Contaminated aircraft cabin air: aspects of causation and acceptable risk†

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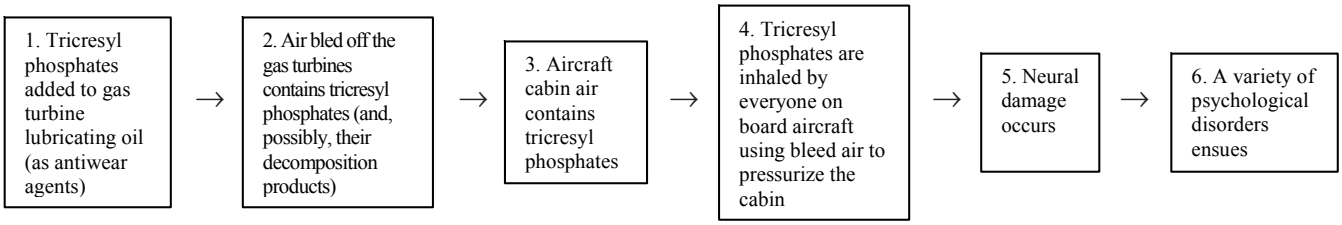
The starting point of this paper is that despite the large amount of available data demonstrating the neurotoxicity of tricresyl phosphates and their presence in aircraft cabin air, and many cases of pilots, cabin crew and frequently flying passengers suffering neurological symptoms consistent with tricresyl phosphate poisoning, the inference that the tricresyl phosphates (which are present in jet engine lubricant) are the cause of the ill health of aircrew and passengers is still widely disputed by airlines, aircraft manufacturers, governments and regulatory agencies. This paper examines how data is transformed into evidence and explores some reasons for opposition to the proposition of causation. It also explores how elimination of the problem can be achieved in a cost-effective manner. Some useful avenues for continuing research are identified.

1. INTRODUCTION

The occurrence of notable cases of ill health, typically involving cognitive dysfunction and other neurological disorders, among pilots flying jet and turboprop aircraft and cabin crew working on such aircraft [1], has led to the proposition of "aerotoxic syndrome" [2], meaning the complex of disorders, mainly neurological, observed in people whose anamnesis includes frequent flying. It is proposed that the chain of causality ("diagram of immediate effects") shown in Scheme 1 exists.[1]



Scheme 1. Diagram of immediate effects for neurological aspects of aerotoxic syndrome.

A great deal of data is already available concerning the matter, gathered over the last 60 years or so [1]. The main efforts have focused on measurement of the concentrations of tricresyl phosphates (TCP) in the aircraft cabin air, and the investigation of the nature of the disorders experienced by those afflicted. Although the measurements are technically rather demanding (e.g., [5]), there now seems to be little doubt that significant concentrations are indeed present. Similarly, there is a particular pattern of physiological and psychological disorder (which is what is called "aerotoxic syndrome") uniquely exhibited by those having flown in aircraft [6, 7]. Since TCP is not a compound to which people are normally exposed, it is not a very daring leap to assert that inhaling TCP is the *cause* of aerotoxic syndrome, especially since it has long been known from animal experiments that TCP causes severe damage to the central nervous system [8].

Despite all this data and what would appear to be a rather strong inference from it, there is nevertheless a good deal of reluctance by some of the key players—notably aircraft manufacturers, airlines, aviation regulators and governments—to accept causation. The UK Committee on Toxicity of Chemicals in Food Consumer Products and the Environment (COT) investigated the matter and issued a statement summarizing their findings in September 2007 [9], which concluded that "it was not possible on the basis of the available evidence ... [to infer] that there is a causal association between cabin air exposures ... and ill health in commercial aircraft crews."

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[1] See [1] for a very comprehensive compilation of data and discussion, [3] for a slightly more recent and much more succinct account, and [4] for a summary of the background.

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More recently Earl Attlee, the UK government spokesman on aviation in the House of Lords, asserted that "we do not have evidence that passenger health is affected by fume events" [10].[2, 3] Some of the possible reasons for this reluctance, which seems to go beyond strictly objective appraisal of the facts, are discussed in §8.

The response of the proponents of the cause of aerotoxic syndrome being tricresyl phosphate inhalation to this apparent reluctance to accept causation has typically been to call for more research aimed at gathering more data. But is more data actually required? Raw data does not necessarily constitute evidence. Is the problem, perhaps, that the facts have not yet been marshalled in an appropriate fashion from which it should be straightforward to determine whether there is causation or not? This paper examines what is apparently still needed in order to be able to assert that there is causation. Interestingly, this does not seem to have been attempted hitherto in any kind of systematic or scientific fashion. Even the aviation medical specialists opposed to the existence of aerotoxic syndrome (cf. footnote 3) admit that there is something wrong with a significant proportion of aircrew.

If adverse health effects are merely associated with confinement in jet aircraft, the only remedial action one can take is to eschew flying in such aircraft. Apart from the loss of livelihood this implies for aircrew, aviation has become well nigh an indispensable part of business life (vacationers are also accustomed to flying to their destinations, but such journeys might only be undertaken once or twice a year) and abandoning it implies considerable disruption.[4] If, on the other hand, causation can be established then definite positive actions can be carried out, such as eliminating the cause, for example by pressurizing the cabin by compressing air taken directly from the exterior rather than bleeding it off the engines.[5] It may be, however, that the cost of such elimination is prohibitive. An alternative would be to treat those afflicted after the event (although it is by no means certain that organophosphate-induced neural damage can be completely reversed). One could also (epi)genetically screen all aircrew and prospective passengers and issue personal masks equipped to trap the neurotoxins to those found to be highly susceptible. A rational approach to remedial action is described in §9.2.

