 142) or no (n = 77) health effects *(8)*. Adverse effects (ranging from acute to long-term symptoms) included cardiovascular, gastrointestinal, general (fatigue,

performance decrement) irritant, neurobehavioural, neurological and respiratory effects (Fig. 1).

FIG 1. STUDY A: BAe 146 AIRCRAFT PILOT HEALTH SURVEY - HEALTH EFFECTS (N = 219)

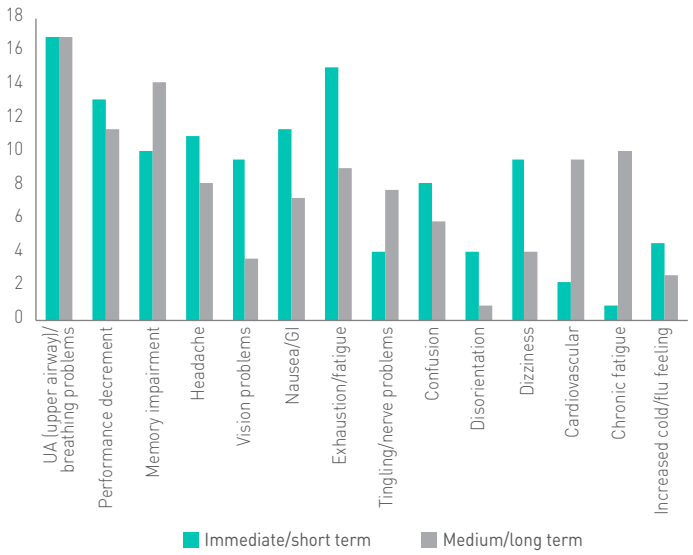
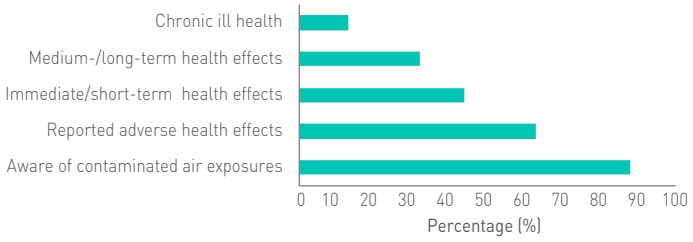


Fig. 2 shows that of the 274 pilots surveyed, 88% were aware of exposure to aircraft contaminated air. In all, 34% reported frequent exposures, 18% reported one to two big events and 7% reported visible smoke or mist events, with most reporting fumes only. In all, 63% reported immediate (i.e. acute, occurring during the flight) to long-term (i.e. chronic, lasting for >6 months) adverse health effects; 44% reported acute or short-term effects (lasting for days to weeks); and 32% reported medium-term (lasting for weeks to months) chronic effects consistent with suspected contaminated air exposures.

FIG. 2. STUDY A: BAe 146 PILOT ADVERSE HEALTH EFFECTS (N = 274)



Of the 274 pilots, 36 (13%) had died or had experienced chronic ill health leading to a permanent loss of fitness to fly. The types of adverse effects and diagnoses described were: neurobehavioural, 64%; neurological and general factors (e.g. chemical sensitivity, chronic fatigue, gastrointestinal (GI) symptoms), 53%; respiratory, 39%; and cardiovascular, 25%. The chronic cohort (13%) reported ill health at 37–433% above the controls. In all, 10% of the pilots had flown the BAe 146 for under 2 years, 54% for 3–10 years and 19% for over 11 years.

STUDY B

A range of findings for study B were identified based on 15 selected incidents (shown in Table 1). In all, 80% of events involved fumes only, 53% took place on the flight deck and 27% took place in both the flight deck and cabin. All events involved non-steady state (i.e. transient) engine operation, with 80% occurring during a climb and or descent. The incidents occurred in seven different aircraft types and 87% were linked to positive maintenance findings of oil leakage. In all, 66% of events involved further reports of fumes both before and after the incident.

