The scientific adequacy of the present state of knowledge concerning neurotoxins in aircraft cabin air

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It is known that organophosphates (tricresyl phosphates) are present in jet engine lubricating oil. Oil may leak into the aircraft cabin if its air supply is bled off the engine. Depending on the type of oil seal, this may always occur to a small degree. The amount of leakage may increase due to faulty maintenance (including during the interval immediately preceding a scheduled maintenance intervention). If there is actual failure of a component of the seal, leakage may be considerable. In any case, leakage tends to be greater when the engine is cold and when the engine is working hard. Furthermore, some oil is pyrolysed in the engine, and the complex mixture of pyrolysis products may also be present in the bleed air. Tricresyl phosphates are potent neurotoxins. This has been most extensively established through animal testing (mainly cats, chickens and rabbits). The effects of human exposure have mainly been deduced by extrapolation from animal exposure and from observing cases of accidental human exposure. Any agent that damages the nervous system is *prima facie* expected to have a very broad spectrum of effects, given the pervasive nature of the nervous system in the control of any large multicellular organism. The proposition examined in this paper is that certain substances, namely tricresyl phosphates and their derivatives, if present in aircraft cabin air and hence inhaled, cause neural degeneration. Sufficient evidence would appear to have accumulated to make this a definite aviation hazard. The frequency of occurrence of acute "fume events", in which a high concentration of neurotoxins is likely to be released into the cabin, cannot be estimated with a high degree of certainty but would appear to be around one in a thousand commercial flights. These constitute a safety hazard. Evidence for almost omnipresent low concentrations of neurotoxins suggests an occupational health hazard for aircrew and frequently flying business passengers, since the tricresyl phosphates accumulate in the body. Priority actions are needed to ensure that especially vulnerable people do not travel in jet aircraft that use bleed air to pressurize the cabin and to develop an appropriate sensor for continuously monitoring cabin air quality.

1. INTRODUCTION

The problem examined in this paper, and indeed throughout the Workshop, of which this paper is just part, is derived from the fact that aircraft cabins (comprising spaces for aircrew and passengers) have to be pressurized to allow them to fly at high altitudes. Early jet airliners such as the Vickers VC10 took in air from outside and it was compressed using conventional compressors. Later on the system of bleeding air off the jet engines was developed. This obviously opens up the possibility of some contamination from the engine entering the cabin atmosphere.[1]

Since in most aircraft the air is bled off the forward part of the compressor, the main expected contaminant is lubricating oil. Seals provide a barrier for oil leaking into the turbine, but near the end of a maintenance cycle, or simply due to poor maintenance, seal parts might become worn and allow oil to leak more readily. Furthermore, some oil seals incorporate a thin film of oil as part of the barrier, and seals may work less well when cold, just after starting the engine.[2]

The oil used to lubricate jet engines (and, more generally, gas turbines) is not a simple long chain hydrocarbon but typically an ester (to allow it to withstand the high temperatures in the engine), to which a few percent of antiwear and antioxidant compounds are added.[3] The most useful antiwear additive has been found

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[1] Although there is no mention of the problem in the Aeronautical Research Council's review covering the years 1949–1954 [1], in 1955 it could be stated [2] that "the contamination in our present airplanes is not toxic." That was, perhaps, a reasonable statement given the state of knowledge of the time.

[2] See ref. 3 for a comprehensive history of bleed air and details of oil seal designs. Note that low pressure (LP) high and high pressure (HP) turbine shaft oil is common to both subsystems and thus LP turbine oil leaks will contain hot, possibly vaporized oil. Presumably the oil would not usually run at vaporization temperature and thus only entrained gas from the HP side would normally appear at the LP seals. See also http://www.exxonmobil.com/lubes/exxonmobil/emal/files/TTopic13_JetEng1.pdf

[3] See, e.g., ref. 4. Oil formulations are discussed in detail in ref. 5.

to be tricresyl phosphate (TCP). This compound belongs to the class of organophosphates, a large group of versatile molecules of great industrial and military importance [6]. The latter derives from their neurotoxicity, and some of the most potent chemical weapons are based on volatile organophosphates such as sarin. The farmer uses chemically related compounds as powerful weapons against pests [7].

The neurotoxicity of TCP was investigated in detail in the 1950s by Henschler in Würzburg [8–10]. The problem is complicated because cresol itself has three isomers, *ortho* (*o*), *meta* (*m*) and *para* (*p*). Thus, ten possible isomers of TCP exist: *ooo*, *mmm*, *ppp*, *oom*, *oop*, *omm*, *opp*, *omp*, *mmp*, *mpp*. Henschler's detailed studies (using rabbits and cats) revealed that the neurotoxicities of the different isomers greatly differed. Prior to his work it was believed that the tri-*ortho* isomer was the only one with significant toxicity. Henschler discovered that the mono-*ortho* and di-*ortho* forms were much more toxic. At low doses, interpolating his data, they would be several orders of magnitude more toxic than the tri-*ortho* isomer [10].

Other substances. The main antioxidant additive is *N*-phenyl-α-naphthylamine (usually abbreviated as PAN, also known as *N*-phenyl-1-naphthylamine) [4]. Compounds of this type are typically carcinogenic but since tumours may only develop decades after exposure it would be difficult to establish a causal link with any particular exposure incident, unless someone was literally drenched in the substance. Given the carcinogenicity, however, it is obviously sensible to minimize exposure.

