Review Article

Is a Cumulative Exposure to a Background Aerosol of Nanoparticles Part of the Causal Mechanism of Aerotoxic Syndrome?

C. Vyvyan Howard[1*], David W. Johnson[2], John Morton[3], Susan Michaelis[4], David Supplee[5], Jonathan Burdon[6]

[1]Centre for Molecular Biosciences, University of Ulster, UK

[2]Department of Chemistry, University of Dayton, Dayton, OH, USA

[3]Chairman European Sealing Association, France

[4]School of Health Sciences, University of Stirling, UK

[5]International Association of Machinists & Aerospace Workers, Missouri

[6]Consultant Respiratory Physician, Melbourne, Australia

Corresponding author: C. Vyvyan Howard, Emeritus Professor, Nano Systems Biology, Centre for Molecular Bioscience, University of Ulster, Coleraine BT52 1SA, UK. Tel: +447917284918; Email: vyv.howard@googlemail.com

Abstract

We present strong evidence for the presence of aerosols of Nano-particles (also termed Ultrafine Particles (UFPs) in aerosol science) in the breathing air of pressurized aircraft using engine bleed air architecture. The physical and chemical nature of engine oils and the high temperatures attained in aircraft jet engines (up to 1,700°C in the oil circulation and up to 30,000°C in the bearings) explain why UFPs are to be expected. A discussion of oil seals used in gas turbine engines concludes that they will permit UFPs to cross them and enter the breathing air supply, in conjunction with a complex mixture of chemicals such triaryl phosphates which are neurotoxic. A consideration of the toxicology of Nano-particles concludes that their continual presence over a typical working lifetime of up to 20,000 hours in aircrew will predispose them to chronic respiratory problems and will exacerbate the translocation of neurotoxic substances across the blood brain barrier.

Introduction

Aircraft design in the 1950s was altered to facilitate pressurization and ventilation of the cabin from 'engine bleed air' drawn off from the compressor stage of the propulsion gas turbine jet engines or auxiliary power units on board the plane. Hitherto cabin pressurization had been achieved with turbo-compressors, drawing air directly from outside, yet these were heavy and costly on fuel consumption. The redesign using unfiltered engine compressor air was thus a cost-saving measure and is found in all current commercial aircraft except one, the relatively recent Boeing 787 (B787) model, which has reverted to the earlier concept of not using bleed air.

Quite soon after the introduction of cabin bleed air, the US military realized that there was a problem with oil fumes coming from the engines [1] with crew becoming ill and instructed some pilots to wear oxygen masks during operations. Gas turbine engines operate at high temperatures and the synthetic lubrication oils must contain additives to reduce engine wear, oxidation and corrosion. The antiwear additives are usually triaryl phosphates, such as Tricresyl Phosphate (TCP), and have neurotoxic properties [2]. The commercially available TCPs consist of a wide range of cresols, phenols and xylenols, not just the 10 TCP isomers, all of which are assumed to have similar reactivity [2,3].

With exposure to engine oil contaminants as aerosols and vapours in cabin air, two modes of exposure are recognised. In normal operation, aircraft with bleed air systems have been

demonstrated to have a background low level mixture of contaminants present [4,5]. These are generally at levels difficult or impossible to routinely detect but their presence is incontestable, as shown in many studies [6-12]. The second form of exposure is when there is a noticeable odour ranging from very short-term transient exposures through to an oil bearing seal failure leading to a more obvious higher dose exposure, usually termed 'fume events'. The principal route of exposure is through inhalation. The pattern of exposure among aircrew is intermittent-continual with cumulative exposure times often summing to many thousands of hours. A noticeable odour may be associated with a very low level of oil [13], as low as a few drops [14]. The odour is often described as a 'dirty sock' type odour, associated with the carboxylic acids related to the thermal decomposition and hydrolysis of the synthetic oil base stocks [15].