Symptoms ranging from in-flight incapacitation to impairment were reported in 93% of events, with the majority (73%) involving pilots and 33% including full or partial incapacitation of two pilots. In all, 53% of events included long-term adverse effects for one or more crew members. Almost 75% of events included adverse effects in more than one crew member and 47% of events reported 10–23 different symptoms. In total, 73% of events were associated with some form of medical investigation soon after the incident, with less than 50% providing a variety of medical findings (shown in Table 2). Chronic medical findings/ diagnoses were found for two thirds of events (shown in Table 2), including cardiovascular, neurobehavioural, neurological and respiratory symptoms, chronic fatigue, multiple chemical sensitivity, aerotoxic syndrome, cancer, soft tissue damage, and chemical exposure. Nine pilots either became unfit to fly or died. Passengers reported adverse effects in 27% of events.

This study highlights links to a variety of operational factors: most events involved non-visible fumes only, low use of emergency oxygen and checklists by pilots, failure to report events as required, inadequate fault identification, with residual events occurring, with most events caused by oil leakage.

TABLE 1. STUDY B: KEY FINDINGS

CATEGORY	Column A
TYPE OF EVENT	Fumes x 12; Fumes & haze or smoke x 3
LOCATION	Flight deck x 8; Cabin x 3; Flight deck & cabin x 4
PHASE OF FLIGHT	Climb & or descent x 12; After start x 1; Various phases x 2
ENGINE OPERATION	Non steady state engine operation x 15
AIRCRAFT TYPES	BAe 146 x 5; A 330 x 2; A 319 x 2; B757 x 3 B737 x 1; B767 x1; B747 x 1
PREVIOUS REPORTS OF FUMES ON AIRCRAFT	10
FOLLOWING REPORTS OF FUMES ON AIRCRAFT	10
MAINTENANCE FINDINGS	Oil x11; Oil & hydraulic x 2; Unknown x 2 (1 possible oil overfill)
LEVEL OF EFFECT (AT TIME OF EVENT)- Pilots & cabin crew	Incapacitation & or partial incapacitation x 7; Incapacitation & impairment x 2; Impairment x 5
LEVEL OF EFFECT (AT TIME OF EVENT) -Pilot(s)	Incapacitation - Full & or partial x 7; Incapacitation & impairment x 1; Impairment- all x 4
2 Pilot incapacitation- Full or partial	5
TIME OF EFFECT	Immediate (in-flight) x 14; Short to medium-term x 12; Long-term x 8
NUMBER OF ACUTE SYMPTOMS REPORTED /INCIDENT	1 - 9 x 8; 10 - 23 x 7
>1 CREW MEMBER AFFECTED	11
PASSENGERS EFFECTED	4
MEDICAL TESTS UNDERTAKEN AT TIME OF EVENT	11
MEDICAL FINDINGS AT TIME OF EVENT	7
MEDICAL FINDINGS/DIAGNOSIS LATER ON	10
LOSS OF PILOT MEDICAL CERTIFICATE/ ABILITY TO FLY	9
LOSS OF CABIN CREW LONG-TERM FITNESS TO FLY	5
USE OF OXYGEN	Both pilots x 6; 1 pilot x 3; All crew x 0
DELAYED USE OF OXYGEN BY PILOTS	5
OXYGEN HELPED	8
EMERGENCY CHECKLIST USED BY PILOTS	2
REPORTING AS REQUIRED	9
AIR ACCIDENT INVESTIGATION BUREAU REPORT	10

