Organophosphates (OPs) have successful properties that means they have been widely used as flame retardants and pesticides. However, their neurotoxic properties have also been long acknowledged and used in more sinister applications such as nerve gases (1). Hundreds of thousands victims have been affected by organophosphates over the last 150 years. This has occurred since its early uses in the 1890s as a treatment to tuberculosis, in the famous ginger Jake poisoning caused by counterfeit alcohol during US prohibition times, and the 1959 Moroccan poisoning, and not to ignore the estimated 200000 annual fatalities in the 3rd world (2). Interest in this group of compounds is growing once again as we try to establish the cause of Aerotoxic syndrome.

In its Guidance note MS 17, The UK Health & Safety Executive (3) warned that OPs of Occupational interest “all act by blocking the normal function of the enzyme acetylcholinesterase at neuronal, autonomic effector organ or neuromuscular junctions and thus interfere with the normal transmission of nerve impulses.” The symptoms listed by HSE correspond, one by one, to those described for OP pesticides and nerve agents by the Centers for Disease Control and Prevention (1) and Eddleston et al. (2), and the symptoms of Aerotoxic syndrome (4).

Due to their widespread use as pesticides, organophosphates are routinely detected in environmental samples. However, a specific concern has arisen in recent decades as hundreds of aircraft crew and passengers, have developed symptoms consistent with exposure to OPs. Organophosphates are not just used as pesticides on crops in fields but are also used in aircraft as flame retardants in engine oil and hydraulic fluids and on material surfaces.

Beside the occupational exposure to OP pesticides and flame retardants deposited on aircraft interior surfaces, OPs contained in aircraft lubricating and hydraulic fluids can enter the cabin air. During a flight the air cabin pressure and temperature are maintained with outside air that is passed through the jet engine. Cabin air is recycled for 50%, whereas the flight deck air is comprised of a continuous stream of bleed air (5). Engine seals in use are known as “wet-seals”, an inherent design feature, whereby a thin film of oil prevents rotating surfaces to come into mechanical contact with each other. Pressure differentials over the seals cause a constant loss of oil and vapours into the core engine. These enter the inlet of the high pressure compressor and, contaminate the bleed air, which is taken downstream. Oil-leaks-by-design can result in odd smells in the cabin and in more extreme cases smoke events as depicted in Figure 1.
This engineering fault has been known since first bleed air systems were designed in 1953, leading to tens of thousands of published scientific articles, engineering and administrative documents as well as occurrence reports worldwide (5). The term Aerotoxic Syndrome (4) was first published in 1999 by an international scientific team to describe the symptoms and exposure conditions reported by aircraft crew from Australia, US, Europe. The term Aerotoxic referred to air and aircraft as well as the toxic compounds and their associated exposures (4). Since the concerns were raised in 1999, several official enquiries have been conducted worldwide. Thousands incident reports have been collected around leading to a large range of statistics, such as 0.84 incidental flights per day in the US (7), 2 flight reports per day in Germany in 2006, 1 flight in 400, or several incidental flights per day in the world (5). Other statistics by US FAA indicate that only 4% of the smoke and fume events are reported to the authorities.

FAA says “we are concerned that if certain mechanical failures occur, the cabin environment may contain contaminants”. Although, Boeing states that “cabin air is safe to breathe”. Research has consistently shown that cabin air meets health and safety standards and that contaminant levels are generally low (references within 6). Over the past 20 years, dozens of official incident/accident reports have confirmed similar facts. However, aircraft crew worldwide have been medically acknowledged for OP exposure and several legal cases have been settled by aviation industry. The aspects of causation of Aerotoxic syndrome have been studied under Hill’s criteria and Bayes ‘rule (8). Despite all of this research the international environmental forensics debate has remained basically unchanged, as the aviation industry, the victims and their experts still debate the major following aspects:

