Health Effects of Contaminants in Aircraft Cabin Air

Summary Report v2.7

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https://www.airpilots.org/file/1277/air-contamination-health-effects-report-oct-13.pdf
http://www.asma.org/asma/media/asma/Travel-Publications/Health-Effects-of-Contaminants-in-Aircraft-Cabin-Air-Report-v2-5-Aug13.pdf

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HEALTH EFFECTS OF CONTAMINANTS IN CABIN AIR (version 2.7)

BACKGROUND SUMMARY – April 2014

INTRODUCTION

The occupants of commercial aircraft are protected from hypoxia by the aircraft cabin being pressurised to below 10,000 feet. The maximum certified cabin altitude will not exceed 8,000 feet during normal operations, to provide a safety margin for those who might be cardio-respiratory compromised. During flight, air is derived from the compression stage of the jet engine or, in the case of the B787, from electrically driven compressors. This bleed air is conditioned and filtered, with an exchange of 10-15 times per hour with outside air and 20-30 times per hour including outside and filtered recirculated air. Pressurisation to sea level, although ideal, is not technologically and economically feasible.

Concerns have been raised by organisations representing pilots and cabin crew about the possible effects on aircrew health of oil/hydraulic fluid smoke/fume contamination incidents in pressurised aircraft. Specific concerns have been raised with respect to organophosphate compounds (OPs) in the cabin air environment and the perceived effects on health of long term low-level exposure (1, 2).

Some aircrew who report incidents experience a variety of symptoms, mainly acutely irritant in nature. Less frequently, some aircrew report longer-term symptoms. However, the epidemiological evidence is hampered by inconsistency in reporting and the numbers are small.

The Global Cabin Air Quality Executive (GCAQE) was established in 2006 to deal specifically with contaminated air issues and cabin air quality affecting air crew (1, 2). It claims to represent more than 20 organisations worldwide, although it appears to have no registered articles of association. The organisation has a high media and political profile in the UK and other parts of Europe.

The UK CAA Mandatory Occurrence Reporting (MOR) System in 2007 noted 116 fume event reports out of 1.3 million passenger and cargo flights, with fume events estimated to occur on 0.05% of flights overall (1 in 2000). Of the approximately 20,000 UK professional pilot population, the UK CAA Medical Department in 2013 were aware of 28 individual cases who have reported symptoms which they attributed to exposure to fumes. Of these 14 have returned to flying or were never assessed as unfit. The remaining 14 remain unfit (the CAA no longer differentiates temporary/long term unfit), although a number would have passed normal retirement age. No new cases have been documented since June 2012 and the CAA is not aware of any other on-going cases (26).

The Australian Parliament conducted a Senate Investigation in 1999 into air safety and cabin air quality. This followed concerns raised by crew members working for Ansett Airlines who reported feeling unwell due to unpleasant odours of engine oil inside BAe 146 aircraft. The Senate report concluded that the BAe 146 had a record of unpleasant odours in the cabin as well as occasional incidents of fumes from lubricating oil. Over a longer period, airline employees had reported a variety of adverse health effects.
In response to the enquiry, BAe redesigned the original air circulation system in the BAe 146. A number of health compensation claims were also filed against Ansett but no damages were awarded at that time. However, in 2010 the Australian Dust Diseases Tribunal awarded damages to a former cabin attendant for lung damage related to a single fume event. No other symptoms of “aerotoxic syndrome” were at issue in that case, nor was the claim related to exposure to neurotoxins.

In the USA similar problems were reported with early RB211-535C powered Boeing 757 aircraft in which overfilling with engine oil could lead to contamination of the environmental conditioning system (ECS).

Also, in the UK, incidents of smells in the cabin were reported on early B757s operated by British Airways, and UK operators of the BAe 146 also experienced oil fume incidents.

Although the evidence suggests that oil fume events of initial concern stem from a design fault on two early series aircraft which has now been rectified, occasional oil smells still occur (~1 in 2000 flights) and campaigners maintain that these are leading to health problems for aircraft occupants. They are also concerned that crew health is being affected by long term exposure to very small amounts of contaminants which may be present in bleed air as a result of leaking engine oil seals, in the absence of specific fume events (1, 2).

These concerns have led to a number of governmental, scientific and industry reviews and investigations of the issue over the past decade.

Organophosphates and their use in Engine Oil

Jet engine oils contain synthetic hydrocarbons and additives, including an organophosphate known as tricresyl phosphate (TCP) which acts as a high pressure lubricant.

The term organophosphate encompasses a variety of chemical compounds with a similar structure. Small differences in this structure alter the chemical properties of the compound and thus any associated health effects.

TCP is a toxic mixture that can cause a wide array of transitory or permanent neurological dysfunction when swallowed in sufficient quantity.

The neurotoxicity of TCP is due to its ortho isomers. The major toxic effect of the ortho isomer, T*o*CP, is impairment of neuromuscular and peripheral nerve synapse function; it is thought to have no toxic effect on centrally mediated cognitive function. Other ortho isomers of TCP include M*o*CP (mono-ortho-cresyl phosphate) and D*o*CP (di-ortho-cresyl phosphate) which have similar toxicity.

The para and meta isomers are not toxic to humans. There have been no independently peer-reviewed recorded cases of neurological harm in humans following dermal or inhalation exposure to TCP, although cases have been reported following ingestion (swallowing) of the ortho isomer.

An unpublished report commissioned by British Airways Health Services from the Medical Toxicology Unit at Guy's Hospital in 2001 stated that "the majority of cases of tricresyl phosphate poisoning have been associated with the swallowing of contaminated food or drink, not with occupational exposure. The most frequent occupational exposures occur during manufacture, packaging, shipping and storage, not at the point of product use, and reports of occupational intoxication are rare". The report authors researched all documented exposures dating back to 1943 and they were all to high concentrations greatly in excess of the amount present in jet oil.