TABLE 2. STUDY B: INDEPENDENT MEDICAL FINDINGS/DIAGNOSES BY MEDICAL STAFF

SHORT-TERM MEDICAL FINDINGS & DIAGNOSES	No.	LONG-TERM MEDICAL FINDINGS & DIAGNOSES	No.
Hydrocarbon fume inhalation/chemical injury on aircraft	1	RADS (Reactive Airways Dysfunction Syndrome) / occupational asthma	6
Adverse effect on the vocal chords and bronchial tubes	1	PTSD (Post Traumatic Stress Disorder)	3
Tricresyl phosphate (TCP) in blood	1	Neurotoxic injury	1
Raised levels of VOCs, nickel, cell degradation	1	Toxic encephalopathy	1
Double hernia due vomiting	1	Neuropathy on vocal chords/limbs	3
Poisoning by non-medical agent	5	MCS (Multiple Chemical Sensitivity)	1
SPO2 70% / 80% (peripheral capillary oxygen saturation)	2	CFS (Chronic Fatigue Syndrome)	1
Abnormal blood results: CK; CK-MB; LDH; GOT (AST); GPT (ALT)	2	Anxiety/depression	1
Traumatic muscle damage and ischemia due excessive athletic sports or contamination	2	Cognitive dysfunction	4
Toxic effect of gas, fumes or smoke	2	Dementia	1
Possible inhibition of the enzyme AChe or other neurospecific esterase caused by organophosphates	2	ADHD (Attention Deficit Hyperactivity Disorder)	1
Toxicopy	2	Seizure disorder	1
carboxyhemoglobin at or above the high normal range - exposure to burned organic chemicals	4	Depression	1
TOCP (Triortho cresyl phosphate) adduct on Bche	1	Aerotoxic syndrome	1
Inhalation injury	1	Chemical injury at work	1
Organophosphate (OP) type poisoning/internal bleeding	1	Neurological chemical injury	1
		CNS injury	1
		G4 GBM (deceased) - (Glioblastoma brain tumour)	1
		Wallerian degeneration	1
		Vocal polyps	1
		Heart attack + phosphate exposure (deceased)	1
		Frontal lobe damage	1
		Optic nerve damage	1
		Migraines	1

OVERVIEW SURVEY

Table 3 lists a range of acute and chronic symptom clusters with low to high prevalence in the selected studies. Study A found moderate acute central nervous systems (CNS), general, GI, neurobehavioural and irritant effects. Moderate levels of chronic cardiovascular, general (fatigue, performance decrement, rheumatological), irritant, neurobehavioural, neurological and respiratory effects were reported. Study B found high rates of acute GI, neurobehavioural, neurological, respiratory, performance decrement and irritant effects, and moderate levels of chronic, GI, neurobehavioural, neurological, respiratory effects and general effects such as chemical sensitivity, fatigue and performance decrement skin and irritant effects.

TABLE 3. OVERVIEW SURVEY

SYMPTOM	Study A		Study B		CLP- Hazard clasification	Literature	Hazard Databases[f]		HYPOXIA	HYPERVENTILATION
	n=142		15 incidents		(harmonized/notified)					
	No of pilots reporting Symptoms		No of incidents/ symptom		- oil, hydraulic, deicing fluid		- oil, hydraulic, deicing fluid			
	Acute	Chronic	Acute	Chronic			Acute	Chronic		
NEUROLOGICAL						X	X	X		
CENTRAL (CNS)						X	X	X		
Incapacity/paralysis; Impaired/loss of consciousness	9 (6%)	1 (1%)	15 (100%)			X	X	X	loss consciousness	semi consciousness
Headache /Pressure in head/ trouble speaking	47 (33%)	21 (15%)	11 (73%)	5 (33%)		X	X	X	headache	headache
Balance problems/erratic movement/ataxia	11 (8%)	7 (5%)	2 (13%)	1 (7%)		X	X	X		
Vision problems/tunnel or double vision/dilated pupils/ nystagmus	11 (8%)	10 (7%)	8 (53%)	1 (7%)		X	X		unresponsive pupils	visual disturbances
PERIPHERAL (PNS) Motor;Sensory;Autonomic						X	X	X		
Shaking/tremors; Inco-ordination/motor response	12 (9%)	17 (12%)	11 (77%)	6 (40%)		X	X	X		shakes/ twitches
Paraesthesiae/numbness in limbs/other; Peripheral neuropathy	12 (9%)	25 (18%)	5 (33%)	7 (46%)	Neurotoxicity, Single & repeat exposure	X	X	X		tingling/ numbness
Sweaty/temperature control/ pallor/flushing/taste	7 (5%)	6 (4%)	3 (21%)	6 (60%)		X	X	X	sweating	sweats/hot/ cold
NEUROBEHAVIOURAL						X	X	X		
NEUROLOGICAL						X	X			
Discomfort/intoxication/disorientation/ confusion	16 (11%)	3 (2%)	10 (66%)	1 (7%)		X	X		confusion/ disorientation	confusion/ disorientation
Behavioural/personaility Changes;unreality/anxiety/ depression	1 (1%)	20 (14%)		7 (46%)		X	X	X	unreality	unreality/ anxiety
Dizziness/light-headedness/ lethargy/drowsiness	21 (15%)	9 (6%)	11 (73%)	3 (20%)	Drowsiness/ dizziness:CNS	X	X	X	light headedness	light headedness
COGNITIVE						X	X			dizziness
Cognitive problems: problem solving/concentration/memory/writing	46 (32%)	58 (41%)	14 (93%)	9 (60%)		X	X	X	cognitive problems	cognitive impairment