2. ASSOCIATION

The first step in looking for the cause of a disease (the identification of which will, hopefully, lead to a cure, most simply by removing the causative agent, if that is feasible) is to establish whether there is association between some environmental features and the features characteristic of the ailment. In the present case the disease is conveniently labelled aerotoxic syndrome. The word "syndrome", which in itself simply means "concurrent symptoms", or a characteristic combination thereof, is deliberately used in a medical context when the morbid condition of the body is less clearly characterized than in the case of a formally defined disease. In particular, especially since the work of Robert Koch, if an infectious agent can be shown to be so strongly associated with the morbid condition that causation can be accepted beyond all reasonable doubt (see the next section, §3), the ailment is confidently labelled "disease". A succinct expression of the difference between "disease" and "syndrome" is, therefore, that the latter is a disease with no known cause.[6] It would perhaps be appropriate to label all maladies initially "syndrome", since the first observations are typically of symptoms only; the elucidation of cause comes later. Similarly with aerotoxic syndrome, the label arose after many pilots and cabin crew were found to be suffering from a distinct set of cognitive and other impairments, not shared by occupations not requiring significant time spent in aircraft cabins [7].

As Singer and Johnson have pointed out [11], damage to the brain and nervous system may result in a confusing array of symptoms, and general practitioners are prone to misdiagnose the syndrome, or fail to diagnose it at all [12]. The body is extensively innervated, and damage to the nerves may affect many vital functions, including muscular control; damage to the brain may affect conscious and unconscious activity. Therefore, any medical condition caused by exposure to a neurotoxin is likely to have a wide range of symptoms. Inevitably, these symptoms have behavioural consequences. The UK Government *Information Note on the Diagnosis of Prescribed Disease C3* (poisoning ... due to anticholinesterase or pseudo anticholinesterase action of organic phosphorus compounds—this wording dates from October 1983)

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[2] Admittedly, no systematic study of *passengers* has yet been made, but they are exposed to the same atmosphere as pilots and aircrew and, hence, can be expected to suffer—or not, as the case may be—similarly to the latter.

[3] A variety of unpublished material, especially lectures and reports emanating from aviation medical specialists attached to airlines, promotes the view that the disorders experienced by aircrew are due to problems such as hyperventilation.

[4] This may change in the future, as more and more new railways are being built on which very high speed trains can run, providing competitive city centre-to-city centre journey times.

[5] The new Boeing 787 "Dreamliner" uses this solution.

[6] Probably the best-known contemporary syndrome is autoimmune deficiency syndrome, AIDS.

makes the special point that "the neurobehavioural symptoms of late organophosphorus poisoning are common in the unpoisoned population ..." [13]. This adds to the difficulty of diagnosis.

It is also important to be aware that there is a considerable variation among the human population in terms of the genetically determined ability of individuals to metabolize xenobiotics. The most important enzymes that break down exogenous toxins are members of the cytochrome P450 family, of which a healthy individual has several dozen variants, able to tackle most chemical structures. Rather like the well known variation in alcohol dehydrogenase expression and activity (especially the contrast between European and Chinese populations), a significant proportion (tens of percent) of the Caucasian population appears to be deficient in the particular cytochrome(s) P450 needed for the decomposition of TCP [14]. Those with the deficiency (of which a general practitioner is unlikely to be aware—it can only be revealed by genetic testing) will be more severely affected by exposure to the neurotoxin. Assuming that the deficiency is not coupled to a predisposition to become an airline pilot, the existence of these genetic variants further confounds the clear emergence of a clearly identifiable set of essential features of the neurological ailment.

3. A.B. HILL'S CRITERIA

In his presidential address, delivered on 14 January 1965 to the Royal College of Medicine [15], Sir Austin Bradford Hill discussed nine aspects of the problem of passing from an observed *association* between an environmental feature and a health problem to a verdict of *causation*. In this section we shall examine each of them in turn, in the same order used by Hill, in which the most important comes first. A brief explanation of each criterion will be given, followed by a summary of the status of aerial TCP-induced neural damage.

3.1 Strength of the association

The stronger the association, the more likely it is to be causal. A comparison of the proportion of afflicted people who suffer exposure to those who do not is usually made. There is no absolute criterion of strength, but it would be prudent to expect a proportion at least an order of magnitude greater in the exposed population compared with the unexposed. For the latter, the general population is usually adequate. For the former, we have a number of health surveys (see Chapter 4 of [1]). More than 20 symptoms are associated with aerotoxic syndrome, some of which, such as "cough", are more widely encountered within the general population than others, such as "eye irritation/pain" and "dizziness/loss of balance". The latter have low occurrence among the relevant age cohort of the general population; their occurrence among aircrew would appear to easily meet the "order of magnitude" criterion. Even if their individual occurrence is as high as almost 30% (as was found for dizziness by an epidemiological study of over 10,000 adults in Sweden [16]) the expected frequency of co-occurrence of the symptoms in the general population can be obtained by simply multiplying the probabilities: e.g., $0.3^{20} \approx 10^{-11}$, whereas a few percent at least of aircrew show *all* the symptoms, indicating an enormous strength of association.

In contrast to the situation with aircrew, information about postflight passenger health seems to be almost entirely anecdotal.

3.2 Consistency

Has the observed association been repeatedly observed by different persons, in different places, circumstances and times? An affirmative answer seems to be generally accepted. Certain aircraft types, such as the BAe 146 (later known as the Avro RJ series) and the Boeing 757, seem to be especially prone to generating the symptoms among aircrew.

3.3 Specificity

This is the question whether the set of symptoms is specifically associated with people flying in aircraft cabins, either as aircrew or passengers. This can really be subsumed into the "strength" criterion, in which one is anyway comparing a specific group of people with the general population.

3.4 Temporality

This criterion is simply whether the proposed cause precedes the appearance of the symptoms. This is also generally accepted. The alternative is rather implausible notion that the particular set of neurological disorders labelled aerotoxic syndrome lead to a desire to fly as often as possible.