A recent paper by Michaelis et al. [16] has described Aerotoxic Syndrome (AS) and presented some epidemiological evidence. Howard et al. [17] have described the probable toxico-pathological mechanism that leads to Aerotoxic Syndrome. This is based on the existing scientific literature concerning repeated low dose exposures to organo-phosphorous compounds [18]. Some stakeholders continue to refuse to accept the existence of Aerotoxic Syndrome, their predominant argument being the low levels of toxicant present in aircraft cabin air are not capable of causing harm or are below exposure limits [8,19,20]. Others accept an association between exposure to the oils and other bleed air contaminants and short-term adverse effects, however they suggest a toxic mechanism or long-term effects are unlikely, yet a link cannot be ruled out [21,22]. This is because the levels identified are suggested to be too low to cause Organophosphate Induced Delayed Peripheral Neuropathy (OPIDN) [21], which is known to result from high dose acute exposures.

This current paper addresses the additional toxicological challenge caused by the continual presence of an aerosol of Ultrafine Particles (UFPs) in gas turbine bleed air, in the presence of a complex mixture of other toxic chemicals and considers its significance in the overall aetiology of Aerotoxic Syndrome.

Formation of Particulate Aerosols in Aircraft Gas Turbine Engines

The chemical (and hence toxicological) nature of fugitive emissions from engine oil seals will be dictated in some measure by the physical conditions (temperature and mechanical stress) to which the lubricating oil has been subjected over a period of time. Apart from the permissible oil consumption, the oil is held either in the oil reservoir or in circulation around the engine. All of the oil, therefore, will circulate through all of the engine during usage and thus have been exposed to high temperatures and very high shear stress.

Turbine engine oils for commercial aircraft have physical and chemical properties governed by the oil's specification. The specification requires stability at 218°C, which approximates the maximum temperature the oil will experience for extended periods of time. The bulk of the oil spends about 95% of its time in the oil reservoir or cycling throughout the lubricated areas at this temperature while the remaining 5% is exposed to far higher temperatures when in potential contact with parts. It is only a very small amount of time that the oil will be in the bearings or other places where exposed to yet higher temperatures. It is easy to measure the bulk oil temperature but far more difficult to estimate the temperatures inside bearings and to account for the effect of mechanical stresses such as shear.

The oil goes through a recirculating system and can (and does) go everywhere within that system. The oil coming into contact with various metallic parts can be exposed to very high temperatures ~1,700°C in the turbine area, rather less in the compressor area. Oil then recirculates and can go to other bearing chambers/areas (cycles through entire engine) including the compressor area and can pass seals there. So, it is clear that the oil is exposed to temperatures up to 1,700°C in some areas of the engine during the normal lubricant duty cycle.

However, 1,700°C, though already well above the typical flashpoint (246°C) [23] for jet engine oils, is not the hottest that oils in gas turbine engines attain. Synthetic ester-based oils do not smoke by the same mechanisms that mineral oils smoke, but under shear they can form an aerosol of Nano droplets that give the appearance of smoke. It is not easy to directly measure the temperatures at the bearing surfaces effectively as it is a function of the temperatures, pressures & sheer forces (bearings 'squeeze' oil) in the metal to metal contact region. However, they can be modelled using a Reynolds equation which has been used to estimate the potential temperatures and pressures to which the oil may be subjected to in contact with bearings. The Reynolds model, [24] estimates that effective temperatures up to 30,000°C can occur for nanoseconds based on the pressures and shear stresses in the bearing. In an operating engine, this would clearly be a recurring event. This level of temperature is almost in the plasma arc range of temperatures. More or less complete thermal degradation of this small oil volume would occur, with subsequent small sized Ultrafine Particles (UFPs) and pyrolysis product formation. High temperatures can cause isomerization of the cresol and xylenol, leading to the formation of ortho isomers. Metal surfaces of the bearings and other parts of the engine can easily catalyze reactions generating gaseous products including carbon monoxide. Additionally, metal surfaces can catalyze addition of aromatic rings to the triaryl phosphates leading to a very large number of products of lower volatility [25]. Less volatile products may be transported as aerosols.

Significance of Nanoparticles to the Toxicology of Triaryl Phosphates in Cabin Air

Research into interactions between UFPs formed under high temperature conditions of gas turbine engines and other chemicals present, such as triaryl phosphates, has never been undertaken (or if it has, it has not been published).

