Chris Winder, editor

BALPA Contaminated Air Protection: Air Safety and Cabin Air Quality International Aero Industry Conference

Proceedings of the BALPA Air Safety and Cabin Air Quality International Aero Industry Conference. Held at Imperial College, London, 20-21 April 2005

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Reports in Safety and Environmental Science
School of Safety Science, The University of New South Wales
August 2005

UNSW SYDNEY·AUSTRALIA

Chris Winder, editor. **Contaminated Air Protection: Proceedings of the Air Safety and Cabin Air Quality International Aero Industry Conference**, held at Imperial College, London, 20-21 April 2005. Published by the British Airline Pilots Association (BALPA) and the School of Safety Science, University of New South Wales, Sydney NSW 2052, Australia, August 2005.

Cost: £25-00 or Aus$55-00 including tax.

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ISBN 0-7334-2282-9

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FOREWORD

Chris Winder[†] **Chris van Netten**[‡]

In December 2000, an International Aviation Air Safety Symposium was held at the Australian Defence Force Academy, Canberra. The symposium was held because aviation air quality had emerged as an occupational health and aviation safety issue (particularly in respect of health problems arising from oil and hydraulic fluid entering the ventilation system of the flight deck and passenger cabin of commercial aircraft (that is, bleed air contamination)). The symposium followed on from the 1999–2000 Australian Senate Inquiry into cabin air safety in the BAe 146, and was held while other inquiries were also looking into this matter (notably, the United Kingdom House of Lords inquiry).

The proceedings of the 2000 symposium (published in 2001) were groundbreaking in many ways because the symposium had examined a variety of environmental exposures and health effects of flight crew members that had not been considered to be part of mainstream aviation.

A great deal has happened since 2000. It is therefore timely that this matter be re-examined, the latest findings reviewed, and feedback from the various stakeholders obtained. The recent Contaminated Air Protection Conference (called for by UK members of parliament, Paul Tyler (now Lord Tyler) and John Smith) focused on past and present research/inquiries into a number of relevant issues, for example, contaminated bleed air, the medical effects being seen in aircrews and passengers, the ways to detect contaminants, the latest medical and scientific thinking on the medical aspects of exposure, the number of exposure events, the filtration technologies available to remove bleed air contaminants, and so on.

The conference was held at Imperial College, London, on 20–21 April 2005. It was sponsored by the British Airline Pilots Association (BALPA), and co-sponsored by Pall Corporation (a manufacturer and supplier of cabin air quality filtration systems), Sofrance (a manufacturer and supplier of filtration and depollution technologies), and the Aviation Organophosphate Information (AOPIS; a website and information resource); it was coordinated by Neil Stewart Associates.

Aviation air quality has been called an "issue" - but calling something an issue just buries it. Poor air quality in some types of aircraft is a problem. The

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word "problem" has negative connotations but is a true reflection of the experiences of aircrew who have to ensure their own safety, and that of the passengers, when exposed to contaminated air while flying.

The attached papers are the presentations made at the Conference. In all, a breadth of topics was presented, and a wide range of issues explored.

The political dimension of this problem was covered at the conference by the presentations of two parliamentarians, Paul Tyler of the UK House of Commons and the Reverend John Woodley, former Senator for Queensland in the Australian Senate and Chair of the 1999–2000 Senate Inquiry into cabin air quality in the BAe 146. Both remained unconvinced by the activities of aviation regulators and the aviation industry as a whole to properly recognise the importance of the problem.

The toxicological dimension of the problem was addressed by two researchers who have been working the longest on aviation air quality from oil leaks, that is, Professor Christiaan van Netten of the University of British Columbia and Associate Professor Chris Winder of the University of New South Wales. One jet oil used extensively in aviation contains ingredients that are known to cause irritation, sensitisation and neurotoxicity. Exposure to mists and vapours from that oil induces symptoms of irritation, sensitisation and neurotoxicity. The symptoms have occurred on a number of aircraft (the MD-80, the BAe 146, and the B757, to name a few) and seemed consistent enough to suggest a specific condition. While significant underreporting of "exposure events" has occurred, the numbers that have been reported were sufficient to warrant much closer attention. The chemicals involved (known ingredients of jet oils) were the neurotoxic tri-cresyl phosphate, the sensitiser phenyl-alpha-naphthylamine, and the environmentally toxic dioctyldiphenylamine, as well as a wide selection of volatile organic compounds and thermal degradation chemicals that are present in the air during exposure events. Professor Vyvyan Howard from the University of Liverpool focused on possible effects on the developing foetus and made the point that, while there were data gaps, any competent risk assessment would indicate that a prudent, precautionary approach is needed.

The medical dimensions of these problems were addressed by a number of physicians who treated flight attendants and pilots after bleed air incidents. Professor Malcolm Hooper of the University of Sunderland drew similarities between the problems of exposed aircrew and other groups with similar problems, such as organophosphate-exposed farmers or Gulf War veterans. Professor Robert Haley of the University of Texas Southwestern Medical Center used the United States experience with Gulf War Syndrome to illustrate the pitfalls and lessons to be learned when attempting to resolve conditions where chronic but non-specific fatigue, pain and cognitive symptoms arise.

Two physicians working in Western Australia, Dr Moira Somers and Dr Andrew Harper, reported on the cases they had seen, that is, 39 and 60 crew

members, respectively. They reported a striking similarity between exposures, symptoms and outcomes. Dr Harper went a step further and subjected his findings to *Bradford-Hill's Criteria of Causation*, considered a cornerstone of the process of establishing causation. He found them to be in agreement, thereby removing one criticism of the medical findings to date (that the medical findings did not meet criteria for causation). Dr Gunnar Heuser, who works in California, reported his findings in 26 flight attendants using physical and neuropsychological examinations, as well as a PET (Positron Emission Tomography) and SPECT (Single Photon Emission Computed Tomography) functional brain scans. His study found significant abnormalities and arrived at a diagnosis of toxic encephalopathy in all cases. Dr Jonathon Burdon and Dr Allan Glanville, respiratory physicians working in Melbourne and Sydney, provided evidence of the respiratory problems in fourteen BAe 146 aircrew who had been exposed to oil mists and vapours. All of these doctors agreed with industry statements that there were short-term effects from exposure to these vapours and mists but, for the first time, their presentations confirmed the existence of long-term, that is, chronic (continuing for longer than twelve months), effects.

The psychological dimension of the problem was addressed by neuropsychologists from Australia and the UK. Dr Sarah Mackenzie Ross of University College, London, reported on the cognitive disabilities in 25 agricultural workers exposed to organophosphate pesticides. Dr Peter Julu and Dr Goran Jamal of Imperial College, London, also reported on their work that looked at organophosphate exposure in sheep dippers. They found that a unique pattern of autonomic dysfunction is part of long-term neurological sequelae of acute organophosphate intoxication or repetitive low-level exposure to the compounds and noted a similarity with pilots tested to date. Leonie Coxon, a clinical and forensic psychologist from Western Australia, reported on her research in workers who are occupationally exposed to neurotoxicants. These workers included eight aircrew flying on the BAe 146 who showed significant cognitive deficits in standardised neuropsychological testing. Professor Abou-Donia of Duke University, Durham, North Carolina has been investigating the toxicity of organophosphorus compounds for over thirty years and provided a wide-ranging review but, most particularly, a description of the condition of organophosphorus ester-induced chronic neurotoxicity, which is characterised by long-term, persistent, chronic neurotoxicity symptoms in individuals who have been exposed to long-term, low-level, sub-clinical doses of these chemicals.

Two papers covered the military aspects of this problem. Dr Bhupinder Singh of the Royal Australian Air Force Institute of Aviation Medicine reported on air leaks in Australian Defence Force aircraft, sources of smoke and fumes, and aircrew protective systems. He also discussed RAAF guidelines for the medical management of exposed aircrew. Dr Wally Masurek of the Australian Defence Science and Technology Organisation reported on contaminant levels in military aircraft. Tri-cresyl phosphate, phenyl-alpha-naphthylamine and dioctyldiphenylamine have been detected in these aircraft, albeit at low levels. Additionally, Professor Christiaan van Netten has detected tri-cresyl

phosphate in swab samples from commercial aircraft, including a sample from a pilot's trousers.

The way forward was also discussed at the conference. Dr Byron Jones of Kansas State University discussed the development of American Society of Heating, Refrigerating and Air-Conditioning Engineers standard 161P for *Air Quality Within Commercial Aircraft*, now available for public comment. Karen Bull of Pall Aerospace discussed the latest technologies for air filtration systems on commercial aircraft. Pascal Contini, from the Sofrance-Snecma Group, discussed how carbon fibres might assist in filtering and treating contaminated air. Stuart Calwell, an attorney from West Virginia, examined some of the legal issues that might arise if injured aircrew were to challenge their employers over exposure to jet oil mists and vapours and their consequent health effects.

Due to the problems associated with carrying sample collection equipment on aircraft, Professor Christiaan van Netten has developed a tiny gas sampler which can be taken on aircraft and used during exposure events to collect air contaminants which can be analysed later. Professor Clem Furlong of the University of Washington has suggested that the study of the normal genetic variability in human populations through toxicant specific biomarkers may provide better answers with regard to toxic exposures and their effects. As such, he has developed a briefcase-sized surface plasmon resonance biosensor system which is capable of detecting airborne toxicants. Dr Laurel Kincl of the University of Oregon discussed the Occupational Health Research Consortium in Aviation research project, which is divided into four components: incident reporting, incident monitoring, sampling feasibility study and ongoing surveillance study. The Aviation Secretary at the International Transport Workers Federation, Ingo Marowsky, restated the need for better maintenance and operating procedures. Finally, BALPA General Secretary Jim McAuslan reflected on the conference findings: there is a problem and it is causing short *and* long-term health effects in aircrews. The problem is happening in the workplace (that is, on aircraft). In spite of the substantial underreporting of bleed air incidents, the problem is already highly significant. Crew and passengers are at risk. With the right will, the problem can be fixed.

Although the conference was organised by a pilot's union, it was poorly attended by the airlines and aviation regulators - which was a pity. Their absence reinforced the feeling by the conference participants that these organisations remain in denial about the aviation air quality problem. To date, the aviation industry has attempted to deal with these problems reactively and somewhat flexibly, as reflected by its response statements to the emerging body of evidence:

- "There are no engine oil leaks."
- "There may be some engine oil leaks, but they are very uncommon."
- "There are more than a few engine oil leaks than we would like, but the oil is safe under normal conditions of use."

- "The oil may contain hazardous ingredients, but not at levels that affect the health of crew."
- "The health problems being reported by our workers are not related to the leaks."
- "If there are health problems, they are related to some other health condition."
- "There may be a few health problems from exposure to oil leaks, but they are transient or mild, and are reversible."

Somewhere in this sad litany of statements comes the crossover from "spin" to reality. Where the contamination of air in flight decks and passenger cabins occurs, or where it is sufficient to cause symptoms of discomfort, fatigue, irritation or toxicity, this contravenes the air quality provisions of aviation design regulations, which date back to the mid-1960s and which every nation adheres to. The current US Federal Aviation Regulation 25.831 states:

> *"Under normal operating conditions and in the event of any probable failure conditions of any system which would adversely affect the ventilating air, the ventilation systems must be designed to provide a sufficient amount of uncontaminated air to enable the crew members to perform their duties without undue discomfort or fatigue and to provide reasonable passenger comfort."*

And

> *"Crew and passenger compartment air must be free from harmful or hazardous concentrations of gases or vapors."*

Similarly, when suggestions such as having a lower pressurisation level in aircraft or building aircraft that do not need bleed air are made, experts in the aviation industry protest and proclaim that it cannot be done. Nevertheless, the new Boeing 787 "Dreamliner" proves them wrong. The sales pitch for this new generation of aircraft notes that it has "no engine bleed systems architecture" and that passengers will get a better experience because of a lower cabin altitude, that is, at 6,000 ft (1,800 m) instead of 8,000 ft (2,400 m).

The Contaminated Air Protection Conference has established that exposure to oil mists and vapours on aircraft constitutes a serious hazard to aircrew and passengers and is capable of producing long-term health problems: the effects are not "just transient or reversible". It's time for aircraft manufacturers and operators to stop pretending that aviation air quality is not important and to join the vision of at least one aircraft manufacturer that has addressed these issues in its latest design. The challenge, at present, is to expand this vision to the already existing fleet of aircraft.

The following conclusions were distilled from the conference:

- There is a workplace problem resulting in acute and chronic illness (among flight and cabin crew).
- The workplace in which these illnesses are being induced is the aircraft cabin environment.

- This problem is resulting in significant flight safety issues, in addition to unacceptable health implications for aircrew.
- Passengers may also be suffering from similar symptoms.

The conference organisers and the editor would like to thank all presenters and participants at the symposium for their participation in the conference and preparation of these proceedings.

August 2005

CONFERENCE PROGRAM

Contaminated Air Protection Conference, Imperial College London 20-21 April 2005

20 April 2005: Day 1

9:15 am Registration and Refreshments

9:40 am *Introductory Remarks* – Jim McAuslan, Secretary, BALPA

Chair: Julian Soddy, Former RAF Test Pilot, BBC Presenter, BALPA member

Session One

9:50 am *Opening Speech* – Paul Tyler, MP CBE, Chair All Party Organophosphate Parliamentary Group, London, UK

10:05 am *Data Review of Instances of In Cabin Fumes from Propulsion System Events* – Ann Azevedo, Chief Scientist and Technical Advisor for Aircraft Safety Analysis, US Federal Aviation Authority, USA

Paper withdrawn at request of author and not included in these proceedings

10:30 am *Hazardous Chemicals on Jet Aircraft* – Chris Winder, Associate Professor in Applied Toxicology, The University of New South Wales, Sydney, Australia

10:55 am Questions and Discussion

11:10 pm Morning break

Session Two

11:40 am *Mode of Action of Developmental Toxicological Consequences* – Dr C Vyvyan Howard, Head of the Developmental Toxicol-Pathology Research Group, University of Liverpool, Liverpool, UK

12:00 pm *Illness Related to Cabin Air: A Survey of Symptoms and Treatment Among Commercial Pilots and Cabin Crew* – Dr Andrew Harper, Occupational and Public Health Physician, Perth, Australia

12:25 pm *Lung Injury Following Hydrocarbon Inhalation in Aircrew* – Dr Jonathan Burdon, Respiratory Physician, former President of the Thoracic Society of Australia and New Zealand, 2001-03, Melbourne, Australia

12:50 pm Questions and Discussion

1:05 pm Lunch

Session Three

2:05 pm *Organophosphate Ester-Induced Chronic Neurotoxicity* – Prof Mohamed Abou-Donia, Professor of Pharmacology and Cancer Biology and Professor of Neurobiology, Duke University Medical Center, North Carolina, USA

2:30 pm *Engine Bleed Air Contamination in Military Aircraft* – Dr Bhupinder Singh, Senior Research Officer, Institute of Aviation Medicine, Royal Australian Air Force (RAAF) Adelaide, Australia and Dr Wally Mazurek, Defence Science and Technology Organisation (DSTO), Canberra, Australia

