

An emerging concern: Toxic fumes in airplane cabins

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Keywords: aerotoxic syndrome, organophosphates, contaminated air, toxicology

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Toxicology is a new science, the complexities of which have been highlighted in the papers contained within this special section. Our understanding of the mechanisms through which various chemicals interfere with nervous system function is constantly evolving and research is unable to keep up with the speed with which new chemicals are produced and put onto the market. Thus there are often controversies surrounding the health-effects of commercially available compounds and disagreement around what constitutes safe exposure limits. This article will introduce readers to an emerging concern in this field, *the potential risk to health of toxic fumes in airplane cabins*. We explore the challenges and methodological issues encountered by researchers who have tried to investigate this issue and highlight the need for further research on this topic. We hope this article will promote discussion amongst academics and clinicians, and lead to the identification of creative solutions to the methodological issues encountered to date.

How does the air become contaminated?

Over the last two decades, aircrew and some passengers around the world have been complaining of ill health following exposure to toxic fumes in airplane cabins (Mackenzie-Ross, 2008; Mackenzie-Ross et al, 2011; Montgomery et al, 1977; Murawski, 2011; Somers, 2005), but it is only recently that this issue has received attention in the UK (Committee on Toxicity of Chemicals in Food Consumer Products and the Environment [COT], 2007). The process by which cabin air can become contaminated is as follows: outside air is drawn into the aircraft and circulated around the engine where it is heated and pressurised to a safely breathable level. On most commercial aircraft types this air is then 'bled off' and pumped into the aircraft, unfiltered (Hunt, Reid, Space & Tilton, 1995). Occasionally this bleed air becomes contaminated by hydraulic fluids, synthetic jet engine oils and combusted or pyrolysed materials. Contamination can occur through mechanical failures, the overfilling of oil or hydraulic reservoirs and faulty seals which allow engine oil fumes to escape into the airflow (Shehadi, Jones & Hosni, 2015). This is commonly referred to by aircrew as a 'fume event'. Exposure to engine oil fumes is potentially hazardous as jet engine oil contains a large number of chemicals some of which are irritating and sensitising (e.g. phenyl-naphthylamine, tri-butyl phosphate) and some of which are neurotoxic (e.g. toluene, xylenes and the organophosphate (OP) tricresyl phosphate (TCP); Winder & Balouet, 2002).

Incidence of contaminated air events

The incidence of contaminated air events is difficult to determine as cabin air is not routinely monitored for the presence of chemical contaminants and airlines are reluctant to share engineering records which document these incidents. Furthermore, the frequency of fumes events is difficult to quantify as underreporting is common among aircrew, possibly due to fears about job security (Winder & Michaelis, 2005). Nevertheless, the aviation industry accepts that occasional fume events occur on commercial aircraft, with certain aircraft types recording more events than others (e.g. the BAe 146 and Boeing 757 aircraft types). And on some

occasions, aircrew and pilots have felt so overwhelmed/ incapacitated by fumes they have had to make an emergency landing (Newman, 2007).

Estimates of how often fume events occur vary widely depending upon whether the information is sourced from regulatory authorities such as the UK Civil Aviation Authority (CAA), from airlines or from trade unions who represent aircrew. For example, between 2004 and 2005, 109 fume events were reported to the CAA, but almost double that figure (204) were reported to the British Airline Pilots Association (personal communication). Figures from the CAA show that since 2010 they have received more than 1,300 reports of smoke or fumes on a British airline and there were 251 incidents of fumes or smoke in the cabin reported between April 2014 and May 2015. In 2007 a Government Scientific Advisory Committee reviewed the evidence on contaminated air and estimated that fume events occur on approximately 0.05% of flights (COT, 2007). And a recent, comprehensive review of officially documented fume events in the USA places this estimate at 0.02% (Shehadi et al, 2015). Whatever, the actual frequency, it is important to note that although discrete fume events do occur, some aircrew report continuous exposure to noxious fumes throughout flight, particularly those who work on the BAe 146 aircraft type (Michaelis, 2010). Thus the estimated frequency of exposure to chemical contaminants in cabin air may be grossly underestimated as aircrew may be exposed to contaminated air on a continual basis as well as being exposed to contaminated air during discreet fume events. Without constant monitoring of on-board air quality, however, it is difficult to reliably assess such a claim.