Purely as a discussion point to demonstrate mechanism, there has been a lot of research into the formation of metals, dioxins and other organo-chlorine moieties on the surface of small particles formed in municipal waste incinerators during combustion. Chang et al. [26] demonstrated a differential deposition of metals: 80% Zn, Pb, Cu on fine particles, only 20% on coarse particles. Cormier et al. [27] reaffirmed that inhalation of fine and ultrafine particles is a major route of exposure to toxic combustion by-products from waste incinerators. Chao et al. [28] showed that particles < 2 μm had the highest dioxin content, comprising 80% of the total particle bound toxicity. They found that in general the smaller the particle the higher the dioxin content. This is all well understood and completely in keeping the toxicological properties of nanoparticles reported by Elsaesser and Howard [29] and others.

What is the relevance of information from waste incineration to aircraft cabin air quality? A lot, it turns out. The temperature ranges of the two processes are in the same range, actually they are somewhat higher in gas turbine engines. The physics governing the formation of ultrafine particles is exactly the same. The chemistry, however, is different. Instead of being primarily the halogen rich environment of a waste incinerator, it is a phosphate rich environment in a gas turbine engine. Because the temperature and other physical conditions remain comparable between the two systems we would expect organic moieties to form on the surface of particles, particularly the smallest respirable UFPs.

Why Do UFPs Get into the Cabin? - Gas Turbine Engine Seal Performance

A recirculatory oil system provides the minimum quantity of oil under high pressure for various purposes including lubrication, cooling and sealing [4]. For example, the main engine shaft bearings grouped together in bearing chambers require a continual supply and removal of oil. Pressurized air from the engine compressor is used to keep the bearing compartment at a lower pressure than the surroundings. This causes an inward flow and prevents an outward leak through the bearing seals and also cools and ventilates the bearing sumps. Oil seals have various functions including prevention of oil leakage outside the bearing chamber, thereby preventing fumes in the cabin, fires and loss of performance. Aero bearing seals are required to operate at high speeds necessitating either a well lubricated seal or one that operates with a clearance [4,30]. All dynamic seals are designed to leak. How much they leak depends on many factors including the style of seal, the balance ratio or tooth pattern, the lubricating regime, operating conditions (speed, temperatures and pressures), compartment condition, wear life and distortion [31].

The two main types of seals used in aero engines, labyrinth clearance seals and mechanical carbon face seals, both rely on compressor sealing air flow across the seal and are responsive to varying engine operating conditions. Labyrinth seals operate with tight clearances often in the range of 200 - 400nm (0.0002 to 0.0004mm), though this is governed by the radial clearance of the bearing. The controlled leakage of air or liquid over restrictions reduces the pressure over the seal. However regardless of the pressure gradient fluid can flow in either direction depending on the pressure, velocity and design. Performance may deteriorate with time, due to component wear and changes in operating conditions. Labyrinth seals do not in isolation provide a complete barrier to leakage [32]. Mechanical carbon seals operate with a micro seal face separation (typically 0.25 -1um), therefore providing very low leakage during normal operation. The high precision flat faces used to form a good seal must be lubricated so as to operate at a reasonable temperature and provide a long life. The oil film is a compromise between being thick enough to provide lubrication and a long seal life, but as thin as possible to minimize oil migration across the sealing faces during normal operation [32]. It is accepted that such seals will leak a very small amount of oil vapor during normal service. Labyrinths operate with a clearance, while the mechanical face seals operate with a lubricated face, with both types of seals designed to limit sealed product migration and therefore limiting emissions, rather than preventing them.

It is commonly assumed that a higher pressure in the gas path than the bearing chamber will keep the oil in the chamber, and that seals will leak only when a failure occurs and that positive pressures across the sealing faces will prevent migration. However, oil can flow both with and against the positive pressure gradients with both types of seals. Additionally, positive pressure gradients are difficult to attain at the near ambient pressures used to seal bearing chambers, allowing a much greater chance of reverse pressure gradients in transient engine modes.

The use of pressurized oil bearing seals therefore provides the mechanism for low-level oil leakage in normal flight. Breathing air for the passenger cabin in all modern transport aircraft, except for the B787, is derived from the engine compressor and is ducted unfiltered via bleed air off takes. Oil passing over the seals in the area of the compressor, has a path to enter the cabin air supply if the leakage or emissions occur prior to the air off take location. The use of pressurized air to both seal the bearing chamber and to provide ventilation for the cabin, guarantees that fugitive low-level oil emissions will enter the breathing air supply during normal engine operation.