2:55 pm *Neurological Impairment in a Group of Airline Attendants After Exposure to Cabin Fumes* – Dr Gunnar Heuser, Clinical Toxicologist, Los Angeles, California, USA

3:20 pm Questions and Discussion

3:35 pm Afternoon break

Session Four

4:05 pm *Biomarkers for Exposure to Organophosphorus (OP) Compounds* – Prof Clement Furlong, Research Professor of Genetics and Medicine, University of Washington, Seattle, Washington, USA

4:30 pm *Assessing over 30 Flight Crew who have Presented as a Result of Being Unwell after Exposure to Fumes on BAe 146 Jets* – Dr Moira Somers, General Practitioner, Perth, Western Australia

4:50 pm *The Effects of Neurotoxic Emissions on the Cognitive Functioning of Workers in Medical, Industrial and Aviation Settings* – Ms Leonie Coxon, Consultant Clinical and Forensic Psychologist, Perth, Western Australia

5:15 pm Questions and Discussion

5:30 pm End of Day One

21 April 2005: Day 2

8:30 am Registration and Refreshments

Chair: Julian Soddy, Former RAF Test Pilot, BBC Presenter, BALPA member

Session Five

9:00 am *Multi-system and Multi-Organ Illnesses in the UK: Gulf War Syndrome ME-CFS, Pesticide Poisoning, MCS and Fibromyalgia* – Emeritus Prof Malcolm Hooper, University of Sunderland, Sunderland, UK, and Chief Scientific Advisor to the UK Gulf War Veterans

9:20 pm *Clinical Diagnosis of Chronic Fatigue-Pain-Cognitive Illness* – Prof Robert Haley, Department of Internal Medicine, University of Texas Southwestern Medical Center, USA

Owing to Prof Haley's ill health, this paper was substituted by:

Neurotoxicity from Exposures to Long Term Low Level Organophosphorus Esters –Dr Sarah Mackenzie Ross, Consultant Clinical Neuropsychologist, Clinical Health Psychology Department, University College London, London, UK

10:40 am Questions and Discussion

9:55 am *Development of a Standard for Aircraft Air Safety* – Dr Byron Jones, Principal Investigator, FAA Center of Excellence for Aircraft Cabin Environment Research (ACER), Kansas State University, Kansas, USA

10:15 am *The Politics of Air Safety* – The Reverend John Woodley, former Australian Senator and Chair of the Australian Senate Inquiry into Cabin Air Quality in the BAe 146 Aircraft

10:40 am Questions and Discussion

10:50 am *The United States Jury System: A Much Maligned but Effective Regulator of Corporate Misconduct – The Dangerous Cockpit, a Case in Point* – Stuart Calwell, The Calwell Practice, PPLC, USA

11:05 pm Morning break

Session Six

11:35 am *Neurotoxicity from Exposures to Long Term Low Level Organophosphorus Esters* – Dr Goran Jamal and Dr Peter Julu, Division of Neurosciences, Imperial College of Science, Technology and Medicine, London, UK

12:00 pm *Cabin Air Filtration – Present and Future* – Karen Bull, Senior Business Development Manager, Pall Aerospace

12:25 pm *Aircraft Air Quality Incidents, Symptoms, Exposures and Possible Solutions* – Prof Chris van Netten, Professor of Health Care and Epidemiology, University of British Columbia, Vancouver, Canada

12:50 pm Questions and Discussion

1:05 pm Lunch

Session Seven

2:05 pm *Adaptation of Near Real Time Biosensor Systems for Monitoring of Cabin Air Quality* – Prof Clement Furlong, Research Professor of Genetics and Medicine, University of Washington, Seattle, Washington, USA

2:30 pm *Activated Carbon Fibers Applied to Air Treatment* – Pascal Contini, Air Quality Program, Sofrance-Safran Group

2:55 pm *ITF-Endorsed Actions to Address Contaminated Aircraft Air* – Ingo Marowski, Aviation Secretary, ITF Aviation Section, International Transport Workers' Federation

3:15 pm *OHRCA Research Project* – Dr Laurel Kincl, Project Manager, Occupational Health Research Consortium in Aviation (OHRCA)

3:35 pm Questions and Discussion

3:50 pm *Closing Speech* – Jim McAuslan, Secretary, BALPA

4:05 pm **Close of Symposium**

From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, p 1.

INTRODUCTION TO THE CONFERENCE

Jim McAuslan

General Secretary of the British Air Line Pilots Association, welcomed delegates to the contaminated air protection conference on behalf of the sponsors – BALPA, Pall Corporation, Sofrance and AOPIS.

BALPA had helped organise the international conference as there was growing acceptance that a problem existed with the quality of cabin air in aircraft, but what was the extent of the problem, what effect did it have on flight crew and how can we avoid it in the first place.

Jim highlighted the breadth of the speaker list – from four continents and from scientific, medical, engineering and research disciplines as well as from legal, political and lobbying backgrounds.

Jim introduced the conference chair, Captain Julian Soddy. Julian was previously a test and line pilot and a very fit man until afflicted by what the aviation authority medical staff diagnosed as organophosphate poisoning. But whilst this had been a very personal experience for Julian, he, like BALPA, would not be pursuing a personal agenda – our aim is to get to the truth.

From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 2-7.

OPENING SPEECH

Paul Tyler, CBE MP
Chair, All Party Organophosphate Parliamentary Group

BIOGRAPHICAL SKETCH

Paul was elected MP for North Cornwall in April 1992 and appointed Liberal Democrat Spokesman on Rural Affairs, Agriculture and Transport. In 1994/95 he also piloted a review of Transport policy which resulted in the approval by Conference of Transporting People, Tackling Pollution and in 1996 he published Country Lives, Country Landscapes, a rural policy paper for the Liberal Democrats. After the 1997 Election he was elected Chief Whip by the newly enlarged Parliamentary Party, and is also Shadow Leader of the house. He serves on the Modernisation Select Committee, and leads Liberal Democrat efforts to make the commons more effective. He has had a prominent role in rural and food industry issues. In 2005, he was elevated to the peerage, and now sits in the UK House of Lords as Lord Tyler.

CONFERENCE INTRODUCTION

Unlike every other contributor to this conference, I am not an expert in anything. Indeed, as a newly retired politician I am – by definition – a totally ignorant layman, a professional amateur.

But even members of parliament have their uses. In December 1999 I received a disturbing report from Sweden, which stated that, on 12 November, an unidentified toxic gas almost caused a catastrophe in a BAe 146 aircraft operated by Braathens Malmo Aviation.[1] With apologies, I repeat what I later reported to the House of Commons:

> *"On the first leg of the three-part trip, the cabin attendants felt strange and experienced incredible pressure. On attendant described the experience as like a 'moonwalk'. On the second leg, the discomfort returned, and the two pilots experienced it too. On the third leg, to Sturrup airport, the cabin manager realized something was seriously wrong, went forward to the cockpit before landing and found that both pilots were wearing their oxygen masks. The captain was as so near to blackout, that in his own words … 'feeling dizzy and groggy despite the oxygen that he had instructed the first officer to take over and land the plane.'*
>
> *"The Swedish Board of Accident Investigation, the airline and the aircraft engine manufacturers all treated the incident as very serious, as well they might. The initial investigation pointed to a leak of a potentially toxic engine lubricant. I was anxious to establish whether that was an organophosphate."*[2]

And that is how I became involved in one of the most extraordinary – and alarming mysteries of our time. Having already spent several years campaigning for a comprehensive inquiry into the forced use of these most dangerous substances (originally developed by the Nazis for chemical warfare), up comes organophosphates (OPs) in yet another risky set of circumstances.

Since then I have pressed successive ministers to insist on international action to get definitive answers to the host of questions that this and so many similar incidents raise. You will hear more details as this conference proceeds. In particular, you will be given details of the only authoritative and independent investigation we have seen so far, undertaken by the Senate of the Australian Parliament. We are extremely fortunate to have former Senator Woodley, who secured and chaired that Inquiry with us, and he will speak tomorrow. He will tell you that crews of the BAe 146 aircraft were undoubtedly affected medically by contaminate air and that it was found to be a serious flight safety issue.

And yet this conference is really the first occasion to bring together a huge range of international experience and expertise to address these issues. The Building Research Establishment (BRE) event here in London in 2003 avoided inviting any union or independent medical and scientific contribution, and that commercial gathering of the industry unsurprisingly concluded that there was no problem.

I and John Smith MP decided that the persistent reports of potentially dangerous incidents demanded a far more thorough investigation than the BRE could provide. Hence my warm welcome to you all to this conference, so efficiently organised by the UK pilot union the British Airline Pilots Association (BALPA).

I should emphasise that BALPA have gone to great lengths to make the examination as comprehensive and unbiased as possible, inviting every leading airline, aircraft manufacturer, lubricant manufacturer, regulator and every person known ever to have had an input into the issues of contaminated air in aviation – whether from the industry or independent outsider – to make a presentation.

They also invited experts on the various medical symptoms which appear to have similar medical characteristics to those reported in flight crews and passengers … I myself have been heavily involved on behalf of those who have suffered acute and chronic illness amongst the troops serving in the 1991 Gulf War and the farmers who used OPs to dip sheep.

I am pleased to tell you that everyone who wished to present a paper has been accommodated – nobody can say that they were not given a chance to make an input.

There have been disappointments. I am frankly amazed that the UK Civil Aviation Authority (UK CAA) declined to present a paper, stating that they

were "unable to field a suitable paper that might add to the medical and/or scientific focus of the conference." It may be encouraging to conclude that they did not think you could not do better that the line you already have here on the program, but it is scarcely reassuring that the UK CAA are on top of the problem.

Clearly, there are still a variety of options on the possible medical effects of exposure to lubricant vapour and mist exposure. I understand that there are some in the industry who deny that there can be any medical effects immediately post exposure, or in the longer term. Some even suggest that the lubricant is safe to bathe in for many hours, and only by ingesting it in large quantities would there be a problem.

It is of considerable concern to all responsible observers that many in the aviation industry – such as the Aerospace Medical Association, some major manufacturers and many airline medical departments – are not here today to listen to this array of expertise. I hope, nevertheless, the Conference will mark a turning point in such apparently complacent attitudes.

While we are missing many major UK airlines, I am delighted to welcome United airlines, who are known to be the first to fit high efficiency particulate air (HEPA) filters on all their aircraft. I suggest that they are again demonstrating their corporate responsibility and duty of care by participating in our proceedings.

The Regulation JAR 25-831 clearly states that: "the air should be free from harmful or hazardous concentrations of gases and vapours" and also that "passengers and crews should not suffer from undue discomfort or fatigue". I remain to be convinced that all airlines fully comply with this regulation: no doubt the lawyers in the audience may have something to say about that.

As a reminder of the problem we are examining, let me make three brief points:

1 Most "exposure events" go un-reported by crews. The BALPA survey of 2002 had 106 pilots experiencing over 1600 exposure events due to air contamination linked to engine oils or hydraulic fluids,[3] but the UK CAA recorded less than 100 events. This is an issue BALPA has raised with the UK CAA but the latter chose to disbelieve the data rather that check it out or act upon it. This under-reporting featured in the findings of the Australian Senate Inquiry. Such exposure events, it was suggested by the Swedish Air Accident Investigation Board and by others, should be re-examined and collated internationally. To date, this has not happened.

2 We are expected to believe – despite what crews' doctors will tell you over the next two days – that what flight crews and passengers are being exposed to on commercial aircraft is too low in quantity to have any harmful or long term effect. The Industry position is argued despite the fact that the UK CAA acknowledged to the House of

Commons on 27 April 2004 that "it did not consider the presence of other substances and effects on low-level exposure." Later, in October 2004, the Minister of Transport was forced to admit to me in the Commons that "the Aviation Health Unit, which was funded by the Department, is currently looking into the potential long term health risks associated with contaminated cabin air." It is difficult to know whether this is a case of buck passing or un-joined-up government.

3 And then we come to the vexed issue of public information. Should not passengers be told when they have been accidentally exposed to contaminated air? At present airlines instruct their crews NOT to inform passengers, unless they ask for help. We know from other work (not least with OP sufferers) that some people are more susceptible to serious illnesses than others. Surely, this is a human rights issue? Passengers should be informed, and they cannot be expected to self diagnose their medical conditions, unless they know that they have had a chemical exposure. Those unusual smells on commercial aircraft are often linked to serious illnesses, as you will hear during this conference.

From my personal perspective, this issue has been buried for nearly thirty years by those with vested interests, and now needs to be addressed as a matter of extreme urgency.

I gather that BALPA has a research proposals with the Aviation Health Working Group, is association with leading university departments, and hopefully this will receive the funding required.

The UK CAA have in the past, I understand, relied on papers published by Marshman in conjunction with BAe, marked as "the data used is the property of BAe systems" and also marked "Restricted Commercial", to seek to prove that all is well. That too, is scarcely reassuring.

Independent research is the only legitimate way forward. Vested interests and commercial pressures cannot be allowed to dominate the investigations, when the risks are so obvious.

So let me, finally, set out the core issues, as I see them.

I believe that this could be a calamity waiting to happen – if a pilot and co-pilot both blacked out as a result of this contamination the consequences could be horrendous.

Leaving aside the responsibility for monitoring and investigating incidents of ill health amongst flight crew with the airlines would be like asking the poachers to take on the job of gamekeepers.

Since 2000, I have been raising in Parliament the concerns of flight crews and passenger groups about reports of incidents of pilots and co-pilots who have suffered from polluted air supplies. From Australia to the USA to Sweden to

the UK there had been alarming cases of engine lubricant leakage, in vapour and mist form, into the cabin atmosphere. The presence of the extremely poisonous Organophosphate (OP) chemicals in these lubricants alerted us to the possibility that these were the cause of both short term and long term illness among both flight crew and passengers. The expert evidence presented today will underline this risk.

One particular type of aircraft seems to have featured all too often in reported incidents – the BAe 146 – which is used by the Queen's flight, and Prince Philip and Princess Anne are said to have complained of unpleasant fumes on flights in 2000. The risks are all too obvious.

Unless the UK Civil Aviation Authority, and its international Equivalents, take a determined initiative to get to the bottom of this problem, the fear will remain that air contamination will one day cause a major disaster: the complacency and buck-passing to those who have a commercial interest in minimising the threat is no longer acceptable.

I warmly welcome you to this conference, which could not be more timely or significant.

REFERENCES

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2 Tyler, P. *UK Parliament Hansard* Col 205WH, 28 June 2000.

3 Michaelis, S. A Survey of Health Symptoms in BALPA Boeing 757 Pilots. *Journal of Occupational Health and Safety, Australia and New Zealand* 19: 253-261, 2003.

From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 8-36.