The reported concentration of TCP used in most aircraft engine oils is less than 3%, of which the ortho isomers constitute less than 0.2% of the total TCP. This results in an overall concentration of ortho isomers of less than 0.006% of the total engine oil.

Consequently TCP mixtures used in engine oils are significantly less toxic than pure T*o*CP (the tri-ortho-cresyl phosphate), for which an Indicative Occupational Exposure Limit Value (IOELV) threshold limit value is set at 100 µg/m³ as an 8h time-weighted average (TWA), with an emergency 15min short-term exposure limit of 300 µg/m³. This is equivalent to the North American occupational exposure limit of 0.1 mg/m^3.

Peer reviewed studies have indicated total TCP concentrations on aircraft during abnormal oil smell conditions significantly below this threshold limit. Those studies able to distinguish between the 10 different TCP isomers have confirmed that even during these abnormal conditions, no neurotoxic ortho-isomers of TCP could be detected (3, 4, 5).

A Canadian study was published in 1998 by the Department of Health Care and Epidemiology of the University of British Colombia (4). Following complaints from crew of health effects thought to be related to oil odour on BAe 146-200 aircraft, the components of cabin air, including TCP were measured. This study was unable to detect any TCP during in-flight measurements, and was unable to detect any health effects associated with the oil odour. Another study of cabin air quality on Boeing aircraft by Harvard University in the USA, also failed to detect any TCP during in-flight measurements (4, 5).

British Airways commissioned a study by an independent specialist on indoor air quality, BRE, the former Building Research Establishment, to investigate this issue in 2001. The BRE study showed that the concentrations of all oil compounds detected in cabin air on the B757 were each less than 100 parts per billion (approx. 0.00125mg/m^3), which is well below the toxicological threshold for humans of 0.1mg/m^3 over 8 hours or the emergency short term limit of 0.3mg/m^3 for 15mins.

In 2004 the UK government Aviation Health Working Group commissioned a study into cabin air quality carried out by the independent BRE. The study analysed a wide range air quality parameters during different phases of flight aboard BAe 146s and older Boeing aircraft, including tests for oil vapours. The project supplemented an earlier 2001-2003 EU-funded research project, CabinAir, which monitored air quality on 50 European airline flights. Both surveys concluded that no air pollutant exceeded recommended health limits; hardly any trace of oil vapour was detected.

A similar finding was reached by another EU-funded project, Health Effects in Aircraft Cabin Environment (HEACE), which examined all aspects of the aircraft cabin working environment during 2001-2005. However, neither of the EU studies specifically targeted the presence of TCP.

In 2005 the British Airline Pilots Association (BALPA) organised a two day conference on contaminated air production at Imperial College London. The conference called upon the government to take action on the grounds of health and safety

In 2007, the United Kingdom Committee on Toxicity (COT) was asked by the Department for Transport (DfT) to undertake an independent scientific review of data submitted by the British Airline Pilots Association (BALPA) relating to concerns of its members about the possible health effects from oil fume contamination on commercial jet aircraft. The COT estimated that cabin air quality events occur on roughly 0.05% of flights (~1 in 2000). It concluded that whilst a causal association between cabin air contamination by oil mists and ill-health in commercial air crew could not be identified, a number of incidents with a temporal relationship between reports of oil/fume exposure and acute ill-health effects indicated that such an association was plausible. The COT recognised that further study of air quality events should therefore be undertaken to determine the types and concentrations of substances present in cabin air (6).

Accordingly, the DfT Aviation Health Working Group (AHWG) commissioned Cranfield University to carry out cabin air monitoring for a range of potential chemical contaminants.

The initial ground investigation in a BAe146 aircraft found low levels of tri-n-butyl phosphate (TBP) and tricresyl phosphate (TCP) in air samples, together

with a range of other volatile or semi-volatile organic compounds (7). These amounts were well below occupational exposure limits.

The subsequent investigation involved in-flight monitoring of the Boeing 757 cargo aircraft and the Boeing 757, Airbus A320/1, BAe 146 and Airbus A319 passenger aircraft (8). An in-flight fume event was observed during the study on the Boeing 757. The data from a particle monitoring device showed that during this event there was a very high number concentration of a very small aerosol, although overall these represented a small mass concentration of oil. Slightly elevated levels of TBP and TCP were again measured, but all were significantly below the relevant Health & Safety Executive specified Workplace Exposure Limits (8, 9)

To complement the Cranfield University work, the AHWG recognised that additional information on potential contaminant residues on internal surfaces could be informative of possible fume events and commissioned the Institute of Occupational Medicine (IOM) to carry out a study. The results were published in 2012.
A total of 86 sample sets were obtained from different aircraft types, ground vehicles and offices. The residues were analysed by gas chromatography/mass spectrometry for TCP, TBP, butyl diphenyl phosphate (BDPP) and dibutyl phenyl phosphate (DBPP). The surface residues in the passenger compartments were generally lower than in the cockpit. The mean amounts of TBP, DBPP and BDPP detected in the aircraft were similar to those in the control vehicles. For TCP the contamination in the control vehicles and the office locations were similar, and slightly lower than found on the aircraft. Estimates of air concentrations consistent with these surface residues were in agreement with other published data (10).

In a similar study in 2009, the University of British Columbia had reported the results of surface wipe samples taken in a Boeing 757 and BAe146 showing the presence of TCP throughout the aircraft. However, this was inconclusive and it was recognised that the results will be influenced by confounders such as the use of cleaning materials, wear and tear of the surface sampled, and proximity to air vents, etc. It was noted that TCP will be found in wipe samples taken in buildings and other public places (23).

In February 2012, an invited international group of aviation, health and toxicology experts participated in a workshop at Hunton Park in the UK, under the auspices of BRE, to consider the issues (12).