3.5 Biological gradient

Do the symptoms increase in intensity with increasing exposure? Exposure is, of course, the product of ambient concentration and the temporal interval during which the human subject is exposed to the toxic compound. Only limited data is available (e.g., [5] for normal flights); nothing appears to have been published for "fume events" (often due to catastrophic and complete failure of an oil

seal), in which visible fumes enter the cabin. Nevertheless, there is plenty of evidence that after a "fume event" aircrew may need to be taken off the aircraft on a stretcher and hospitalized. The effects of chronic low-level exposure will depend on the rate at which the toxin is eliminated from the body. Doubtless individuals vary in their abilities in this respect. Flights are discrete events separated by an interval on the ground, during which some detoxification might be possible. The dose, in a plot of response *vs* dose, might simply be the number of flights.

There is certainly a present lack of data for establishing a quantitative biological gradient, since a blood test for a marker of TCP inhalation has only recently been developed.[7] In the absence of individual blood tests carried out on aircrew and passengers, one has to rely on estimates of chronic TCP exposure based on sample measurements carried out within the cockpit or cabin. An average concentration of 0.23 μg m^{-3} has been recorded, with a maximum of almost 40 μg m^{-3} [5], for normal flights without a "fume event".

Full quantification would require some numerical measure of the severity of symptoms. Doubtless this could be devised. It might, however, be sufficient to use a binomial diagnosis (cf. §4.2)—either one has the syndrome or one does not.

3.6 Plausibility

Does the proposed causal link fit in with existing knowledge? Experiments with laboratory animals have established the neurotoxicity of TCP (with considerable differences in the potencies of the different isomers) [8]; studies of humans accidentally exposed to TCP or chemically similar substances corroborates the animal work. After the landmark experiments of Henschler, later studies clarified the nature of the neural damage: short-term cholinergic toxicity and longer-term organophosphate-induced delayed and/or chronic neurotoxicity [17].

3.7 Coherence

This criterion is interpreted by Hill to mean medical plausibility, whereas he makes the previous criterion refer to biological plausibility. Note that it is not necessary for a biological mechanism for the medical condition to have been established in order to be able to reasonably assert causality.

3.8 Experiment

In practice, this criterion concerns semi-experimental evidence. For example, the new Boeing 787 ("Dreamliner"), which entered commercial service with All Nippon Airways (ANA) last November, pressurizes its cabin using air taken directly from the exterior: do aircrew working on this aircraft still develop aerotoxic syndrome? Icelandair will switch to NYCO lubricating oils that have less neurotoxicity than the oils mainly used otherwise in civilian jet aviation:[8] will the strength of the symptoms drop in consequence (cf. §3.5)? Poor or infrequent engine maintenance is considered to result in underperforming oil seals that leak more TCP into the cabin than otherwise; do aircrew working for airlines with a good maintenance policy suffer weaker symptoms than those working for airlines with a poor policy?

3.9 Analogy

In terms of neurotoxicity, TCP is closely related to organophosphate pesticides, whose adverse health effects on farmers and horticulturalists has long been recognized [18, 19], including from chronic, low-dose exposure [20, 21]. It is also related to Gulf War syndrome, for which organophosphate exposure is recognized as a likely causal agent [22].

4. TESTS OF SIGNIFICANCE

As René Descartes remarked, "lorsqu'il n'est pas en notre pouvoir de discerner les plus vraies opinions, nous devons suivre les plus probables" [23]. One has a proposition, namely that exposure to tricresyl phosphates in the atmosphere promotes a variety of symptoms that, in combination, constitute "aerotoxic syndrome". To what extent is this proposition backed by the evidence? There are two main approaches to answer this question.

4.1 Bayes' rule

The so-called "Bayesian method" relies upon Bayes' formula (which he refused to publish during his lifetime because of legitimate concerns about its applicability and interpretation).[9] It links the "posterior probability" (i.e., the conditional probability that our hypothesis H is supported by the available evidence E) to the likelihood (see §4.2):

[7] Described in the contribution of O. Lockridge to the Global Cabin Air Quality Executive (GCAQE) Fifth Annual Forum, 25 April 2012, London.
[8] Announced at the Global Cabin Air Quality Executive (GCAQE) Fifth Annual Forum, 25 April 2012, London.
[9] See, e.g., the note by Feller on p. 124 of [24].

$$P(H|E) = \frac{P(E|H)P(H)}{P(E)} \quad (1)$$

where $P(H)$ is the prior probability of the hypothesis and $P(E)$ is the probability of the evidence (data). The factor $P(H)$ is highly problematical. If one applies Laplace's *principle of insufficient reason* (ascribing equal probabilities to events whose actual probabilities are unknown), and if there is an infinite number of possible hypotheses, then $P(H)$ becomes zero for every hypothesis. In practice, attention is limited to a finite, small number of candidate hypotheses and $P(H)$ is simply a personal estimate of plausibility—in other words an expression of preconceived beliefs. This is obviously unsatisfactory (for one thing it fails Hill's criterion of consistency, §3.2).

4.2 Likelihood

The likelihood $L(H|E)$ of the hypothesis H given evidence (data) E, and a specific model, is proportional to $P(E|H)$ [25]. Since we usually wish to compare different hypotheses (given the same data), the arbitrary constant of proportionality can be eliminated by computing the *likelihood ratio*, denoted $L(H_1, H_2|E)$ for two hypotheses H_1 and H_2. Furthermore, likelihood ratios of two hypotheses on independent sets of data (e.g., E_1 and E_2) may be multiplied together to yield the likelihood ratio on the combined data:

$$L(H_1, H_2|E_1\&E_2) = L(H_1, H_2|E_1) \cdot L(H_1, H_2|E_2) \quad (2)$$

as can be proved using the multiplication rule for probabilities, since both the left-hand and right-hand sides of (2) are, by definition [25]:

$$\frac{L(H_1|E_1 \,\&\, E_2)}{L(H_2|E_1 \,\&\, E_2)} = \frac{P(E_1 \,\&\, E_2|H_1)}{P(E_1 \,\&\, E_2|H_2)} = \frac{P(E_1|H_1)}{P(E_1|H_2)} \cdot \frac{P(E_2|H_1)}{P(E_2|H_2)}. \quad (3)$$

Often the hypotheses are framed in terms of getting a particular result with a (continuously distributed) probability p. In this case it is convenient to take the likelihood ratios with respect to the value of p giving the maximum likelihood. Plotting the ratios versus p under this convention gives a *likelihood curve* with a maximum of 1.