HAZARDOUS CHEMICALS ON JET AIRCRAFT: CASE STUDY – JET ENGINE OILS

Chris Winder
School of Safety Science, The University of New South Wales

BIOGRAPHICAL SKETCH

Assoc Prof Chris Winder, BA (Hons), GradCert in OHS Management, MSc, PhD, FSIA is Associate Professor in Applied Toxicology, School of Safety Science, University of New South Wales (formerly Senior Lecturer 1992-95 and the Head of School 1997-2003). Former positions include: Senior Lecturer in Occupational Health, the School of Occupational Health, University of Sydney (1990-1996); Senior Lecturer in Toxicology at the National Institute of Occupational Health and Safety (1987-1992); Coordinator, Hazard Evaluation Program, Worksafe Australia (1987-1990); Director and Chief Toxicologist, Chemicals Section, Worksafe Australia (1985-1987); Principal Toxicologist, Commonwealth School of Health (1984-1985); Postdoctoral Research Fellow, University of Sydney (1983-1984); Senior Research Fellow, Neurotoxicology Laboratories, Royal Postgraduate Medical School, London (1979-1983). Chris has published over 150 research papers, reviews, book chapters and monographs. He is author of the 1984 book *The Developmental Neurotoxicity of Lead*. In 1987, Chris edited the Proceedings of an international Symposium on Occupational Cancer (*Cancer Forum* **12:** 1-54, 1987), and in 1989, he edited the Proceedings of an NIOHS workshop on occupational asthma in the aluminium industry (*Journal of Occupational Health and Safety – Australia and New Zealand* **5:** 379-440, 1989). He also prepared the NOHSC/WorkCover report: *Survey of Industrial Solvent Use in the Rockdale Area* in 1993. Chris was the principal consultant for the CCH publication *Managing Workplace Chemical Safety*. In 2001, he co-edited the Proceedings of a *Symposium on Aviation Air Quality* held at the Australian Defence Force Academy (ADFA), and in 2004, was co-editor of the second edition of *Occupational Toxicology*.

ABSTRACT

The cabin of an airplane is a specialised working environment and should be considered as such. The oils and hydraulics used in airplane engines are toxic, and specific ingredients of such materials are irritating, sensitising and neurotoxic. If oil or hydraulic fluids leaks out of engines, this contamination may be in the form of unchanged oil/fluid, degraded oil/fluid from long use in the engine, combusted oil/fluid or pyrolised oil/fluid, in the form of gases, vapours, mists and particulate matter. If leak incidents occur and the oil/fluid is ingested into bleed air and is passed to the flight deck and passenger cabins of airplanes in flight, aircrew and passengers may be exposed to contaminants that can affect their health and safety. Where contamination of air in flight deck and passenger cabin occurs that is sufficient to cause symptoms of discomfort, fatigue, irritation or toxicity, this contravenes the air quality

provisions of Federal Aviation Regulations, most notably FAR 25.831. Symptoms of immediate or short term nature and reported by exposed staff in single or few leak incidents are consistent with the development of irritation and discomfort. Symptoms of a long term nature (that is, sustained symptoms for at least six months) reported by some exposed staff following small to moderate numbers of leak incidents are consistent with the development of an irreversible discrete occupational health condition, termed aerotoxic syndrome. Features of this syndrome are that it is associated with air crew exposure at altitude to atmospheric contaminants from engine oil or other aircraft fluids, temporarily juxtaposed by the development of a consistent symptomology including short-term skin, gastro-intestinal, respiratory and nervous system effects, and long-term central nervous and immunological effects.

INTRODUCTION

Air quality is an important aviation problem. Problems arise from a number of factors, including:

- The problem of hypoxia. Commercial flight levels typically range from 31,000 to 42,000 ft, and the aircraft cabin is pressurised to an hypobaric environment equivalent to 8,000 ft (2,315 m).
- The problem of ventilation. Studies indicate[1] that it is common that all modes of transport have ventilation rates less than current ASHRAE 62 guidelines for commercial buildings.[2] This finding, of itself, does not imply poor air quality. However, it suggests that initiatives to reduce air quality should be resisted and indicates that opportunities to improve air quality should be encouraged. For example, a Canadian study of one aircraft type and airline found that 245 of 33 commercial flights did not satisfy the ASHRAE air ventilation criteria of fifteen cubic feet/occupant, and that 18 of 33 flights had less than ten cubic feet/occupant.[3]
- The problem of contamination of air. Chemical exposures in aircraft are not unheard of. In 1953, The US Aeromedical Association first expressed their concerns about the toxicity risks of cabin air contamination by hydraulics and lubricants.[4] The oils and hydraulics used in aircraft engines can be toxic, and specific ingredients of oils can be irritating, sensitising (such as phenyl-alpha-naphthylamine) or neurotoxic (for example, ortho-containing triaryl phosphates such as tri-ortho-cresyl phosphate). If oil or hydraulic fluid leaks occur, this contamination may be in the form of unchanged material, degraded material from long use, combusted or pyrolised materials. These materials can contaminate aircraft cabin air in the form of gases, vapours, mists and aerosols. Other risks have been identified more recently, either as part of the chemicals routinely used in maintaining airplanes,[7] or as products of the passnegers or cargo.[1]
- Problems of combustion and emergency situations.[8] Passenger protective breathing equipment tests conducted by the UK Air Accidents Investigation Branch (AAIB) identify contaminants in

combustion situations such as carbon monoxide, hydrogen cyanide, hydrogen fluoride, hydrogen chloride, nitrogen oxides, sulphur dioxide, ammonia, acrolein, and other hydrocarbon compounds.[9]

Notwithstanding normal operational activities or emergency situations, a range of other situations can arise whereby aircraft cabin air can be contaminated.[10] These include:

- uptake of exhaust from other aircraft or on ground contamination sources,
- application of de-icing fluids,
- hydraulic fluid leaks from landing gear and other hydraulic systems,
- excessive use of lubricants and preservative compounds in the cargo hold,
- preservatives on the inside of aircraft skin;
- large accumulations of dirt and brake dust may build up on inlet ducts where auxillary power units extract air from near the aircraft belly;
- ingestion of oil and hydraulic fluid at sealing interfaces, around oil cooling fan gaskets and in worn transitions;
- oil contamination from synthetic turbine oil;
- engine combustion products (for example, defective fuel manifolds, seal failures, engine leaks).

Other air quality problems include ethanol and acetone, indicators of bioeffluents and chemicals from consumer products.[11] One additional problem is the lower partial pressure of oxygen that is present in the cabins of planes flying at altitude.[15]

International aviation legislation such as the US Federal Aviation Regulations (FAR) and airworthiness standards for aircraft air quality state "*crew and passenger compartment air must be free from harmful and hazardous concentrations of gases or vapors.*"[16] Where contamination of air in the flight deck and passenger cabin occurs that is sufficient to cause symptoms of discomfort, fatigue, irritation or toxicity, this contravenes such standards and legislation.

THE CHEMICAL PRODUCTS USED IN AVIATION

The aviation industry has used fuels, lubricants, hydraulic fluids and other materials that can contain a range of toxic ingredients. Aircraft materials such as jet-fuel, de-icing fluids, engine oil, hydraulic fluids, and so on, contain a range of ingredients, some of which are toxic.[17,18,19,20] Significant contaminants include: aldehydes; aromatic hydrocarbons; aliphatic hydrocarbons; chlorinated, fluorinated, methylated, phosphate or nitrogen compounds; esters; and oxides.[21]

A complex approval process exists for ensuring that materials used in aviation are manufactured to relevant standards. For example, jet fuels are specified

by the American Society for Testing and Materials (ASTM D 1655 *Standard Specification for Aviation Turbine Fuels*)[22] and the United Kingdom Ministry of Defence (MOD Standard 91-91),[23] and the jet engine oil specification of the US Navy MIL-PRF-23699 is used for jet oils. This process of approval and re-approval for new product formulations has meant that there is some resistance to modifying formulations (for example, for health and safety reasons).

Consequently, changing approved formulations is not conducted without significant justification. In the case of the jet oil additive tricresyl phosphate (TCP, discussed below), manufacturers have been reluctant to modify product formulations by substituting toxic TCP additives that perform well in critical applications. This has meant that potentially toxic products have continued to be available and used long after their toxicity has been recognised.[24] It is not known if an approved formulation containing, for example 3% tricresyl phosphate, is considered a change in formulation if the proportion of individual isomers in the TCP mixture is altered, but the 3% remains unchanged. However, as Mobil indicate, only the base stock esters have been modified over the past thirty or so years, suggesting that the mixture of isomers in TCP stock has not been changed.

Fuels are based on the type on engine type (piston, turbo or jet) and operating conditions. They are similar to other petroleum products that have a boiling range of approximately 150°C to 300°C. The freezing point and flash point are the principle differences between the finished fuels. The main fuels used are the kerosene based Jet A (used in the USA or Jet A-1 (used around the world). Jet B is a modified fuel for use in cold climates. Chemical additives allowed for use in jet fuel are also defined in product specifications.[25]

Over two million workers year are occupationally exposed each year to jet propulsion fuels. Approximately 220 billion litres of these kerosene-based jet fuels are annually consumed.[26]

Kerosene-based hydrocarbon fuels are complex mixtures of over 200 aliphatic and aromatic hydrocarbon compounds (C_6 to C_{17}), including varying concentrations of potential toxicants such as benzene, n-hexane, toluene, xylenes, trimethylpentane, methoxyethanol, naphthalenes (including polycyclic aromatic hydrocarbons [PAHs], and certain other C_9-C_{12} fractions such as n-propylbenzene, trimethylbenzene isomers). Table 1 lists some of the components of an early sample of Jet Fuel A.[27]

Table 1: Jet A Constitution

Constituent Composition	**% Volume**	
Simple Alkanes		53.7
Includes:		
Decane	16.5	
Undecane	36	
Methyl Alkanes		3.77
Cycloalkanes		0.79
Monocyclic Aromatic Hydrocarbons		31.8
Includes:		
Benzene	0.02	

Constituent Composition	% Volume	
Butylbenzene	2	
1,2-Diethylbenzene	0.24	
1,2-Diethyl-3-propylbenzene	5.4	
1,4-Diethyl-2-ethylbenzene	0.2	
Ethylbenzene	0.02	
1-Methyl-4-propylbenzene	3.3	
Propylbenzene	3-5	
1,2,4,5-Tetramethylbenzene	9	
Toluene	trace	
1,2,3-Trimethylbenzene	6.6	
Xylenes	0.07	
Polycyclic Aromatic Hydrocarbons		0.63
Includes:		
Naphthalene	0.14	
2-Methylnaphthalene	0.34	
1,3-Dimethylnaphthalene	0.15	

This is consistent with proprietary commercial information, as available on product MSDS (although the aromatic fraction may have been reduced over the years (see Table 2).

Table 2: Jet A Constitution (from Product MSDS)

Component	% present
Saturated Hydrocarbons (Paraffins and Cycloparaffins)	70-80%
Aromatic Hydrocarbons	17-20%
Unsaturated Hydrocarbons (Olefins)	3-6%

Lubricants are classified into either:

- mineral petroleum oils either straight mineral of the appropriate viscosity or blended with additives or part synthetic multigrade oils for piston engines; or
- mineral based (mainly for earlier models of jet engines) or synthetic or turbojet, turboprop or turbofan engines.

Oil types include: mineral oils; semi-synthetic oil; synthetic oils; jet oils; turbine oils; piston engine oils, gear oils.

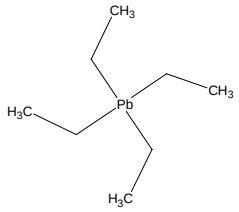
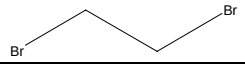
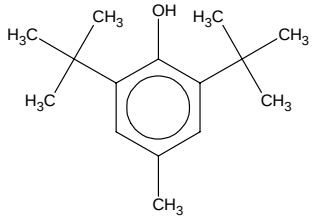
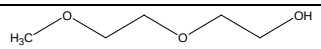
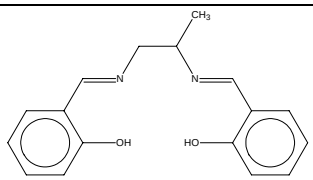
Hydraulic Fluids are usually of the mineral or synthetic, normal or superclean type.

Greases usually containing mineral or synthetic base oils with metal soaps or organic thickeners or inorganic fillers.

Speciality chemicals include antiseize compounds; bonded parts; coolants; corrosion preventatives; damping fluids; de-icing fluids; dry lubricants; instrument oils; lubricity agents; protectives; sealants, adhesives, epoxy resins; shock strut fluids.

A range of aviation chemicals in shown in Table 3.

Table 3: Aviation Chemicals

Product	Type	Ingredients	Formula
Jet Fuels			
	Jet A and Jet A-1	A kerosene based fuel, based on ASTM Specification D1655)	Varies, depending on manufacturer
	Jet B	A wide cut blend of gasoline and kerosene, rarely used except in very cold conditions	Varies, depending on manufacturer
	Aviation gasoline		Varies, depending on manufacturer
Aviation fuel additives			
	Anti-knock additives	Tetra-ethyl lead (TEL)	
		Ethylene dibromide	
	Anti-oxidants	2,6-ditertiary butyl-4-methyl phenol	
	Electrical conductivity/ static dissipater additives	Stadis®450	Proprietary mixture
	Corrosion inhibitor/ lubricity improver	"DCI-4a"	Proprietary mixture
	Anti-icing additives	Di-ethylene glycol monomethylether	
	Metal deactivators	N,N'-disalicylidene-1,2-propane diamine	
	Biocides		
	Thermal Stability Improver additives	(mainly military applications) – "+100"	Proprietary mixture
	Leak detection	Tracer A®	Proprietary mixture
Lubricants, based on			
	Mineral oils		Proprietary mixtures
	Synthetic oils		Proprietary mixtures
Hydraulic fluids			
	Mineral types		Proprietary mixtures
	Synthetic types		Proprietary mixtures
Greases			

Product	Type	Ingredients	Formula
Speciality Chemicals			
	Antiseize compounds		Proprietary mixtures
	Coolants		Proprietary mixtures
	Corrosion preventatives		Proprietary mixtures
	Damping fluids		Proprietary mixtures
	De-icing fluids		Proprietary mixtures
	Dry lubricants		Proprietary mixtures
	Instrument oils		Proprietary mixtures
	Lubricity agents		Proprietary mixtures
	Protectives		Proprietary mixtures
	Sealants, adhesives, epoxy resins		Proprietary mixtures
	Shock strut fluids		Proprietary mixtures
	Bonded parts		Proprietary mixtures

Inhalation is an important route of exposure, with exposure to uncovered skin being a second, less significant route (for example, following exposure to oil mists or vapours). Ingestion is unlikely.