The Hunton Park workshop reviewed evidence associated with cabin air fume events. It was concluded that there are no published peer reviewed reports of acute organophosphate poisoning with analytical confirmation of the diagnosis after cabin air fume exposures. Similarly, there are no published peer reviewed reports of organophosphate-induced delayed neuropathy after cabin air fume exposure, with no evidence to support a causative association between cabin air fume exposure and short or long term nerve damage. However, the workshop noted lack of clarity and consistency in reporting definitions and terminology which may lead to difficulties in establishing the

true incidence of events. It was also observed that there is a need for standardisation in the methodology and calibration of the sampling and analytical procedures carried out when making the relevant cabin air quality measurements reported so far.
The workshop agreed that there is a need for consistent guidance on the medical assessment of crew members following a cabin air fume event. It was noted that there is similarity between the reported symptoms of some crew members after fume events, particularly when emergency oxygen masks have been used, and the classical symptoms of hyperventilation.

The Australian Government Civil Aviation Safety Authority independently convened an Expert Panel on Aircraft Air Quality in 2012 which reached similar conclusions (13, 14).

A study by Schindler et al was published in Archives of Toxicology in 2013 (15) A total of 332 urine samples of pilots and cabin crew members in common passenger aircraft, who reported fume/odour during their last flight, were analysed for three isomers of tricresyl phosphate metabolites as well as dialkyl and diaryl phosphate metabolites of four flame retardants. None of the samples contained o-TCP metabolites above the limit of detection (LOD 0.5 lg/l). Only one sample contained metabolites of m- and p-tricresyl phosphates with levels near the LOD. Median metabolite levels of tributyl phosphate (TBP), tris-(2-chloroethyl) phosphate (TCEP) and triphenyl phosphate (TPP) (DBP 0.28 lg/l; BCEP 0.33 lg/l; DPP 1.1 lg/l) were found to be significantly higher than in unexposed persons from the general population. Median tris-(2-chloropropyl) phosphate (TCPP) metabolite levels were significantly not higher in air crews than in controls. The authors concluded that health complaints reported by air crews can hardly be addressed to o-TCP exposure in cabin air. (Note that the German abbreviation o-TCP is synonymous with ToCP as used elsewhere in this paper.)

The conclusions contrast with a recent descriptive study published by Abou-Donia et al (16). The study reports the results of assays performed to detect circulating autoantibodies in a panel of 7 proteins associated with the nervous system (NS) in sera of 12 healthy controls and a group of 34 flight crew members, including both pilots and attendants who experienced adverse effects after exposure to air emissions sourced to the ventilation system in their aircrafts (*sic)* and subsequently sought medical attention.
The authors state these results suggest the possible development of neuronal injury and gliosis in flight crew members anecdotally exposed to cabin air emissions containing organophosphates. The study concludes that increased circulating serum autoantibodies resulting from neuronal damage may be used as biomarkers for chemical-induced CNS injury.
The study is descriptive and the numbers are small. If the list of symptoms in figure 2 of the study were to be presented to a sufficiently large, randomly selected section of the population, it is likely there would be a background pattern of positive responses for one or more of the complaints listed. With respect to measuring IgG, it is known that IgM rises first and the subsequent IgG response is open to interpretation. Furthermore, it seems doubtful

whether clinical and biochemical improvements are as closely and as directly linked as the authors would suggest.
The clinical significance of many of the tests reported in this context is not clear and is difficult to understand in terms of clinical toxicology.

HUMAN TOXICOLOGY

Virtually every chemical, including water, can produce an adverse effect on the human body in sufficient amount. Toxic agents can be classified by the potency or relative dose required to elicit a specific adverse effect, which creates a spectrum of poisons with potencies differing by many orders of magnitude.

Absorption is the process by which a toxic substance enters the body. In the aviation environment inhalation is the most common pathway with vapours (gaseous component), fumes (oxides of metals) and solid particles entering the respiratory system. The depth of penetration is determined by water solubility, particularly for gases. For fumes and dust particles, aerodynamic size determines the depth of penetration. Particles may be trapped in the nasopharyngeal region, the trachea or penetrate into the lung alveoli.
There are other routes of entry. The eyes and nasal mucosae readily absorb water-soluble particles and respond to acids and bases. The skin, however, is waterproof and lipid proof, and highly resistant to absorption of most chemicals. Ingestion through the gastrointestinal tract provides opportunities for chemicals requiring an acidic environment (the stomach) or alkaline environment (oesophagus and duodenum) to be solubilised and absorbed.

The next phase of exposure is *distribution*. Chemicals are dispersed throughout the body on the basis of pH-based solubility or solubility in fat, and eventually reach the target organ as a result of specific binding sites in the cells.

Ultimately a toxic substance will be *eliminated* via a number of excretion systems. Many chemicals are excreted via the kidneys in urine, whereas other are excreted via the liver in bile. Other chemicals such as solvents can be excreted as vapour through the lungs, while other chemicals are deposited in the hair, skin and nails.

The human body has its own defence mechanisms which protect against harm from certain levels of hazardous substances. However, if these levels are exceeded it is possible for health to be affected, either immediately (acute effects) or sometime after the first exposure (chronic or delayed effects).

Individuals can vary in their *response* to toxic insult because of age, health status, previous exposure or genetic differences. It has long been recognised that some individuals are more susceptible to adverse effects when exposed to certain chemicals; the genetic basis for differences in susceptibility is being increasingly understood. However, a susceptibility to adverse effects still requires a clinically significant level of the chemical to be absorbed by the body in sufficient quantities and over sufficient time periods in order to

produce a toxic effect. Occupational exposure levels for chemicals are set to take account of individual differences in susceptibilities and to provide a significant margin of safety.
In addition, it can be difficult to disentangle the physical, psychological and emotional components of well-being, and there is no doubt that different people may respond in different ways on different occasions.