4.3 Application to aerotoxicity

Because of its superior objectivity, we prefer the likelihood approach. Let us assume a binomial model—that is, each passenger on a flight constitutes an independent trial. H_1 is what we might call the Attlee hypothesis—the probability of contracting neurological disease (aerotoxic syndrome) on a flight is zero.[10] H_2 is that there is a certain probability p of developing aerotoxic syndrome after a flight. Let the number of passengers showing aerotoxic symptoms after a flight be a, and the number of those who not showing them be b. Then

$$P(E|p) = \frac{(a+b)!}{a!b!}\, p^a(1-p)^b. \quad (4)$$

and hence the likelihood of p for this data is

$$L(p|E) = kp^a(1-p)^b \quad (5)$$

where k is the arbitrary constant of proportionality, chosen so that the maximum value of L is 1. All available flight datasets (a_1, b_1, a_2, b_2 ...) can be combined multiplicatively. Since the sum of all the as is not zero,[11] p cannot be zero, hence the Attlee hypothesis is disproved, even if each flight constitutes an independent set of independent trials. If, however, as seems to be the case, the neurotoxicity depends on the cumulative exposure, at the next stage of sophistication we need to consider that p actually depends on the number of journeys flown. It would then be realistic to construct the likelihood curve for data from (say) aircrew and passengers who had flown approximately 100 times. In order to be able to deal with all possible numbers of flights for which data is available, one might instead inquire how many trials are necessary to produce one case of aerotoxic syndrome. Since in this paper the purpose of this section is merely to sketch out how probability and likelihood can be used to reach firm conclusions, we shall not go into more details here. Such details would, ultimately, necessarily have to include the intervals between flights (during which some detoxification presumably takes place) as well as data on diet and other aspects of lifestyle. p very likely also depends on the genetic constitution of the flyer.

5. THE RESULTS OF JUDICIAL INQUIRIES

Until now it appears that only one legal case concerning aerotoxicity, brought by a flight attendant against her employer, has been successfully consummated—*Turner vs Eastwest Airlines Ltd* [27], heard before the Dust Diseases Tribunal (DDT) of New South Wales and upheld by the Court of Appeal of that state. The plaintiff became ill after a single fume event that occurred on 4 March 1992. The judgment of J. Kearns included the

[10] Earl Attlee's remark [10] applied to passengers. Passengers and aircrew are, however, breathing essentially the same air, therefore at this level of approximation we can apply the hypothesis to passengers and aircrew indifferently. A more refined approach would take into account the fact that although the cockpit is not hermetically sealed off from the cabin, it receives *only* bleed air, whereas cabin air is partially recirculated via HEPA filters; and that flight attendants are usually on their feet and moving around whereas passengers are mostly seated and stationary; etc.

[11] See, e.g., [26] for evidence of aerotoxic syndrome having been developed by a passenger.

statement ([27], ¶151): "in coming to the view I do about the plaintiff's condition and its cause, I am particularly impressed by a six-year history before before 4 March 1992 of the plaintiff's being cough-free, by the nature of the event of 4 March 1992, by the potential toxic effects of pyrolysed oil, by the plaintiff's immediate reaction and by her continuing symptoms." In other words, the court determined that toxic particles in the cabin air *were the cause* of long-term adverse health effects (see also [28] for more details). The fume event occurred in 1992, suit was filed in 2001, and the judgment was made in 2009. The defendant's appeal was dismissed in 2010.

A further case was brought in 2009 by a flight attendant (Terry Williams) against the manufacturer of the aircraft (McDonnell Douglas, now part of Boeing). As in *Turner vs Eastwest Airlines Ltd* [27], the plaintiff became ill after a single fume event that occurred in 2007. This case was settled by Boeing on 6 October 2011 (with details of the settlement remaining undisclosed).

Passengers who were on an international flight in 2007 on which a fume event apparently occurred filed suit against the various parties involved (including the aircraft manufacturer, the engine manufacturer, the manufacturer of components of the bleed air system and the airline) in 2009 (*Sabatino vs Boeing Corp.*, see [28]), but this case has not yet reached any conclusions.

Whereas the two cases involving flight attendants concerned aerotoxicity as an occupational hazard, passengers' welfare on international flights is governed by the Warsaw Convention (updated by the Montreal Convention), which is essentially limited to considering the consequences of *accidents*. While a fume event might well be regarded as an accident, chronic exposure on normal flights (as found by [5] and [6], for example) is evidently not.[12]

6. OFFICIAL OPINION

In the UK, the government places great reliance on its Committee on Toxicity of Chemicals in Food Consumer Products and the Environment (COT), which provides supposedly independent advice to the Department of Health (DH) and other ministries. In in its 1999 report on organophosphates [30], the COT concluded that the balance of evidence did not support the existence of long-term neurological effects from chronic exposure to organophosphates. In its 2007 statement on aircraft cabin air [9], it could not conclude that there is a causal association between cabin air exposures and ill health in commercial aircraft crews.[13] Furthermore, the COT could not even formulate a "specific hypothesis regarding which chemicals to monitor", despite all the previous work of Henschler and others pointing to the uniquely neurotoxic behaviour presented by the tricresyl phosphates. The formulation of hypotheses, which are then subjected to test, is of course the foundation of scientific work. One cannot advance very far without them.[14]

Advisory bodies such as the COT have a general problem affecting the credibility of their work. As the Countess of Mar has pertinently remarked in a debate about the impartiality of the advice given by government advisory committees [31]: "I do believe that these committees are independent of government, but I am not so certain that they are independent of the industry which they were set up to regulate ... the scientific community is very close-knit and because the numbers of individuals in specialties is small, they will all know one another. They are dependent upon one another for support, guidance, praise and recognition. If they wish to succeed, they must run with the prevailing ethos of their group, department or specialism. History is littered with stories of the establishment refusing to accept new scientific discoveries and of the ostracism of the discoverers ..." (columns 1555–1556). She continued, "these expert committees are often required to make decisions upon incomplete evidence, so the only verdict they can give is that of 'not proven' ... they rely upon what may be called 'constructive ignorance' by being content to rule on the evidence which is before them and avoid a search for information that may lead to a different decision. That is not being impartial" (columns 1558–1559). Given that state of affairs, Earl Attlee's remark quoted earlier [10] becomes less surprising (but not less excusable), since he no doubt relies (perhaps unthinkingly) on what "expert" advisory committees have told him.[15]

[12] European regulations stipulate that "Crew and passenger compartment air must be free from harmful or hazardous concentrations of gases or vapours" [29].