The levels of individual oil substances detected in normal engine operation at background levels have been repeatedly identified as shown above. It is acknowledged that there will be a permanent low level of oil leakage below the limits of detection based on current technology [9]. Confirmation of lower-level oil leakage may be very difficult with defined maintenance procedures [14,33] and for those associated with transient engine operations [22].

However, Jones et al. have more recently reported that "Measurements showed that oil contamination in the compressor will result in a fog of very fine droplets in the bleed air under most operating conditions" [34]. The droplets were found to be in the 10-150 nm range, with it suggested many of the droplets to be even smaller than 10nm. "Oil contamination leads to a large number of particles in the bleed air" with peak UFP concentrations in the 50-70nm range and particle size becoming increasingly small with low contamination rates [34].

Figure 1 shows the air supply ducting of a Boeing B737 bleed air system aircraft. Note the blackened appearance of the ducting.

Figure 1: Air supply ducting of a B737 aircraft [35].

Figure 2 is a portion of ducting taken from a non-bleed air aircraft using a turbo-compressor to supply the air direct from outside the aircraft. Clearly this ducting is much cleaner than the bleed air ducting.

Figure 2: Turbo compressor ducting of a non-bleed air aircraft, Vickers VC 10 [35].

Figure 3 shows a section of the interior surface of an unused air supply duct of a bleed air aircraft that is free from particulate material [7].

Figure 3: Unused air supply ducting [7].

Figure 4 shows the interior surface of used bleed air aircraft ducting which is coated with a film of black particulate material, suggested to be associated with oil particulate matter and corroborates the appearance of the manifold in Figure 1.

Figure 4: Used aircraft air supply ducting [7].

Toxicology of Nanoparticles

There is evidence that, in addition to the complex mixture of fugitive chemical emissions continually present in cabin air, there is also an aerosol of Ultrafine Particles (UFPs). The size range of UFPs is, by definition, the same for Nano-particles, namely 1-100nm. This has been confirmed by Jones et al. [34] who made measurements of appreciable levels of UFPs in bleed air from gas turbine engines. This should come as no surprise because high temperature 'Hot Spots' in the lubrication oil pathway have been reported by Dr. David Johnson, referred to in a previous section of the paper, all of which exceed the smoke point for lubrication oils. The highest temperature is approaching plasma arc temperatures. At these temperatures several sequelae are assured. UFPs will be formed. Organic molecules, such as the triaryl phosphates present in the vapor phase will condense on the very high specific surface of the UFP aerosol and will remain there.

Elsaesser and Howard [29] have reviewed the toxicology of nanoparticles. The main points of relevance are: - When particles in the Nano-scale are made, they become chemically much more reactive, very much in the mode that heterogeneous catalysts operate. This works even for materials that are chemically inert in bulk, such as gold and platinum. These very small particles develop a surface chemistry, Fenton chemistry, which is a function of their small size. A common factor between UFPs in biological matrices is that they induce inflammation, largely irrespective of what they are made of - it is a small size related property. Particles in the UFP size range are preferentially deposited to the deepest alveolar regions of the lungs, where gas exchanges between air and blood are conducted. UFPs can cross the alveolar membranes into the blood stream [36] by endocytosis (in the same way that viruses do) and have been measured travelling to most organs in the body, including the CNS [37]. UFPs can also act like Trojan Horses as they can cross the Blood Brain Barrier (BBB), which has evolved to keep unwanted chemicals at bay. Pharmaceutical companies are already exploiting this aspect to increase drug penetration into the brain. They coat Nano-particles with the drug of interest and this then 'piggybacks' across the BBB, again by endocytosis. Thus, the drug, in this case, avoids the metabolic defense mechanisms of the BBB while adherent to the surface of the Nano-particle.

What are the health consequences of being chronically exposed to an aerosol of UFPs for hundreds or thousands of hours during the professional lifetime of typical flight crew? The effect of having a continual aerosol of UFPs within a complex mixture of fugitive engine vapors in cabin air will be to increase exposure of the brain to neurotoxic chemical influences leading to target organ toxicity. This will be because some of the vapor-phase volatile organic compounds will have condensed onto the surface of UFPs which can act as Trojan Horses and cross the BBB.