In summary, to conclude this introductory section, a known neurotoxin, tricresyl phosphate, is present in the lubricating oil used in jet engines and a pathway for admitting it into the aircraft cabin exists. The lipophilic nature of the neurotoxins, tricresyl phosphate isomers, signifies that it accumulates in tissues, from which it follows that there may be no safe upper exposure limit. Given the current scale of the air transport industry (according to figures from the International Air Transport Association (IATA) in 2009 about 2300 million people flew on 35 million flights; in the USA alone there are probably at least 25,000 commercial flights daily), if this state of affairs is considered to pose a problem clearly it has the potential for significant human impact.[4] Furthermore, for the last 30 years air travel has grown approximately 5% each year.

2. HAZARDS FROM INHALATION

Since Henschler's pioneering studies, evidence for the neurotoxicity of the tricresyl phosphates has continued to be accumulated and it can nowadays be considered to be well established [12]. The primary mechanism of action of these and other organophosphates is attributed to their ability to inhibit the enzyme acetylcholine esterase (AChE, also known as choline hydrolase), which catalyses the hydrolysis of the neurotransmitter acetylcholine after its release at a synapse. If the hydrolysis is blocked, no further nerve signals can be transmitted.

Effects have been classified as cholinergic toxicity (due to inhibition of AChE), which is rapid, and longer term, persistent effects: organophosphate-induced delayed neurotoxicity (OPIDN) and organophosphate-induced chronic neurotoxicity (OPICN) [13, 14]. These compounds appear to physically damage the neural structures. What is still not clear are the dynamics of the processes of damage and repair. The effect of a single, sharp exposure to a high concentration c is likely to be very different from a long-term, low-level exposure [15, 16] even though the value of the integral $\int_0^t c(t)\,\mathrm{d}t$ is the same in both cases.

Substances with a large apolar moiety such as TCP will tend to accumulate in fatty tissues, from which they will only be slowly released. The internal dynamics of these compounds within a medium as complex as the human body, with a variety of sources (mainly lungs and skin) and sinks, is far from being understood. The liver is the main organ for eliminating TCP; unfortunately the first metabolic product, cresyl saligenin phosphate (2-(*o*-cresyl)-4*H*-1,3,2-benzodioxaphosphorane-2-one (CBDP) is the metabolite of tri-*o*-cresyl phosphate) appears to be even more toxic than TCP itself [17–19], further complicating the dynamics.[5]

High temperatures are encountered within jet engines. Indeed, the formulation of jet oil is expressly formulated to withstand high temperatures, and one of the attractions of tricresyl phosphate is its relative stability [6]. It was an early concern that the lubricating oil could be pyrolysed and it was shown that the pyrolysis products are typically more toxic than the original compounds [22, 23]. Since that early work no further quantitative studies appear to have been carried out.[6]

The precise identities of the pyrolysis products are not known. Establishing their toxicities in more detail will be

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[4] The problem is not solely confined to aircrew and passengers. Aviation technicians and loaders are also at risk [11], as are technicians in nonaviation environments (e.g., offshore oil platforms) where gas turbines are widely used.
[5] Cf. the diminution of dopamine activity in Gulf War syndrome patients [20, 21].
[6] Note that a study on the thermal behaviour of trimethyl phosphate, triethyl phosphate and triphenyl phosphate was reported in 1984 [24].

a complicated challenge, not least because their multiplicity enables synergy. Furthermore, since the early work, operating temperatures of jet engines have increased (in order to increase their fuel efficiency), with unknown effects on the results of pyrolysis.

Naturally, anything that damages the neural structures of a higher organism will have profound behavioural consequences, ranging from motor neuron problems (if the affected nerves connect muscles) to altered thought patterns (if there is damage in the brain). One of the great and ongoing challenges is to correlate alterations in physical structure with behavioural alterations [25]. Terms such as myalgic encephalomyelitis (ME) have emerged to describe the complex set of symptoms that appear to result as a consequence of the neural damage. There has also been the temptation to diagnose patients suffering from physical neural damage as suffering from purely psychiatric disorders, a rather naïve view that is really not justified given the present state of knowledge. The complexity of the symptoms of sufferers engendered the suggestion of introducing the term aerotoxic syndrome as a convenient label for them [26].

Even today, after about a century of commercial aviation history, flying in an aircraft is still less natural than other forms of travel, such as in a motor road vehicle, a railway carriage or a ship. This feeling of naturalness changes with time. An early railway guide asks, "What are the evils with which tunnels are charged? They are, the excitation of an injurious feeling of dread in persons not accustomed to pass through them—a density of atmosphere, its dampness, its admixture with carbonic-acid gas—the sudden transition from darkness to light, and the consequent effect on the eyes" [27]. The peculiar psychological features of environment are omnipresent; only familiarity enables them to become assimilated with normal behaviour. Neglect of this rather obvious principle is responsible for many missed diagnoses in aviation medicine, which would seem quaintly antiquated were it not for the often very serious consequences for the persons misdiagnosed.

Thus, raising awareness, firstly among physicians, of the physical health effects of exposure to lubricating oil-related atmospheric contamination is in itself important [28, 29]. There is also the aspect of physical differences in the aircraft cabin environment compared with the normal terrestrial situation. High altitude commercial passenger aircraft are typically pressurized as if one were on a high mountain (typically, 6000 to 8000 feet above sea level), leading to a reduction in blood oxygen saturation [30].