A number of recently published studies reported acute or persisting biological or health effects such as human liver dysfunction, emotional dysfunction, abnormal electroencephalograms, shortened attention spans, decreased sensorimotor speed and immune system dysfunction from single, short term repeated exposure, or long term repeated exposure of humans or animals to kerosene-based hydrocarbon fuels, to constituent chemicals of these fuels, or to fuel combustion products.[28,29,30,31,32,33,34,35] Other reports suggest that other aviation chemicals may be toxic.[21,36,37]

Occasionally, such exposures may be of a magnitude to induce symptoms of toxicity. In terms of toxicity a growing number of aircrew are developing symptoms following both short term and long term repeated exposures, including dizziness, fatigue, nausea, disorientation, confusion, blurred vision, lethargy and tremors.[38,39,40] Neurotoxicity is a major flight safety concern especially where exposures are intense.[41]

Taken together, these indicate that air quality on aircraft is a significant aviation safety issue.[42]

CASE STUDY: THE TOXIC INGREDIENTS OF JET OILS

The engine oils that are used in jet engines are precision oils that need to operate in extreme conditions. Some commercial jet oils have been in use as engine oils in aviation for decades. For example, Mobil USA note that Mobil Jet Oil II (a jet oil with close to half the market share) "has been essentially unchanged since its development in the early 1960s" and "most changes have

involved slight revisions of the ester base stock due to changes in raw material availability".[43]

Therefore, jet oils are specialised synthetic oils used in high performance jet engines. The have an appreciable hazard based on toxic ingredients, but are safe in use by engineering personnel who handle the product routinely provided that:

- health and safety iinformation such as labels, material safety data sheets, manufacuturers manuals and the like are obtained and consulted;
- a suitable risk assessment is carried out that identifies hazards and assesses risks, and recommends suitable controls and precautions;
- maintenance personnel follow the appropriate controls and safety precautions as recommeded in health and safety information and risk assessments; and
- the oil stays in the engine.

Aircraft engines that leak oil may expose others to the oils through uncontrolled exposure. Airplanes that use engines as a source of bleed air for cabin pressurisation may have this source contaminated by the oil if an engine leaks. If such leaks occur, exposed crew and passengers do not have access to the health and safety information, risk assessments or advice on controls that engineering staff have; where such information or advice is lacking, they may be at additional risk.

Using a typical commercial Jet Oil (Mobil Jet Oil II), various sources, such as the supplier's label on the cardboard box the cans are shipped in, the product Material Safety Data Bulletin (MSDB), and information from the manufacturer, list the following ingredients:[21]

- synthetic esters based in a mixture of 95% C5-C10 fatty acid esters of pentaerythritol and dipentaerythritol;
- 1% of a substituted diphenylamine;
- 3% tricresyl phosphate (Phoshoric acid, tris(methylphenyl) ester, CAS No 1330-78-5);
- 1% phenyl-alpha-naphthylamine (PAN) (1-Naphthalenamine, N-phenyl, CAS No 90-30-2);
- a last entry "ingredients partially unknown" is also noted on some documentation.

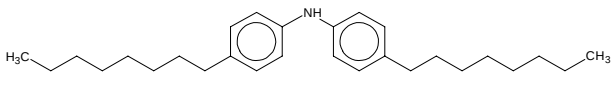
Of these ingredients, the most toxicologically significant components are the substituted diphenylamine, phenyl-alpha-naphthylamine (PAN) and tricresyl phosphate (TCP).

The Substituted Diphenylamine

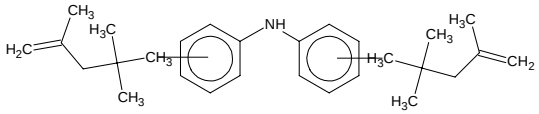
The substituted diphenylamine is variously reported as Benzamine, 4-Octyl-*N*-(4-Octylphenyl), (CAS No 101-67-7) or 0.1-1% N-Phenyl-benzeneamine,

reaction product with 2,4,4-Trimethylpentene (CAS No 68411-46-1), and used as an antioxidant, in concentrations not greater than 1% (see Figure 1).

Figure 1: Substituted Diphenylamines



Benzamine, 4-Octyl-N-(4-Octylphenyl)



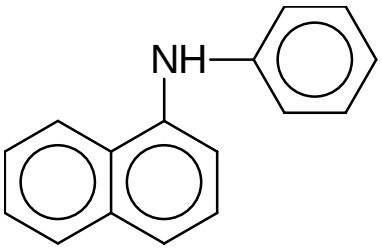
N-Phenyl-benzeneamine, reaction product with 2,4,4-Trimethylpentene

There is little toxicity data available for this ingredient, although it is not believed to be toxic by single exposure (no data on long term exposure). The disclosure of this ingredient in hazard communication by identity probably relates to its environmental effects, such as poor biodegradability and toxicity to aquatic invertebrates.[49]

N-Phenyl-alpha-naphthylamine

N-Phenyl-alpha-naphthylamine, (CAS No 90-30-2), also known as Phenyl-alpha-naphthylamine (PAN), is a lipophilic solid used as an antioxidant used in lubrication oils and as a protective agent in rubber products (see Figure 2). In these products, the chemical acts as a radical scavenger in the auto-oxidation of polymers or lubricants. It is generally used in these products at a concentration of about 1% (its concentration in jet oils). The commercial product has a typical purity of about 99%. Named impurities are: N-Phenyl-2-naphthylamine (CAS No 135-88-6, 500 to below 5000 ppm), 1-Naphthylamine (below 100-500 ppm) and 2-Naphthylamine (below 3 to 50 ppm), aniline (below 100 to 2500 ppm), 1-naphthol (below 5000 ppm), 1,1-dinaphthylamine (below 1000 ppm).

Figure 2: N-Phenyl-1-naphthylamine



PAN is readily absorbed by mammalian systems and rapidly biotransformed.[50] Both urine and feces appear to be the main routes of excretion.[51]

By single dosing, PAN has a short term low toxicity, with LD_{50}s above 1 g/kg. The chemical has a similar mechanism of toxicity to many aromatic amines, of methaemoglobin production. PAN is not irritating in primary skin and eye irritation studies. However, in a guinea pig maximisation test, PAN was shown to be a strong skin sensitiser.[52] This result is supported by case studies in exposed workers.[53,54] At the concentration used (1%), Mobil Jet Oil II meets cut off criteria (1%) for classification as a hazardous substance in Australia for sensitisation properties.

Most genotoxicity studies report negative results, suggesting little genotoxicity potential.[51]

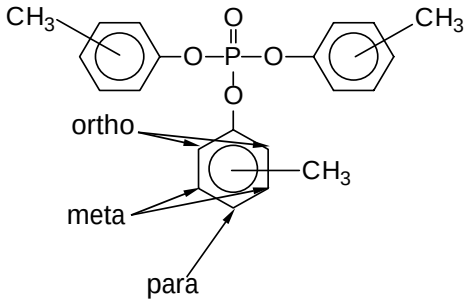
Most repeated dose toxicological studies focus on its potential carcinogenicity. An experimental study, using both PAN and the related compound N-phenyl-2-naphthalenamine administered subcutaneously to mice found a heightened incidence of lung and kidney cancers.[55] While the methodology used in this study makes evaluation of the results problematic (use of one gender, small sample sizes, limited number of dose groups, subcutaneous administration as an inappropriate route of exposure, and so on). A high incidence of various forms of cancer was also found among workers exposed to antirust oil containing 0.5% PAN.[56] While these animal and human results offer only limited information, they are at least supportive of a mild carcinogenic effect.

This must be contrasted with the results of long term carcinogenicity bioassays in rats and mice conducted by the US National Toxicology Program with the structurally related N-phenyl-2-naphthylamine (studies were not carried out on PAN), which have not reported any carcinogenic potential for this chemical.[57]

Tricresyl phosphate

Tricresyl phosphate, (CAS No 1330-78-5) is also known as Phosphoric acid, tris(methylphenyl) ester or Tritolyl phosphate. TCP is a blend of ten tricresyl phosphate isomer molecules, plus other structurally similar compounds, including phenolic and xylenolic compounds. TCP is a molecule comprised of three cresyl (methylphenyl) groups linked to a phosphate group. The location of the methyl group in the cresyl group is critical for the expression of neurotoxicity, with ortho-, meta- or para- prefixes that denote how far apart the hydroxyl and methyl groups are on the cresol molecule. Technically, there are 27 (3^3) different combinations of meta, ortho and para cresyl groups in TCP (see Figure 3). Since the apparently different three-dimensional structures of the molecule are not chemically locked in place, they are not optical isomers. Therefore, structures with similar numbers of cresyl groups (such as ppm, pmp and mpp) are considered the same molecules. This gets the apparent 27 structures down to the real ten isomers conventionally described.

Figure 3: Structure of Tricresyl Phosphate



TCP molecule showing designation of o, m and p cresyl groups

CAS Number descriptors for tricresyl phosphate chemicals have been introduced to differentiate between ortho-cresyl and non-ortho-cresyl isomers:

- CAS No 78-30-8 Tricresyl phosphate (containing o-o-o, o-o-m, o-o-p, o-m-m, o-m-p, o-p-p isomers);
- CAS No 78-32-0 Tricresyl phosphate (containing m-m-m, m-m-p, m-p-p, p-p-p isomers).

TCP is a compound with a toxicity typical of the organophosphorus compounds. Human toxicity to organophosphorus (OP) compounds has been known since at least 1899, when neurotoxicity to phosphocreosole (then used in the treatment of tuberculosis) was reported.[58] The study of OP toxicity is extensive, and generally characterised by a toxicity of inhibition of the esterase enzymes, most particularly cholinesterases[59] and neurotoxic esterases.[60] The mechanism of effect is phosphorylation.[61]

Signs of low level intoxication include headache, vertigo, general weakness, drowsiness, lethargy, difficulty in concentration, slurred speech, confusion, emotional lability and hypothermia.[62] The reversibility of such effects has been questioned.[63]

Signs of poisoning are usually foreshadowed by the development of early symptoms related to acetylcholine overflow and include salivation, lacrimation, conjunctivitis, visual impairment, nausea and vomiting, abdominal pains and cramps, diarrhoea, parasympathomimetic effects on heart and circulation, fasciculations and muscle twitches.[64] This is the basic site of inhibition for all OP molecules.[65,66]

A second reaction with certain OPs (including TCP) leads to further neurotoxic and neuropathological changes. This is inhibition of neurotoxic esterases (NTE) which produces a progressive distal symmetrical sensorimotor mixed peripheral neuropathy, called organophosphorus induced delayed neurotoxicity (OPIDN).[66,67] The mechanism of toxicity is now fairly well understood, as indeed are the organophosphorus structures which are predicted to cause OPIDN.[68]

OPIDN has a severe pathology. It is quite likely that such a severe condition would be presaged with a range of clinical and pre-clinical signs and symptoms. These have been reported extensively, and an "intermediate syndrome" was defined in 1987.[69]

More recently, chronic exposure to organophosphates has been associated with a range of neurological and neuropsychological effects.[70,71,72,73,74] Such symptoms (mainly neurological and neurobehavioural symptoms) may also be seen in exposed individuals who have been sufficiently fortunate in not having exposures that were excessive enough in intensity or duration to lead to clinical disease.

A distinct condition - chronic organophosphate neuropsychological disorder (COPIND) has been described, of neurological and neuropsychological symptoms.[75] These include:

- diffuse neuropsychological symptoms (headaches, mental fatigue, depression, anxiety, irritability);
- reduced concentration and impaired vigilance;
- reduced information processing and psychomotor speed;
- memory deficit and linguistic disturbances;

COPIND may be seen in exposed individuals either following single or short term exposures leading to signs of toxicity,[71] or long term low level repeated exposure with (often) no apparent signs of exposure.[73] The basic mechanism of effect is not known, although it is not believed to be related to the esterase inhibition properties of organophosphorus compounds. It is also not known if these symptoms are permanent.

In addition, since the introduction and extensive use of synthetic organophosphorus compounds in agriculture and industry half a century ago, many studies have reported long-term, persistent, chronic neurotoxicity symptoms in individuals as a result of acute exposure to high doses that cause acute cholinergic toxicity, or from long-term, low-level, subclinical doses of these chemicals.[76,77,78] The neuronal disorder that results from organophosphorus ester-induced chronic neurotoxicity (OPICN), which leads to long-term neurological and neurobehavioral deficits and has recently been linked to the effects being seen in aircrew despite OP levels being too low to cause OPIDN.[79]

Furthermore, OPICN induced by low-level inhalation of organophosphates present in jet engine lubricating oils and the hydraulic fluids of aircraft could explain the long-term neurological deficits consistently reported by crewmembers and passengers, although organophosphate levels may have been too low to produce OPIDN.[80]

While the description above relates to the general toxicity of OPs, they are characteristic of exposure to tricresyl phosphate. The ten isomers that make up TCP are toxicologically different, and it is well established that the ortho containing isomers are the most toxic.[81,82,83] Of the ten isomers of TCP, six contain at least one ortho-cresyl group: three mono-ortho (MOCP) isomers, two di-ortho (DOCP) isomers and tri-ortho-cresyl phosphate (TOCP). Other, similar ortho- containing chemicals, such as the xylenols and phenolics, are also present in commercial TCP formulations in small amounts. Manufacturers of TCP have reduced the levels of ortho-cresyl and ortho-ethylphenyl isomers to reduce the potential for neurotoxicity of products containing TCP.[24] How much these refinements had removed the toxic impurities outlined above is not known. Indeed, toxicity was still being detected in commercially available products in 1988,[84] and questions have been raised about the lack consistency between stated ingredient data and

actual amounts of toxic isomers present in commercial formulations, and their impact on exposed individuals.[21]

In evidence to the Australian Senate Aviation Inquiry in 1999, Mobil USA noted that Mobil Jet Oil II contains less than 5 ppb (0.005 ppm) TOCP.[85] This is an impressively low amount, and suggests that the neurotoxic potential from a chemical containing such a low level would be vanishingly small.

However, concentrations from other neurotoxic ingredients are not so readily available. In the Mobil USA evidence to the Australian Senate Aviation Inquiry, it became apparent that DOCPs were present in TCP at a concentration of 6 ppm, and MOCPs were present at a concentration of 3070 ppm. As these ingredients are present in higher concentrations than TOCP, and have a significantly higher toxicity than TOCP, it is suggested that a statement of low TOCP content is misleading as it underestimates the toxicity of the –OCP ingredients by a factor of 30,000 (see Table 4).[86]

Table 4: Tricresyl Phosphate: Toxicity of Isomers

Isomer	Concentration (ppm)	Relative Toxicity	Equivalent Toxicity
TOCP	0.005	1	× 1
DOCP	6	5	× 30
MOCP	3070	10	× 30700
		Total	**× 30731**

Tricresyl phosphate will also contain mixed esters of orthophosphoric acid with different cresyl radicals, of the mono- and di-cresyl types. The important issue with this data is that the level of <u>all</u> ortho-cresyl phosphates should impact on the regulatory classification of materials containing TCP.

MONITORING STUDIES

Until recently, most studies that have been carried out to measure atmospheric contamination in aircraft by engine oil leaks or hydraulic fluids are sufficiently flawed on procedural and methodological grounds as to render their conclusions invalid.[87] For example, they feature:

- an inability to collect poorly volatile contaminants
- inadequate sample collection times;
- inadequate sample volume;
- inappropriate storage of samples;
- no chain of custody;
- not taking account of altitude;
- studies were conducted on the ground (sometimes with airplane doors open.

Further, no monitoring has occurred during an oil leak.[11]

NUMBERS OF LEAKS

There is a spectrum of defects and malfunctions in an airplane engine ranging from the trivial, to the serious, to the catastrophic. As trivial malfunctions can escalate into serious events, it is necessary to ensure that all types of malfunctions are identified, investigated and rectified.