Health complaints amongst aircrew

Pilots and cabin crew work in unique physical conditions where they are exposed to jet fuels, changes in temperature, pressure, gravitational forces, radiation and hypoxia. They also experience unusual routines, shift work, long hours of duty and time zone changes. The long-term impact of these factors on the health of aircrew remains unclear, but many aircrew report health complaints such as fatigue, dizzy spells, insomnia, stress, anxiety and marital conflict and evidence suggests they have increased rates of certain diseases and neurological conditions such as melanoma, cataracts and motor neuron disease (Nicholas, Butler, Lackland, Tessier, Mohr & Hoel, 2001). Despite this, specific data on incidence, prevalence and potential causes of ill health among aircrew is lacking. In the last two decades, an increasing number of aircrew have reported symptoms of ill health to regulatory authorities, which they attribute to exposure to neurotoxins in engine oil fumes. However, very little research has been undertaken on this issue, making it impossible to draw firm conclusions. According to de Boer, Antelo, van der Veen, Brandsma and Lammertse (2015) between two to three pilots out of every 1000 retire from work on ill health grounds every year suffering from neurological symptoms such as tunnel vision, memory impairment and headaches; a figure which has doubled over the last two decades. However, the cause of these symptoms remains unclear.

Causation

Some researchers have suggested chronic exposure to OP compounds (particularly TCP) in engine oil may be to blame (Winder and Balouet, 2002). To reflect this, in 2000 Winder and Balouet proposed the term 'Aerotoxic Syndrome' to describe the common symptoms reported by aircrew following exposure to toxic fumes in aircraft cabins, and encompasses both short and long-term effects such as ear/nose/throat irritation, skin conditions, nausea and vomiting, respiratory problems, headaches, dizziness, weakness and fatigue, sensory changes and nerve pain, tremors, chemical sensitivity and cognitive impairment (e.g. Abou-Donia, 2003; Cox & Michalis, 2002; Coxon, 2002; Mackenzie Ross, Harper & Burdon, 2006; Mackenzie Ross et al, 2011; Michaelis, 2010; Montgomery, Weir, Zieve & Anders, 1977). In addition, recent studies have reported evidence of neuropsychological impairment (Heuser, Aguilera, Heuser, & Gordon, 2005; Mackenzie Ross et al, 2006; Mackenzie Ross, 2008; Mackenzie Ross et al, 2011; Reneman et al, 2015) and neurological damage (Heuser et al, 2005); evidence of nervous system degeneration (Abou-Donia, Abou-Donia, El Masry, Monro & Mulder, 2013; Abou-Donia, van de Groot & Mulder, 2014); and altered white matter microstructure, cerebral perfusion and activation (Reneman et al, 2015) in aircrew and pilots.

Although these studies have shown those working in the airline industry complain of an array of symptoms and/or show evidence of neurological damage, none of these studies have been able to determine cause. Indeed, without any objective measurement of exposure, it is very difficult to claim that contaminated air is to blame.

The only studies published to date that have attempted to explicitly measure and link ill-health with exposure to cabin fumes have relied solely on self-report questionnaires. In these studies, pilots and air crew were asked to report whether (and how often) they had experienced fume events or noxious smells whilst flying, as well as being given a health survey where they could report any symptoms that they believed they had experienced as a consequence (Cox & Michaelis, 2002; Harper, 2005; Michaelis, 2003). These studies found that an array of symptoms were typically reported immediately following exposure, including headache, cognitive impairment, fatigue, eye, nose, throat irritation, respiratory problems, nausea and skin irritation. They showed a temporal relationship with exposure and usually resolved within a few hours following cessation of contact, although a number of individuals reported persistent chronic ill health lasting months or years following exposure, particularly following repeated exposures over time.