Concentrations of carbon dioxide are usually several times higher than in a normal terrestrial environment, and relative humidity is significantly lower. Other contaminants, such as ozone, may be present. The toxicity of TCP should be established under similar conditions. One imagines that these other factors, which may well interact synergistically, will exacerbate rather than alleviate the toxicity.

Since the tricresyl phosphate isomers boil at rather high temperatures, around 200 °C [10],[7] it is a moot point whether they are actually present as vapours or aerosols in an aircraft cabin. Walsh et al. [32] have found that vaporization can engender isomerization. This does not change the fundamental chemical nature as does pyrolysis, which takes place at significantly higher temperatures, but could, for example, convert one of the less toxic isomers into a more toxic one (and vice versa).

There are well documented examples of human intoxication following inhalation of engine oil fumes (e.g., ref. 33). Until recently, however, it would have been very difficult to definitively establish the nature of the fumes to which the sufferer had been exposed. The development of blood assays based on specific biomarkers for exposure to tricresyl phosphate is a major landmark in this regard [34].

3. OCCURRENCE, REPORTING AND STANDARDS

From the previous sections, it is clear that the neurotoxic TCPs are present in jet oil and may leak into the cabin. Jet engines need regular refilling with oil, although to date it has been difficult to obtain comprehensive and reliable data for the oil consumption, which would give an upper limit to what might leak into the cabin.[8]

The oil itself is not volatile (the TCPs boil at over 200 °C, with slight differences between the isomers) and hence is likely to be present as an aerosol, not as a vapour.[7] If odours are detected in the cabin, they are likely to be those of pyrolysis products more volatile than the TCP itself, which may be present at the same time but is itself odourless [31]. They would indicate that leakage is taking place (due to some problem with the oil seal)—they could be considered as markers for presumably higher concentrations of unpyrolysed substances (the ester oil "base", considered to be relatively non-toxic, and the additives).

In extreme cases the cabin actually fills with smoke. Figure 1 shows a photograph taken by a passenger of such an occurrence, which constitutes what is known as a "fume event". For the fume, or smoke, to be visible it must consist of particles at least several hundred nanometres in

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7   According to ref. 31, tri-*o*-cresyl phosphate decomposes upon or before boiling.
8   A pilot has guessed that it might be "half a quart an hour", which equates to 100–200 mm^3 s^{-1} in S.I. units.

diameter. Presumably these are made from carbon coated with other pyrolysis products and burnt oil. Oil droplets may also be present.

Figure 1. A fume event on US Airways flight #432 from Phoenix, Arizona to Maui, Hawaï on 17 September 2010. The airplane was a B757. The flight was diverted to San Francisco.

Technical defects must, of course, be formally reported but deciding what is significant is essentially at the discretion of the captain. In view of the risk of incapacitation, the presence of TCP in the cabin must be considered as significant, although the threshold above which it becomes so cannot be definitively stated at present. Because of the lack of appropriate background knowledge, much of which is associated with a variety of separate academic disciplines and not widely disseminated, the captain may not even be aware of the potential danger of TCP and of the clues to its presence.

Most countries have rules for reporting aviation incidents [3]. For example, the UK Civil Aviation Authority (CAA) has a mandatory occurrence reporting (MOR) scheme [35], according to which suspected ingress of toxic fumes into the cabin should be reported.[9]

Murawski and Supplee have used the reporting records in the USA and have concluded that there is an average of 0.86 events per day [36]. It is, however, widely acknowledged that significant underreporting of cabin air-related incidents occurs—in practice, a pilot would rather not fill in a form if it can be avoided, and because of the lack of monitoring equipment there is inevitably a wide band of discretion regarding the presence of toxic fumes. Hence, the actual number of fume events might be significantly higher. There is, indeed, considerable uncertainty regarding their frequency of occurrence.[10]

The reporting schemes make no provision for lower-level contamination events which, because of their brevity or slightness of intensity, are not considered by the aircrew to pose an operational hazard.

Given the relatively involatile nature of the tricresyl phosphates, it is to be expected that they will condense and accumulate on all the internal surfaces within an aircraft cabin. There has been considerable unofficial sampling of such contamination ("swab tests") by passengers, the results from which point to an alarming history of TCPs in aircraft cabins; this is now being investigated more thoroughly by the Institute of Occupational Medicine (IOM) in Edinburgh, and the results are due to be reported later on this year. The CAA [37] analysed contamination of the inner surfaces of cabin air supply ducts and found both tricresyl phosphate and other materials consistent with the pyrolysis products of engine oil.

The American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) has promulgated a standard for cabin air quality [38], which certainly recognizes the hazards from engine oil contamination and specifies chemical sensors for sampling the air before it enters the cabin or cockpit, but makes no more detailed prescriptions. The European standard EN 4618 [39], which was prepared by the standardization office (ASD-STAN) of the Aerospace and Defence Industries Association of Europe (ASD) on behalf of the Comité Européen de Normalisation (CEN) covers similar ground. Somewhat surprisingly, however, tricresyl phosphate is not considered to be a suitable marker compound, apparently because of the perceived lack of a suitable measurement method.