[13] This conclusion was carefully qualified by "on the basis of the available evidence in the BALPA submission or that sourced by the Secretariat and the DH Toxicology Unit"—in other words the information was somewhat selectively (or incompetently) gathered and, hence, the report fell short of the usual standards of scientific integrity.

[14] Sir Isaac Newton's famous utterance "hypothesis non fingo" is sometimes taken (at least in the English-speaking world) as an authoritative repudiation of hypotheses in general. This is simply taking the remark out of context. Newton of course formulated many hypotheses. He refused, however, to be drawn into airy speculation on ultimate causes—in which realm hypotheses are useless because they cannot be tested.

[15] In the same debate (*loc. cit.*), Lady Mar aptly quoted from *A Pride of Tigers* by S. Marshall: "I fell to wondering why it is that 'experts' so often get things wrong. Once they become experts they know all the answers, so they don't ask questions. They

Official opinion often shelters behind the "workplace exposure limits" (as they are now known in the UK; they have been called "maximum exposure limits" and "occupational exposure standards"; the EU directs "indicative occupational exposure limit values"), which prescribe the maximum permissible exposures to which workers may be subjected. Such limits were often established many decades ago and there is considerable inertia in the process to update them on the basis of new knowledge. Besides, they are essentially established for the terrestrial factory, office or workshop environment. The pressurized cabin of an aircraft flying at high altitude is very different, perhaps most physiologically notably due to the low oxygen level. We need to inquire what are the effects of exposure to TCP, pyrolysed oil etc. *in combination with* a low oxygen level.

7. MEDICAL OPINION

Mainstream medical opinion, as represented by medical examiners, airline medical doctors and professors of aviation medicine among others, has been peculiarly reluctant to accept the possibility of neurological damage among aircrew as a result of chronic exposure to tricresyl phosphate (the only serious neurotoxic candidate among the aircraft cabin air contaminants, apart from the pyrolysis products of lubricating oil, which are rather ill-defined), let alone as a result of acute exposure as in a fume event. For example, the recently published edited book entitled *The Neurosciences and the Practice of Aviation Medicine* [33] makes no mention of anything related to aerotoxic syndrome, despite its almost 500 pages and evident aim to be comprehensive.

One of the main problems in reaching a satisfactory diagnosis of the ill health resulting from exposure to neurotoxic substances is that the "complexity ceiling" of medical diagnosis appears to be rather low. According to a University of Illinois study by Miller and McGuire (quoted by Fabb [34]), about 85% of medical examination questions require only recall of *isolated bits* of factual information. The very notion of a syndrome requires the weighing of many factors simultaneously; current medical education and training does not, apparently, inculcate this ability.

The medical world is well known to be notoriously conservative. Established views are frequently held with an almost religious fervour. A good analogy is tap water fluoridation, which has been (for more than half a century) and continues to be strongly promoted by the UK health ministry (now called the Department of Health), despite the accumulated evidence that any benefits of fluoride for teeth are confined to topical application; systemic administration is at best of neutral effect and may be actually harmful [35]. All the more if a syndrome is complex and difficult to diagnose, let alone treat, if the mainstream ignores it many individual doctors will simply follow suit.

8. IS FECIT CUI PRODEST

Even nowadays, more than a century after the Wright brothers, aviation retains something of an aura of pioneering modernity. This may explain some of the reluctance to interfere with it. The main document regulating liability for international air traffic is still the 1929 Warsaw Convention, which restricts considerations of passenger health to the occurrence of accidents. Many aviation regulatory agencies, such as the Civil Aviation Authority (CAA) in the UK, have both a safety and an economic remit [36]; the CAA is indeed mainly financed by the aerospace industry. This situation should not in itself give rise to concern. I.K. Brunel was flatly opposed to government supervision of railways: "[railway engineers] understood very well how to look after the public safety ... they had not only more ability to find out what was necessary than any inspecting officer could have, but they had a greater desire to do it" [37]. Even if Brunel's high principles are rarer today than formerly, no aerospace manufacturer or airline wishes to degrade public safety, for loss of business would quickly result. Only the greed of individual company directors might result in even that basic principle being overlooked [38], for the sake of short-term financial gain. Doubtless there is already considerable industry motivation to prevent fume events, the occurrence of which is hard to deny even if the only consequence is ill health (cf. §5; due to the potential of the tricresyl phosphates to produce paralysis there is also a safety issue). Chronic, low-level exposure is a different matter. Infrequent flyers, which still constitute the vast majority of the flying public, are unlikely to link possible post-flight ill health to neurotoxic exposure and the symptoms of frequent flyers (including aircrew) may only incontrovertibly appear after many years of exposure. Practically the issue can, therefore, be

simply reach out and take the most likely ready-made explanation from the peg and use it, whether it fits the case in point or not." Within the scientific literature on expertise, this is known as the "classic expert's mistake". Experts can often solve a problem rapidly because their past experience allows them to see the similarity between the present problem and a past one. If the problem is completely new, they are no more expert than anyone else ("anyone else" not being the proverbial "man on the Clapham omnibus" but someone possessing a solid and extensive general scientific background). A fairly recent illustration of this is Richard Feynman's identification of the engineering defects that led to the crash of the space shuttle *Challenger* in 1986 [32].