However, it is important to note that these studies relied on subjective measures of self-reported exposure. Given the variation in human sensory sensitivity, the fallibility of memory and the fact that these self-reported levels generally appear to be much higher than those officially reported to industry (and therefore cannot be objectively confirmed), it is difficult to determine the reliability/validity of this data. Secondly, none of these studies utilised control groups to determine whether the rate or type of health complaints differs from that seen in the general population or in pilots who have not experienced fume events. Therefore, it remains difficult to draw valid conclusions regarding the likely cause of the health complaints made by

aircrew. This is especially true, as there are a number of other factors associated with working in the aviation industry which could otherwise explain the ill health observed in aircrew such as shift work, jet lag, exposure to radiation, pathogens and pressure changes; along with pre-existing or new and unrelated medical conditions (Abeyratne, 2002; Hocking, 2002; Rayman, 1997). Furthermore, the symptoms reported by aircrew are often non-specific, diverse and common in other occupational groups, clinical populations and even the general population making it difficult to determine their clinical significance without more detailed information. Thus future research in this area should use more established robust, valid and clinically sensitive measures to establish ill health with good sensitivity and specificity, alongside objective confirmation of exposure, thus enabling symptomology to be explicitly linked with exposure measures, something that is sorely missing in this field.

It is also worth asking why more passengers are not reporting ill-health immediately after flying. There are several reasons why this might be the case, for example it may be that they are unaware that any contamination event has taken place (airlines are not obliged to inform passengers), and therefore would not associate ill health with flying; or perhaps they are simply not exposed to the same levels of fumes as aircrew. But it could also suggest that contaminated air may not, in fact, be responsible for the symptoms reported by aircrew and pilots, a possibility that should be investigated thoroughly, as the toxicity of cabin air has yet to be clearly established.

Toxicity of cabin air - Air-quality monitoring studies

At present, the number, type and quantity of chemicals which might enter the cabin during a fume event remains unknown. In 2007 the UK Department for Transport commissioned Cranfield University to sample the air quality on board 100 flights, with the aim of identifying the levels of various chemical compounds that were present in cabin air during various stages of flight (Crump, Harrison & Walton, 2011). Several volatile and semi-volatile organic compounds were detected during routine flight, including carbon monoxide, toluene and TCP (which is used as a lubricant and anti-wear additive in jet engine oils and hydraulic fluids). However, the authors reported that the levels detected in cabin air fell within safe exposure standards, despite there being no aircraft safety standards with regard to TCP. A more recent study, conducted in partnership with KLM airlines, measured levels of TCP isomers in the cockpit of over 20 flights, and found non-ortho isomers (but not ToCP) were present in low concentrations on 10 out of 20 flights, but the authors concluded such low levels were unlikely to be responsible for alleged Aerotoxic Syndrome (de Ree et al, 2014). The Cranfield and de Ree et al studies are often interpreted as showing that the chemicals detected in cabin air cannot be responsible for the ill health reported by aircrew, however there are several considerations that should be taken into account before accepting this conclusion:

(1) No fume events were observed on any of the flights that were monitored in these studies. This is hardly surprising, given the relative rarity of cabin air contamination according to official estimations. For example, using COT's (2007) estimate that

fume events occur on approximately 0.05% of flights, for a fume event to be reliably observed and measured, one would need a sample size of 2000 (not 100, or 20). The only study to have come close to measuring levels of TCP during a fume event was that by Solbu et al (2011). Whilst undertaking a cabin air monitoring study, one of their target aircraft reported a fume event, however on-board monitoring was not in situ when the event actually occurred. Instead, they took various air-quality measurements whilst the plane was grounded, both before and after the engine was repaired. They found significantly elevated TCP levels when the engine leak was still present, but the relationship between ground measurements and the level of contaminants which might have been detected during an in-flight fume event is unclear. As such, the possible exposure that passengers and aircrew may face during a fume event remains unknown.

(2) These papers have only explored the presence of limited chemicals in the cabin. As compounds may be captured and measured in different ways, researchers must choose which chemicals should be monitored in the cabin – they do not detect everything that is present. To date, the predominant focus has been on TCP; a neurotoxin whose effects have been known since the 1930s, following the mass paralysis of thousands of individuals who consumed a drink called ‘Ginger Jake’ which had been contaminated by the substance (Kidd & Langworthy, 1933). However, TCP (which only accounts for around 3% of engine oil makeup [Michaelis, 2011]) is not the only toxic ingredient in oil fumes. For example, other substances present in engine oil, include trixylenyl phosphate (TXP), phenyl naphthylamine (PAN), acrolein, amines, carboxylic acid, carbon monoxide, formaldehyde, toluene, and xylene all of which have the capacity to do harm (Anderson, 2014). And while Crump et al (2011) included a small selection of these other substances as target compounds, neither they nor the other air-monitoring studies considered looking for new substances that may be formed by combining chemical compounds. For example, the neurotoxin trimethylolpropane phosphate (TMPP) may be formed from TCP and trimethylolpropane ester at high temperatures (Wright, 1996). Thus a lot remains unknown about the potential ill health effect of exposures to mixtures of contaminants.