4. OFFICIAL INVESTIGATIONS

Given the immense and still growing commercial importance of aviation, interest in the matter has not been confined to academic laboratories or military research

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[9] Prior to 2005, such ingress only had to be reported when emergency procedures were used. Given the present lack of chemical metering instrumentation on board aircraft, actual ingress cannot be sensed anyway other than through the pilot's nose.
[10] See ref. 3, Ch. 6.

stations. The growing number of pilots and cabin crew suffering adverse occupational health effects prompted governments to take an interest in the matter. In the year 2000 a select committee of the House of Lords of the UK parliament examined the matter [40]. This followed a judicial, rather than a scientific, style of inquiry.[11]

The relevant part of the report is Chapter 4, "Elements of healthy cabin air". Unfortunately (because it is thereby condemned to superficiality) the report is very much at the level of the lay person. Although the authors, laudably, wish to "help clarify the present muddle" (§4.1), since the present muddle has arisen through a lack of knowledge and the lack of a proper scientific appraisal of what data is already available, in order to make progress it is necessary to tackle the matter from an advanced scientific viewpoint, yet the report begins with "To maintain life, the body needs oxygen" (§4.2). Beginning at that level, it is not to be expected that it will get very far along the road to clarification. A few paragraphs further on, we meet the surprising statement that "Aircraft cabins are no different from many air-conditioned ground environments such as office and hotel buildings ..." (§4.16), although this seems to be contradicted by some subsequent comments on the special atmospheric features of the cabin at cruising altitudes in §4.19. It is unfortunate that consideration of TCP focuses almost exclusively on tri-*ortho*-cresyl phosphate (TOCP), whereas it had already been discovered more than 40 years earlier that the mono- and di-*ortho* isomers are much more potent neurotoxins [10].

The Safety Regulation Group of the CAA[12] carried out research on the possible effect of cabin air contamination on a pilot's ability to safely fly and land aircraft [37]. The experimental part was a careful, high-quality study, the main conclusions being that the ducts carrying bleed air from the engines to the cabin were contaminated with substances consistent with the pyrolysis products of engine oil. Mixed isomers of TCP were also found. In their interpretation of the data, the authors of the report inclined towards the view that irritant, rather than dangerously toxic, substances were likely to be present in the cabin air, and that tricresyl phosphate was unlikely to be present in sufficient quantities to constitute a danger to health. The latter inference was derived from a toxicological review of the literature. Unfortunately this review was seriously inadequate. TOCP was considered to be the most toxic isomer (neglecting the work of Henschler [8–10]) and the only symptom of intoxication considered was OPIDN (cf. §2). Exposure limits from the UK Health and Safety Executive are quoted; this is presumably ref. 41, which gives a long-term (8 h) exposure limit of 0.1 mg m^{-3} for TOCP alone; however, it is clearly stated in that document that "workplace exposure limits are approved only for use where the atmospheric pressure is between 900 and 1100 mbar".[13] In other words they are invalid for the environment of an aircraft cabin pressurized to 8000 feet above sea level. The report ends with a rather curious, and irrelevant, estimate of the oral dosage of oil required to produce OPIDN. Making use of anyway erroneous toxicity data, the conclusion is that "an average man would therefore be able to ingest 7 metric tonnes of pyrolysed oil per day for 74 days without effect" (*sic*).

The UK Government's Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked by the Department for Transport to undertake an independent scientific review of aircraft cabin air contamination and ill health in aircraft crew data submitted by the British Airline Pilots Association (BALPA). Although the members of the COT are academic scientists, this review [43] also appears to have been conducted in the style of a judicial inquiry (cf. [40]). Thus, the usual scientific method is not adopted. A particularly egregious statement is "no specific hypotheses regarding which chemicals to monitor could be pursued at the present time" (§67). This is despite the impressive collection of literature listed in the report (266 items, including some duplications, supplied by BALPA and a further 169 items identified by the COT)—which nevertheless omits Henschler's papers [8–10] and other key references.[14]

Hence, something akin to Laplace's *Principle of Insufficient Reason* is followed, in which adventitious perfume (for example) is *a priori* as important as TCP, and hence justifies the same expenditure of effort on

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[11] The main difference is that the investigator in a judicial style of inquiry will only look at the evidence presented. If the matter is a controversial one with proponents and opponents, each side will carefully select the evidence to boost their case. In contrast, the scientific investigator has a duty to try to get all the evidence before making inferences.

[12] Note that although the CAA is the official regulatory body for aviation in the UK, it is financed through subscriptions from the aviation industry (aerospace manufacturers and airlines).

[13] Ref. 31 gives the same exposure limit for the construction and general industry. It seems indisputable that "this standard cannot be applied to pilots, who are required to perform complex cognitive tasks requiring short-term memory, judgment, reaction time, neuromuscular coordination and orientation" [42].

[14] (Note added in proof.) For an extensive and detailed critique, see Michaelis, S., Winder, C., Hooper, M. and Harper, A. *Critique of the UK Committee on Toxicity Report on Exposure to Oil-Contaminated Air on Commercial Aircraft and Pilot Ill Health*. Unpublished report (2008).

monitoring it. This attitude is underlined in the recommendation that "approaches to exposure measurement should address the widest possible range of potential contaminants from oil/hydraulic fluid" (§87). Given infinite resources this might be feasible but even then it would be unnecessary. Overall, the report [43] is rather sloppy, the writing suggests a lack of sufficient breadth of expertise to properly address the issues involved, and is somewhat inconsistent and evasive. Hence, it is not very surprising that the conclusions include such banalities as "it would be prudent to take appropriate action to prevent oil or hydraulic fluid smoke/fume contamination incidents" (§85).