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	No of pilots reporting Symptoms		No of incidents/ symptom		- oil, hydraulic, deicing fluid		- oil, hydraulic, deicing fluid			
	Acute	Chronic	Acute	Chronic			Acute	Chronic		
Giggling/euphoric			2 (13%)			X	X		euphoria	
GASTROINTESTINAL							X	X		
Nausea/vomiting/ Diarrhoea	25 (18%)	14 (10%)	14 (93%)	5 (33%)	Harmful if swallowed	X	X	X	nausea/ vomiting	
Cramps/bloating/pain/digestive problems		2 (1%)	4 (27%)	2 (13%)	Harmful/ fatal if inhaled	X	X	X		bloating/ belching
RESPIRATORY					Respiratory tract irritant					
Breathing problems/cough/ chest discomfort/wheezing/ lung irritation	15 (11%)	34 (23%)	11 (73%)	4 (27%)	Respiratory sensitization Allergy/ asthma / difficulty breathing	X	X	X	breathing problems	breathing problems
CARDIOVASCULAR										chest pain
Chest pain/ tightness/variable heart rate/palpitations/BP	6 (4%)	21 (14%)	5 (33%)			X	X		variable heart rate/ palpitations	irregular heart rate/ palpitations
GENERAL: rheumatological; miscellaneous; soft tissue					Target organ toxicity-single/ repeat					
Joint/muscle pain/aches/ twitches/weakness	8 (6%)	23 (16%)	4 (27%)	2 (13%)	Liver; urinary tract; heart;	X	X	X		weakness
Feeling unwell/performance decrement	33 (23%)	54 (38%)	15 (100%)	3 (20%)	Respiratory; systemic; CNS	X				
Fatigue/chronic fatigue/exhaustion	27 (19%)	65 (46%)	3 (20%)	6 (40%)	blood; kidneys	X	X	X	fatigue	exhaustion
Chemical sensitivity	3 (2%)	13 (9%)		5 (33%)		X				
Vocal/nasal/ throat polyps/ swelling			1 (7%)	1 (7%)		X				
IRRITATION										

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	n=142		15 incidents		(harmonized/notified)					
	No of pilots reporting Symptoms		No of incidents/ symptom		- oil, hydraulic, deicing fluid		- oil, hydraulic, deicing fluid			
	Acute	Chronic	Acute	Chronic			Acute	Chronic		
Eye, nose, throat & voice irritation/burning/redness/ hoarseness	41 (29%)	14 (11%)	15 (100%)	3 (21%)	Eye irritation	X	X	X		dry mouth
SKIN					Skin irritant/					
					skin sensitization					
Skin reaction/blisters/rash (uncovered areas); Burning scalp/alopecia	7 (5%)	11 (8%)	4 (27%)	5 (34%)	Harmful- skin exposure	X	X	X	bluish/red skin	
IMMUNE SYSTEM					Genetic defects	other	other	other		
Recurrent respiratory tract infections/altered immune system	11 (8%)	12 (8%)		1 (7%)	Damage: fertility/ unborn	X				
CANCERS		9 (6%)		1 (7%)	Carc 1B/2 - bladder; liver	X		X		

e X indicates symptom present.
f Hazardous Substances Data Bank, International Chemical Safety Card, US National Institute for Occupational Safety and Health.