The aviation industry itself acknowledges that air quality exposure events are primarily due to oil leaking into the air supply. All parties acknowledge that a problem exists, and has existed for a long time.[88] However, they then paradoxically deny that leaks are a serious matter, suggesting that it is not it is an air safety issue, rather an OHS, general health or comfort issue.[89] Regulatory agencies indicate that "serious impairment" includes the loss of crew's ability to see flight deck instrumentation or perform expected flight duties. However, they also suggest this excludes purely psychological aspects of the concern of odours, and concerns about long-term exposure.

When a leak occurs, it may be dismissed by the pilot as being a nuisance, in that it appears to have no apparent effect. Or it may be considered minor and reported within the company and fixed without record (anecdotally, some pilots report leak events to ground crew verbally or unofficially, for example, on scrap paper or even cocktail napkins). In this, there is inappropriate subjective interpretation of the terms "undue discomfort" and "harmful or hazardous levels of gases or vapours" specified in aviation regulations, and this interpretation errs on the side of convenience. Or a record may be made, but not considered sufficiently serious to report to aviation regulators, either voluntarily or as part of mandatory requirements. Lastly, as aviation regulations impose strict guidelines on how aircraft defects are defined, must be reported, investigated and dealt with, some leaks may actually be reported to aviation regulators.[90] These reports tend to cover the serious problems, but not always so. However, with substantial under-reporting and a culture of complacency between operators and regulators, no aviation regulatory authority can honestly consider that the reports they receive from the industry represent anything other than a very small tip of a very large iceberg of leak events.

From review of available sources and reported and accessible information, it is apparent that only a small fraction of the known incidents are reported.[90] Table 5 shows an analysis of various voluntary and mandatory sourced collections of leak events (taken from[90]).

Table 5: Rates of Aircraft Smoke/Fume/Oil and Other Fluid Contamination

Report type/ Country	Year(s)	Aircraft type	Number of reports	Comment
BALPA/UK	2001	B757	1667+	1667+ reports of smoke or fumes mostly thought to be from oil in air conditioning system
MOR*/ UK CAA	1988-Jan 2004	B757	104+	"Smoke and or fumes" – oil/smoke/fumes/de-icing/ hydraulic fluid • 16 reports 1988 - 1998 • 88 reports 1999 – January 2004
MOR*/ UK CAA	1985-2003	BAe 146	85+	"Smoke and or fumes" – oil/smoke/fumes/de-icing/hydraulic fluid • 11 reports 1985 - 1995 • 68 reports 1996 – 2003

Report type/ Country	Year(s)	Aircraft type	Number of reports	Comment
Other UK data	1998-2004	B757	47	Reports sent via email or airline reports (but not on CAA data base)
Other UK data	2002-2004	BAe 146	23	Airline reports not on CAA data base
UK CAA	1989-1999	5 Jet types	128	Smoke/gas fumes (non-mandatory) • 1 event every 22,265 flights • B757 (21), BAe 146 (17)
UK AAIB	2000-2002	BAe 146/ B757	19	Smoke/fumes incidents • B757 -10 • BAe 146 - 9+
BAe/UK	1985-2000	BAe 146	439	• 36 operators report 227 cases of contaminated air -1985 - 2000 • 1 operator reports 212 cases of tainted cabin air 1996 -1999
Aircraft Defect Reports/ Australia	1991-1999	BAe 146	775	Mandatory reports in aircraft technical log. Number of reports • 1992 – 418 reports = 1 every 66 flights • 1997 - 189 • 1999 (6 months)- 168 reports = 1 every 131 flights
Odour Occurrence Reports/ Australia	1991-2000	BAe 146	791	Optional (voluntary) BAe 146 odour occurrence reports.
CASA/ Australia	1996-2002	BAe 146	22	Examples of oil seal bearing defects, fumes and crew impairment
ATSB/ Australia	1991-2002	BAe 146	32	Oil/hydraulic fume - smoke or odour incidents
FAA/US	1986-2000	Various	8268	SDRS - Smell, fume, odour, gas, toxic fume, or toxic gas
AFA/US	1989-1998	MD80	760	900 reports at 1 airline - (73% on MD80)
FAA/US	1989-1999	Various	167	Accidents and Incidents Data Systems (AIDS) • 23 (14%) - Air quality events connected to air contaminants in ventilation system – 1 every 3,590,000 departures • 60 events of ventilation toxic contaminant events + smoke in cockpit/cabin - (1978-1999)
FAA/US[91]	1992-2000	Various	4360	Fumes generated by engine/APU clearly present • less that 1 in 1000 events were a serious threat to flight safety or immediate serious physical harm
NTSB/US	1990-2000	Jet transport	5	Smoke/fumes
TSB/Sweden	1999	BAe 146	1	All crew members "temporarily effected by probably polluted cabin air"

Some of the more significant data includes:

- One BAe 146 operator reports oil/fumes every 66 flights in 1992 reducing to every 131 flights in 1999; and 775 mandatory aircraft technical log reports in two and a half years.[92]
- The British Airline Pilots Association (BALPA) survey of B757 pilots showed that 106 pilots reported in excess of 1667 exposure events mostly thought to be associated with oil contamination of the air supply.[93]
- FAA Service Difficulty Reports Search (SDRS) - 8268 cases of smell, fume, odour, gas, toxic fume, or toxic gas from 1986 to 2000.[94]
- 760 reports of contamination at one US airline on the MD80 aircraft from 1989 -1998.[95]
- BAe 146 odour occurrence report - 791 optional reports.[96]
- BAe reports from aircraft operators - 439 reports from 1986 to 2000, including 212 from one operator in over three years.[97]

Although the data in Table 5 is unlikely to be complete, it is not possible to conclude that leak rates are so low that they should be dismissed.

In conclusion, evidence is available that suggests that there are a substantial number of leak incidents on airplanes, especially on certain models of aircraft. Many of these leaks go unreported to aircraft operators. Of those leak incidents that are reported to aircraft operators, many are not reported to regulatory authorities. Of those leak incidents that are reported to regulatory authorities, not all are added to relevant databases. Ultimately, only a very small number of leak incidents are investigated fully.

Further, as already noted, this information must also be evaluated against substantial under reporting. The information available clearly varies greatly dependent on the source. It can be seen that there are a substantial number of reports on particular types of aircraft.

EFFECTS OF HAZARDOUS CHEMICALS LEAKS ON CREW

Where exposure may be to high levels of airborne contaminants, it is not unreasonable for signs of irritancy and discomfort to be observed. Similarly, it is not unreasonable to consider that a person exposed to a chemical that contains 1% of a sensitiser and 3% of a neurotoxicants might show signs of irritancy and neurotoxicity. These symptoms are often reported in air crew who may be exposed to aircraft fluids.

The earliest case found in the literature of toxicity following jet oil exposure and adverse health problems in air crew was reported in 1977.[98] A previously healthy member of an aircraft flight crew was acutely incapacitated during flight with neurological impairment and gastrointestinal distress. His clinical status returned to normal within a day. The aetiology of his symptoms was related to an inhalation exposure to aerosolised or vapourised synthetic lubricating oil arising from a jet engine of his aircraft. This paper notes that analysis of two samples of military specification oil contained less than 3.5 ppm and 140-175 ppm of TOCP. Analysis of oils from commercial airlines was found to contain 3.5 to 56 ppm of TOCP.[98] This data confirms high levels of TOCP in early oils. Bearing in mind Table 4 above show that the concentrations of MOCP and DOCP isomers are orders of magnitude above the TOCP concentrations, the true –OCP concentration of exposures to these oils is severely underestimated by being expressed in TOCP concentrations alone.

Other studies of exposures in aircraft exist in the literature, including a 1983 study of eighty nine cases of smoke/fumes in the cockpit in the US Air Force,[99] a 1983 study of Boeing 747 flight attendants in the USA (this paper linked symptoms to ozone),[100] a 1990 study of aerospace workers,[101] and a 1998 study of BAe 146 flight crews in Canada over a four-month period.[38] A recent report of seven case studies considered representative of the common symptoms of irritancy and toxicity described similar symptoms,[39] and a follow up survey by the same research group reported similar findings in a larger

group of fifty crew respondents.[102] Two union based studies in pilots provide additional data.[93 103]

These studies investigated different exposures and situations, and the range of symptoms in these studies was quite broad, affecting many body systems. However, there are common themes in symptom clusters in these studies, as shown in Table 6 below.

While this Table shows a long list of symptoms, it is possible to characterise many symptoms more consistently. For example, different papers report dizziness or loss of balance or light-headed or feeling faint or feeling intoxicated or disorientation. It would be incorrect to regard such symptoms as being entirely different from each other – they point to a basic neuropsychological dysfunction affecting balance. But rather than dismissing such symptoms as being multitudinous and variable,[104,105] it may be more appropriate to re-categorise symptoms with clearer definitions, so that the artificial distinctions between symptom reporting can be clarified, and a shorter list of "symptom clusters" be developed (as shown in the first column of Table 6).

Table 6: Studies Reporting Signs and Symptoms in Aircrew from Jet Oil Leaks

Symptom Cluster	Sign or Symptom / Reference / Number of cases	99 89	100 248	101 53	38 112	39 7	102 50	103 21	93 106
Loss of consciousness/ Inability to function	Fainting/loss of consciousness/grey out	4%	4%			3/7	14%		
	Respiratory distress, shortness of breath, respiration requiring oxygen		73%		2%	4/7	62%	26%	4%
Symptoms of direct irritation to eye, airways or skin	Irritation of eyes, nose and throat					7/7		32%	37%
	Eye irritation, eye pain	35%	74%	57%	24%	4/7	76%		
Respiratory symptoms secondary to irritation	Sinus congestion	35%	54%		5%	2/7			
	Nose bleed		17%			1/7	4%		
	Throat irritation, burning throat, gagging and coughing	2%	64%	57%	43%	2/7	76%		
	Cough		69%			2/7	12%		
	Difficulty in breathing, chest tightness		68%			3/7	62%		
	Loss of voice		35%			1/7			
Skin symptoms secondary to irritation	Rashes, blisters (on uncovered body parts)			36%		4/7	48%	16%	8%
Gastrointestinal symptoms	Nausea, vomiting, gastrointestinal symptoms	26%	23%	15%	8%	6/7	58%	5%	15%
	Abdominal spasms/cramps/diarrhoea	26%				3/7	20%	5%	16%
Neurotoxic symptoms	Blurred vision, loss of visual acuity	11%	13%		1%	4/7	50%	5%	4%
	Shaking/tremors/tingling	9%			3%	3/7	40%		
	Numbness (fingers, lips, limbs), loss of sensation			8%	2%	4/7		10%	12%
Neurological symptoms related to basal nervous system function	Trouble thinking or counting, word blindness, confusion, coordination problems	26%	39%	42%		6/7	58%	21%	22%
	Memory loss, memory impairment, forgetfulness			42%		7/7	66%	26%	11%
Cognitive/neuro-	Disorientation	26%			15%	4/7		16%	8%

Symptom Cluster	Sign or Symptom / Reference / Number of cases	99 89	100 248	101 53	38 112	39 7	102 50	103 21	93 106
psychological symptoms related to higher nervous system function	Dizziness/loss of balance	47%			6%	4/7	72%	16%	3%
	Light-headed, feeling faint or intoxicated	35%	54%		32%	7/7		21%	33%
Nonspecific general symptoms	Chest pains	7%	81%		6%	2/7	22%		
	Severe headache, head pressure	25%	52%		26%	7/7	86%	21%	33%
	Fatigue, exhaustion					7/7	62%	21%	30%
	Chemical sensitivity			32%		4/7	72%	26%	10%
	Immune system effects							21%	3%
	Behaviour modified, depression, irritability	26%	20%	60%		4/7	40%		
	General increase in feeling unwell							21%	27%
	Change in urine		3%	6%			4%		
	Joint pain, muscle weakness, muscle cramps		29%			2/7	38%	5%	30%

THE COCKPIT/CABIN ENVIRONMENT

The cockpit or cabin of an aircraft is a unique environment. It is a specialised working environment for the air crew that cannot (indeed, must not) be equated with workplaces at sea level, or workplaces where specialised ventilation and escape are possible.[106]

The process of aircraft pressurisation means that the working environment is hypoxic. Flying crew are required to conduct complex operations requiring high order cognitive skills and coordination expertise. Flight attendants may be required to direct emergency procedures requiring composure and confidence. Anything that may have an impact on the delivery of these tasks can have serious consequences.

A lowered level of oxygen may in turn may have an impact on the emergence of adverse health problems to toxic exposures.

For these reasons, the application of conventional occupational health and safety procedures to this specialised environment are inappropriate. Examples of these include:

- ventilation rates for buildings;
- absence of safety information, risk assessmenst and advice on control of risks;
- the use of permissible exposure standards. A common assertion by aviation companies is that "all chemical exposures are within acceptable TWA exposure standards". These:
  - apply only to the specified chemical,
  - do not protect "nearly all workers",
  - cannot protect sensitive workers – they are NOT no effect levels,
  - poorly consider periods of peak exposure,
  - ignore skin exposure,
  - ignore exposures to other contaminants,

- must not be applied to people other than workers (ambient standards are often 100-1000 times lower),
- must not be applied to unusual environments (for example, the cabin of an airplane);

- extenuating circumstances on board aircraft (including humidity and cabin pressure) have not been studied to the extent that a suitable exposure standard can be identified that incorporates these factors or identifies interactions between factors;[108]
- it is incorrect to assume the exposure standard for TOCP as being "adequately protective" for a TCP containing mixture of TCP isomers as other ortho isomers (MOCPs, DOCPs) are at least 5-10 times more toxic than TOCP;[109]
- procedures for assessing the risks of exposures to more than one chemical, that may act in synergy to produce toxicity (for example, carbon monoxide and lowered oxygen);
- under circumstances of exposure to mixtures of contaminants, levels may be well below recommended levels in currently accepted exposure standards - yet still generate complaints or signs and symptoms, because they act in synergy with other contaminants or because some standards may be outdated and not have incorporated more recent scientific and medical evidence;[108]

Occupational exposure standards must also not be applied to non-workers, for example passengers.

COMBUSTION AND PYROLYSIS PROCESSES

Further, an oil leak from an engine at high pressure and temperature may burn or pyrolise before it enters the cabin. This produces carbon-containing materials which, in the presence of energy and oxygen, produce the two oxides of carbon: Carbon dioxide (CO_2) and Carbon monoxide (CO). The first of these (CO_2) is produced in the presence of an abundance of oxygen, the second (CO), where stoichiometric concentrations of oxygen are lacking (usually in conditions of incomplete combustion). Both of these oxides are gases, one (Carbon monoxide) is quite toxic at low concentrations, causing toxic asphyxiation. Single or short term exposure to CO insufficient to cause asphyxiation produces headache, dizziness, and nausea; long term exposure can cause memory defects and central nervous system damage, among other effects.[110]

Many combustion and pyrolysis products are toxic. The toxic asphyxiants, such as carbon monoxide, have already been introduced above. Some thermal degradation products, such as acrolein and formaldehyde are highly irritating. Others, such as oxides of nitrogen and phosgene, can produce delayed effects. Still others, such as particulate matter (for example, soot) can carry adsorbed gases deep into the respiratory tract where they may provoke a local reaction or be absorbed to produce systemic effects.