The House of Lords conducted a further inquiry in 2007. Their report [44] took account of some significant developments since the earlier work [40], some of which had resulted from it.[15] The quality of this report was significantly higher than that of the earlier work [40], and resulted in some incisive recommendations. Of particular importance to this Workshop was "We recommend that the AHWG-sponsored research to identify the substances produced during a fume event be completed urgently. It should be followed up by an epidemiological study on pilots to ascertain the incidence and prevalence of ill health in air crew and any association there might be with exposure to the chemicals identified in the AHWG-sponsored study, paying particular attention to the synergistic effect of these chemicals" (§4.50, repeated in §5.17).

The AHWG-sponsored study referred to in ref. 44 was the "Cabin Air Sampling Study" that had been commissioned from Cranfield University, whose first report [45], issued in 2008, was a disappointment. Its purpose was to identify the most suitable experimental technique for monitoring contaminants. Unfortunately, those responsible for the work seem to have been heavily influenced by the COT report [43] which, as already mentioned, took a catholic approach to the contaminating substances of interest, and suggested the use of photoionization detectors (PID). The peer reviews of the draft of the report (extracts from which are printed on pp. 12–14 of the final version of the (first) report [45]) concluded that "it is difficult to understand how ... the report can state: '1, The PID is a suitable instrument for detecting fume incidents in aircraft cabins.' This unsupported conclusion is repeated and implied to be true in the main report." The authors' response to this criticism was "We feel that the PID will prove a suitable instrument when it is performing to its advertised specification." Responses to some of the other criticisms were in similar vein. Inadequate

as the methodology was, it nevertheless revealed that tricresyl phosphate was present in the aircraft cabin.

The "functionality test" [45] paved the way for the full study [46], which was published in May this year and it is no exaggeration to say that it is a very poor piece of work. Some of the more obvious shortcomings include: inadequate monitoring technology (having ignored the criticisms of the PID from the preliminary study [45]); failure to measure even one fume event during the 100 flights monitored; incomplete experimental details (including absence of information on the actual engine types powering the aircraft being monitored); and a seeming lack of understanding of the principles of statistical inference. The highest concentration of TCP detected was $0.038\ \mathrm{mg\ m^{-3}}$. The measured concentrations were compared with "available workplace exposure limits"—presumably refs 31 and/or 41. That they are irrelevant does not seem to have occurred to the authors. Surprisingly, a considerable portion of the report was devoted to a survey of contaminants in indoor domestic environments, with which the aircraft cabin measurements were compared. All this did not deter the authors from concluding that "there was no evidence for target pollutants occurring in the cabin air at levels exceeding available health and safety standards", the statement that was repeated in the UK House of Commons on the day of publication of the report (10 May 2011) by the Minister of State, Department of Transport (Mrs Theresa Villiers) [47] and which has since been widely quoted by aerospace manufacturers and airlines.

It should be emphasized that for a relatively involatile, lipophilic substance such as tricresyl phosphate, especially in view of its even more toxic metabolic breakdown products, there may effectively be no threshold exposure limit below which it can be deemed to be safe. Provided the appropriate cytochrome P450 enzymes are available in the liver, organophosphates such as TCP can be hydrolysed; the question is whether the detoxification happens faster than toxic injury. Such detailed knowledge of the reaction kinetics is not yet available; we can, however, say with fair certainty that for an appreciable proportion (10–20%) of the population, prolonged exposure to a TCP concentration of $0.038\ \mathrm{mg\ m^{-3}}$ is likely to lead to central and peripheral nervous system damage and, hence, chronic neural illness. Since no fume event was measured, the presumably much higher concentrations during such an event remain, regrettably, unknown, but already cases of near-incapacitation of pilots experiencing such events are known (ref. 3, pp. 547 ff.).

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[15] Including the formation of the Aviation Health Working Group (AHWG) chaired by the Department for Transport, and the Aviation Health Unit (AHU) set up within the CAA.

5. THE RESPONSIBILITIES OF AIRLINES

The basic legal framework within which airlines operate is derived from the 1929 Warsaw Convention [48]. Safety issues are confined to actual accidents. Chronic issues, such as exposure to elevated levels of cosmic radiation when flying in the stratosphere, are not covered. Chronic low level exposure to TCP would, presumably, also fall in that category.

It might reasonably be argued that a sudden fume event resulting from, for example, an oil seal failure is an accident, in which case the Convention's provisions would apply.

The European Air Safety Agency (EASA) does stipulate that "Crew and passenger compartment air must be free from harmful or hazardous concentrations of gases or vapours" [49]. This is rather vague and in particular it is open to interpretation whether "harmful" refers to the average occupant of the aircraft cabin or to the most vulnerable occupant. The stipulation continues "In meeting this requirement, the following apply: (1) Carbon monoxide concentrations ... . (2) Carbon dioxide concentration ... ". No other substances are explicitly mentioned. One should perhaps be mindful that the House of Lords echoed earlier criticisms of the House of Commons, stating that "it is clear that this organisation [EASA] is not yet ready to do its job" (ref. 44, §2.11), which should temper any expectations of effective EASA action in the near future.

The European standard EN 4168 [39] has recently been promulgated. Rather surprisingly, it in effect asserts that TCP cannot be measured and is a bad marker.[16]

There has certainly been extreme reluctance on the part of the airlines to admit any responsibility for health deterioration through occupational causes. This is understandable because of the present difficulty in establishing a definite causal link. Given the broad spectrum of symptoms of sufferers, as would be expected for any neurological ailment, it is obviously necessary to establish such a link in order to prevent erroneously ascribing someone's ill health to the specific occupational cause that is being proposed. Carelessness in this regard would open the doors to potentially very large numbers of liability claims being made against airlines.