(3) The authors have not given sufficient consideration to the fact that cumulative low level exposure over time (as opposed to a one off fume event) may be harmful to health. Indeed, rather than being reassuring the Cranfield (Crump et al, 2011) and de Ree (2014) studies illustrate that potentially neurotoxic chemicals enter the cabin even under normal flying conditions, a fact which is surely rather alarming.

(4) None of these studies looked investigated the relationship between air quality measures and symptom reporting.

Establishing exposure - biomarkers of exposure

Alternative methods have been used by some researchers to obtain objective measurements of exposure, which involve the identification of biological markers that may follow contact with specific components of engine oil. For example, Liyasova et al (2011) developed an assay to determine exposure to TCP by focusing

on its toxic metabolite. They analysed blood samples taken from 12 passengers within 24-48 hours of disembarking from a plane. Six tested positive for TCP, but at very low levels. None of the subjects reported symptoms of toxicity nor did they notice any noxious smells during flight or visible fumes, giving further credence to the notion that low-level exposure can occur on routine flights. Interestingly, 4 subjects provided further blood samples 3-7 months after their last air flight at which point all traces of TCP had vanished. However, further research is needed to determine the sensitivity and specificity of Liyasova et al's blood test and what the relationship might be between blood test results and adverse health effects.

Additionally, Abou-Donia et al (2013) have suggested that measurement of serum auto-antibody levels might be useful in terms of demonstrating nervous system damage following exposure to engine oil fumes. They detected increased levels of various auto-antibodies which are released into the blood stream following damage to the central nervous system (e.g. IgG, NFP, tubulin, tau proteins, MAP-2, MBP, S100B protein and GFAP) in 34 aircrew who experienced adverse health effects after being exposed to engine oil fumes. In addition, they undertook a prospective study of a pilot who was initially symptom-free, but became ill after flying 45 hours in 10 days. As the pilot's condition worsened, the level of circulating autoantibodies increased; and after a year away from flying, these levels then reduced. Although Abou-Donia's test might be useful for detecting neuronal damage, it does not indicate the mechanism through which it has occurred. In other words, it remains to be determined whether exposure to neurotoxic substances in cabin air is the cause of neuronal damage, or some other aspect of flying or some other completely unrelated pathological process. Thus, although it is important to identify potential biomarkers of exposure, this work is in its infancy and further research is needed to clarify the precise relationship between biomarkers, exposure and adverse health effects.

Conclusions

It is imperative we get a definitive answer to the question of whether exposure to engine oil fumes on board commercial aircraft causes ill health. To date, no firm conclusions have been drawn due, in large part, to the absence of objective and reliable measures of the chemical contaminants in cabin air. Previous work has documented various physical and neuropsychological symptoms amongst airline pilots and crew who subjectively report a history of exposure to noxious fumes during flight (e.g. Abou-Donia, 2003; Cox & Michalis, 2002; Coxon, 2002; Mackenzie Ross et al, 2006; 2011; Michaelis, 2010; Montgomery et al, 1977), but causation has yet to be established. Outside of the research domain, several lawsuits have been brought against the airline industry by employees who attribute their ill health to occupational exposure to pyrolysed engine oil, for example *Turner v Eastwest Airlines* and *Terry Williams v Boeing*. In both cases it was accepted that the claimant's health had been adversely affected by exposure to engine oil fumes (Lambert-James & Williams, 2014). More recently a former British Airways (BA) pilot, Richard Westgate, died in December 2012 following a prolonged period of ill health which he attributed to repeated exposure to contaminated air. The British coroner who is investigating his death was so disturbed by the evidence he had seen,

that he wrote to BA and the CAA to express his concerns. In 2014 an air steward died suddenly in his sleep after suffering from ill health for about a year. Post-mortem findings suggest his death may have been caused by exposure to contaminated air (Hills, 2015).