ignored especially since almost any remedial action will involve change (and is, hence, troublesome) and expense. Furthermore, undertaking remedial action will doubtless be perceived by potential plaintiffs as an admission of past guilt.[16] For any manufacturer or airline wishing to innovate in this matter, however, there would be an immediate competitive advantage in offering a healthy cabin environment, which Boeing seems to have realized with its B 787. This aircraft has other merits apart from the lack of bleed air, which is nevertheless one of its most valuable features. Since, however, there are of the order of 10,000 Boeing aircraft with conventional (i.e., using bleed air) cabin ventilation systems still flying in the world, the potential competitive advantage has to be weighed against the admission of liability for having used bleed air in all these older aircraft, which might lead to expensive compensation claims (cf. §5) and new legislation requiring extensive retrofits (although, presumably, the latter will provide substantial business opportunities to whoever provides the hardware).

The position of governments is rather ambiguous. Among their duties is the promotion of the health and well being of their citizens. But this requires revenue. Just as governments heavily tax tobacco, ostensibly to discourage smoking (reinforcing the almost universal statements of the dangers of smoking obligatorily printed on the packets nowadays) but in reality to raise revenue for other activities (which might include the construction of hospitals), governments also heavily tax passenger aviation. Any decline in passenger numbers will diminish these revenues. The aerospace industry, both manufacturers and airlines, is economically very important in Europe and North America. No government would wish to jeopardize it. In the European Union the supremacy of economic principles such as the single market, which aviation strongly supports, is even formally entrenched in its treaties. We see in the views of governments a parallel to the conservativism prevailing in the medical world, and for similar reasons. Changing the status quo is perceived as a threat. It takes effort to move out of or change the direction of the main stream and, besides, the matter is complex and requires hard intellectual effort to properly understand it. Hence, one sees certain views being dogmatically defended with what can only be described as religious fervour, not open to rational counterargument. Despite having an extensive web of health and safety legislation, citizen wellbeing is only one of a great many diverse vested interests. Table 1 summarizes some of the expected viewpoints of the stakeholders.

Table 1. Stakeholder viewpoints regarding aerotoxic syndrome.

Stakeholder	Viewpoint	Reason
Passengers	pro	wish to preserve their health
Aircrew	1) pro	wish to preserve health; want a safer working environment
	2) contra	wish to continue to work; want their employer to remain solvent
Insurance companies	contra	wish to avoid payouts
Regulators[a]	1) pro	wish to fulfil their statutory duty of keeping aviation safe
	2) contra	wish to keep aviation economical
Government	1) pro	wish to keep their citizens safe and healthy[b]
	2) contra	wish to keep home industries profitable
Aerospace industry (conservative and backward looking)	contra	wish to avoid payouts for liability and more expensive construction costs
Aerospace industry (progressive)	pro	see business opportunities in making aircraft safer and healthier; perceive that the long-term survival of the industry demands a solution
Airlines (short-term outlook)	contra	perceive that any admission may lead to payouts and costly retrofitting
Airlines (long-term outlook)	pro	inevitably passengers and aircrew will demand a safe breathing environment

[a] As Bennett [36] has pointed out, aviation regulators are somewhat unusual in that they typically seek to promote both safety and economic health of the industry.
[b] If *at an affordable cost* is added, the opinion of the government may switch from pro to contra.

[16] Here we have a good example of how the concept of Christian forgiveness would enable an impasse to be overcome.

Note that, as already mentioned, some of the most important stakeholders have an ambiguous viewpoint. In the absence of a clear, objective way of assessing risk, and the costs of alleviating it, policy is likely to be made in a correspondingly ambiguous fashion. This points to the advantage of devising an objective and quantitative assessment of the cost:benefit ratio (see §9.2). Objectivity needs to be really strong in order to defend impartiality against attacks. As an editorial in *The Lancet* pointed out some time ago, "all policymakers must be vigilant to the possibility of research data being manipulated by corporate bodies and of scientific colleagues being seduced by the material charms of industry. Trust is no defence against an aggressively deceptive corporate sector" [39].

9. ASSESSING COST:BENEFIT RATIO

Many human activities are dangerous. During the early decades of motoring, commenting on the alarming increase of fatalities, it was remarked that "the general use of automobiles ... seems also to have created a disregard for the safety of others, and even for the value of human life" [40]. By the often slow and fumbling process of trial and error, the regulation of activities such as motoring (and aviation) reaches a compromise between the diverse wills of diverse stakeholders (users and manufacturers of the technology as well as "innocent bystanders"), which continues to evolve.

Nevertheless, one might imagine that in a rational world, once a threat is perceived steps are taken to eliminate it. According to the scheme presented in §1, the causal chain could be broken in a number of places:

Between 1. and 2. By replacing tricresyl phosphates by a non-neurotoxic antiwear agent;

Between 2. and 3. By capturing the noxious substances before they reach the cabin; or by taking the air for the cabin directly from the external atmosphere;

Between 3. and 4. By requiring aircrew and passengers to wear masks or smokehoods;

Between 4. and 5. By ensuring that aircrew and passengers exceeding the safe dose (which depends on genetic constitution) are given appropriate antidotal treatment following a flight;

Between 5. and 6. By correctly diagnosing the neurological (and other) damage and prescribing appropriate remedial treatment.

State 5 in Scheme 1 is the contentious one. Even if only *association* between the environmental condition and the set of symptoms is admitted, however, some remedial action preventing the reaching of that state would be a sensible precaution (i.e., application of the precautionary principle).[17]

The last item in the above list does, however, require some knowledge of the mechanism of the effect, which can of course only be acquired once causation is admitted.