Progress is nevertheless being made. Just before this Workshop, Boeing made an undisclosed out-of-court settlement to the former air stewardess Terry Williams whose health had been seriously damaged through occupational causes, probably linked to TCP exposure. It took about 10 years of legal action to reach this conclusion. Now that we are close to having blood biomarkers for TCP exposure (cf. [50]) it should become much easier to unambiguously link neurological effects back to TCP exposure, especially when this occurred due to a single "fume event".

6. POSSIBLE TECHNICAL SOLUTIONS

Humanity involuntarily engages in many dangerous activities, some of which have become so inextricably associated with our whole way of life, indeed our very civilization, that prohibiting them is not a feasible option. Motoring is probably still the most prominent example of such activities, but air travel is rapidly increasing as well and it has become well-nigh inconceivable to imagine a world without flying.[17] It follows that every effort needs to be made to make flying as safe as possible. In the past, safety systems have focused on the prevention and alleviation of accidents. Having achieved a largely accident-free state, attention can now turn to ensuring wellbeing on board.[18]

In order to obviate the possibility of inhaling TCP (and any other substance of comparable toxicity), the following options would appear to be available, in order of decreasing difficulty:

1. Eliminate bleed air by compressing the air using a separate compressor, as on early jet airliners such as the Vickers VC10. Interestingly, this is also being done in the new Boeing 787 "Dreamliner", which is just entering commercial service.[19] There may be additional reasons for doing this, such as the need to eliminate flows of hot air through a structure incorporating many novel composite materials.

2. Eliminate TCP from jet oil. This is being attempted,[20] but it is proving remarkably difficult to achieve the same high-temperature antiwear capability. Recent progress in understanding the molecular mechanisms of antiwear action gives grounds for some optimism [52]. A further development barrier arises through the fact that any new oil will have to go through an exhaustive certification procedure.[21]

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[16] Interestingly, the CEN delegated the work of producing this standard to the organization ASD-STAN, which is an office of the Aerospace and Defence Industries Association of Europe (ASD).

[17] But see ref. 51 for an alternative scenario.

[18] A sudden "fume event" raises a safety issue because the pilots may be incapacitated.

[19] According to a memorandum submitted by Boeing to the House of Lords (ref. 44, p. 115), "The Boeing 787 will have a no-bleed architecture for the outside air supply to the cabin. This architecture eliminates the risk of engine oil decomposition products from being introduced in the cabin supply air in the rare event of a failed engine compressor seal."

[20] Notably by NYCO SA, Paris. See ref. 44, pp. 131–132.

[21] Mobil Jet Oil II appears to have been certified in the early 1960s. There has been considerable evolution in jet engine design since then.

3. Incorporate filters or adsorbents in the air line between the bleed off the engine and the entry into the cabin. One problem with this approach seems to be that the existing spectrum of technologies are designed either to eliminate dust (i.e., fine particles) using microporous membranes (i.e., true filtration) or to eliminate small molecules via adsorption on the surface of a substance with a high specific surface area and broad nonspecific affinity (e.g., "activated carbon") [53,54]; high boiling point oils like TCP present a different kind of challenge. Another problem is that both filters and adsorbents become saturated and, therefore, need regular replacement. Experience with the HEPA filters used to purify recirculated cabin air shows that some airlines never replace these filters. At the very least, sensors (item 5 below) will be required to monitor when the filters/adsorbents are saturated. A further problem is that the adsorbed contaminants may react chemically to produce different substances, which may be even more toxic than the original ones and which, if they desorb, present a fresh hazard. The vast materials synthesis potential of nanotechnology offers a new way to address the problem, by tailoring the materials to specifically avoid the disadvantages of the conventional ones. One question that will have to be answered is whether to concentrate capture efforts on TCP, which is probably the most dangerous substance, and ignore the others. Against this approach is the knowledge of the presence of possibly even more dangerous pyrolysis products whose identities are, as yet, unknown [21, 23].

4. Screen aircrew and passengers for susceptibility to organophosphate poisoning. It would appear that susceptibility is genetically determined; it depends on the available and potentially available variety and quantity of cytochrome P450 enzymes in the liver. There are possibly different degrees of susceptibility, according to which the occupational risk, or risk from frequent flying, may be too great or even a single flight might constitute an unacceptably high risk of health damage. Research work still needs to be done in this area but it seems likely that genetic screening would be useful.[22] It would certainly be easier to accomplish than a liver biopsy.

5. Retrofit sensors for continuously monitoring chemical contamination of the cabin atmosphere. There is already a considerable literature on measuring TCP contamination [46, 55–57,], and even a personal sampler has been proposed [58]. Given the general needs for noninterference with aircraft control systems and miniaturization, integrated optical nanosensors would appear to be called for (e.g., the monofibre chemical meter [58]). The question whether the sensor should respond to a single selected marker analyte or to a broad spectrum of contaminants needs to be answered. Sensors should be provided in the bleed air ducts and at various points in the cockpit and passenger compartments. The sensors would firstly provide an objective physicochemical indication of the presence of contamination, and secondly they would provide information to guide the captain in deciding what action to take. For example, if an oil seal failed on one engine, the bleed air from that engine could be immediately shut off; the remaining engine or engines would normally be able to provide sufficient air to continue normal ventilation. If contamination is already present in the cabin, depending on its degree the captain could decide on an emergency landing or landing at the next available airport, and so forth.

