



ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



Editorial

The Lung in Aerotoxic Syndrome

El pulmón en el síndrome aerotóxico

In most aircraft cabin and flight deck ventilation use outside air mixed with air recirculated from the cabin. In all transport aircraft, except the Boeing B787 Dreamliner, cabin air pressurization, heating, and ventilation are achieved using unfiltered air supplied both from the gas turbine engines and from the auxiliary power units (APU) on the ground.¹ When the air that comes from the outside moves through the engine compressor it gets very hot. It must be cooled down by heat exchangers and then go to the air conditioning packs (Fig. 1). This outside air that comes from the engine/APU compressors is commonly known as bleed air and is unfiltered. Jet engine oils may leak into the breathing air because seals used in bleed air systems do not completely prevent low levels of contamination from reaching the cabin air.¹ Reliable aircraft air quality monitoring is lacking. The generic term “aircraft fume events” refers to the detection of abnormal odors, fumes, smoke, or haze in the cabin. An important device for air cleaning is HEPA (High Efficiency Particulate Air) filters. They treat the recirculated cabin air only in order to remove some of the odors and volatile organic compounds (VOC). The HEPA filters are also effective eliminating airborne microorganisms, dust, fibers, and allergens.

The term Aerotoxic Syndrome (AS) has been coined to describe the spectrum of clinical features exhibited after aircraft fume events exposure.² There is variability in the reported incidence of onboard fume events. In the US alone, an average of at least two to three contaminated bleed air events have been estimated to occur every day based on official reports.³ However, most non acute exposures are likely to be underreported.^{2,3} Additionally, it is now recognized that exposure to low levels of bleed air contaminants may occur on all flights.^{1,2}

Fume events in aircraft are described in a variety of ways. Most have no visual identifying features, such as mist or smoke.² Oil fumes are typically described as smelling like dirty socks/smelly feet, foul, musty or oily odors, while hydraulic fluid is often described as acrid. The dirty socks or smelly feet description, often used, is increasingly understood to be related to the thermal degradation and hydrolysis of the oil base stocks.

The causative agents are also diverse. For instance, a hazardous substance used in most aircraft engine oils are triarylphosphates (TAP), specifically tricreshyl phosphate (TCP), an organophosphate (OP) compound with proven toxicity.^{4,5} Moreover, the high temperatures attained in aircraft jet engines generate a complex thermally pyrolysed mixture.^{5,6} A wide variety of VOCs have been identified in cabin air monitoring studies.⁷ Other contamination

sources may include hydraulic fluids or flame retardants emanating from the highly flame-protected environment of airplanes.² An in vitro study has shown that exposure to these fumes may cause relevant lung toxicity.⁸ Ultrafine particles (UFP) aerosols may also be frequently detected in commercial flights, sometimes in high concentration.⁹ It has been stated that these UFPs could be a carrier that enhance the deposition of potential toxic substances, such as TAP, to lung tissue.⁹ Nanoparticles released by aircraft ventilation systems have also been associated with a risk of respiratory and neurological toxicity.¹ OPs are present in the oil and small nanoparticles appear to be predominantly comprised of oil.^{9,10} The cumulative exposure to the background aerosol of nanoparticles are suggested to be part of the causal mechanism of AS.¹

AS encompasses a constellation of symptoms and individual susceptibility and variation in symptoms are considerable.^{1,2,11,12} The complete list of symptoms and clinical findings are not necessarily found in all any individual cases. A study that reported extensive findings from two different cohorts showed that there may be acute and chronic patterns of adverse effects, affecting the central nervous system (CNS) and peripheral nervous system (PNS) (motor, sensory, and autonomic nervous systems involvement), the respiratory and the gastrointestinal tract, skin, and the cardiovascular system.² The CNS and PNS symptoms are rather nonspecific leading to a diffuse pattern of neurological symptomatology, which is consistent with OP modes of action.¹³ An increased levels of autoantibodies against neuronal and/or glial proteins is often found, which is consistent with non-specific chemical-induced nervous system injury.¹⁴

The respiratory symptoms after fume events exposure rank only second to neurological symptoms in their frequency.^{1,2,11,12} Generally, cough, dyspnea, chest discomfort, and wheezing are the usual respiratory features of AS.^{11,12} In some cases, the duration of symptoms may be just a few days or weeks, but sometimes respiratory complaints may last over many months and even longer. Irritant-induced asthma has been reported in patients with AS.^{11,12,15} Some cases could also be diagnosed as reactive airway dysfunction syndrome (RADS).¹² Persistent cough, wheezing, and documented bronchial hyperreactivity (BHR) many months after fume events is the hallmark of RADS. Spirometry may help to document BHR. Diffusion capacity for carbon monoxide (D_{LCO}) is usually normal. Limits between RADS and irritative asthma are sometimes quite difficult to be drawn. Lung imaging techniques are usually normal.^{11,12}

<https://doi.org/10.1016/j.arbres.2022.03.021>

0300-2896/© 2022 SEPAR. Published by Elsevier España, S.L.U. All rights reserved.