The scientific literature on the toxicological consequences of repeated low dose OP exposure has been reviewed by Terry [18]. We believe it is wrong to not mention the toxicology of complex mixtures but wanting to maintain a 'One chemical at a time' approach. The current approach of the toxicological consequences to consider candidate chemicals, for which trigger limits can be set, is a standard approach in classical toxicology. However, it should be stated explicitly that, on the current evidence in the peer reviewed scientific literature, the proposed 'One chemical at a time' approach will do absolutely nothing to address health problems that air crew and frequent flyers suffer from.

Evidence of Impacts on the Respiratory System in Air Crew

Respiratory complaints among aircrew are particularly common. Published studies [16,38-44] have drawn attention to respiratory abnormalities in previously healthy aircrew who were predominantly non-smokers, and who experienced symptoms following an aircraft cabin fume event. These complaints are consistent with lung injury secondary to hydrocarbon and particulate inhalation. In many cases, these effects have been irreversible. Breathlessness, cough and chest pain or tightness are reported in most subjects. Other presenting symptoms have been those of wheezing, occasionally haemoptysis and complaints of upper respiratory tract irritation; sinusitis and epistaxis are also common. Recurrence of symptoms with return to duty is commonplace.

Inhaled particulates have always been a matter of concern in respiratory health. Lung diseases caused by exposure to, and the inhalation of, toxic fumes and dusts are well recognized to cause conditions, such as occupational asthma, silicosis, asbestosis, lung cancer and mesothelioma, to name just a few. Toxic chemical substances and particulates (PM10s and smaller) generated from the burning of fossil fuels have also been a major cause of respiratory ill-health for centuries. Nanoparticles have always been present in the environment and it is now becoming clear that they

may have toxic effects on the lung and other organ systems [45]. This is of concern as nanoparticle technology is being examined as a useful way to deliver treatment for lung and other diseases [46], but the emerging literature also shows that some UFPs may not be innocuous. As previously discussed, thermal degradation of aircraft engine oils at extreme temperatures will produce UFPs which, together with other engine oil contaminants will enter the bleed air and then the aircraft cabin. As a result, aircrew and passengers will be exposed to their potentially toxic effects together with those of other larger particles also contained in the bleed air. The potential for illness, as a result of exposure, will be increased by cumulative exposure, whether by regular short-term exposures or by less frequent longer exposures.

The respiratory tract is the common portal of entry for these toxic substances, although entry through the skin and alimentary tract is also recognized. Thus, it is not surprising that recurrent acute and chronic sinusitis and symptoms referable to the lower respiratory tract, such as cough and breathlessness, are common complaints among aircrew. Furthermore, not only is the respiratory tract the main portal of entry, in most cases, but it is also systemically more exposed than other organ systems, as it receives the total cardiac output, thus, at least, theoretically increasing the possible toxicity [47]. The emerging evidence for the toxic effects of UFPs on the respiratory tract are largely based on animal studies. Several studies have shown that carbon nanotubes will cause systemic immune responses, pulmonary inflammation and fibrosis [48-50] and the toxic effect of multi-walled carbon nanotubes is increased in conditions characterized by underlying inflammation, such as asthma [45]. The results of early animal studies indicate that UFP toxicity is real and may lead to and account for currently observed human ill-health, at least in susceptible individuals.

Evidence of Impacts on the Nervous System in Air Crew

The spectrum of neurological signs and symptoms associated with Aerotoxic Syndrome have been reported by Michaelis et al. and Howard et al. [16,17] When considered together they constitute a group of non-localizing functional deficits which are consistent with a diffuse toxic encephalopathy. This clinical picture is in many ways directly comparable with the symptoms suffered by farmers suffering from 'dippers' flu' [51], the common aetiological factor being exposure to organo-phosphorous compounds.

A toxico-pathological explanation of the influence of continual low dose exposure to a complex mixture of OPs has been given by Howard et al. [17] A major consideration in the aetiology of neurological damage in Aerotoxic Syndrome is the protracted length of exposure that occurs in the normal working lifetime of air crew, as discussed above. It is known from the scientific literature that some of the interactions between low dose OPs and biological matrices are delayed and irreversible in nature [52,53]. For example, co-valent binding of OPs to tyrosine and lysine residues can result in the modification of many more proteins than was previously recognised. [54,55] The majority of human protein misfolding diseases (currently 42 are recognised) manifest themselves as chronic degenerative diseases of the central nervous system.

