1. HISTORY

The history of the toxic effects of organophosphates (OPs) goes back to the 1920s and in the UK a significant landmark was the report by the Government’s then Chief Scientific Officer, Sir Solly Zuckerman, in 1951 [1]. This report, concerned principally with the spraying of OPs in the farming industry, drew on expert testimony from the Medical Research Council about the mode of action and dangers to man of OPs and identified the following as major issues:

- Successive small doses ... may progressively lower cholinesterase levels without producing symptoms ... rendering individuals increasingly susceptible to further doses.
- Owing to the slow restoration of cholinesterase to its normal level, this susceptibility will persist for a long time, maybe for some weeks.
- Chronic toxicity and cumulative poisoning may result from repeated absorption of parathion.
- Routes of absorption comprehensively recognized as inhalation, dermal and ingestion.

and made these recommendations:

- Working periods to be limited to not longer than 10 hours per day and not more than 6 days per week.
- Supervision providing instruction for employees is essential.
- Precautions to include warnings to general practitioners and hospitals in areas where spraying is being undertaken.
- Protective clothing should be worn.

All this advice has been honoured more in the breach than the observance. The use of OPs has been extended with almost total disregard to those warnings despite a number of inquiries into the adverse health effect on farmers after long delays and the Government’s enforcement of OPs in sheep dips. Many OPs have, however, been withdrawn from use [2].

Initially, because of the well known action of OPs as inhibitors of acetylcholinesterases (AChEIs), which control cholinergic transmission at nerve synapses, most early studies were concerned with AChEs and the closely related butyrylcholinesterases (BuChEs), which occur mainly in blood plasma. Other serine enzymes have now been identified that are more sensitive to OPs. These include:

- Paraoxonase, PON1, which protects against atherosclerosis and occurs in plasma and the liver [2–7].
- Neuropathy target (toxic) esterase (NTE), which hydrolyses lysophospholipids in the brain [8].
- Acylpeptide hydrolase (APH), which plays key rôles in the brain and other tissues [9, 10].

A range of novel proteins in the brain were reported to be very sensitive to OPs [11]; the senior author of that paper has served as a member of the Government Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) and despite changes in the membership and chairmanship COT has continued to resist any recognition of the biomedical effects of OPs, especially tricresyl phosphates in aerotoxic syndrome (AS). Abou-Donia has reviewed the chronic toxicity of OPs [12]. A disturbing development in passenger welfare is the recognition that three separate studies now link brain development to OP exposure in utero (reviewed in [17]; this work has recently been extended [18]).

2. THE EVIDENCE

Much has already been accumulated and extensively reported and summarized by Michaelis in her Manual [13] and recent PhD thesis [14]. Estimates of enforced retirement among pilots flying the BAe 146 were reported in one survey as 7.4% with some 25% of cabin crews and pilots reporting significant symptoms [13, 14]. Small numbers of passengers are also reporting AS symptoms (see Furlong’s paper1).

New studies were reported at this conference by Passon2 showing up to 25% long term sickness among those completing the survey and including high levels of cancers, peripheral neuropathy and sarcoidosis. Such studies are easy to dismiss for a variety of reasons: small

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1 Emeritus Professor of Medicinal Chemistry, University of Sunderland. E-mail: hooperseundus@talktalk.net
2 This issue, pp. 201–207.
numbers, self-selecting group etc.) but they do provide hard evidence that contradicts the assertions of all official groups, including aerospace and insurance company doctors and unions, government representatives, panels and committees. In the Lawrence\textsuperscript{3} case there appear to be sound grounds for legal action and significant compensation claims for mistreatment and false diagnosis and an appalling failure of the duty of care. The Boeing compensation award to the air hostess Terry Williams [15] for the effects of her exposure to contaminated cabin air may well be the tip of an iceberg [16] that will comprehensively expose the failures of all those groups responsible for the health and welfare of pilots, cabin crews and passengers. The issue of cabin air is now being raised in hard-hitting TV documentary programmes shown in Germany.\textsuperscript{4}

The unwillingness of Government to accept any of these studies and reports as a basis for funding larger studies is incomprehensible and suggests a blind ideology linked to callous and inhumane attitudes that only serve to protect a wide variety of vested interests.