The globally harmonized hazard classification system (i.e. CLP) for levels of substances present in oil and hydraulic and de-icing fluids lists a wide range of mandatory (harmonized) and non-mandatory (notified) hazard warnings. These include CNS, inhalation, neurotoxic and skin warnings; single and repeat exposure organ toxicity (systemic, CNS, respiratory and other); eye, skin and respiratory irritation; respiratory and skin sensitization; and genetic, reproductive and carcinogenic hazards. Key hazard databases (e.g. Hazardous Substances Data Bank, International Chemical Safety Card, US National Institute for Occupational Safety and Health) include a range of acute and chronic hazards associated with substances present in aircraft fluids, including cardiovascular, carcinogenic, GI, general, irritant, neurobehavioural, neurological, respiratory and skin effects. The available literature on exposure to aircraft fluids covers all categories identified. The adverse effects of hyperventilation and hypoxia cover some of the same categories.

DISCUSSION

Bleed air contamination has been recognized since the introduction of the bleed air system in the 1950s and remains a problem through to the present day *(2, 7, 11–14)*. All current transport aircraft, except for the Boeing 787, use the bleed air system to provide cabin ventilation. Transient, low-level oil leakage over the engine oil seals into the aircraft air supply occurs during normal flight operations, with less frequent, higher level leakage under certain operational conditions (e.g. seal wear or seal failure) *(4)*. The use of pressurized air from the engine compressor to both seal the oil-bearing chamber and supply cabin bleed air provides a mechanism for low-level oil leakage in routine engine operations *(4, 15)*. While many experts have suggested that oil leakage is associated only with rare failure events, others now recognize that chronic exposure is caused by the so-called tiny amounts of oil vapours released by oil leaking continuously over the seals during engine power changes *(4, 16)*. The manufacturer of aircraft described in study A acknowledged that all engines leak oil, that the amount of oil leaked by their engines was previously greater than the industry average, and that there was a general health and safety problem, but no in-flight safety issues *(17)*.

Although there have been many attempts to determine the frequency of oil fume events from available reports, underreporting is widely recognized *(8, 12)*. Thus, the population exposed to low-level oil fumes in flight is considered to comprise all crew and passengers. In 2015, this represented 3.5 billion passengers and around 0.5 million crew members.

The debate on cabin air contamination commonly focuses on ad hoc air-monitoring findings undertaken during normal flight operations. However, a number of smaller case studies have been undertaken over the last 6 decades. An early case study reported eye, nose and throat irritation, nausea, chest tightness, breathing difficulties, fatigue, light-headedness, dizziness, faintness, headache, vision problems and a metallic taste *(1)*. A number of case studies describing cardiovascular, general, GI, irritant, neurobehavioural, neurological and respiratory effects of cabin air have also been reported (see Table 4.11 in *(8)*). Further case studies have focused on exposure to a mixture of volatile organic compounds and OPs *(18, 19)*. The results presented here are consistent with the findings of these studies.

A syndrome consists of a group of signs and symptoms, some or all of which consistently occur together (although not all need be present), and can be recognized as a distinct entity. It has been suggested that aerotoxic syndrome, first described in 2000 *(20)*, is not a medical entity. Additionally, the reported symptoms are suggested to be "so broad and non-specific and can have many causes that it is difficult to define or discern a precise illness or syndrome" *(14)*. Physicians make a diagnosis on the merits of the case at hand and will then prescribe appropriate treatment. However, the information required for identifying a syndrome is not available at the level of the individual patient, but rather at the population level – it is epidemiological in nature. The symptoms associated with chronic low-dose exposure to OPs are acknowledged to be nonspecific and diffuse. For these reasons, clinicians who only treat one exposure case at a time may feel able to dismiss the concept of aerotoxic syndrome.