This body of science has to date been based solely on exposure to OP chemicals. In the case of aircraft cabin air, it is now important to consider the additional impact of UFP aerosols and how they will interact with respect to target organ toxicity in the CNS. The evidence presented in the toxicology section above clearly indicates a mechanism by which the continual presence of nanoparticle aerosols admixed with a complex mixture of OPs will increase the target organ sensitivity of the brain. Therefore, the presence of UFPs should be included as part of the aetiological mechanism for neurological harm in Aerotoxic Syndrome.

Summary

There is incontrovertible evidence for the presence of UFP aerosols in commercial aircraft under normal operating conditions. We have produced photographic evidence and cited published literature to support this. The high temperatures known to be present in gas turbine engines mean that the production of UFP aerosols is inevitable under normal working conditions. The only barrier to keeping UFPs out of the cabin breathing air is, therefore, the engine oil seals. UFPs on the size range measured in fugitive emissions of gas turbine engines (predominantly 50-70 nm) can act like gases and diffuse by Brownian motion. It is therefore not surprising that they can cross oil seals (clearance values 200-400 nm) along with other vapour phase molecules derived from the engine lubrication oil. It is logical to conclude that the oil seals will act as a filter to remove any larger particles, that may have developed as a result of agglomeration, and lead to the UFP size distribution reported in the scientific literature.

Knowledge about the toxicological sequelae of exposure to UFPs has increased considerably in the past decade, very much as a consequence of the development of nanotechnology. Furthermore, the large scale epidemiological studies of the effects of poor air quality on the health of populations is leading to drastic plans to ban the presence of diesel and petrol cars from cities, such is the level of health concerns. The protracted cumulative lengths of time that aircrew spend in the aircraft cabin environment lead to the conclusion that health impacts must be expected. The smaller the particle the more reactive it becomes and also the more mobile in the body. A general property small nanoparticle in biological matrices appears to be their ability to induce inflammation. Thus, the very nature of the UFP aerosol found in bleed air is of concern - it is at the lower end of the size distribution which is known to be the most harmful.

The presence of UFPs in cabin air will exacerbate cardio-respiratory disease through the mechanism of chronic low-grade inflammation. The ability of inhaled UFPs to enter the blood stream and subsequently cross the blood-brain barrier is likely to increase the rate at which neurotoxic substances enter the brain by 'piggybacking' on particle surfaces. This will be a function of extended exposure times, which for aircrew can be thousands of hours. In the light of current published knowledge, UFP aerosols must be considered to be part of the aetiology of Aerotoxic Syndrome. There is a pressing requirement for filtration of engine bleed air as a short-term remedial measure. In the longer term the current engine bleed air architecture needs to be phased out.

References

1. Reddall H (1955) Elimination of engine bleed air contamination. SAE paper: 550185.

2. Mackerer C, Barth M, Krueger A, Chawla B, Roy TA (1999) Comparison of neurotoxic effects and potential risks from oral administration or ingestion of tricresyl phosphate and jet engine oil cotaining tricresyl phosphate. J Toxicol Environ Heal Part A 56: 293-328.

3. Mackerer C, Ladov E. Mobil Submission (14a): In: Inquiry into air safety - BAe 146 cabin air quality Vol 3. Canberra: Parliament of the Commonwealth of Australia, 2000.

4. Michaelis S (2016) Implementation of the requirements for the provision of clean air in crew and passenger compartments using the aircraft bleed air system. (MSc thesis) Cranfield University, UK.

5. Michaelis S (2016) Oil bearing seals and aircraft cabin air contamination. Seal Technol 4: 7-10.

6. Spengler JD, Vallarino J, Mcneely E, Estephan H (2012) In-flight / onboard monitoring: ACER's component for ASHRAE, 1262, Part 2. Boston: RITE/ACER, RITE-ACER-CoE-2012-6.

7. CAA (2004) CAA PAPER 2004/04. Cabin Air Quality. Gatwick Airport South, UK.

8. Crump D, Harrison P, Walton C (2011) Aircraft Cabin Air Sampling Study; Part 1 and 2 of The Final Report. Cranfield: Institute of Environment and Health, Cranfield University, UK.