A leak of such an oil from an engine operating at altitude would see most of the oil pyrolise once it leaves the confined conditions of temperature and pressure operating in the engine. While it seems reasonable that any ingredients with suitable autoignition or degradation properties that allow such a transformation after release from the engine could be radically transformed, it is possible to speculate in only general terms about the cocktail of chemicals that could form. Presumably it would include carbon dioxide, carbon monoxide, partially burnt hydrocarbons (including irritating and toxic by-products, such as acrolein and other aldehydes, and TCP (which is stable at high temperatures). These contaminants will be in gas, vapour, mist and particulate forms. These contaminants could not be classified as being of low toxicity. The possible problems that might arise from exposure to such a cocktail cannot be dismissed without proper consideration.

AEROTOXIC SYNDROME

What emerges in the analysis of this information, is a pattern of symptoms related to local effects to exposure to an irritant, overlaid by development of systemic symptoms in a number of body systems, including nervous system, respiratory system, gastro-intestinal system, and possibly immune system and cardiovascular system. These symptoms may be expressed specifically to these symptoms, or may be seen more generally, such as headache, behavioural change or chronic fatigue.

The symptoms reported by exposed individuals as shown in Table 6 are sufficiently consistent to indicate the development of a discrete occupational health condition, and the term aerotoxic syndrome is introduced to describe it (Etymology: *aero* refers to aviation, *toxic* to toxicity of exposure and associated symptoms). Features of this syndrome are that it is associated with air crew exposure at altitude to atmospheric contaminants from engine oil or other aircraft fluids, temporarily juxtaposed by the development of a consistent symptomology including short-term skin, gastro-intestinal, respiratory and nervous system effects, and long-term central nervous and immunological effects (see Table 7).

Table 7: Aerotoxic Syndrome: Short and Long Term Symptoms

Short term exposure	Long term exposure
❍ **Neurotoxic symptoms:** blurred or tunnel vision, nystagmus, disorientation, shaking and tremors, loss of balance and vertigo, seizures, loss of consciousness, parathesias; ❍ **Neuropsychological or Psychotoxic symptoms:** memory impairment, headache, light-headedness, dizziness, confusion and feeling intoxicated; ❍ **Gastro-intestinal symptoms:** nausea, vomiting; ❍ **Respiratory symptoms:** cough, breathing difficulties (shortness of breath), tightness in chest, respiratory failure requiring oxygen; ❍ **Cardiovascular symptoms:** increased heart rate and palpitations; ❍ **Irritation** of eyes, nose and upper airways.	❍ **Neurotoxic symptoms:** numbness (fingers, lips, limbs), parathesias; ❍ **Neuropsychological or Psychotoxic symptoms:** memory impairment, forgetfulness, lack of co-ordination, severe headaches, dizziness, sleep disorders; ❍ **Gastro-intestinal symptoms:** salivation, nausea, vomiting, diarrhoea; ❍ **Respiratory symptoms:** breathing difficulties (shortness of breath), tightness in chest, respiratory failure, susceptibility to upper respiratory tract infections; ❍ **Cardiovascular symptoms:** chest pain, increased heart rate and palpitations; ❍ **Skin symptoms:** skin itching and rashes, skin blisters (on uncovered body parts), hair loss; ❍ **Irritation** of eyes, nose and upper airways; ❍ **Sensitivity:** signs of immunosupression, chemical sensitivity leading to acquired or multiple chemical sensitivity ❍ **General:** weakness and fatigue (leading to chronic fatigue), exhaustion, hot flashes, joint pain, muscle weakness and pain.

This syndrome may be reversible following brief exposures, but features are emerging of a chronic syndrome following significant exposures.[39,40,102]

CONCLUSIONS

The presence of contaminants in flight decks and passenger cabins of commercial jet aircraft should be considered an air safety, occupational health and passenger health problem:

- Incidents involving leaks or engine oil and other aircraft materials into the passenger cabin of aircraft occur frequently and are "unofficially" recognised through service bulletins, defect statistics reports and other sources. The rates of occurrence of incidents are higher than the aviation industry cares to admit, and for some models of aircraft are significant. These need appropriate reporting, follow up investigations and health investigations for those exposed.
- The oils used in aircraft engines contain toxic ingredients which can cause irritation, sensitisation and neurotoxicity. This does not present a risk to crew or passengers as long as the oil stays in the engine. However, if the oil leaks out of the engine, it may enter the air conditioning system and cabin air. Where these leaks cause crew or passenger discomort, irritation or toxicity, this is a direct contravention of the US Federal Aviation Authority's and the European Joint Aviation Authorities' airworthiness standards for aircraft ventilation (FAR/JAR 25.831).
- As indicated by manufacturer information and industry documentation, aviation materials such as jet oils and hydraulic fluids are hazardous

and contain toxic ingredients. If such fluids leak into the air supply, cabin and flight deck, toxic exposures are possible. Presently, the aircraft manufacturers, airline operators and the aviation regulators deny that this is a significant problem.

- Leaks of oil and other fluids into aircraft may be considered of a nuisance type, but where they affect the health and performance of crew, or the health of passengers, this is to be considered a flight safety and health issue and must be given appropriate priority.
- Pilots continue to fly when experiencing discomfort or irritation or symptoms of toxicity. There is a lack of understanding by pilots regarding the toxicity of the oil leaks, occupational health and safety (OHS) implications and the necessity to use oxygen. This is further compounded by the airline health professionals who, when confronted with a pilot who has been exposed in a fume event and who is concerned about its consequences, have a poor understanding of the short and long-term medical issues that may arise and tend to be dismissive about their implications.
- Attempts by the industry to minimise this issue, such as acceptance of under-reporting of incidents, inadequate recognition of the extent of the problem, inadequate adherence/interpretation of the regulations, inadequate monitoring, inappropriate use of exposure standards and care provided to crew reporting problems, have perpetuated this problem.
- The health implications both short and long-term, following exposure to contaminants being reported by crew and passengers must be properly addressed. A syndrome of symptoms is emerging, called aerotoxic syndrome, suggesting these exposures are common and a sufficiently large enough group of affected individuals exists.
- Where contaminants impair the performance or affect the ability of pilots to fly planes, as has been reported for a number of incidents, this is a major safety problem. Where contaminants cause undue discomfort or even transient health effects in staff and passengers, this is a breach of FAR 25.831 and other regulations.

Statements by organisations in the aviation industry have attempted to deal with this problem reactively and somewhat flexibly, as evidence emerged:

- "There are no engine oil leaks."
- "Well, there may be some engine oil leaks, but they are very uncommon."
- "Well, there more a few engine oil leaks than we would like, but the oil is safe under normal conditions of use."
- "Well, the oil may contain hazardous ingredients, not at levels that it affects the health of crew."
- "The health problems being reported by our workers are not related to the leaks."
- "Well, if there are health problems, they are related to some other health condition."

- "Well, there may be a few health problems from exposure to oil leaks, but they are transient or mild, and are reversible."

Where contamination of air in flight deck and passenger cabin occurs, or where this is sufficient to cause symptoms of discomfort, fatigue, irritation or toxicity, this contravenes air quality provisions of Aviation Regulations, most notably FAR/JAR 25.831.

In fact, contaminants in the air of an occupational environment should, under normal circumstances, alert management to a potential problem.[106] There is a nested hierarchy of factors which influence the genesis of aerotoxic syndrome, from design of aircraft, engines and oils, to operational aspects and organisational culture, through to injury and disease (see Figure 4).

Figure 4: The Genesis of Aerotoxic Syndrome

However, much of the focus is at the lower levels of this hierarchy, with action basically targeting affected workers. Better attention further up the hierarchy might be more useful.

Rather than just responding to a problem reactively, this needs action on a number of fronts:

1 Better designed aircraft, engines and APUs are needed that don't leak.

2 Better designed aircraft environmental systems are needed that do not rely on bleed air.

3 Better, more safer, chemical products are needed to be used in this industry.

4 Standard, open, non-retributive systems for the reporting of leaks are needed.

5 Organisations in this industry need to acknowledge their occupational health and safety responsibilities as mandated by legislation and

should develop and implement appropriate systems that allow those responsibilities to be met (because their existing systems don't).

6 All reports of leaks should be recorded and all such records should be openly available.

7 Risk assessments of exposures are needed that are inclusive, not exclusive, of workers and passengers.

8 Better health systems are needed that treat affected employees with sympathy and respect and not contempt.

9 Better models are needed for monitoring, diagnosis, treatment, rehabilitation and compensation of affected workers. This is urgently needed for the legacy that already exists of pilots and flight attendants who have been affected, forced out of he industry and have been in the wilderness ever since.

10 And of course, research. Research is needed into better engineering systems, less toxic chemicals, better diagnosis, better treatment, better risk assessments and representative epidemiological surveys of employees in the industry. Proper medical and scientific research needs to be undertaken in order to help airline management and crew to better understand both the short-term and long-term medical effects of being subjected to air contamination. This research must be independently funded and objectively reported. At best, it must be free of bias from vested interests that are so skilful at obscuring the issue.

Over the past fifty years, the concept of duty of care has emerged as one of the most important legal responsibilities for employers. In the workplace, the duty of care of an employer to its workers has been crystallised into OHS legislation. Aviation safety is something that a person outside of the industry would understand to cover all aspects of safety, including the health and safety of its workers. However, this does not seem to be how all industry insiders see it. Many in the industry see aviation safety as being about making sure the planes keep flying. Both the aviation regulators and the airlines themselves think that OHS is not their business - which is strange, because if *they* do not look after the health and safety of workers in the industry, then who will?

ACKNOWLEDGEMENTS

I gratefully acknowledge the support and ongoing contributions of my colleagues Dr Jean-Christophe Balouet and Ms Susan Michaelis in the development of this paper.

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From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 37-42.

THE CURRENT STATE OF RISK ASSESSMENT OF ORGANOPHOSPHATE COMPOUNDS IN JET LUBRICATION OILS FOR THE UNBORN CHILD

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BIOGRAPHICAL SKETCH

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INTRODUCTION

To understand the regulatory stance to the questions raised over the use of Tricresyl phosphate (TCP) in jet engine lubrication oils, and exposure of workers to such oils, it is necessary to review the nature of the risk assessment process. This will then be set in the context of some of the current knowledge about the toxicology of organophosphate compounds. One aspect of this toxicology, the possible effects of exposure on the developing fetus, will be examined in more detail.

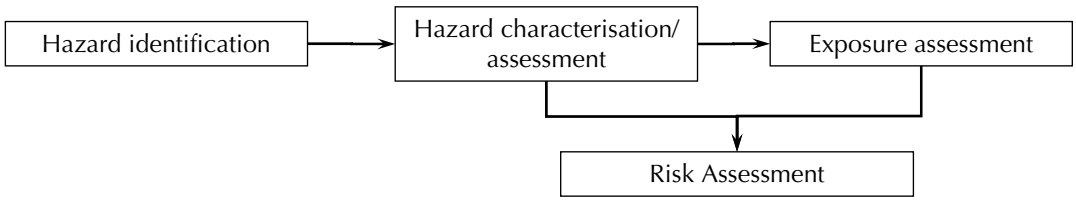
RISK ASSESSMENT

The main tool used to regulate the use of toxic substances is risk assessment. Therefore it is essential in any discussion of the likely impact of the use of TCP in jet engine lubricants that the basis and nature of risk assessment and its limitations are understood. Regulatory change used to come about retrospectively, by reacting to events. New technologies and/or industries

would emerge with little or no regulation. When negative health or environmental effects were detected later, restrictions would be imposed. More recently, it was perceived that an anticipatory stance would be a better approach. New developments are now subjected to risk assessments. This can represent an improvement on simple reaction to disaster. However, some aspects of risk assessment can be surprisingly subjective when data gaps exist.

A risk assessment goes through several steps (see Figure 1).

Figure 1: The Risk Assessment Process



1) **Hazard identification** – which requires insight into the system or process under scrutiny. The risk assessor has to be able to imagine what might go wrong, given a set of information.

2) **Hazard characterisation/assessment** – which can only be performed on hazards that have been identified, requires the application of scientific experimentation and is therefore costly and time consuming. Furthermore if something adverse is found, then definitive action is required. This might, for example, mean the phasing out of a product.

3) **Exposure assessment** – is required when human exposure to toxic substances is being considered, and requires further scientific investigation, usually from survey samples of food or the population, for example. It can be very expensive to perform adequately, particularly in view of the fact that there are almost never any base-line studies performed prior to the introduction of new substances.

4) **Risk assessment** – Finally, the information collected in steps 1) – 3) can be combined into a risk assessment. The validity of this final step is totally reliant on the rigour and completeness of the earlier steps, and especially depends on the assumptions made at each stage.

A hazard is something that can cause harm. For example if you cross the road, you might be hit by a bus. That is a hazard. But the statement does not quantify the likelihood of being hit by a bus each time you cross the road. That risk depends on many factors – the frequency of buses, the time of day, the weather, your attentiveness, your visual and auditory acuity and so forth.

In fact, risk assessment was devised by engineers to assess the integrity of structures, designed and built to certain specifications. Thus, when a civil engineer designs a bridge, he or she can take into account the geometry, materials used, geology of the region, force of the water and wind and so on. Models can then be made of scenarios with adverse weather and traffic

conditions, earthquakes, ships hitting piers and so on. A design can then be developed, including a margin of safety. Bridges are typically over-designed by a factor of 5. Aircraft are over-designed by factors of between 1.1 and 1.2. The tighter the design limits, the more testing has to be applied to the components, to reduce the chance of failure to as near zero as is possible. Such engineering problems are at least finite but even so they can go wrong. The Millennium Bridge in London, which "wobbled" unexpectedly, and the early de Havilland Comet airliner metal fatigue disasters serve to illustrate as examples. In the latter case, the square windows prove to be fatally weak when operating at the low temperatures experienced at altitude. Testing had been done at ground temperature – **a failure of hazard characterisation**.

A risk assessment will only address identified hazards, and there seems little doubt that hazard identification is the most difficult step with newly developed technologies. It is often the unpredicted hazards that are the most problematic. When it is not possible or it is too expensive to obtain reliable or exhaustive hazard assessments, then predictions can be made about what **might** happen, using **data models**. A major reason why risk assessment has failed to protect society on a number of occasions is through the use of unrealistic assumptions or modeling. These have, on occasion, been dubbed ***fact-free models***.[1]

WHERE IN THE RISK ASSESSMENT PARADIGM DOES JET OIL II FIT?

Hazard Identification

Let us examine the likely range of potential hazards that might be considered for TCP and its contaminants. There is no doubt that the acute toxicology of these compounds is well characterised, as discussed elsewhere in this volume. Another set of problems likely to require addressing are the chronic effects of repeated low dose exposure by crew members who work continually in the same environment. Yet another scenario to consider is that of the likely effects of exposure on pregnant women. When a woman is in the early phase of pregnancy she will often not be aware that she is pregnant. Yet the period of organogenesis in the embryo, from days 28 to 56, is one of critical vulnerability to teratogenic agents. Have current risk assessments considered single or repeated exposures to TCP and contaminants?