This overview study is the first to report extensive findings from two different cohorts. There were clear, consistent acute and chronic patterns of adverse effects, including CNS and peripheral nervous system

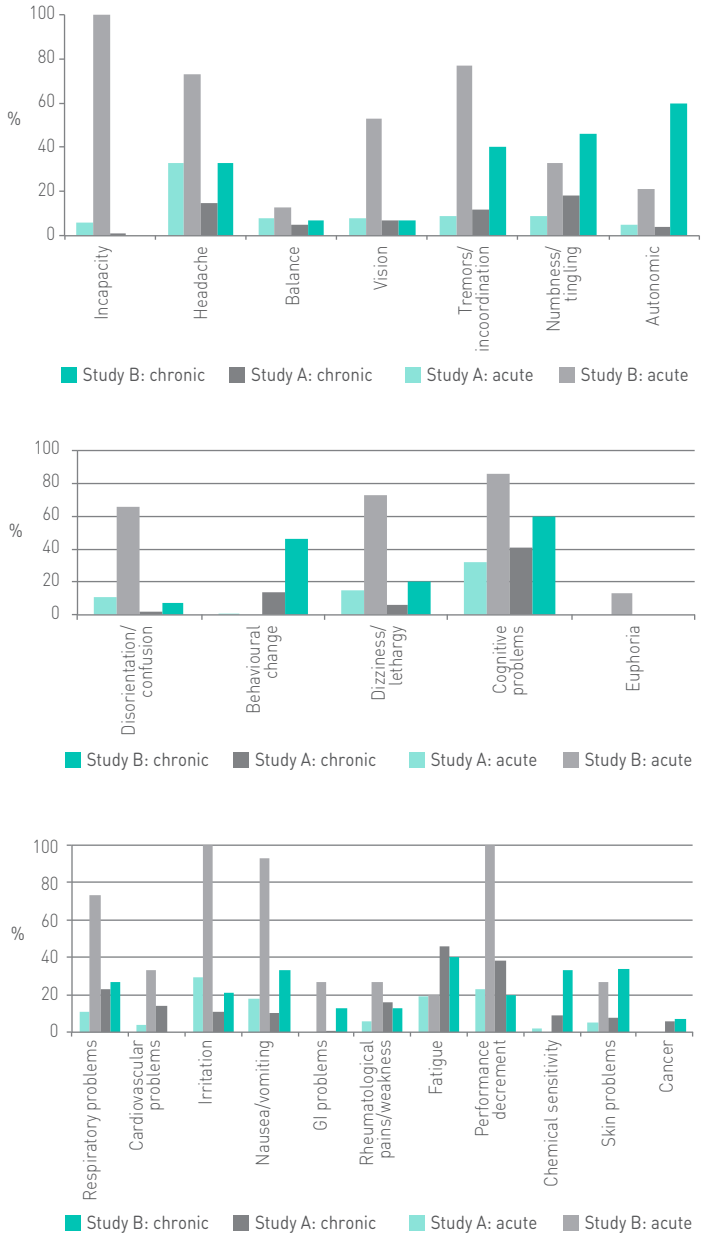
(PNS; motor, sensory and autonomic nervous systems); neurobehavioural (neurological and cognitive systems); gastrointestinal; respiratory; cardiovascular; general (rheumatological, performance decrement, fatigue, soft tissue damage); irritant, skin and sensitizing effects.

Study A found that aircrew had a high level of awareness of working in a contaminated air environment, along with a higher rate of repeated, low-level background fume events, while study B identified acute exposures occurring in addition to general chronic exposures. Therefore, the so-called acute-on-chronic effects of exposure to OPs and pyrolysed mixtures must be considered. As shown in Fig. 3, studies A and B identified different rates of symptoms; however, there is a clear pattern of primarily neurological and respiratory symptoms.