9. EASA (2017) CAQ Preliminary cabin air quality measurement campaign. EASA_REP_RESEA_2014_4. Cologne: European Aviation Safety Agency.

10. Houtzager M, Havermans J, Bos J (2013) TNO 2013 R11976- Investigation of Presence and Concentration of Tricresyl Phosphates in Cockpits of KLM Boeing 737 Aircraft During Normal Operational Conditions. The Hague: TNO 2013 R11976.

11. Rosenberger W, Netz-Piepenbrink S, Wrbitzky R (2013) Untersuchungen Zum Vorkommen Von Mono- Und Diortho-Trikresylphosphaten In Der Innenraumluft Von Flugzeugen. Gefahrstoffe - Reinhaltung der Luft 73: 138-143.

12. Eckels S, Jones B, Mann G, et al. (2014) Aircraft recirculation filter for air-quality and incident assessment. J Aircr 51: 320-326.

13. Barcelo LV (2013) A clean APU means clean cabin air. Airbus.

14. Occupational Health and Safety Tribunal Canada. 2015 OHSTC 14 - Case No.: 2011-62 and 2012-06 - Air Canada V CUPE. 2015-08-27.

15. ASHRAE (2012) ASHRAE Guideline 28-2012: Air quality within commercial aircraft.

16. Michaelis S, Burdon J, Howard C (2017) Aerotoxic Syndrome: A New Occupational Disease? Public Health Panorama 3: 141-356.

17. Howard C, Michaelis S, Watterson A (2017) The Aetiology of 'Aerotoxic Syndrome' - A Toxico- Pathological Viewpoint. Open Acc J Toxicol 1: 1-3.

18. Terry AV (2012) Functional consequences of repeated organophosphate exposure: potential non-cholinergic mechanisms. Pharmacol Ther 134: 355-365.

19. Bagshaw M (2013) Health effects of contaminants in aircraft cabin Air.

20. de Ree H, van den Berg M, Brand T, Mulder GJ, Simons R, et al. (2014) Health risk assessment of exposure to tricresyl phosphates (TCPs) in aircraft: A Commentary. Neurotoxicology 45: 209-215.

21. COT (2013) Position paper on cabin air. Committee of Toxicity. London, UK.

22. CAA. Health information for passengers: Cabin air quality. London: Civil Aviation Authority, 2017.

23. Johnson DW (2016) Lubricants for turbine engines. In: Agarwal RK. Recent progress in some aircraft technologies. INTECH Open. Pg No: 35-53.

24. Johnson D (2017) Lubricant and lubricant additive degradation: Implications for cabin air quality. In: International Aircraft Cabin Air Conference, Imperial College, London. 19-20 September 2017.

25. Johnson DW, Morrow S, Forster NH, Saba C (2002) Vapor-phase lubrication: Reaction of phosphate ester vapors with iron and steel, Chem. Mater 14: 3767-3775.

26. Chang MB, (2000) Characteristics of heavy metals on particles with different sizes from municipal solid waste incineration J. Hazardous Materials A 79: 229-239.

27. Cormier SA, Lomnick S, Backes W, Dellinger B (2006) Origin and health impacts of emissions of toxic by-products and fine particles from combustion and thermal treatment of hazardous wastes and materials EHP 114: 810-817.

28. Chao MR (2003) Size distribution of particle-bound polychlorinated dibenzo-p-dioxins and dibenzofurans in the ambient air of a municipal incinerator. Atmospheric Environment 37: 4945-4954.

29. Elsaesser A, Howard CV (2012) Toxicology of nanoparticles. Adv Drug Deliv Rev 64: 129-137.

30. Flitney R (2014) A Description of The Types of High Speed Rotary Shaft Seals in Gas Turbine Engines And The Implications For Cabin Air Quality. J Biol Phys Chem 14: 85-89.

31. Michaelis S, Morton J (2017) Mechanisms of oil leakage into the cabin air supply & the regulatory implications. In: International Aircraft Cabin Air Conference, Imperial College London, 19-20 September 2017.

32. Flitney R (2007) Seals and Sealing Handbook. 5th edn. Burlington: Butterworth-Heinemann.2007

33. Airbus. Environmental Control system decontamination. Reference 21.00.00018. First issue, 07 November 2013. A318;A319;A320;A321. Toulouse: Airbus, 2013.