The human senses, particularly the sense of smell, are generally very effective in detecting potentially hazardous substances at a level well below that which causes harm (the major exception being carbon monoxide). For most volatile organic compounds, the concentration level for detection by a normal healthy human is around 1,000 times less than the concentration level which is likely to harm health.
In the UK, the Health and Safety Executive (HSE) sets the exposure limits (OELs) for hazardous substances at work and these are published by the HSE in Document EH40 (www.hse.gov.uk). The European legal limits are known as Indicative Occupational Exposure Limit Values (IOELVs), and are broadly in line with the UK HSE occupational exposure standards.

Absorption and Distribution of Chemicals

Foreign or exogenous chemicals (xenobiotics) must be absorbed from the surrounding environment and transported to their target site in the body for a toxic effect to occur. The chemical has to cross many cell membranes which form a lipoprotein barrier to the outside as well as maintaining the integrity of the cell. Most xenobiotics are transported by simple methods and not complex carrier-associated processes (there are exceptions such as paraquat transport into lung cells) (25).
Lipid solubility is one of the major factors determining the extent and rate of simple diffusion through a lipoprotein membrane. Lipophilic molecules diffuse more readily than those which are hydrophilic, the rate of transport being dependent on the partition coefficient (ie the ratio of solubility in octanol/water). Non-ionised molecules are often more lipophilic, and ions generally more hydrophilic. So the movement of electrolytes, such as organic acids and bases, is related to the degree of ionic dissociation and the lipid solubility of the non-ionised form of the compound.
The cell membrane controls the movement of chemicals in or out of the cytoplasm; there are several methods of transport:

- *Simple diffusion*. Does not require energy expenditure and is the principal method of transport for most lipid soluble, non-ionised compounds. Fick's law states that the rate of gas diffusion through a tissue medium is proportional to the tissue area and the difference between the gas partial pressures on the two sides, and inversely proportional to the tissue thickness.
- *Filtration* allows water, ionic and hydrophilic molecules of appropriate size to pass through small pores (~0.4nm diameter) in the cell membrane.
- *Facilitated diffusion* is carrier-mediated, and transports chemicals with specific common structures across the cell membrane.
- *Active transport* allows the absorption of substances against a concentration gradient.

- *Phagocytosis* and *pinocytosis* enables particulates and solutions to be taken into the cell by the extrusion or invagination of an area of the membrane.

Inhalation Kinetics

The constant diffusion of gases between the alveoli and the pulmonary vessels leads to the composition of alveolar air differing from ambient atmospheric air. At a body temperature of 37 degC water vapour exerts a pressure of 47mmHg, remaining constant at all altitudes due to metabolism. When gas partial pressures are calculated, water vapour pressure must be subtracted from the total pressure.

The partial pressure of carbon dioxide in the alveolar air is about 40 mm Hg, although this reduces with increasing altitude due to the effect of physiological hyperventilation, and this similarly has to be taken into account when calculating alveolar partial pressures.

It is important to note that it is the partial pressure (related to concentration) of an individual gas which drives the exchange.

The lung tissue barrier (alveolar membrane) separating air and blood is only 0.5 - 1.0μ thick and the 300 - 400 million alveoli provide a large surface area for diffusion. In accordance with Fick's law, the transfer of gases through the alveolar membrane depends on the area and thickness of the membrane, and the partial pressures of the gases in the blood and in the alveoli.
The media on either side of the alveolar membrane are being continuously renewed; the air is changed 12 - 15 times per minute and the pulmonary blood flows at 3.5 - 5 litres per minute at rest, at sea level. This leads to efficient elimination of volatile chemicals.

Factors influencing the inhalation kinetics of a volatile compound include the environmental air concentration, duration of exposure, rate of alveolar ventilation, cardiac output, blood and tissue solubility and the degree of metabolism of the chemical. Volatile compounds are usually inhaled as a gas mixture with air and most are completely miscible in all proportions. The concentration of gases and volatile compounds in a mixture is expressed in terms of partial pressure, which is not equivalent to concentration. However, the relative concentrations of dissolved materials can be expressed in terms of partial pressures which add up to a total pressure of 100%. Solubility is inversely related to the temperature and proportional to the pressure of the chemical in the ambient gas. The partial pressures of constituent volatile compounds vary with the absolute pressure but, at a fixed pressure, the concentration of each gas or vapour varies directly with its partial pressure and indirectly with the total pressures of the gas/vapour mixture.

Thus any inhaled gas will be part of the total gas mix in the alveolus, and its absorption depends on the partial pressure exerted by that gas. Taking the RB211 engine as an example, the maximum engine oil possible in the bleed air is 0.4kg (20). Of this, 3% is TCP of which around 0.1% is T*o*CP. In the

unlikely worst case scenario of the total discharge of an engine's lubricant into the engine bleed system, 0.4kg of oil would pass into the cabin ventilation system. This would give a peak cabin atmosphere T*o*CP level of 0.025 mg/m^3, reducing rapidly due to normal cabin ventilation. This peak level would thus be a quarter of the 8hr workplace limit of 0.1 mg/m^3, and less than a tenth of the 15min emergency workplace limit of 0.3 mg/m^3.

Alveolar absorption depends on Dalton's Law of partial pressures, as well as Fick's Law, and the partial pressure of bleed air contaminants would therefore be a very small proportion of the total alveolar gas pressure, reducing rapidly. Of the published levels of T*o*CP detected in cabin air, most are less than 0.005 mg/m^3. Another way of expressing gas concentration is as parts per billion (ppb), and for TCP 1 ppb is approximately 0.007 mg/m^3. [To assist visualisation, in terms of time 1 ppb would be analogous to expressing 1 second in 32 years.]

It would be highly unlikely, if not impossible, for such small concentrations of contaminant to cross the alveolar membrane so as to cause organosphosphate poisoning through inhalation. It is important to note in this regard that there are no published peer reviewed reports of acute organophosphate poisoning with analytical confirmation of the diagnosis after cabin air fume exposures.