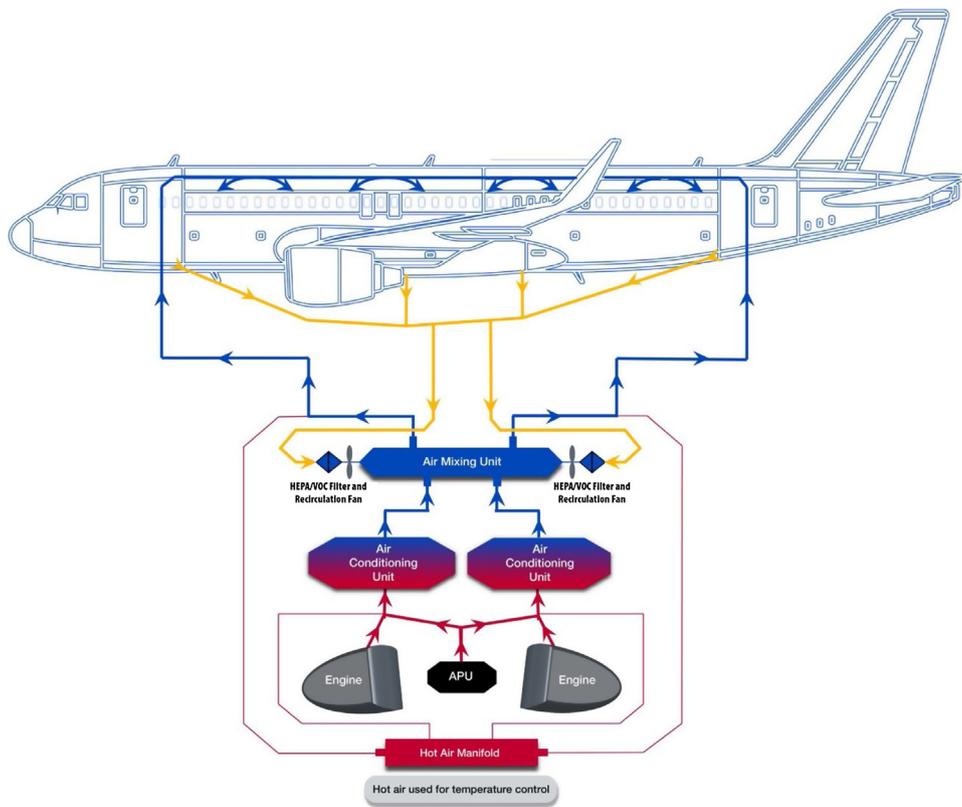


Fig. 1. Schematic representation of the air delivery system in an aircraft. APU: Auxiliary Power Unit. HEPA: High Efficiency Particulate Air. VOC: Volatile Organic Compounds. From *How Cabin Air Filters Work – Commercial Fixed Wing* | Pall Corporation. Retrieved from <https://www.pall.com/en/aerospace/commercial-fixed-wing/how-cabin-air-systems-work.html>. Copyright 2022 by Pall Corporation.

Some patients may also fulfill the criteria of multiple chemical sensitivity (MCS), another long-term possible respiratory presentation of AS. Chronic, dry cough, which is easily triggered by exposure to low concentrations of chemicals commonly present in normal environment is a hallmark of MCS related to AS.¹²

Nowadays, many clinicians are not aware of the existence of AS; hence, when patients require medical assistance after a fume event, the lack of a good, standardized protocol precludes general recommendations on the immediate identification of the implicated chemical toxins, on the type of pulmonary and neurological studies to perform, and on the therapeutic management of the disease.² Urine and blood samples should be obtained without delay after a fume event and strict technical requirements should be mandatory.² A standardized protocol to properly approach cases suspected of AS is currently drawn up by a team of international experts on the subject.

Not all aircrew or passengers are affected by fume events.² A good description of why this may be occurring is available for review.^{1,2,9} The potential for illness is said to be increased by cumulative exposure of regular short-term exposures or by less frequent longer exposures.^{1,13} This would have obvious connotations for aircrew, maintenance staff and frequent fliers.

Additionally individual vulnerability may be influenced by P450 enzymes. However, little is known about which P450s generate toxic metabolites from TAPs, or the genetic variability of the P450s involved.⁴

This editorial aims at raising awareness on this newly emerging disease, particularly on the respiratory symptoms, and calls for the implementation of standardized protocols to manage AS. Further research is warranted to clarify which chemical substances and UFP exposures are potentially causative, which populations are more susceptible and which preventive and therapeutic measures

should ideally be implemented.² Minimization of potential contaminating sources and/or improved reduction of pollutants by air cleaning should be mandatory to diminish the risk of AS. A progressive replacement of conventional airplanes that have been using bleed air systems by new models utilizing electrically sourced air supply would enhance public health.²

Conflicts of interest

Susan Michaelis undertakes limited consultancy work for the Global Cabin Air Quality Executive, Horsham, UK. E-mail address: susan@susanmichaelis.com.