The medical findings and diagnoses, while significant and consistent with exposure to substances in aircraft fluids and to complex, thermally degraded mixtures, have not been well recognized within the aviation industry. Primary data has been lost for a number of reasons, including lack of a recognized medical protocol, lack of an aircraft air-monitoring system, a general reluctance to volunteer information on an issue that is not accepted by the airline industry, lack of education about aircraft contaminated air, difficulties associated with maintenance investigations for bleed air contamination, and reluctance by airlines to investigate such events. There is a clear disincentive to report health effects when a commercial pilot's licence and career depend on good health *(8, 21)*.

The lack of an internationally accepted protocol for investigating aircraft fume events hampers our understanding of the consequences of such exposure. A useful protocol should include: checklists for sampling aircraft air and surfaces, along with adequate numbers of appropriate collection and storage containers; and specimen collection (blood, urine) using standard methods from crew and passengers within maximum time limits or at stated collection times. Adopting such protocols would enable the collection of standardized, consistent data which would, in turn, facilitate a better understanding of the medical consequences of fume exposure. Progress in this field is hampered by a general lack of medical training in toxicology.

FIG. 3. STUDIES A AND B: PREVALENCE OF CHRONIC AND ACUTE (A) NEUROLOGICAL, (B) NEUROBEHAVIOURAL AND (C) NON-NEUROLOGICAL SYMPTOMS



TCP has neurotoxic properties *(22)*, but the widespread belief that only *ortho* isomers of TCP are dangerous is invalid. The 99.7% of non-*ortho* isomers of TCP and TAP can cause nerve demyelination and inhibit various enzymes, including those linked to cognition *(23–25)*.

It is widely accepted that high concentrations of OP compounds poison enzyme systems and have direct toxicological influences on living cells. These properties were first exploited for the development of nerve gases and later for insecticides. Although OPs can bind to

many different enzymes, their best-known actions are on cholinesterases and neuropathy target esterase (NTE). The principal mode of action is to disturb the process of acetylcholine metabolism, a natural neurotransmitter substance found in the CNS and PNS. Neurotransmitters normally have a short half-life because they are rapidly destroyed by specific enzymes. This prevents their build-up; if further signal is required, then more neurotransmitter is secreted from neurons. When OPs poison acetylcholinesterase, the resulting increase in acetylcholine concentration overstimulates acetylcholine receptors, causing CNS and PNS symptoms. People exposed to a fume event have reductions in acetylcholinesterase and NTE activity *(18)*. CNS symptoms include ataxia, drowsiness, headache, poor concentration and visual disturbances, with higher doses leading to coma. PNS symptoms include altered muscle tone, tremor and paraesthesae (pins and needles).

However, OPs can have more subtle effects at lower doses, particularly with repeated exposures. Terry reviewed non-cholinergic mechanisms of OP toxicity, including covalent binding of OPs to tyrosine and lysine residues, which suggests that numerous proteins can be modified by OPs *(26)*. In addition, OP concentrations of up to three orders of magnitude below those required for cholinesterase inhibition can (i) cause oxidative stress and neuroinflammation and (ii) affect known OP targets such as motor proteins, neuronal cytoskeleton proteins, axonal transport, neurotrophins and mitochondria.

Tri-*o*-cresyl phosphate has been shown to cause primary axonal degeneration and subsequent secondary demyelination *(27)*. Thus, the symptomatology of OP exposure tends to be rather nonspecific. Indeed, it is relevant that multiple sclerosis, a demyelinating disease, can present as almost any combination of neurological symptoms – it can thus be described as protean. In a similar way, OP exposure damage tends not to cause a clear-cut set of localizing signs and symptoms that are instantly recognizable as a syndrome, but rather to a pattern of diffuse neurological symptoms. This is consistent with their mode of action and the resulting diagnosis of diffuse toxic encephalopathy.

The very-low-dose effects described by Terry *(26)* support the exposure pattern among aircrew described in the present studies – chronic, continual, low-dose exposure with occasional acute-on-chronic, higher-dose episodes. This scenario could explain the apparent differential vulnerability between aircrew and passengers. Supporting evidence for this hypothesis was provided by an in vitro study in which pre-exposure of neuroblast cells to very-low-dose OPs made them much more susceptible to neurotoxic damage compared with non-pre-exposed cells upon further challenge by a higher dose of a variety of OPs *(28)*.