In effect, there are three possible categories of response:

1. Eliminate the cause (the first three items in in the previous list);

2. Treat those affected *post hoc* (the last two items in the previous list);

3. Do nothing.

Although the last item has zero implementation cost, there is a considerable cost burden due to subsequent ill health, partly due to loss of economic activity and partly due to medical treatment, the costs of which are borne by the state in many countries [26]. With that in view, providing masks or smokehoods to all passengers (much as lifejackets are provided at present) might at first sight appear to be the most cost-effective measure that one could take. Nevertheless, it has hitherto not been met with great favour by airlines (or governments) because it is very likely that there would be a significant drop in passenger numbers (and hence taxation revenue) if everyone was required to wear a mask, not so much because of the discomfort but because what is at present knowledge of the health risk of flying held by tiny minority would become widespread and many passengers would react by minimizing the amount of flying they undertook.

Progress in deciding what to do is presently hampered by the lack of a universal quantitative approach to assess the costs and benefits. In the next section the conventional approach will be briefly surveyed, followed by an introduction to the new J-value approach.

9.1 Conventional impact and risk assessment

Impact or regulatory impact assessment (sometimes abbreviated as IA or RIA) has become a requirement in many countries, including the UK, prior to the introduction of any proposal that affects the costs of business or public sector activities. It is a formal process insofar as prescriptions for carrying out the process are published by government, but the prescriptions are typically arbitrarily canonical and do not form part of a logically consequential scheme. Key points (sometimes called "possible stages") are: "development" (definition of the policy, gathering of evidence); "options" (their identification and testing

[17] This is, in effect, also stated by the COT: "it would be prudent to take appropriate action to prevent oil or hydraulic fluid smoke/fume contamination incidents" [9].

through "preconsultation"); "consultation" (with the public, leading to refinement of the options); "final proposal" (in which costs and benefits are more carefully assessed for the preferred option); "implementation"; and "review" (evaluation of actual costs and benefits). One of the main difficulties of the conventional approach is the difficulty of quantifying the benefits. This is one of the specific advantages of the J-value approach (§9.2). The conventional or traditional approach manages quantification by restricting it to an estimate of the costs of failure. These, when multiplied by the probability of failure, give a figure for "expected costs" and if they exceed the cost of implementation of a safety measure, then the measure should be implemented. The temporal basis is typically annual but could of course be longer or shorter, as relevant.

Environmental risk assessment sometimes uses a hypothetical *maximally exposed individual*. In the aviation case, this could be a pilot flying the maximum legally allowed hours and constantly exposed to the highest level of TCP measured (40 μg m^{-3} [5], for normal flights without a "fume event").

9.2 The J-value

The J-value (J) is the ratio of the actual cost of a safety measure to the maximum reasonable cost [41], which will be elaborated upon below. Hence, if (for example) $J = 3$, three times as much is being spent as is necessary (i.e., there is a net disbenefit). On the other hand, $J = 1/3$ indicates that the measure is excellent value for money: up to three times more could be spent on it while still retaining a net benefit. Generally speaking, the actual expenditure $\hat{c}$ on a measure should be straightforwardly available. The main challenge is to determine the maximum reasonable cost.

A human being is a living creature. The ultimate aim of any living creature is survival (in the language of cybernetics, the creature must ensure that its essential variables are in the ranges corresponding to the living state). The ultimate merit of any proposed action can, therefore, be judged according to its impact on survival. If a proposed action requiring expenditure shortens human lifespan, the J-value will necessarily be negative and, therefore, can be rejected without further computions. Most actions are only proposed on the ultimate basis that they will prolong lifespan.

One can take as an example a measure to prevent leakage of radioactive waste from a nuclear power station into the sea [42, 43]. Expenditure is required to design and construct the antileakage works. The prolongation of life can be assessed on the basis of the avoidance of certain cancers that exposure to the radioactive waste induces. Epidemiological data can be used to determine the number of cancers that are thereby avoided, and combined with similar data establishing the mortality rate in order to end up with the number of premature deaths that are avoided through the introduction of the safety measure.

It only remains to put a value on the human life that is thereby prolonged. This is a well documented actuarial problem (e.g., [44, 45]). Rather than using a fixed value, however, the formula Thomas et al. propose [41] makes use of the *life-quality index* Q, defined as

$$Q = G^q X_d \tag{6}$$

where G is mean *annual* income of the group of people being considered (which might be an entire nation or, indeed, the whole world), q is a function of the fraction of time w spent working ("work–life balance"):

$$q = w/(1-w) \tag{7}$$

and X_d is the discounted life expectancy of the group. This function has indeed the anticipated properties that quality of life increases with increasing annual income and with increasing life expectancy.[18] Safety measures have to be paid for out of income G, resulting in a decrease $-\Delta G$, but in return (discounted) life expectancy increases by an amount X_d, and the life quality index changes to a new value $Q + \Delta Q$. Expanding eqn (6) and neglecting higher powers and cross product terms (since ΔG and ΔX_d can be assumed to be small) we obtain after rearrangement [41]

$$\frac{\Delta Q}{Q} = q\frac{\Delta G}{G} + \frac{\Delta X_d}{X_d} \tag{8}$$

the right-hand side of which must be equal to or greater than zero in order for there to be a net benefit, implying that

$$-\Delta G \le \frac{G}{q}\frac{\Delta X_d}{X_d}; \tag{9}$$

the total cost of the measure is then $X_d \Delta G$. The annual cost c for a population of size N is $-N\Delta G$, the minus sign signifying loss of income. Using eqn (9) to eliminate ΔG, we obtain

$$c = \frac{NG}{q}\frac{\Delta X_d}{X_d}, \tag{10}$$

which is our measure of "maximum reasonable cost". Recalling our original statement of the definition of the J-value,

$$J = \hat{c}/c\,, \tag{11}$$

[18] The literature suggests $w \approx 1/8$, implying $q \approx 0.14$. Thomas et al. [41] found their results to be insensitive over $0.12 \le q \le 0.2$.

which expands to

$$J = \frac{\hat{c}qX_d}{NG\Delta X_d}. \qquad (12)$$

9.3 Application to aviation

Table 2 sketches out input for computing and comparing J-values for the various options suggested at the beginning of §9.

Table 2. Input for J-value calculation.