Jorge Roig: no conflict of interest; Jonathan Burdon: no conflict of interest. E-mail address: jbardon@bigpond-net.au.

References

1. Howard CV, Johnson DW, Morton J, Michaelis S, Supplee D, Burdon J. Is a cumulative exposure to a background aerosol of nanoparticles part of the causal mechanism of aerotoxic syndrome? *Nanomomed Nanosci Res*. 2018;139:1–8, <http://dx.doi.org/10.29011/JNAN-139.100039>.
2. Michaelis S, Burdon J, Howard CV. Aerotoxic syndrome: a new occupational disease? *Public Health Panorama (WHO)*. 2017;3:198–211 <https://apps.who.int/iris/handle/10665/325308>
3. Shehadi M, Jones B, Hosni M. Characterization of the frequency and nature of bleed air contamination events in commercial aircraft. *Indoor Air*. 2016;26:478–88, <http://dx.doi.org/10.1111/ina.12211>.
4. Furlong CE. Exposure to triaryl phosphates: metabolism and biomarkers of exposure. *J Biol Phys Chem*. 2011;11:1–11, <http://dx.doi.org/10.4024/28FU11A.jbpc.11.04>.
5. Winder C, Balouet J-C. The toxicity of commercial jet oils. *Environ Res*. 2002;89:146–64, <http://dx.doi.org/10.1006/enrs.2002.4346>.
6. Houtzager M, Noort D, Joosen M, Bos J, Jongeneel R, van Kesteren P, et al. Characterisation of the toxicity of aviation turbine engine oils after pyrolysis (AVOIL), Cologne, Germany: European Aviation Safety Agency; 2017 <https://www.easa.europa.eu/document-library/research-reports/easarepresea20152>

7. Schuchardt S, Bitsch A, Koch W, Rosenberger W. EASA research project: CAQ preliminary cabin air quality measurement campaign. Final report EASA_REP_RESEA_2014.4. Cologne, Germany: European Aviation Safety Agency; 2017 <https://www.easa.europa.eu/document-library/research-reports/easarepresea20144>
8. He R, Houtzager M, Jongeneel W, Westerink R, Cassee F. In vitro hazard characterization of simulated aircraft cabin bleed-air contamination in lung models using an air-liquid interface (ALI) exposure system. *Environ Int.* 2021;156:106718, <http://dx.doi.org/10.1016/j.envint.2021.106718>.
9. Michaelis S, Loraine T, Howard CV. Ultrafine particle levels measured on-board short-haul commercial passenger jet aircraft. *Environ Health.* 2021;20:1–14, <http://dx.doi.org/10.1186/s12940-021-00770-7>.
10. Fushimi A, Saitoh K, Fujitani Y, Takegawa N. Identification of jet lubrication oil as a major component of aircraft exhaust nanoparticles. *Atmos Chem Phys.* 2019;19:6389–99, <http://dx.doi.org/10.5194/acp-19-6389-2019>.
11. Hageman G, Pal TM, Nihom J, MackenzieRoss SJ, van den Berg M. Three patients with probable aerotoxic syndrome. *Clin Toxicol (Phila).* 2019;58:139–42, <http://dx.doi.org/10.1080/15563650.2019.1616092>.
12. Roig J, Domingo C, Burdon J, Michaelis S. Irritant-induced asthma caused by aerotoxic syndrome. *Lung.* 2021;199:165–70, <http://dx.doi.org/10.1007/s00408-021-00431-z>.
13. Naughton SX, Terry AV Jr. Neurotoxicity in acute and repeated organophosphate exposure. *Toxicology.* 2018;408:101–12, <http://dx.doi.org/10.1016/j.tox.2018.08.011>.
14. Abou-Donia MB, Abou-Donia MM, ElMasry Eea. Autoantibodies to nervous system-specific proteins are elevated in sera of flight crew members: biomarkers for nervous system injury. *J Toxicol Environ Health A.* 2013;76:363–80, <http://dx.doi.org/10.1080/15287394.2013.765369>.
15. Shaffo FC, Grodzki AC, Fryer AD, Lein PJ. Mechanisms of organophosphorus pesticide toxicity in the context of airway hyperreactivity and asthma. *Am J Physiol-Lung Cell Mol Physiol.* 2018;315:L485–501, <http://dx.doi.org/10.1152/ajplung.00211.2018>.

Jorge Roig^{a,*}, Susan Michaelis^b, Jonathan Burdon^c
^a *Department of Pulmonary Medicine, Clínica Creu Blanca, Barcelona, Spain*
^b *Occupational and Environmental Health Research Group, School of Health Sciences, University of Stirling, United Kingdom*
^c *St Vincent's Hospital, Melbourne, Australia*

Corresponding author.
E-mail address: jroig@separ.es (J. Roig).