Many have seen the development of the Boeing 787, which takes air for the cabin directly from outside, as tacit admission by the industry that the problem of cabin air contamination is part of a fundamental design flaw in all current commercial aircraft [19].

The common feature of all these conditions is that despite the obvious complaints and disabilities of sufferers, routine blood test results are usually normal. The reluctance of physicians and others to engage with these complex conditions has lead to a great division between those who find sound experimental and investigative evidence for underlying biomedical damage and defects and those who seek to assert that they are somatiform (i.e., psychiatric/psychological) in origin and label them accordingly. This approach has been applied across the board by some psychiatrists [22] (Table 1).

Table 1. Functional somatic syndrome labels for chronic, complex conditions and syndromes.

<table>
<thead>
<tr>
<th>Functional somatic syndromes: one or many? [22]</th>
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<tbody>
<tr>
<td>Gastroenterology</td>
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<td>Gynaecology</td>
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<tr>
<td>Rheumatology</td>
</tr>
<tr>
<td>Respiratory medicine</td>
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<tr>
<td>Infectious disease</td>
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<tr>
<td>Neurology</td>
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<tr>
<td>Dentistry</td>
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<tr>
<td>Allergy</td>
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| Key: IBS, irritable bowel syndrome; PMS, premenstrual syndrome; PVFS, postviral fatigue syndrome; TMJ, temporal mandibular joint; ENT, ear, nose and throat; MCS, multiple chemical sensitivity. |

- Lack any basic similarity to known mental disorders (i.e., they are outside of current mental health paradigms).
- Convert firm knowledge into speculative assertions without any critical voices being heard.
- Those postulating them typically use evasive arguments and have a lamentably poor record of research into causes, particularly where biochemical and environmental factors are concerned. Furthermore,
- Industrial/Government/commercial/insurance interests seem to be actively influencing the course of what is ostensibly a scientific discussion. [20, 21, 23–25]. There is ample evidence of inappropriate diagnoses.
and mistreatment that leads to serious mental and physical illness in those suffering from such conditions [26–29].

A prominent medical spokesman for the industry firmly aligns himself with the somatoform/psychiatric view of aerotoxic syndrome when he states [30]

The symptoms attributed to cabin air exposure are “similar to those seen in a wide range of conditions, including chronic fatigue syndrome, Gulf War syndrome, Lyme disease, chronic stress and chronic hyperventilation.”

This statement betrays some ignorance and obfuscation of the nature of AS by using terms that are inexact and confuse rather than clarify. Lyme disease should read chronic Lyme disease, which is associated with ME-like symptoms [31] and affects only a small proportion of those who contract Lyme disease, usually readily treated with established antibiotics. The use of the misleading term “chronic fatigue syndrome” rather than the more established “myalgic encephalomyelitis” (classified as a neurological condition by the WHO) gratuitously belittles the illness called ME, as fully explained by Hyde and others [27, 32].

The attempt to claim that hyperventilation is responsible for the chronic and progressive illness suffered by so many sick cabin crew and pilots defies the evidence, which includes paralysis and loss of physical and cognitive functions that persist long after the precipitating event and in some cases gives rise to an excess of severe neurological diseases such as Parkinson’s Disease (PD) and motor neuron disease (MND, also called Lou Gehrig disease in American literature on Gulf War illness/syndrome) as well as some cancers.

4. THE SCIENCE

Major scientific presentations made at the Workshop further established the adverse biomedical effects of organophosphates, particularly tricresylphosphates, known to be present in jet engine oils.

Figure 2 summarizes five independent strands of advanced biomedical evidence from internationally acknowledged experts that all point to conclusive evidence that OPs have serious acute and chronic effects.

The chemistry of the reaction of cresyl saligenin phosphate with the active site of cholinesterases has now been published [33] and undergirds the investigations of Furlong who, in a series of papers, developed a specific assay for the identification of key enzymes affected by OPs that are “decorated” with TCP molecules [34]. A blood test has been developed that can be used immediately after any “fume event” to show unambiguous and specific exposure to TCPs. Professor Furlong reported a similar study with the more sensitive acyl peptide hydrolyase (APH), present in mouse and human brains.