No	Action	F[a]	Cost	Benefit	J[b]
0	None	8	high	low	> 1
1	Replace TCP by a non-neurotoxic antiwear agent	6	low	high	< 1
2	Capture noxious substances before they reach the cabin	4	high	moderate	> 1
3	TCP sensors	4	high	high	~ 1
4	Take air for the cabin directly from the external atmosphere	8	high	very high	< 1
5	Require aircrew and passengers to wear masks	7	low	moderate	< 1
6	Screen aircrew and passengers	6	high	high	~ 1
7	Correctly diagnose neurological damage and prescribe appropriate treatment	5	high	high	~ 1
8	Place a warning statement on airline tickets—*caveat emptor*	7	very low	low	< 1

[a] Estimate of feasibility on a scale of 0 (reckoned to be completely unfeasible) to 10 (technically feasible and could easily be implemented).
[b] Indicative estimate of the J-value based on cost/benefit.

Here is some explanation for the entries in Table 2. Although option 0 appears easy to implement the main obstacle is the growing criticism of present inaction from aircrew, frequent flyers, scientists, medical doctors and others. Having $J > 1$ should rule it out. Option 1 is presently the subject of active research and development. If all organophosphates can be eliminated from gas turbine lubricant, one may nevertheless be left with some pyrolysed lubricant base stock that has previously been shown to be toxic [46]. Option 2 appears feasible but research into the specific problem of TCP capture (and possibly the capture of pyrolysed lubricant base stock) is still needed, hence there is no technical solution immediately ready for implementation. Besides, it is inadequate on its own: sensors (option 3) would be required to guard against capture malfunction. Option 3 is long overdue. If the fitted devices are sensitive enough, they can be used as indicators of incipient oil seal failure, signalling the need for prompt maintenance—although "sensitive enough" needs to be qualified by awareness that for some particularly susceptible individuals there may be no safe threshold for TCP exposure.

Sensors would also allow the captain to shut down any malfunctioning bleed air inlet ("malfunctioning" is used on the premiss that a perfectly functioning bleed air system would contain no TCP or other toxic substance at all; it is not certain whether this is practically realizable). There is a plethora of candidate sensing devices that have been invented in research laboratories; they need to be assessed and adapted for TCP detection. Option 4 seems to be the optimal solution. The Boeing 787 demonstrates its feasibility. The extra weight required by the dedicated compressors is offset by the ultralight composites used to build the airframe. Option 5 is a very simple solution, but the efficacy of any mask or smokehood deployed would need to be properly tested. Genetic screening (option 6) for susceptibility to TCP poisoning has long been feasible and the cost is becoming low enough for it to be routinely applied to all passengers, who would only need to be tested once in their lifetime. As a consequence, some people might be advised not to become pilots or flight attendants, or fly in any aircraft using bleed air cabin pressurization. This option, therefore, presupposes that having a substantial proportion of the population (possibly tens of percent) unable to fly would be acceptable. Option 7 needs to be implemented in any case for all those who are already suffering the consequences of inhaling TCP. On the basis of the maxim "prevention is better than cure", however, it cannot be considered as a general solution. Option 8 has the lowest possible cost associated with its implementation, no technical barrier, and the experience of placing similar statements on

cigarette packets is to hand for assessing the likely consequences.

Note that the J-value approach uses averages and considers an entire country or supranational entity. It does not—at its present level of approximation—consider on which specific sectors the costs fall and to which sectors the benefits accrue. National solidarity is assumed. There is nothing in the principle of the approach to prevent more detailed consideration of reality, however. Whether to do this is, however, a political decision, rather like a policy of compulsory medical insurance that, in effect, gets healthy members of the population to pay for their weaker brethren.

10. CONCLUSIONS

The association between the presently used highly effective antiwear additives in jet engine lubricant, tricresyl phosphates, which are known neurotoxins, and the deleterious health effects on pilots and cabin crew and passengers, who are chronically exposed to low levels of the substances whenever they are on board an aircraft, seems strong enough to be able to accept causation. Knowledge advances by the formulation of such hypotheses, which can then be scrutinized more and more strictly. Blanket denial of causation, as presently practised by several official agencies, can well be called intellectual Luddism: it is retrogressive and effectively prevents remedial action. While there is still useful research on the issue to be done, enough is already known to be able to make sensible decisions on what action to take. The J-value approach to cost–benefit analysis is commended as a rational basis for such decisions.

Until now most attention has been focused on *fume events* in *flight*. This is understandable given the legal framework (the Warsaw Convention) within which aviation operates. Low-level chronic exposure is, however, probably of much greater significance for health and possibly even for safety.[19] Furthermore, contamination (both low-level, through normally operating oil seals, and due to fume events) may come from the auxiliary power unit (APU), which is simply a small gas turbine, from which air is also bled, used while the aircraft is on the ground. The contribution of the APU to the problem, while well documented anecdotally, appears to have been overlooked so far in the supposedly comprehensive investigations. Low-level chronic exposure puts the "TCP in aircraft cabins problem" on a par with other widespread environmental hazards such as asbestos, radioactivity, halocarbons, polychlorinated biphenyls and tetraethyllead. All these cases have certain common features, such as early observations, or laboratory experiments, of the mechanism of harm, large-scale industrial production, extensive observations (since, because of industrial production, the hazard became widespread), regulation and, ultimately, elimination. In each case the timescales for the overall cycle have been long with respect to human generation time—of the order of a century. Given that knowledge of the problem of TCP (and oil pyrolysis substances) in aviation has been around for 50 or 60 years, one hopes that it will not take another 40 or 50 for the problem to be eliminated.

Note added in proof: Flight Attendant Turner "was a seated passenger" on the flight during which a fume event occurred (ref. 27, ¶22; cf. §4.3 including footnotes 10 and 11). The author thanks Capt. John Hoyte for having pointed out this detail to him.

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[19] The two are linked insofar as low-level chronic exposure may sensitize the person thus exposed to react more adversely than otherwise to a high-level acute exposure as in a fume event.

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