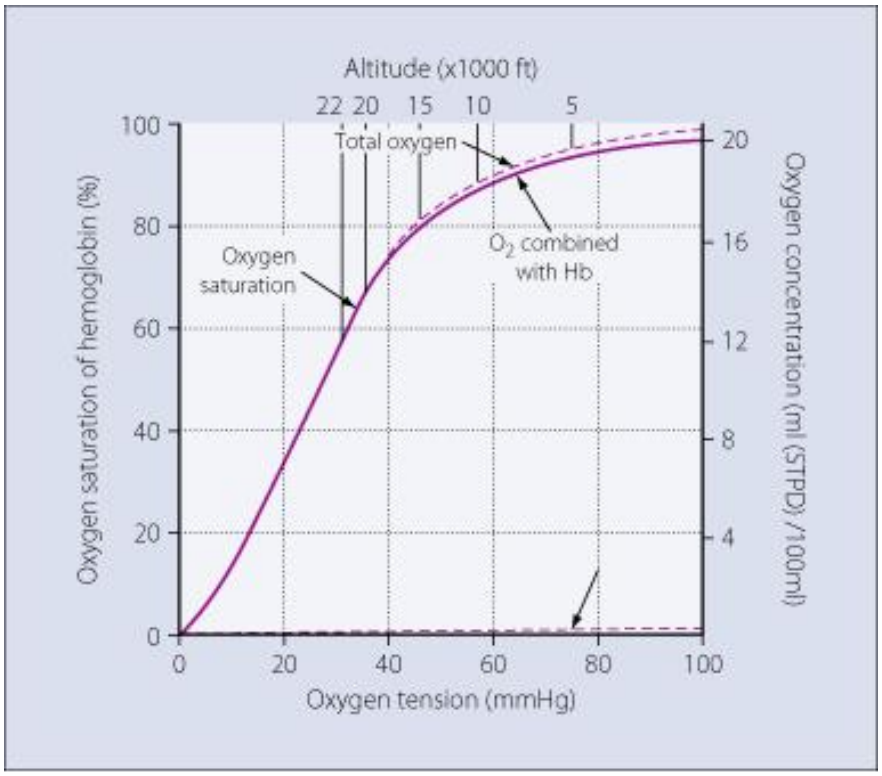
EFFECTS OF ALTITUDE

Ascent to altitude is associated with a fall in air pressure paralleled by decreases in density and temperature. Thus at 18,000 feet in the Standard Atmosphere atmospheric pressure is half its value at sea level and the ambient temperature is about -20 degC.

The behaviour of gases is explained by the Gas Laws.
Boyle's Law can be expressed as $V_1/V_2 = P_1/P_2$ where V_1 is the initial volume, V_2 is the final volume, P_1 is the initial pressure, and P_2 is the final pressure. At a constant temperature, the density of a given mass of gas varies directly as its pressure, so the expressions for pressure can be substituted by expressions for density (D).
Charles's Law shows that at a constant pressure the volume of a gas is proportional to its absolute temperature.
Combining the two laws gives the General Gas Law which is $P_1V_1/T_1 = P_2V_2/T_2$

When considering gas mixtures, Dalton' Law states that the total pressure of a gas mixture is the sum of the individual or partial pressures of all the gases in the mixture. The partial pressure of each gas in the mixture is derived from $P_1=F_1xP$, where P_1 is the partial pressure of gas 1, F_1 is the fractional concentration of gas 1 in the mixture, and P is the total pressure of the gas mixture.

The relationship between the oxygen saturation of haemoglobin and oxygen tension is reflected in the shape of the oxyhaemoglobin dissociation curve reproduced below:



Inspection shows a plateau indicating that the oxygen saturation does not fall below 90% until the altitude exceeds about 10,000 feet (which equates to an alveolar oxygen tension of approximately 55 mm Hg). As altitude rises above 10,000 feet the percentage saturation of haemoglobin falls precipitously resulting in hypoxic, or hypobaric, hypoxia.

In moderate hypoxia, such as when breathing air at 25,000 feet, cardiac output and heart rate are increased but overall peripheral resistance is reduced, so that mean arterial blood pressure is unchanged. Cerebral blood flow is increased, although the degree of increase is modified by the magnitude of coexisting hypocapnia which results from increased respiratory minute volume. Thus cerebral and cardiac perfusions are increased at the expense of less vital organs.
Respiration increases under the hypoxic drive to help alleviate cerebral hypoxia but is ineffective, and the symptoms and signs of hyperventilation develop alongside those of hypoxia. Hyperventilation is a normal response to a fall in alveolar oxygen partial pressure to below 55 – 60 mm Hg and may be the dominant clinical feature. Symptoms both of hypoxia and hyperventilation

can include light-headedness, feelings of unreality and anxiety, paraesthesiae, visual disturbances and palpitations (24).

Effect of Altitude on Absorption

Exposure to breathing air at cabin altitudes between 10,000 and 30,000 feet never results solely in a reduction in the oxygen tension in the alveolar air since there is always a simultaneous decrease in the alveolar carbon dioxide concentration. The effect on alveolar ventilation rate is thus due to the combined effects of a lowered alveolar oxygen concentration and hypocapnia. There is a very considerable individual variation in the degree of increase in alveolar ventilation caused by a given reduction in alveolar oxygen tension; amongst individuals exposed to the same level of oxygen deprivation some will achieve a lower alveolar carbon dioxide tension than others.
The tensions of oxygen and carbon dioxide in the alveolar air of resting subjects breathing air at reduced barometric pressure reflect the changes in the inspired oxygen tension and the changes in alveolar ventilation caused by hypoxia.
It has been shown that there is no increase in pulmonary ventilation (breathing rate) until the alveolar oxygen tension is reduced to about 65 mm Hg (17). This occurs at an altitude of about 8,000 feet. It is only when the barometric pressure is reduced further that pulmonary ventilation is increased.

However, none of these effects are significant at cabin altitudes below 10,000 feet. It can be seen from the oxyhaemoglobin dissociation curve that the reduction in alveolar oxygen partial pressure is small, resulting in a desaturation of less than 10%. The published air quality standards remain valid at cabin altitudes up to 10,000 feet (24).

