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The Aetiology of 'Aerotoxic Syndrome'- A Toxico-Pathological Viewpoint

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Background

The term 'aerotoxic syndrome' was coined in 2000 [1] to describe a collection of predominantly neurological and respiratory signs and symptoms found in some commercial aircrew, which includes pilots and cabin crew. From the 1950's, aircraft were redesigned to provide pressurized cabin air directly from the compressor stage of the engine, known as bleed air. This allowed for the fuel consuming turbo compressors used prior to that date to be dispensed with. However, it also led to the exposure of aircrew and passengers to fugitive emissions from aircraft engines. This bleed air remains, to date, supplied to the cabin unfiltered.

Gas turbine engines require the use of vapors-phase lubricants, including additives, which can withstand the extremely high operating temperatures and pressures found in normal use. The most widely used anti-wear additive is tri-cresylphosphate (TCP), an organophosphate compound which is neuro toxic. TCP used in gas turbine lubricating oils is not pure but comes as a technical grade complex mixture of isomers and other associated triaryl phosphate (TAP) compounds. The complexity of this mixture is further enhanced by an ester base stock, amine antioxidants, proprietary ingredients and the addition of pyrolosis products, as the oil ages through use.

There are two main exposure scenarios:

1. acute higher dose 'fume events' where there is generally only a detectable odour and, on occasion, a visible haze. These are associated with acute irritation of mucosa, primarily of the respiratory system, eye irritation, breathing problems and nausea. Acute neurological /neuro behavioral side effects have also been reported, ranging from mild headache, cognitive problems, dizziness to incapacitation.

2. chronic repeated low-dose exposure of aircrew on a day to day basis to a complex mixture of fugitive jet engine emissions.

The current design of the majority of commercial airliners guarantees this continual background exposure because all oil seals 'weep' small amounts of lubricant in normal operation [2]. The exposure times can amount cumulatively to thousands of hours per individual. Frequent flyer passengers would also accumulate large numbers of hours of exposure, though not to the same extent as professional aircrew. The symptoms reported are predominantly neurological and respiratory and tend to be diffuse in nature. They include inability to concentrate, memory problems, breathing problems, headache, fatigue, numbness, tingling, confusion, dizziness, cardiovascular effects and performance decrement. These symptoms setting out a clear pattern of acute and longer-term effects, in many cases supported by medical findings and diagnoses, have been reviewed recently by Michaelis, Burdon and Howard [3].

Currently:

1. On the one hand there are a number of aircrew who have been acutely impaired in flight incidents, with others becoming chronically ill, many of whom have had to retire as a result. This is acknowledged by many aircrew organizations and some doctors and scientists.

2. On the other hand, arguments are put forward that the levels of contaminants in aircraft cabin air are too low to be able to cause the illnesses complained of, which are largely dismissed as being psychological/psychiatric in nature, common in the general population or, alternatively, as hyperventilation. This opposed position is acknowledged by a number of airline operators, aircraft manufacturers, some scientists and regulatory and airline industry bodies. It is that conundrum which this paper addresses.

Aetiological Considerations

There is an enormous literature on the acute toxicity of

organo-phosphate pesticides and nerve gas agents through acetyl-cholinesterase inhibition, which will already be familiar to the readership. This aspect was reviewed by the UK Committee on Toxicity in the context of cabin air quality [4]. They concluded, considering only the one isomer tri-orthocresyl phosphate (TOCP), that it would not cause organo-phosphate delayed neuropathy (OPIDN), which is acknowledged to be a sequel of high dose exposure involving acetyl-cholinesterase inhibition. However, OPIDN is definitely not the clinical picture observed in Aerotoxic Syndrome [3].

The effect of repeated low dose OP exposure has been reviewed by Terry [5]. He describes a number of mechanisms by which OPs can cause harm at exposure levels below those required to cause lowering of acetylcholine esterase. These include covalent binding of OPs to tyrosine and lysine residues, which suggests that numerous proteins can be modified by OPs. In addition, the mechanisms of oxidative stress and neuro inflammation and the known OP targets of motor proteins, neuronal cytoskeleton, axonal transport, neurotrophins and mitochondria. This type of exposure has been associated with prolonged impairments in attention, memory, and other domains of cognition, as well as some chronic illnesses where these symptoms are manifested, precisely the spectrum of symptoms reported for air crew by Michaelis et al. [3]. A more recent paper by Terry's group [6], detected antero grade axonal transport deficits associated with the oxon metabolite of chlorpyrifos at 0.1nM in vitro, in cultured embryonic rat neurons, a very low concentration.

The clinical picture is further complicated by at least three factors:

1. the complexity of the mixture to which air crew are being exposed. Some work has been done on the enhancement of OP toxicity in mixtures [7] and it is clear that the traditional 'one chemical at a time' toxicology will not suffice.

2. The wide variability between individuals to metabolize and detoxify OP compounds. A good example of this is provided by studies on British farm workers who developed 'dippers flu' as a consequence of handling OP sheep dips. A paper by Cherry et al showed that R allele at position 192 on PON1 was associated with a higher probability of illness from dippers flu's [8].

3. Low dose repeated exposure to OPs has been demonstrated in vitro to increase the vulnerability of neurons to a subsequent high dose event [9]. Thus the prospect of an 'acute-on-chronic' mechanism must be considered, where those cumulatively pre-exposed for hundreds or thousands of hours would be more vulnerable to harm from a subsequent high dose fume event.

Discussion

There is no dispute about the fact that fugitive jet engine emissions are found in aircraft cabin bleed air. The recent detailed study investigating the pattern of effects, findings and diagnoses, was supported by maintenance investigations confirming oil fume leakage in 87% of the identified incident cases with suspected oil contamination in another 7% [3]. The difficulty in maintenance investigations identifying the oil leakage sources has been acknowledged within the aviation industry, along with recognition [10] of permanent low-level oil leakage with additional discontinuous fume events sourced to engine oil leakage. However, there is debate about the significance of this. When there is a differential susceptibility of various exposure groups to harm then we have to seek an explanation, this is one of the tenets of occupational medicine. What is observed is an increased vulnerability of aircrew, when compared with passengers, to the set of signs and symptoms collectively known as aero toxic syndrome. This is seen after reported acute fume events as well as in the absence of high dose events. An Airbus A380 diverted into Vancouver due to 'toxic gas type fumes', with 25 crew taken to hospital [11]. Fumes on a Boeing 767 with a confirmed oil leak led to crews being hospitalized with 5 of the 6 crew, including the 2 pilots, no longer able to fly [12]. Other reports commonly refer to chronic lower-dose exposures [13].

Following the logic of Sir Bradford Hill in considering causation: Temporality-Aero-toxic syndrome was never reported prior to the introduction of engine bleed air pressurization systems, though it was detected soon afterwards [14]; it is biologically plausible that the mixture of chemicals in bleed air, many of which are known neuro-toxins, could lead to the symptoms described; animal experimental data supports the diagnosis [5]; there is epidemiological evidence [3] to support the causation argument. Specificity -The fact that the symptomatology is rather non-specific is seized upon to explain clinical findings as being of a psychological/psychiatric nature, rather than an organic illness. However, consistency of the pattern of symptoms exists, supporting an organic aetiology [3].

On the balance of probabilities, a causal link between repeated exposure to a low dose mixture of fugitive turbine engine oil emissions, based on current scientific knowledge, seems more likely than not and, in our opinion therefore, to be responsible for aero-toxic syndrome.

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