As such it is surprising that, to date, no substantial efforts have been made by government or industry to establish the levels of chemical contaminants which enter the aircraft during a fume event or to establish the impact of cumulative, low level exposure over time. Injury might be preventable if contamination detection and bleed air filtration systems were installed in all commercial aircraft. While the existence of a relationship between contaminated cabin air and ill-health may be a potentially expensive and inconvenient truth; the costs of ignoring the possibility of such a relationship are too high to ignore.

Methodological considerations for future researchers

Given the degree of scientific uncertainty that still surrounds this issue, it is the authors' contention that future research needs to be proactively supported and commissioned in this area. Establishing whether or not the symptoms reported by patients are the result of neurotoxic damage is notoriously difficult. As such, Hill (1965) proposed a list of criteria which neurotoxicological studies should strive to meet to establish causation. These include providing clinical and epidemiological evidence that demonstrate consistent and specific patterns of ill health following exposure to the substance(s) of interest; establishing a temporal link between exposure and symptom onset and evidence of a dose-response relationship; a biologically plausible model for the effects; coherence of the proposed link with existing evidence; and the investigation and elimination of alternative potential causes. Thus far, few of these criteria have been satisfactorily met. As such, future research in this area needs to take a multi-disciplinary approach in order to address the neurotoxicological questions that remain unanswered which include the following:

What is the clinical incidence of ill-health amongst aircrew and passengers. No large-scale epidemiological study has been conducted to date. Research of this kind would need to utilise clinically sensitive and meaningful measures of ill health with established sensitivity and specificity, and establish whether or not the profile of symptoms seen in this group is different to that observed in other (non-exposed) cohorts and the general population. Sensitive and meaningful measures of neurological injury also need to be identified. Results from routine medical evaluations often fail to reveal any abnormalities in patients who have been exposed to toxic substances which can result in neurotoxic syndromes being misclassified as psychiatric disease. Neuropsychological assessment is more sensitive but results are non-specific and need to be interpreted in the context of other medical information. Modern imaging techniques, such as PET scans have proven useful in addiction research and may have a great deal to offer toxicological research and so too might MRI diffuse tensor imaging or fMRI.

Objective and reliable measures of exposure need to be developed, such as air monitoring devices (which would need to be fitted to a large enough fleet of planes to increase the likelihood of capturing a fume event) and biomarkers of exposure. It is not until we can objectively measure chemical exposure that we can explore the link with health outcomes.

Researchers need to directly and explicitly measure the association between different levels of exposure and ill-health symptoms. This should consider the possible effects of both cumulative low level exposure to contaminants, as well as discreet fume events. Research on other occupational groups, particularly individuals who work with pesticides, suggests both acute poisoning events and cumulative low level exposure may be harmful (e.g. Mackenzie-Ross, McManus, Harrison & Mason, 2013).

Researchers need to consider the possibility that more than one chemical contaminant may be involved in the aetiology of ill health. To date the primary focus in this area have been on TCP which comprise only about 3% of engine oil (Michaelis, 2011). Thus air quality studies should measure more than one potential contaminant and consideration needs to be given to the possibility that chemical compounds combine at high temperatures and may form more toxic compounds in the process.

Other potential causes of ill health must be excluded. White et al (this issue) illustrates how difficult it can be to identify the cause of ill health in some occupational groups where multiple factors exist which could account for their symptoms. Whilst this paper concentrated on military veterans, many of their points can be applied to the context of aviation, and parallels can be drawn between the Gulf War and Aerotoxic Syndromes.

Researchers need to consider the possibility that individual differences may give way to different expressions of illness. Collectively, the papers in this special section by Debes, Weihe and Grandjean (this issue), Rodriguez-Barranco et al (this issue), Rohlman et al (this issue) and Sanchez-Santed (this issue) all illustrate how some members of the population may be at increased risk of ill-health as a result of their developmental stage/age, health status or genetic variability in their ability to detoxify chemicals.

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