6. Educate aircrew more comprehensively about the issue, especially so that they recognize the symptoms of incipient oil seal problems and can promptly take appropriate action (donning oxygen masks, landing at the next available aerodrome, ordering passengers to don activated carbon masks and so forth).

7. Issue activated carbon masks (with filtration/adsorption capability) to all passengers, to be donned should a "fume event" (i.e., major leakage of oil into the cabin, as in Fig. 1) occur.[23]

8. Print a health warning, akin to those nowadays found in many countries on cigarette packets, on flight tickets.[24]

9. Encourage prompt reporting of any suspected oil leakage into the cabin so that appropriate engine maintenance can be carried out without delay—this lies well within the existing procedural framework.

In addition, the development of biomarkers for intoxication [60] will assist prompt diagnosis and the application of appropriate therapy to passengers and aircrew having experienced a fume event.

7. FINDING A WAY FORWARD

At present the aviation industry appears to have entered an impasse. The organophosphate issue seems to have

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[22] This could solve the problem for passengers; those lacking the relevant genes would be advised not to fly in aircraft with bleed air-pressurized cabins. For aircrew it may not be considered acceptable since in effect they would be deprived of a job because of their genetics.

[23] Note that fume events seem to occur far more frequently than ditching, for which eventuality relatively heavy life jackets are stowed at each seat.

[24] Possible wording could be "Travel by jet airliner may seriously damage your brain". One can anticipate that this will be resisted by the airline industry, for though it might remove liability, it is also likely to discourage people from flying.

become a veritable bugbear and extraordinarily strenuous attempts are made to deny both the actual contamination and the link with adverse health effects. The "Aircraft Cabin Air Sampling Study" [46] already referred to is the most recent example of attempting to deny the actual contamination and its possible consequences.[25]

It is most unfortunate that the study was commissioned to be carried out by an organization (Cranfield University) that has a strategic alliance with one of the members (BAE Systems) of the Aerospace and Defence Industries Association of Europe (ASD), the parent body of ASD-STAN, which is charged with preparing aviation standards on behalf of CEN and through this work one may infer that ASD is opposed to admitting the presence of hazardous levels of TCP in aircraft cabins.[26]

In short, the report appears to be a clumsy attempt to provide pseudoscientific "evidence" for the lack of a health and safety hazard.

Even where the presence of significant toxins is admitted, there is obfuscation regarding the link between them and the collection of symptoms that are now conveniently labelled as aerotoxic syndrome. In this regard the Committee on Toxicity's statement [43], eschewing hypotheses and denying association (which does not have to be causal to provide a sound basis for action) is particularly reprehensible. Although this committee is supposedly constituted from experts, one wonders in what field their expertise actually lies. They have disregarded scientific progress and promoted obscurantism—both, apparently, known failings among toxicologists [61].

Presumably the industry is concerned that if the problem is admitted, it will not only be faced with the expense of having to find a technical remedy (see §6) but also with potentially very costly liability suits from employees, former employees and passengers whose health has been adversely affected by TCP exposure. Furthermore, the flying public may be severely discouraged from undertaking any but the most essential journeys by air once awareness of the problem becomes widespread. Since any work to find a technical remedy

amounts to an admission of the problem, there is no serious attempt being made within the industry to undertake such work. The Boeing 787 seems to be the sole exception to this state of affairs which will, in the years to come, likely give that company a decisive advantage compared with its ostrich-like competitors.[27]

Nevertheless, in so far as there now appears to be an incontrovertible link between even low-level organophosphate exposure and physiological abnormality in the brain, liability seems to be ultimately unavoidable and it would, therefore, be prudent to take all practically possible steps to minimize exposure, starting with what can be achieved within existing procedural frameworks [62].

Airline employees (and their unions) are placed in a difficult position, for if individuals flag up their health problems their pilot's licences may be withdrawn, and if the problem becomes more widely known to the public, plummeting passenger numbers and liability suits may force airlines into bankruptcy. This in itself raises a safety issue, for it implies that there are currently pilots flying with damaged central nervous systems, who might be well able to cope with routine flights but adversely challenged by any sudden emergency.

In the past it has certainly been difficult to provide firm evidence for a link between organophosphate exposure *in the aircraft cabin* and ill health. In the absence of chemical meters continuously monitoring organophosphate levels one cannot "prove" that organophosphates (notably, TCPs) were present in the atmosphere on a particular flight.[28]

Similarly, in the absence of reliable blood (or other biofluid) test convenient enough to be carried out shortly after landing one cannot "prove" that a given individual was exposed to TCPs and absorbed them. But it can be confidently anticipated that a suitable blood test will soon be available [60]. Furthermore, knowledge of the brain activity patterns characteristic of TCP intoxication is constantly increasing [63]. The ability to provide significant and substantial evidence for both the actual exposure and its adverse health consequences is imminent. Once this happens, it will obviously no longer be possible to credibly deny the problem [64].

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[25] Seemingly in order to obfuscate the issue, a large spectrum of compounds was measured with a technique that might have been appropriate for many of them but not for the most important one, namely tricresyl phosphate. Despite having been commissioned to do so, the study failed to measure even one "fume event". Finally, although the matter is first and foremost an occupational hazard in a very special environment, the on-board contamination was merely compared with a typical domestic setting at sea level in order to establish whether exposures cause ill health.