Individual susceptibility to damage by OP exposure appears to be highly variable. Some people have constitutionally low levels of liver enzymes, such as paraoxonases, that detoxify OPs in the liver. It was demonstrated that farmers with lower paraoxonase levels are more likely to suffer from dippers flu as a result of exposure to OP sheep dips *(29)*. This finding may help explain why not all aircrew appear to be equally affected by fume events. It also goes some way toward explaining the apparent differential susceptibility between aircrew and passengers.

Respiratory symptoms are likely to be secondary to direct irritation or damage to lung tissue. Substances that are not toxic individually may become highly toxic within a pyrolysed mixture *(13)*. There is growing evidence that the response to low-level exposure to mixtures of toxic substances can differ from the response to acute, high-dose exposure to single toxins *(30, 31)*. The predominance of respiratory symptoms (second only to neurological symptoms) in these studies should be considered direct evidence of the presence of appreciable levels of irritants in cabin air during fume events.

Some researchers suggest there is no causative agent or that there is a temporal association only between exposures and adverse effects *(7, 9)*. However, the findings from the present study are consistent with previous reports which accept that the Bradford Hill causation criteria are met in eight out of nine categories (the exception was a dose–response relationship) *(8)*. This study identified a cause–effect relationship for exposure and symptoms and diagnosis; thus, disease findings are linked to occupational and environmental exposure. Causation is also accepted elsewhere *(32)*.

Numerous arguments have been used to deny the recognition of aerotoxic syndrome as a new occupational disease. Levels of contaminants are often reported to be below exposure standards. However, the use of such standards does not apply to the public, at altitude or to a complex pyrolysed mixture *(33)*. Furthermore, industry accepted standards are designed to protect most (but not all) of exposed individuals. It is well recognized that some individuals will develop disease at environmental concentrations well below these standards. Furthermore, the effects are said to be inconsistent with tri-*o*-cresyl phosphate-associated, OP-induced delayed neuropathy, while ignoring all other indicators of toxicity; thus, nocebo is the suggested mechanism *(7)*. The studies reported herein identify PNS neuropathy along with one case of OP-induced delayed neuropathy (characterized by Wallerian degeneration) associated with confirmed oil findings, among a range of other effects and diagnoses.

Hyperventilation and hypoxia were also suggested to be responsible for the observed symptoms *(9)*, but this was based upon reports of selected symptoms only. Although hyperventilation may occur in stressful situations, to argue that fume-affected aircrew suffer from a hyperventilation syndrome simply because their symptoms resemble those seen in a hyperventilating person is to ignore the fact that overbreathing also occurs in individuals with cardiac, lung and neuromuscular disorders. Furthermore, if symptoms are, in fact, due to stress-related hyperventilation, this would call into question the industry's selection process for aircrew. Hypoxia will prompt hyperventilation, but if this is accepted as the cause of the symptoms, then it follows that the fume inhalation must have caused organic injury. Additionally, this rationale ignores the strong correlation between observed symptoms and the hazard classification process and databases.

CONCLUSIONS

Aircraft air supplies contaminated by pyrolysed engine oil and other aircraft fluids can reasonably be linked to acute and chronic symptoms, findings and diagnoses, thus establishing causation. Other potential causes of symptoms have been suggested. However, these fail to recognize that:

- the design mechanism allows chronic low-level exposure to a complex mixture during both normal flight and specific incident events with confirmed leakage;
- observed effects are consistent with those of recognized hazards;
- acute effects and operational limitations reduce flight safety;
- chronic effects are common; and
- passengers occupy the same environment as crew.

Over 3.5 billion passengers and 0.5 million aircrew were exposed to low levels of engine oils in 2015 *(34–36)*. There is an obvious need for a clearly defined internationally recognized medical protocol, occupational syndrome and disease recognition, and health and environmental data collection.

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