AEROTOXIC SYNDROME

A syndrome is defined as a set of symptoms which occur together, or the sum of signs of any morbid state, or a symptom complex. It follows that there should be a consistent set of common symptoms which together make up a given condition.
Individuals reporting that they suffer from the so-called aerotoxic syndrome describe a wide range of individual symptoms and signs, with insufficient consistency to fulfil the requirements for the definition of a medical syndrome. Many of the reported acute symptoms are largely the same as those reported by participants in all phase 1 drug trials, being normal symptoms experienced by most people on frequent occasions. It is recognised that 70% of the population experience one or more of them on any given day.
The Aerospace Medical Association reviewed the scientific evidence and concluded that there was insufficient consistency and objectivity to support the establishment of a clearly defined syndrome (18). The US National Academy of Sciences performed a similar review and reached the same conclusion (19), as did the Australian Government CASA Expert Panel on Aircraft Air Quality in 2012 (13, 14).

Thus the concept of the 'Aerotoxic Syndrome' is not recognised in the aviation medicine community.

Of the UK professional pilot population of approximately 20,000, in 2013 the CAA log of pilots who have reported symptoms which they attributed to exposure to fumes has 31 cases, of which 3 are duplicates, leaving a total of 28 individuals. Of these 14 have returned to flying or were never assessed as unfit. The remaining 14 remain unfit (the CAA no longer differentiates temporary/long term unfit), although a number would have passed normal retirement age. No new cases have been documented since June 2012 and the CAA is not aware of any other on-going cases (26).

Following a review of the log document, the CAA Medical Department determined that this information has no medical validity because:

- the inclusion of an individual is based entirely on the individual's subjective perception of the cause of their condition;
- there are no objective or diagnostic medical criteria for inclusion;
- there is no consistency in the symptoms and signs reported by the individuals or their treating doctors;
- it is likely that there is incomplete reporting of cases where a pilot experiences brief symptoms at the time of an event.

There are known to be individual genetic differences in sensitivity to smells and chemical exposures, but there is no consistency in reported symptomology. The concentration of oil products in the cabin air is very low and greatly diluted in the free stream air.
Taking the RB211 engine as an example, the maximum engine oil possible in the bleed air is 4kg. Of this, 3% is TCP of which around 0.1% is T*o*CP. In the worst case scenario of the total discharge of an engine's lubricant into the engine bleed system, 0.4kg of oil would pass into the cabin ventilation system. This would give a peak cabin atmosphere T*o*CP level of 0.025 mg/m^3, reducing rapidly as a result of normal cabin ventilation. The peak level would be a quarter of the 8hr workplace limit of 0.1 mg/m^3, and less than a tenth of the 15min emergency workplace limit of 0.3 mg/m^3 (20).
Alveolar absorption depends on Dalton's Law of partial pressures, as well as Fick's Law (see above), and the partial pressure of bleed air contaminants is a small proportion of the total alveolar gas pressure. Comparisons have been made with the symptoms reported by farmers exposed to organophosphates in sheep dip, but the concentrations and periods of exposure are many magnitudes of difference as well as the route of chemical entry into the body being different.

Symptoms reported by some crew members who have been exposed to fumes in the cabin are similar to those reported by individuals complaining of a range of conditions such as sick building syndrome, chronic fatigue syndrome, Gulf War syndrome, Lyme disease and chronic stress. In all these conditions, there is lack of consistency in reported symptoms and signs and wide individual variability.

The UK Government Committee on Toxicity published a position paper in 2013 (27). In summary, the paper concluded:

- a toxic mechanism for the reported long term illness is unlikely
- further cabin air sampling would be technically feasible but prohibitively expensive
- collection and analysis of more comprehensive data in relation to fumes events, evaluated against a suitable control sample, would be informative and might help to target either further research or measures to reduce the number of incidents
- further studies involving collection and analysis of biological samples would be feasible and useful.

Specifically, amongst the conclusions the paper stated:

"12 vii. More generally, the Committee considers that a toxic mechanism for the illness that has been reported in temporal relation to fume incidents is unlikely. Many different chemicals have been identified in the bleed air from aircraft engines, but to cause serious acute toxicity, they would have to occur at very much higher concentrations than have been found to date (although lower concentrations of some might cause an odour or minor irritation of the eyes or airways). Furthermore, the symptoms that have been reported following fume incidents have been wide-ranging (including headache, hot flushes, nausea, vomiting, chest pain, respiratory problems, dizziness and light-headedness), whereas toxic effects of chemicals tend to be more specific. However, uncertainties remain, and a toxic mechanism for symptoms cannot confidently be ruled out.

13. Finally, it should be emphasised that illness can be disabling whether it occurs through toxicity or through nocebo* effects, and therefore there is a continuing imperative to minimise the risk of fume incidents that give rise to symptoms."

[* In medicine, a **nocebo** (Latin for "I shall harm") is a harmless substance that creates harmful effects in a patient who takes it. The **nocebo effect** is the negative reaction experienced by a patient who receives a nocebo. Conversely, a placebo is an inert substance that creates either a positive response or no response in a subject who takes it. The phenomenon in which a placebo creates a positive response in the subject to which it is administered is called the placebo effect. Both nocebo and placebo effects are entirely psychogenic. Rather than being caused by a biologically active compound in the nocebo or placebo itself, these reactions result from a subject's expectations about how the substance will affect him or her. Though they originate exclusively from psychological sources, nocebo effects can be either psychological or physiological.]