All Furlong’s work is in agreement with wider enzyme studies, especially on paraoxonase (PON1), associated particularly with GWS/I. OP pesticides and pyridostigmine bromide (another AchEI) have been causally linked to GWS/I [7]. Using advanced imaging techniques, Haley and colleagues have identified hippocampal dysfunction associated with regional changes in cerebral blood flow and paradoxical changes in response to cholinergic challenge in sick Gulf War veterans [35]. This test provides diagnostic evidence for profound and extensive damage to the central nervous system following exposure to acetylcholine esterase inhibitors (AchEIs). The hippocampus is particularly associated with memory processes, which are reported as dysfunctional in people with AS.

Using well established tests Mackenzie Ross showed how some neuropsychiatric processes are damaged by low-level exposure to OPs and, building on her recent paper [36] dealing with farmers exposed to OPs, found similar deficits in memory, response speed, fine motor control, mental flexibility and strategy-making in sick pilots even after controlling for the effects of mood. Anxiety and depression were badly affected.

Whilst fuller studies are needed it is apparent that there is little funding for such work, the results of which look as though they would completely destroy the official commitment to the psychiatric understanding of AS and related conditions.

Figure 2 also draws attention the work of Abou-Donia and his colleagues, which has demonstrated that synergistic effects of disparate compounds can arise when mixtures of chemicals are present [25, 37, 38]. This exposes the fallacy that individual exposures to chemicals
judged to be below the threshold of toxic effects measured for a single compound provide sound grounds for claiming that exposures in complex mixtures of chemicals such as those found in engine oils, lubricants and antifreeze are “safe” provided the individual compounds are individually present below those thresholds.

Furthermore, the old paradigms in toxicology are no longer valid (Table 2). In particular, many modern dose–response curves are not monotonic; they have an inverted U-shape indicating that the compound may be active at concentrations below the threshold of the linear régime (Figure 3, and briefly reviewed in [25]). Such unexpected responses are outside the old toxicological models used to assert that threshold values of individual compounds pose no threat to human health. This is now known not to be the case and the industry needs to take cognizance of these new aspects of toxicological science and undertake more rigorous studies in the light of this information.

Table 2. Changes in toxicology paradigms.

<table>
<thead>
<tr>
<th>Old</th>
<th>New</th>
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<tbody>
<tr>
<td>High level contamination overwhelms detoxification and other defence mechanisms</td>
<td>Low level contamination hijacks control of development</td>
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<tr>
<td>“The dose makes the poison”</td>
<td>Non-monotonic dose–response curves are common, in which low level exposure causes effects that disappear at higher levels</td>
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<tr>
<td>Only high levels of exposure matter</td>
<td>Impacts caused at what had been assumed to be “background” levels</td>
</tr>
<tr>
<td>Focus on adults</td>
<td>Periods of rapid growth and development (prenatal through puberty) are most sensitive to exposure</td>
</tr>
<tr>
<td>A small number of “bad actors”</td>
<td>Many chemicals formerly thought safe are biologically active and capable of interfering with signalling systems</td>
</tr>
<tr>
<td>Immediate cause and effect</td>
<td>Long latencies are common; fetal programming can lead to disease and disabilities decades later</td>
</tr>
<tr>
<td>Examine chemicals one compound at a time</td>
<td>In real life, mixtures are the rule. They can lead to effects at much lower levels than indicated by simple experiments with single chemicals. Synergy is significant</td>
</tr>
<tr>
<td>Focus on traditional toxicological endpoints like mutagenesis, carcinogenesis, cell death</td>
<td>Wide range of health endpoints, including immune system dysfunction (both hyper- and hypo-activity); neurological, cognitive and behavioral effects; reproductive dysfunctions; chronic diseases</td>
</tr>
<tr>
<td>One-to-one mapping of contaminant to disease or disability</td>
<td>Same contaminants can cause many different effects, depending upon when exposure occurs during development and what signals it disrupts. Multiple contaminants can cause the same endpoint if they disrupt the same developmental process</td>
</tr>
</tbody>
</table>

Figure 3. Very low dose effects below the linear dose–response threshold.

A further important contribution from Abou-Donia’s group is the identification of autoantibodies to internal proteins from damaged neurones; the antibodies are released following OP exposure [39]. This test provides unequivocal evidence of a neurotoxic exposure and is used by sick pilots and cabin crews seeking to, demonstrate the validity of the link between their neurological illnesses and their OP exposure, understand their sickness and support their claims for compensation.