Hazard Characterisation

In this paper it is intended to solely address what is known about the potential for fetal toxicity, in this section. Other hazards mentioned in the previous section are addressed in other contributions at this conference. This is likely to be the hazard that could be realised at the lowest levels of exposure.

Exposure Assessment

We can, and indeed must, assume that TOCP is potentially hazardous to the fetus. The regulatory risk assessment stance considers that if there is no exposure to the hazard then no risk exists. Therefore, it is of crucial

importance to know whether exposure is actually occurring and, if yes, then to what extent. An examination of the available information reveals that in all probability exposure is occurring. However, reliable quantitation as to the level of exposure is currently lacking.

Normal mode of action of nerve cells – a simple explanation

Nerve cells, called neurons, are the constituents of the brain that process information. They have a large receptive surface, in the form of a branching structure called a dendritic tree. The neuron passes information on to the next one in the chain through its single axon, which may branch to another tree and terminate on a number of other neurons.

Neurons "communicate" to each other by sending pulse coded "electrical" signals down their axons which are then transformed into chemical signals from the end of their axons to the receptive surface of the next neuron at a structure called a synapse. These chemicals are called "transmitter substances." When they are secreted into the synaptic cleft, they alter the resting membrane potential of the receptive neuron. Any particular neuron will then average all the inputs coming to its receptive surface at any one time and "decide" whether to "fire" another pulse of information down its axon.

In any system, such as the brain, there has to be a system in place to allow any signal to decay. This is achieved by enzymes that are present in the region of synapses. They inactivate the transmitter substances quite rapidly after they are secreted and therefore prevent them from having a protracted effect. If there is a requirement for the stimulus to continue, then more transmitter substance will need to be secreted. In this way physiological control of synaptic activity is maintained.

Mode of action of Organophosphate (OP) compounds

One of the abundant transmitter substances in the nervous system is acetyl choline (ACh). It is excitatory in a number of systems. These include the motor end plate of all voluntary muscles in the body and in the autonomic nervous system. When ACh is secreted into synaptic clefts, it comes into contact with the enzyme acetyl choline esterase (AChE), which inactivates it. This is the abovementioned control mechanism for ACh. Organophosphate pesticides and nerve gases work by inactivating AChE. This allows for a build up of ACh at the post synaptic target neurons and they become over stimulated, giving rise to the symptoms of acute OP poisoning.

Consequences for policy

We can all agree that if there are fume events in aircraft leading to the appearance of acute OP-like toxicity in air crew or passengers, then that is likely to be dangerous and steps should be taken to remedy the state of affairs.

Sensitivity of the Unborn Child

However, the biological effects that are likely to occur at the lowest concentrations are those that could affect the fetus. Fetal development is controlled by genes which mediate their effects through a variety of cell signaling molecules. Examples of cell signaling molecules include hormones and neurotransmitter substances. They act in the body at very low concentrations in the range of parts per trillion. Most pharmaceutical and pesticide risk assessments look at effects occurring in the "pharmaceutical" range of concentrations, usually more likely to be in the parts per million range. TCP and its metabolite TOCP have been shown to have developmental neurotoxicological potential through the use of the neurite outgrowth assay.[2,3] Furthermore, OPs have been shown to have the potential for acting more than additively in mixtures.[4,5] The concentrations demonstrated in these papers are consistent with effects at levels that could influence the concentration of cell signaling molecules. Thus, although these are *in vitro* measurements, and that means care must be taken in extrapolating such results to *in vivo* situations, it is a given that OPs can be neurotoxic and the literature above does assist in hazard identification, **Step 1** of any risk assessment.

Step 2 would be to perform a hazard characterisation. What is the outcome of pregnancy in cabin staff, who have worked for different periods of time in different aircraft during critical periods of development? A controlled retrospective epidemiological study should be feasible.

Step 3 is an exposure assessment. In many airlines female cabin staff are permitted to work through the period of organogenesis of their pregnancies. Recommendations for pregnant staff flying were introduced in 1976 and at the time, were related to the changing mechanics of body size, posture, and increasing unsteadiness of the pregnant crew-member. These recommendations included that pregnant employees cease flying at thirteen weeks, with an absolute prohibition of flying after the twentieth week of pregnancy. With minor modifications, these have been retained in the aviation industry.[6,7]

Risk Assessment

To perform a realistic risk assessment of the presence of OPs in jet engine lubrication oils it would be necessary to perform an exposure assessment of cabin staff through monitoring cabin air and cabin surfaces. Biomonitoring of cabin staff for exposure would also be desirable. There seems to be rather little data available in either category.

Therefore an overall risk assessment (**Step 4**) for the hazard identified, namely fetal damage, is not currently attemptable because of data gaps. There is the prospect of being able to fill the data gaps by suitable studies being instituted. A prudent, precautionary approach would suggest that these should be

undertaken while there is any risk of exposure of pregnant women to neurotoxic substances in cabin air.

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ILLNESS RELATED TO CABIN AIR: A SURVEY OF SYMPTOMS AND TREATMENT AMONG COMMERCIAL PILOTS AND CABIN CREW

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BIOGRAPHICAL SKETCH

Andrew Harper is an Occupational and Public Health Physician in private practice in Perth Western Australia. He graduated in Medicine from the University of Sydney in 1966 and trained in Public Health at Harvard. His work has included community medicine, academic epidemiology, general practice and occupational medicine with experience in Australia, Canada, USA and Africa. He has a particular interest in occupational chemical injury and has been involved in a number of cases of community and occupational chemical exposure in Western Australia over the last ten years. He is a Fellow of the Australasian Faculty of Occupational Medicine and a Fellow of the Australasian Faculty of Public Health Medicine both within the Australasian College of Physicians.

INTRODUCTION

Commercial pilots and flight attendants have been reporting illness related to cabin air contamination for a number of years.[1,2] The Australian Senate Enquiry concluded that engine oil enters the aircraft through the air conditioning system and is causing acute and middle term adverse health affects.[3] Disabling symptoms continue to occur. Pilots and flight attendants are concerned over the perceived failure by the airline industry and governments to address the problem.[4,5]

Particular concern is being felt by British pilots.[6] This lead the British Airline Pilots Association (BALPA) and the Association of Flight Attendants (AFA) in conjunction with the School of Safety Science of the University of New South Wales to propose an exploratory survey to document illness and treatment among crew associated with contaminated cabin air exposure. The aim was to determine the presence and nature of the problem.

METHODS

The design was a simple self-selected case series of affected crew. Pilots' and flight attendants' unions in Britain, Australia and the US canvassed their members to submit a description of their illness and treatment in relation to contaminated cabin air. Data collection was not structured and subjects were self-selected. The data were analysed descriptively in terms of occupation, country of employment, aircraft type, dates of fumes events, timing of onset of symptoms within the flight, types of symptoms, duration of symptoms, work

capacity and disability, diagnosis, treatment, effects on other crew and passengers. Descriptive statements made by the subjects and reported comments from their doctors were examined. A descriptive analysis was performed.

RESULTS

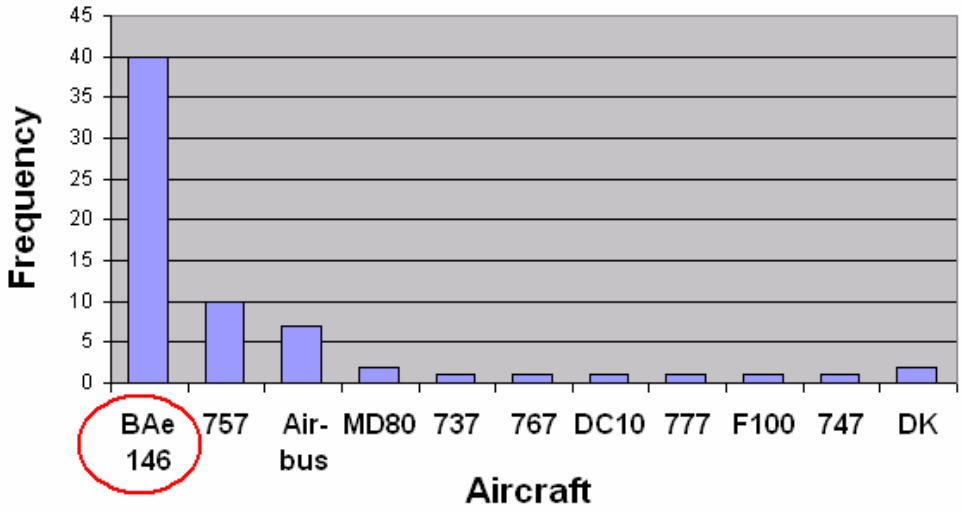
Respondent Details

A total of 60 affected crew responded. They included 39 pilots and 19 flight attendants. Two crew did not specify their occupation. 51% worked in the United Kingdom, 37% in Australia, 10% in the USA and 2% in Egypt.

Aircraft Type

The BAe 146 aircraft was overwhelmingly the most frequently involved in exposure events (see Figure 1) but a number of other aircraft were reported.

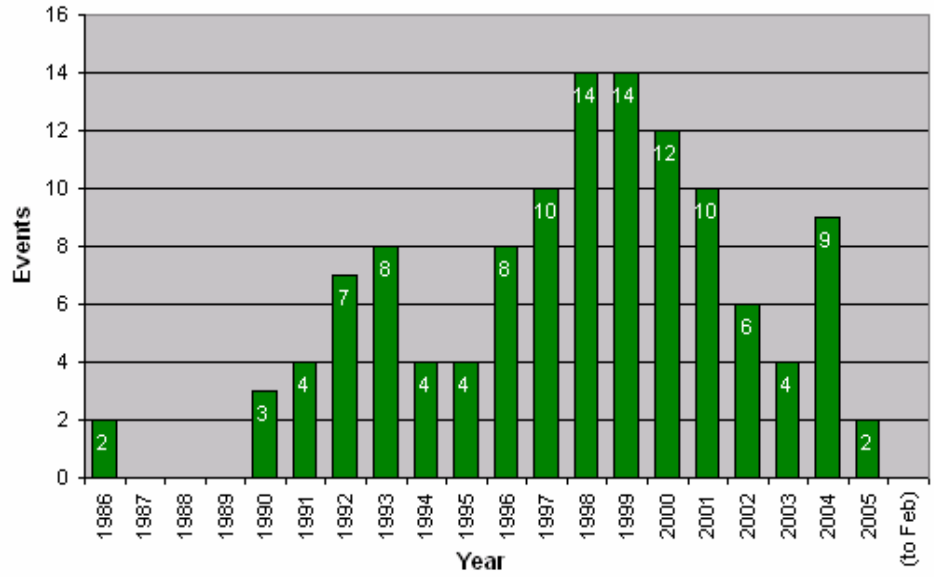
Figure 1: Aircraft Type



Exposure Events

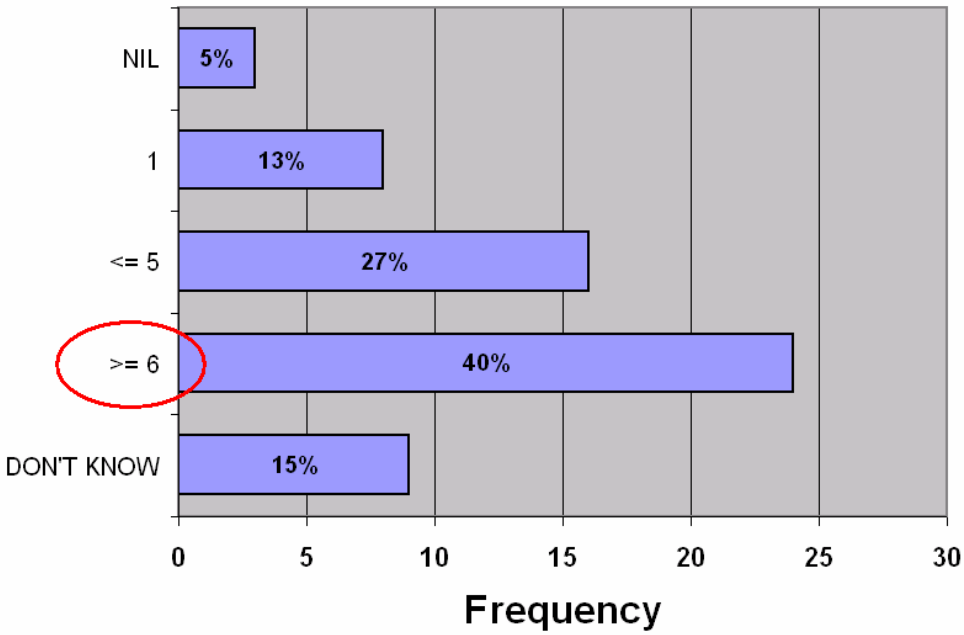
The years in which exposure events were reported are displayed in Figure 2, dating from 1986, peaking in the late 1990's but continuing up to the time of the study.

Figure 2: Exposure Events by Year



Exposure events were experienced most commonly prior to take off and during ascent (see Figure 3). Fewer events occurred during cruise and descent. 40% of the crew reported experiencing six or more exposure events and approximately half of the sample reported being aware of at least one other crew member being affected concurrently.

Figure 3: Number of Exposure Events by Respondent

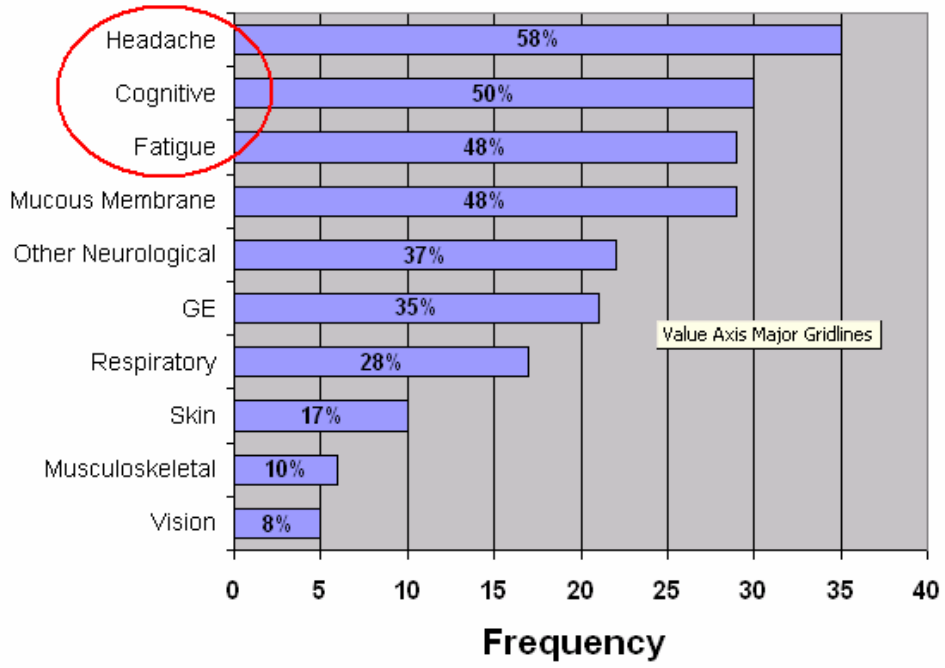


Sixteen in the sample also reported passengers being affected.