[26] The rejection of TCP as a measurable marker for contamination (ref. 39, footnote to Table 1) is especially revealing in this regard, given the many works dealing with TCP measurement in aircraft cabins that have already been published [46, 55–58]—including the Cranfield University report [46] itself!

[27] Its attitude is, however, necessarily highly ambivalent, because at the same time a large number of its older, bleed-air aircraft will remain in service for many years to come and could attract retrospective liability claims.

[28] Passengers may wish to take swabs from the interior surfaces of the cabin and send them to a chemical laboratory for analysis. Almost certainly, accumulated TCPs will be found on every jet aircraft.

At the very least, the present oppressive atmosphere of denial must be blown away to allow genuine sufferers to receive the diagnosis and treatment that will, hopefully, allow them to start moving along the road to recovery. The next priority is to minimize the actual contamination. Even without updating any technology, comprehensive reporting of problems when they do occur will assist appropriate engineering maintenance. The quantitative monitoring of contamination through sensorization of the airframe (i.e., installing chemical sensors) is the obvious practicable technology update. If the aerospace industry acts energetically in response to the latest knowledge, in accord with the principles of the "knowledge-based economy", hopefully this will give it the confidence to be able to move forward constructively.

Is more research needed before taking concrete action? There seems already to be overwhelming evidence in favour of the proposition that tricresyl phosphate *is* leaking into aircraft cabins (e.g., ref. 46) and causing both chronic illness through relatively low-level but long-term exposure as well as acute illness (incapacitation) through a sudden fume event that might properly rank as an accident. A large-scale epidemiological study with a control group would of course be decisive in this regard (cf. ref. 65) but would also be very expensive and it may be that all the existing data, including much hitherto unpublished or unanalysed material, if centrally collated and properly analysed, will suffice if further evidence is still considered to be necessary. The case would already seem to be made if one uses Sir Austin Bradford Hill's criteria [66].

A complete understanding of the mechanisms of toxicity would certainly require identification of the oil pyrolysis products that may enter the cabin along with both unaltered and isomerized tricresyl phosphates, but this is a luxury not essential for taking effective action to combat the problem.

One area that has definitely been neglected is establishing whether there are synergies not only between different toxins—and we do now have quite a variety of data for different substances [46]—but between the inhalation of TCP under the particular conditions typical of a pressurized airliner flying at high altitude, and between the neurotoxin TCP and other attriting factors including disruption of the circadian rhythm ("jetlag" [67]), cosmic radiation [68] and disturbance to the immune system [69]. All of these factors, omnipresent in long-distance travel by jet aircraft, seem likely to exacerbate damage to the central nervous system by TCP.

Finally, the concentrations of potential toxins still need to be measured, in a statistically appropriate fashion, during actual "fume events".

8. SUMMARY AND CONCLUSIONS

The proposition enunciated at the beginning of this paper, namely that certain substances present in aircraft cabin air cause neural degeneration, has been considered and, taking due account of the available evidence, can be accepted as valid. Moreover, one can be more specific and point to the mono- and di-*ortho*-tricresyl phosphates as being the most hazardous substances.

The evidence for the risks seems to be overwhelming. In other words, it is already sufficient to justify taking remedial action. Further research is not required in this sense. What is, however, still lacking is an attempt to calculate how much could reasonably be spent on developing technical remedies. This will be the subject of a future paper.

If suitable chemical sensors can be retrofitted to aircraft cabins, air travel by jetliner will become much safer, both occupationally and otherwise. The development of such a sensor would appear to be a high-priority research and engineering task. If it becomes a regulatory requirement to fit such sensors, their sales should provide a sufficiently attractive return on the investment for a commercial company to undertake this development.

Meanwhile, vulnerable people should be identified whenever possible and advised not to travel by jet airliners fitted with bleed air technology. Given that there is some evidence for reproductive toxicity of TCP [70], pregnant women should at least be made aware of the risk. It seems self-evident that whenever a fume event occurs, passengers should be promptly informed of the true state of affairs in order that they can, if they wish, seek medical advice upon landing.

Regarding potential liability, the earlier positive remedial action can be undertaken, the less the liability will be. At present it might still be possible for all sides to agree on a "no-fault" settlement (even though there is already a considerable history of knowledge of the hazards of bleed air) as a way out of the impasse. Once chemical meters or blood tests or both are available, one can expect that the need for judicial certainty will be satisfied and the issue can no longer be evaded in the courts.

"The constant increase of environmental contamination by chemical compounds is one of the most important and unsolved problems burdening mankind" [71]. Tricresyl phosphate is just one of the very useful chemical compounds created by man but is, like so many others, linked to deleterious effects as well as beneficial ones. Actually, the need for additional (high) technology to make flying safe is simply another consequence of what A.O. Hirschmann called "maintenance compulsion" [72]. Modern civilization provides many examples. Many years

ago Lord Adrian raised the problem of potential genetic deterioration through mutations caused by radioactivity, as a consequence of nuclear power generation as well as medical X-rays. Fortunately a rough estimate of the possible effects showed that they were not particularly alarming [73]. Anything that promotes neural degeneration is, however, a matter of particular concern because our abilities to cope with the demands placed on us by high technology (as well as its effect of alleviating labour) might well require increasing intelligence, especially considering that coping may call for the development of even higher technology.

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