IRRITABILITY

Irritation is a state of over-excitation and undue sensitiveness of the nervous system in response to a stimulus. For example, irritant receptors in the lungs stimulate reflex constriction of the bronchioles in response to smoke and smog. Similarly, sneezing, sniffing and coughing may be stimulated by irritant receptors in the nose, larynx and trachea.
Some gases are known to be irritants and as a rule they are chemically corrosive. They injure surface tissues and induce inflammation of the air passages and the parenchymal region. Organophosphates are not classified as irritant gases.
Individuals vary in their response to sensory stimuli, including smells. Genetic differences are thought to cause some people to have enhanced sensitivity to low levels of some volatile chemicals; they experience a range of irritant symptoms affecting well-being.

HYPERVENTILATION

Hyperventilation is a normal response to emotional stress, particularly anxiety, apprehension and fear. Even low levels of stress, which may not be perceived as such by the individual, commonly give rise to hyperventilation. It is also a natural response when resistance to breathing is encountered, such as when using an emergency oxygen mask.
Obviously not every case of 'aerotoxic syndrome' is caused by hyperventilation, but it offers a plausible explanation for some reported events.

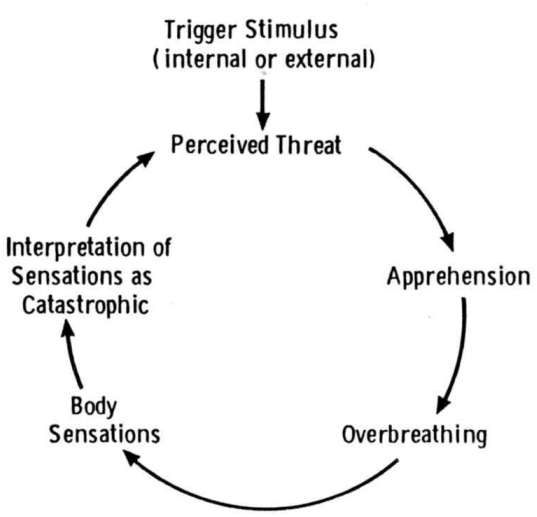
In the aviation environment it is generally recognised that hyperventilation is a common condition. Studies have shown that a large proportion of aircrew under training hyperventilate, as do experienced aircrew when confronted with an unusual event or in-flight emergency. A 2009 study raised concerns about the prevalence of unrecognised hyperventilation amongst airline pilots and the potential risk to flight safety (21).
Symptoms can include light-headedness, headache, feelings of unreality and anxiety, paraesthesiae, visual disturbances, palpitations, cognitive impairment, loss of concentration and, in extreme cases, muscular tetany and paralysis (22, 24).
The nervous system and blood vessels are very sensitive to the acidity of the blood, which is reduced during hyperventilation. It causes a marked constriction of blood vessels in the brain and skin and an increase in blood flow through the muscles. The reduction in blood flow through the brain leads to a reduction in the oxygen available to the cerebral tissues, giving effects similar to hypoxia affecting mental performance. The shallow breathing reduces gaseous exchange in the alveoli which may result in a fall in peripheral blood oxygen concentration, adding to the hypoxic effects.

Whereas in general medicine, the hyperventilation syndrome may not always be readily recognised as a clinical entity, falling as it does between

physiology, psychiatry, psychology and medicine, the condition of hyperventilation is readily accepted in aviation medicine.
However, diagnosis can be difficult in the absence of a simple measurement. The physiological diagnosis of hyperventilation is breathing in excess of metabolic requirements, thus implying arterial hypocapnia (low CO_2 tension) and an abnormally high respiratory drive. However, in chronic cases measurement of the alveolar partial pressure of carbon dioxide (PCO_2) is difficult and can be profoundly affected by the total physiological inputs to respiration and the conscious state of the individual. There can be a tendency to hyperventilate even though the resting PCO_2 is normal.

There are a number of factors which may perpetuate hyperventilation. Apart from renal compensation, there appear to be physiological mechanisms resetting the PCO_2 to a lower level independent of chemoreceptor setting. Habit may be a perpetuating mechanism, as may be misattribution of symptoms of hypocapnia (symptoms not dissimilar to those of carbon monoxide toxicity).
The interaction of factors contributing to chronic hyperventilation remains uncertain. One possible scenario is that an acute episode of hyperventilation, such as might occur on perceived exposure to oil fumes, leads to symptoms which are misdiagnosed or incorrectly diagnosed. The symptoms can be alarming and as a consequence, the individual's anxieties are increased and further consultation sought, leading to perpetuation of the disorder. However, providing satisfactory proof of such a model is difficult, and in the presence of worrying physical symptoms without an obvious cause the individual and his/her medical advisers may be reluctant to consider such a diagnosis.
With such a wide range of reported symptoms and signs amongst crew members who are anxious that they have been exposed to oil fumes, it is fatuous to suggest that all cases are the result of hyperventilation. However, it should be considered in the differential diagnosis.

Hyperventilation Syndrome:



CONCLUSION

There has been an increase in reported incidents of in-flight smoke/fume events since 1999, with a small number of crew members reporting adverse health effects which they associate with the events.
The source of oil contamination of engine bleed air was identified in early versions of the BAe 146 and the Boeing 757 and suitable modifications were implemented. A range of chronic health effects continue to be reported by some crew members.

The toxic effects of organophosphates are specific and are due to impairment of neurotransmission in the peripheral nerves, giving rise to muscular weakness and paralysis. In terms of medical toxicology, it is impossible to explain the wide range of symptoms and signs reported by some crew members as a unified result of TCP exposure.
Symptoms reported by some crew members who have been exposed to fumes in the cabin, particularly when emergency oxygen masks are used, are the same as those seen in acute or chronic hyperventilation. Obviously not every case of 'aerotoxic syndrome' is caused by hyperventilation, but it offers a plausible explanation for some reported events.
In some cases, the symptoms may be due to irritation associated with enhanced chemical sensitivity to certain volatile organic compounds.

The reported symptoms are wide-ranging with insufficient consistency to justify the establishment of a medical syndrome. It has been noted that many of the acute symptoms are normal symptoms experienced by most people frequently; some 70% of the population experience one or more of them on any given day.