Mulder described his important work of collecting real-time exposure data from pilots, cabin crews and passengers. By careful consideration of the biochemical pathways associated with the production of key neurotransmitter molecules he has also devised a treatment protocol that many sick cabin crew and pilots are finding useful to alleviate some of the worst symptoms.

5. THE POLITICS, REGULATORS, VESTED INTEREST AND DEMOCRACY

Government policy seeks and funds research to provide policy-based “evidence” that is in tune with its predetermined aims. These aims are in turn influenced by lobbyists for the aero industry, the insurance industry and
Government departments such as the UK Department for Work and Pensions (DWP), which is responsible for sickness benefits. Evidence based on independent science and medicine is ignored or belittled. It has been admitted that government funds research to support policy [40]. This is evident in the funding for large experimental studies that have failed to address the question of cabin air contamination or, as in the latest Cranfield study [41], have carried out studies that are at best tangential to the problem. This latter study was very heavily criticized as bad science lacking the necessary rigour to properly address the questions associated with cabin air contamination.

The other ploys used by the industry and regulators is to manufacture doubt [42] and call for ever more experiments that avoid addressing head-on the question—in this case of cabin air contamination.

The cryptic phrase “human sacrifice—road speed” in the title of this presentation points to the willingness to sacrifice human life and health in the interests of economics and profit. A proposal of the present UK Government is illustrative: for (unspecified) economic gain, the maximum speed limit on major roads should be raised from 70 to 80 mph [43], which will give rise to an estimated 20% increase in road deaths [44]. In the same way the health and well being of pilots and cabin crews are being sacrificed at the behest of economic gain and vested corporate interests. Susceptible aircraft passengers are being similarly sacrificed. It is advisable to listen to the economists who have challenged the view that “economics is king” and must be served at whatever cost [45, 46]. Vested interests and their pressure groups, both of which are outside the democratic processes of government, must be exposed even if, as recently, they involve government departments such as the UK Department for Work and Pensions (DWP), which is responsible for sickness benefits. Evidence based on independent science and medicine is ignored or belittled. It has been admitted that government funds research to support policy [40]. This is evident in the funding for large experimental studies that have failed to address the question of cabin air contamination or, as in the latest Cranfield study [41], have carried out studies that are at best tangential to the problem. This latter study was very heavily criticized as bad science lacking the necessary rigour to properly address the questions associated with cabin air contamination.

The Workshop has presented incontrovertible and overwhelming scientific evidence in support of AS that must be acted upon immediately by governments, regulators and all other agencies involved in order to prevent further chemical poisoning of pilots, cabin crews and passengers. This goal could be achievable in present aircraft by retrofitting appropriate filters in the ducts bringing air from the engines into the cabin. At the very least, some kind of contamination monitoring devices should be retrofitted. The Boeing 787 has already demonstrated the essential changes needed in future aircraft design. Furthermore, truth and justice demand that support for sick pilots, cabin crews and passengers should be given without argument or delay.

ACKNOWLEDGMENT

The author thanks Professor Vyvyan Howard for having provided Fig. 3.

REFERENCES


6 The Bill “could benefit Djanogly ‘in multiple ways’... the Justice Minister piloting controversial plans to cut legal aid and curb payouts—a move that could benefit the insurance industry by £1 billion per year... Has investments of at least £1/4 million... as a minority partner in family firm of insurance underwriters” [47]. He “failed to declare that his children were minority shareholders in his brother-in-law’s businesses... which advertise ‘no win, no fee’ compensation claims” [48]. “Justice minister... criticised for not declaring relative’s company which supplied staff to industry he regulates” [49].


29. Voices from the Shadows. This powerful testimony to medical misdiagnosis and neglect illustrates the desperation of those suffering from complex and chronic illnesses like ME and AS and the neglect of many by modern clinicians. http://voicesfromshadowsfilm.co.uk


40. Hansard 11th May 2000: 461W- 462W The Office of Science and Technology monitors all government funding of research grants and controls official science policy and it is “policy” which determines the research which is funded: “The Department funds research to support policy”. Quoted in Marshall, E.P., Williams, M., Hooper, M. What is ME? What is CFS? Information for Clinicians and Lawyers (December 2001). http://www.ahummingbirdsguide.com/wmarwillhoopwimewicfs.htm