**Exposure:** industry supports the view that incidental exposure events during flights are rare, however underreported they are; and that OP concentrations in normal flights are too low to cause symptoms. They do acknowledge the presence of TCP at low concentrations as measured on the majority of tested aircraft. However, it could be argued that official measurement campaigns have not dealt with incidental exposure on flights where leaks have occurred, and have been selective on sought compounds, i.e; looking for ToCP which is the least abundant and toxic TCP in aircraft fluids,. The sampling and analytical protocols are also debated. Should sampling be undertaken on fresh oil, used oil, bleed air vapour and how can you target sampling an incidental fume / smoke event? Also there are significant analytical challenges with the need to quantify all TCP isomers and screen for the presence of, and identify, any new compounds generated by pyrolysis.

**Symptoms:** Conditions have been described such as OPIDN (OP Induced Delayed Neuropathy) or COPIDN (Chronic OP Induced Delayed Neuropathy) or as COPIND (Chronic OP NeuroPsychological Disorder) (9,10). However, industry representatives view several of the
symptoms reported by crew members as non-specific, such as salivation, lacrimation, difficulty breathing, tachycardy evolving with time to bradycardy, coughing, dizziness, nausea, diarrhea and fatigue which could be easily caused by or also wrongly misattributed to jetlag. The most worrisome symptoms reported by crew members are neurotoxic, including impaired short term memory, altered coordination, blurred vision and speech. These cause significant immediate concerns for flight safety to aircraft crew and indeed passengers. There are also long term concerns; do people exposed on board an aircraft develop neurological symptoms in the future?

Toxicology: most of the debate centres on tricresyl phosphate (TCP), which is present in lubricating oils at approximately 3-5%. Industry supports the principle of a no-threshold level, indeed The World Health Organisation (11) state that because of considerable variation among individuals in sensitivity to tri-o-cresyl phosphate (ToCP), it is not possible to establish a safe level of exposure. However, Craig and Barth (12) have more recently calculated a no-effect level; others argue the use of a linear no-threshold limit, versus the hormesis principle (13) or Non-monotonic dose-response (14) by which the dose response may not be linear. All parties acknowledge that OPs are neurotoxicants, however it is more difficult to establish the toxicity of the jet oil vapour as new compounds may be synthesised by pyrolysis and these could play an important additive or synergistic role. There is also the added complication due to the large variation in individuals and their ability to metabolise and eliminate OPs. Approximately 4% of the human population poorly metabolises OPs (8), and crews / frequent flyers may have had already their cholinesterase levels depleted by previous exposures and therefore be more susceptible. The effect of the Auto-immune system is first looked at by Abou Donia (9) in response to a low dose of OPs causing neuronal cell death in the brain. Neuro filaments of these decaying cell pass the damaged Blood-Brain-Barrier into the bloodstream and trigger an IgG mediated T-memory cell response. The amplification factor of the immune system is several orders of magnitude greater than the original dose-effect response. Consequential irreversible damage to the peripheral nervous system and organs like the heart have been observed (15).

Conclusions
There is an ever growing list of aircraft personnel that are reporting symptoms consistent with exposure to OPs. Luckily, many of these crew members recover and return to their flight duties, however too many staff have lost their jobs, and even more sadly, several have passed away. UK Coroner Payne, recently issued a regulation to prevent further deaths following the death of Captain Richard Westgate, which was linked to OP poisoning. Two more post-mortem cases (Bass, Brady) have since been identified with similar findings as a possible cause of death (Lymphocytic Myocarditis). Still, the aircraft crew and passengers are poorly informed as to what toxic chemicals they have been potentially exposed to. Therefore, in cases where symptoms do develop they are often not able to get proper medical care.

When many legal cases associated with Aerotoxic syndrome have been settled or handled by Courts in the past, dozens of cases are still on, facing the same disputes, for almost 20 years. This is where environmental forensics is needed to improve our environment, health and wellbeing, for facts not vested opinions.
Acknowledgements
The authors thank Dr Michel Mulderx & Mathew Robson for their constructive comments on this article.

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