Individuals can vary in their response to potential toxic insult because of age, health status, previous exposure or genetic differences.
In addition, it can be difficult to disentangle the physical, psychological and emotional components of well-being, and there is no doubt that different people will respond in different ways on different occasions.
It is not understood why most occupants of pressurised aircraft do not report symptoms despite having the same exposure as those who do.

Finally, so far as scientific evidence has been able to establish to date, the amounts of organophosphates to which aircraft crew members could be exposed, even over multiple, long-term exposures, are insufficient to produce neurotoxicity.

Investigations of aircraft cabin air world-wide have failed to detect levels of TCP above well-established and validated occupational exposure limit values. The partial pressure in the alveolar gas mixture of any TCP contamination of the cabin air is so low that it is unlikely to cross the alveolar membrane.

Genetic or particular susceptibility to a particular adverse effect of certain chemicals on the part of an individual does not alter the need for there to have

been a sufficient chemical exposure to cause the injury or damage. For the reasons set out above, the possible exposure levels to ToCP on aircraft are so low relative to what is required to create a toxic effect through inhalation that a toxic injury is simply not medically feasible with current understanding.

Aviation medical professionals throughout the world continue to monitor the scientific evidence and remain receptive to objective peer-reviewed evidence.

REFERENCES

1. GCAQE Press Release 19 April 2012. GCAQE: http://www.gcaqe.org
2. Inhalable toxic chemicals on board aircraft – ITCOBA Seminar, Cranfield, Oct 2011. Journal of Biological Physics and Chemistry, Vol 11, No 4. http://www.itcoba.net/
3. van Netten C (1998). Air quality and health effects associated with the operation of the BAe146-200 aircraft. Applied Occupational and Environmental Hygiene 13:733-739
4. Spengler JD, Burge H, Dumyahn T, Muilenberg M, Forester D (1997). Environmental Survey on Aircraft and Ground-based Commercial Transportation Vehicles. Harvard School of Public Health, Harvard University, Cambridge, MA.
5. Dumyahn, TS, Spengler, JD, Burge, HA, Muilenburg, M (2000). Comparison of the Environments of Transportation Vehicles: Results of Two Surveys, *Air Quality and Comfort in Airliner Cabins, ASTM STP 1393*, N.L. Nagda, Ed, American Society for Testing and Materials, West Conshohocken, PA 2000
6. Committee on Toxicity of Chemicals in Food Consumer Products and the Environment: Statement on the Review of the Cabin Air Environment, Ill-health in Aircraft Crews and the possible relationship to Smoke/fume Events in Aircraft. http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2007/cotstatementbalpa0706
7. Muir H. (2008). Cabin air sampling study functionality test. Cranfield: Cranfield University. https://dspace.lib.cranfield.ac.uk/handle/1826/2389
8. Cranfield University Institute of Environment and Health. (2011). Aircraft Cabin Air Sampling Report (Part 1 of the Final Report) https://dspace.lib.cranfield.ac.uk/handle/1826/5305
9. Cranfield University Institute of Environment and Health. (2011). Aircraft Cabin Air Sampling Report (Part 2 of the Final Report) https://dspace.lib.cranfield.ac.uk/handle/1826/5306
10. Lamb J, McGonagle C, Cowie H, Cherrie JW. Cabin Air – surface residue study. IOM Research Report TM/11/06. March 2012
11. Spengler JD, Wilson DG. Air Quality in Aircraft. Proceedings of the Institution of Mechanical Engineers, Part E: Journal of Process Mechanical Engineering November 1, 2003 vol. 217 no. 4 323-335
12. BRE Cabin Air Quality Workshop. Aviat Space, Environ Med; **83**(10): 1023. October 2012

13. Navathe P. What does EPAAQ add to our Knowledge? Proceedings of IATA Aviation Health Conference, London. Oct 2012
14. www.casa.gov.au/cabin/epaaq/index.htm
15. Schindler BK, Weiss T, et al. Occupational exposure of air crews to tricresyl phosphate isomers and organophosphate flame retardants after fume events. Arch Toxicol (2013) **87**:645–648
16. Abou-Donia MB, Abou-Donia MM, et al. Autoantibodies to nervous system-specific proteins are elevated in sera of flight crew members: Biomarkers for nervous sytem injury. Journal of Toxicology and Environmental Health, Part A, **76**:363–380, 2013
17. Gibson TM. Hyperventilation in aircrew: a review. Aviat Space Environ Med 1979; **50**: 725-33
18. Hudson MF. Cabin Air Quality in Commercial Aircraft: Is there any cause for concern? A Review of the Current Evidence. Aviat Space Environ Med; 82(3). March 2011:280-281
19. www.nap.edu/catalog.php?record_id=10238 pp180-181
20. The United Kingdom Parliament - Select Committee on Science and Technology – Fifth Report (04-10-2006): 4.39
21. Karavidas KK, Lehrer PM. In-flight hyperventilation among airline pilots. Aviat, Space, Environ Med 2009; 80 (5): 495-6
22. Brown EB. Physiological effects of hyperventilation. Physiological Reviews 1953; **33**: 445-71
23. van Netten C. Final Report on Aircraft Wipe Sample Analysis for Tricresyl Phosphate Isomers (Feb 2009). University of British Columbia, Vancouver BC. www.spph.ubc.ca
24. Ernsting J, Ward J, Rutherford OM. Cardiovascular and respiratory physiology. In Rainford DJ, Gradwell DP (eds). Ernsting's Aviation Medicine 4ed (2006) ISBN-10 0 340 81319 9: 13-40
25. Blain PG. Absorption of chemicals and mechanisms of detoxification. In Baxter PJ, Adams PH, Aw T-C, et al (eds). Hunter's Diseases of Occupations 9ed (2000) ISBN 0 340 67750 3: 67-80
26. Head of Aviation Health Unit, UK Civil Aviation Authority Medical Department (September 2013). Personal communication.
27. http://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2013/cotpospacabair