34. Jones B, Roth J, Hosni M (2017) The nature of particulates in aircraft bleed air resulting from oil contamination. LV-17-C046. In: 2017 ASHRAE Winter Conference Papers. Kansas State University, USA.

35. Loraine T (2017) Origins of Contaminated Air. In: International Aircraft Cabin Air Conference, Imperial College London, 19-20 September 2017.

36. Nemmar, Hoet PHM, Vanquickenborne B, Dinsdale D, Thomeer M, et al. (2002) Passage of inhaled particles into the blood circulation in humans. Circulation 105: 411-414.

37. Oberdorster G, Elder A, Rinderknecht A (2006) Nanoparticles and the brain: cause for concern? J. Nanosci Nanotechnol 9: 4996-5007.

38. Cox L (2001) A Pilot Perspective on the Issue of Cabin Air Quality. Proceedings of the Aircraft Air Quality Symposium, Canberra, 7th December 2000. Reports in Safety and Environmental Science 2001: 83-118.

39. Glanville AR, Burdon J (2004) Toxic planes: The respiratory effects of flying. Respirology 9: A55.

40. Rayman RB, McNaughton GB (1983) Smoke/fumes in the cockpit. Aviat Space Environ Med 54: 738-740

41. Taskin DP, Coulson AH, Simmons M, Spivey GH (1983) Respiratory symptoms of flight attendants during high altitude flight: Possible relation to cabin ozone exposure. Arch Occupat Environ Health 52: 117-137.

42. Burdon J (2014) Respiratory symptoms and lung injury after inhaling fumes on aircraft: toxic fumes or hyperventilation? J Biol Phys Chem 14: 103-106.

43. Winder C, Fonteyn P, Balouet JC (2002) Aerotoxic syndrome: a descriptive epidemiological survey of aircrew exposed to in-cabin airborne contaminants. J Occup Heal Saf - Aust NZ 18: 321-338.

44. Michaelis S (2010) Health and flight safety implications from exposure to contaminated air in aircraft. (PhD Thesis) UNSW, Sydney.

45. Bonner JC (2010) Nanoparticles as a potential cause of pleural and interstitial lung disease. Proc Am Thorac Soc 7: 138-141.

46. Bahadori M, Mohammadi F (2012) Nanomedicine for respiratory diseases. Tanaffos 11: 18-22.

47. Erdely A, Hulderman T, Salmen R, Liston A, Zeidler-Erdely PC, et al. (2009) Cross-talk between lung and systemic circulation during carbon nanotube respiratory exposure. Potential biomarkers. Nano Lett 9: 36-43.

48. Lam CW, James JT, McCluskey R 2004) Pulmonary toxicity of single-wall carbon nanotubes in mice 7 and 90 days after intratracheal instillation. Toxicol Sci 77: 126-134.

49. Shevedova AA, Kisin ER, Mercer R (2005) Responses to single-walled carbon nanotubes in mice. Am J Physiol Lung Cell Mol Physiol 289: L698-L708.

50. Muller J, Huaux F, Moreau N, Misson P, Heilier JF, et al. (2005) Respiratory toxicity of multi-walled carbon nanotubes. Toxicol Appl Pharmacol 207: 221-231.

51. Cherry N, Mackness M, Mackness B, Dippnall M, Povey A (2011) "Dippers" flu and its relationship to PON 1 polymorphisms. Occup Environ Med 68: 211-217.

52. Costa LG (2006) Current issues in organophosphate toxicology. Clinica Chimica Acta 366: 1-13.

53. Lotti M, Moretto A (2005) Organophosphate-induced delayed polyneuropathy. Toxicological Reviews 24: 37-49.

54. Grigoryan H, Schopfer LM, Thompson CM, Terry AV, Masson P, et al. (2008) Mass spectrometry identifies covalent binding of soman, sarin, chlorpyrifos oxon, diisopropyl fluorophosphate, and FP-biotin to tyrosines on tubulin: a potential mechanism of long-term toxicity by organophosphorus agents. Chemico-Biological Interactions 175: 180-186.

55. Rigoryan H, Li B, Anderson EK, XueW, Nachon F, et al. (2009) Covalent binding of the organophosphorus agent FP-biotintotyrosine in eight proteins that have no active site serine. Chemico-Biological Interactions 180: 492-498.