Symptoms – Range, Onset, Diagnosis and Treatment

The symptoms experienced were diverse and affected a wide range of body systems. Neurological symptoms including impaired concentration, difficulty thinking, dizziness, making errors and altered depth perception were the most common along with headache, fatigue and mucous membrane irritation. A number of subjects reported gastrointestinal, respiratory, skin and musculoskeletal symptoms (see Figure 4).

Figure 4: Numbers of Symptoms



The onset of symptoms was sudden in 50% of cases but approximately one third did not comment on the time of onset. For more than half of the subjects symptoms became chronic persisting for months or years.

The diagnoses reported were diverse. The commonest were Multiple Chemical Sensitivity, Chronic Fatigue Syndrome, Sinusitis, Toxic Encephalopathy, Depression, Reactive Airways Disease and Toxic Exposure. Regarding treatment, a number reported use of oxygen in flight.

Subsequent medical treatment did not follow a pattern with the exception of treatment of upper respiratory symptoms often labeled as sinusitis and treated surgically in four cases. Crew commonly commented they felt the severity of their illness was underestimated and symptoms were under treated.

Work capacity was affected and 35% reported being chronically unfit to fly.

Comments of crew and doctors are illustrated by the following quotations.

Regarding exposure there were a number of descriptions of the conditions inside the aircraft which ranged from the smell of “rotten socks” to comment such as:

- "There was grey-black smoke in the cabin and from row 3 the last 3 or 4 rows of passengers were not visible. I alerted the Purser who alerted the Captain and we actually thought there was a fire in the rear toilet".

A number of crew reported

- "Extreme light-headedness."
- "No ability to focus or concentrate."
- "Feeling drunk as a skunk."
- "Having trouble judging distance to touch down."
- "I obviously did not have the presence of mind to consider handing over control to the First Officer."
- "I felt ill often but dismissed it, most of the time".

Concern over the problem is reflected in statements such as

- "I was worried that either one or both pilots one day would end up incapacitated in this particular aircraft"(BAe146).
- "Toxic exposures are not only a health hazard but are a very real threat to the safety of flight and to the flying public".

Pilots commented on their reluctance to report exposure events.

- "I did not want to be labeled as an alarmist."
- "Job security and promotion prospects are a major reason why pilots do not document contamination defects."
- "There is a culture in the airline in which you try to look to profitability of the aircraft, and if you can get away with it, you are expected to take the stiff-upper lip approach and ignore any problems which you may want to be convinced are of nuisance value only and do not concern health and safety."
- "There was a marked reluctance from other pilots to effectively report occurrences of fumes".
- "I was severely victimised by management".

Doctor's comments range from admitting to being "completely baffled" to stating that "toxic effects are not occurring". One medical authority commented that

- "Because there exists no documentation of exposure to specific air contaminants, and because the reported symptoms are non-specific (and could possibly be related to a number of different factors), a determination of exposures or the work relatedness of symptoms experienced in the past is not possible".

A more comprehensive perspective was expressed by one doctor

- "The phenomena of reactions to the BAe 146 cabin fumes cannot currently be fully explained, proved or disproved by the science of medicine, but that does not preclude the fact that those individuals that claim to be suffering such effects would appear to have symptoms of

extreme illness in some cases. Rather than being rubbished and labeled as shysters or of unsound mind, these individuals are in fact our own modern day canaries. They are telling us that something is definitely wrong and we as a community should be listening to them very carefully to enable sober research of the issue".

DISCUSSION

Despite a case series being a very basic form of investigation, the above results are an important barometer. Exposure events continue to occur and to affect the ability of pilots to fly as well as incapacitating flight attendants. There is an apparent wide variation in response to exposure events, presumably due to variation in individual susceptibility. For some crew the severity of disability is moderately severe and sufficient to jeopardise aircraft safety. Disability is not only acute but chronic in a proportion of cases. The occurrence is predominantly in one type of aircraft but does occur across a number of aircraft designs. The health effects are not limited to crew but also affect passengers. Exposure events appear to have a pattern related to the stage of the flight. Generally the onset of symptoms coincides with an odour or fume event.

A worrying dimension to the problem is a reluctance to report the incidents. Pilot behaviour in this regard appears to be variable. There is uncertainty surrounding the decision to report and document. This reluctance appears to relate to perceived management expectations, such that pilots are reluctant to be labeled as over-reacting. Consequently they are reluctant to acknowledge that there is a problem or to use oxygen as this needs to be documented. Fundamentally they are reluctant to jeopardise their careers.

The response of the medical profession is highly variable. At one end of the spectrum there is rejection of the existence of a toxic cause. This includes a tendency to minimise the severity of symptoms and a tendency towards inaction on the grounds of insufficient evidence. In the centre of the spectrum there is an admission of ignorance. In a number of cases however treatment has gone as far as surgical intervention. Towards the other end of the spectrum there is acknowledgement of the presence of disabling illness but this remains couched in the realisation that further enquiry and research is needed.

The question of work-relatedness of these symptoms is of central concern. For this purpose Bradford Hill's Criteria of Causation provide a framework which Bradford Hill himself described as "the application of common sense".[7] His criteria help answer the question: "is this illness occupational?" With regard to *consistency*, there is a repetition of circumstances, observations and experiences among crew in different aircraft in different places and at different times. There is *specificity* in the observations in that the onset of symptoms among pilots and flight attendants is specific to those who are flying and is not reported among ground staff. There is a close *time relationship* between exposure to fumes or smells within the aircraft and the

onset of symptoms. There is minimal lag time and the initial onset of symptoms is not being reported at other times. The occurrence of symptoms is *plausible* both biologically and in terms of engineering. Organophosphate additives to engine oil are known to be neurotoxic and the use of bleed air to supply the air conditioning system within the cabin explains how cabin air is contaminated. A cause and effect interpretation of the association between illness and flying has *coherence* with the biology and natural history of a neurotoxic disorder. Each crew member in describing symptom onset following exposure with subsequent recovery and then recurrence provides their own *experimental experience* as in the "n of one" concept. With regard to development of non-specific illness following exposure at work to synthetic chemicals the cabin air experience is *analogous* to a number of other occupational groups notably the Australian F-111 maintenance workers, Vietnam veteran and agricultural workers. This reasoning suggests a causative relationship.

The alternative question to answer is whether or not there is any explanation for this problem which is not work-related and does not arise from a chemical toxin within the cabin air. Possible alternative explanations are the occurrence of a psychological disorder, an infection, malingering, an artifact in the observations, a non-work related chemical toxin or some alterative medical diagnosis. Having considered all these alternatives, each one appears improbable. Despite this view there is strong opposition to accepting cabin air illness as a significant problem. Bradford Hill has sounded a warning regarding new health problems. He has said that an observed association "may be new to science or medicine and must not therefore be too readily dismissed as implausible or even impossible" (Hill, p 293). As seen in the history of medicine, new illness precedes research, and scientific understanding of disease lags behind the occurrence. When faced with a material difference between two groups but with limited evidence Bradford Hill advised concluding "not proven" rather than "no problem" (Hill, p 287).

The implication of the results of this case series is that aircrew are experiencing a real problem, a dangerous problem and a disabling and chronic problem which is continuing. Medically the condition is commonly undiagnosed. The problem is environmental and work-related and when it occurs it is nearly universally accompanied by cognitive and neurological symptoms.

Acknowledgement of illness associated with cabin air by employers and government appears to be quite inadequate. Preventive measures are not in place and safety practices for the events are not standardised. Medical management is ill-defined and treatment being received by those affected is limited. Management of affected crew by employers is failing to address safety and health implications. The initiative into addressing the problem is coming from those who are affected, namely pilots and crew, but authorities are acting as though they are reluctant to heed the warnings. Affected crew are finding ways to manage their own symptoms relatively independently of the medical profession as commonly occurs with chemically related illness.

Airline cabin chemical illness needs to be acknowledged. Primary prevention through elimination of exposure is needed. Safety procedures for exposure events need to be upgraded. Prompt medical assessment for affected crew should be routine as should be comprehensive medical treatment. Health surveillance of affected crew needs to be implemented and an appropriate procedure for workplace management of exposed and affected crew is needed. Supportive and rehabilitative health care should address the spectrum of symptoms experienced. Occupational rehabilitation is required for those disabled.

The problem of cabin air contamination highlights the necessity to give priority to health and safety of crew and passengers over business interests, which means reversing the current situation. The airlines and airline authorities need to acknowledge the problem and implement the precautionary principle rather than postponing action because of incomplete scientific understanding. The existence of a public health problem is undeniable. Doctors need to take a comprehensive occupational and medical history in order to diagnose the problem and not rely upon physical examination and laboratory tests which in this type of medical condition, fail to reveal the diagnosis. The solution to air cabin ill health will depend upon collaboration cooperation and coordination among all stakeholders. The current divisions between employer and employee are holding back progress and are perpetuating the problem.

Acceptance of uncertainty is very difficult for the medical profession but what is required is a willingness to take public health action well in advance of full scientific understanding of causative mechanisms. Our history of public health is too easily forgotten. In 1854, John Snow interrupted a cholera epidemic by the forthright practical action of removing the handle from the Broad Street pump.[8] This was 29 years before the discovery of the cholera bacterium. He used the available information to take responsible action. Let us follow his example.

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LUNG INJURY FOLLOWING HYDROCARBON INHALATION IN BAE 146 AIRCREW

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BIOGRAPHICAL SKETCH

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INTRODUCTION

The toxic effects of inadvertent inhalation of aviation fuels and lubricants are not well described but are thought to include both respiratory and neurocognitive features. The purpose of this paper is to describe respiratory and other symptoms and detected physiological and pathological abnormalities in a group of fourteen BAe 146 flight crew who presented complaining of symptoms following exposure to fine aerosols or fumes during and/or after aircraft flights.

The inhalation of foreign material is a common everyday occurrence but is especially important in the workplace setting. Despite improvements in occupational hygiene, occupational lung disease continues to be an important problem in Western society. For example, recent years have seen a marked reduction in the incidence of mineral dust diseases (pneumoconioses) such as silicosis and asbestosis but others, such as occupational asthma, continue to pose a significant problem. Furthermore, the importance of indoor or closed area pollution and its association with respiratory disease is now appreciated.

The respiratory tract achieves importance in the occupational health setting because it is exposed to potentially contaminated environmental air. Approximately 14,000 litres of air are inspired during the course of a forty-hour working week, increasing with escalating physical activity. Thus the potential for airborne substances to cause injury to the respiratory tract is important in this setting. Inhaled substances vary in their potential to cause lung disease. Some have a characteristic odour or rapidly cause significant airway irritation and are quickly recognised. Other substances which are not so easily perceived may continue to be inhaled, often for prolonged periods,

without being recognised (for example, carbon monoxide). It is, therefore, incumbent on those individuals and organisations involved to appreciate that early recognition of hazards and risks to health are of paramount importance, that prevention is better than cure and that lung injury may not be reversible.

Occupational lung diseases may involve any part of the respiratory system. In order to better understand the factors involved in the genesis of lung injury and disease secondary to inhaled fumes, aerosols and particulates it is important to briefly review the anatomical and physiological features of the respiratory tract. This is particularly important, as the lung has marked regional differences in terms of physiology and function. The respiratory system can be usefully be considered as having four compartments as follows:

- the nasopharyngeal compartment, from the nostrils through the nasal passages, throat to the larynx and vocal cords;
- the tracheobronchial compartment, from the vocal cords to the main airway (trachea), the right and left main bronchi, the progressively smaller airway subdivisions down to the respiratory bronchioles (with an internal diameter less than 0.5 μm);
- the pulmonary/parenchymal compartment, from the respiratory bronchioles to the alveoli or air-sacs;
- the pleural space (the space between the lining of the lungs, and the lining of the ribs);

The alveoli have a rich blood supply, which ensures a direct and unique link between the body and the external environment. The alveoli present an enormous surface area to the inspired air, which ensures rapid exchange of oxygen and carbon dioxide between the blood stream and atmosphere. Thus the lung is particularly suited for the uptake of gases, it is also prone to the development of disease as a result of deposition of particulates and absorption of volatile compounds causing injury.

Materials that can inflict direct injury to lung tissue can lead to respiratory malfunction. This can cause a spectrum of pathological changes including death. Thus the importance of inhalation as a route of exposure to noxious substances in the workplace cannot be over emphasised. It is not possible, within the limits of this presentation, to discuss anymore than briefly the effects of inhaled foreign material on the lung and the mechanisms by which they cause disease. Inspired material may take the form of solid aerosols (powders, dusts, smoke), liquid aerosols (mists, fogs, fumes) and gases or vapours. Depending on their chemical and physical nature (for example, size, morphology) various chest disorders may result.

Broadly speaking, lung diseases can be regarded as those affecting the airways, those affecting the interstitial tissue (the substance of the lung excluding the airways) and some affect both. The following is a list of some examples of these diseases and of their aetiological agents and is illustrative only. Many other factors and agents can affect lung function and structure.

Airway disorders

- Bronchitis (smoke, mineral dusts)
- Bronchiolitis (chlorine, ammonia)
- Asthma (wood dusts, formaldehyde, isocyanates, grain dust eg flour)
- Reactive airways dysfunction syndrome (chlorine, ammonia)

Interstitial disorders

- Pneumoconioses (dust disorders)
- Fibrogenic (ie scar inducing) dusts (asbestos, silica, tungsten carbide)
- Non-fibrogenic dusts (coal dust)

Immunological

- Extrinsic allergic alveolitis (animal proteins, e.g. birds, fungal elements)
- Lipoid pneumonia (oil, fats)

Alveolar filling disease

- Adult respiratory distress syndrome (phosgene)
- Alveolar proteinosis (silica)
- Lipoid pneumonia (fine oil mists)

CLINICAL STUDY

In this study we report a retrospective case series of fourteen BAe 146 flight crew from all states of Australia. They presented complaining of symptoms following exposure to fine aerosols or fumes during or immediately following aircraft flights. In this report we describe the respiratory symptoms and physiological and pathological abnormalities.

There were ten flight attendants, all female, and four pilots, three male and one female. The flight attendants were 34 ± 5 years (mean ± SD) and eight were non-smokers. The pilots were older, mean age (± SD) 52 ± 8 years and three were non-smokers. Maximal potential exposure duration was 65 ± 52 months for the flight attendants compared with the pilots of 250 ± 125 months. One pilot and seven of the flight attendants recalled discrete high-dose exposure episodes provoking symptoms. None of the subjects had a past history of chest complaints.

All fourteen subjects complained of breathlessness and cough (productive in three with haemoptysis in one). Five flight attendants reported wheezing. All ten flight attendants had recurrence of symptoms with return to cabin duties. The pilots reported a similar pattern of symptoms.

Nine of the flight attendants complained of difficulties with speech, short-term memory and an acute onset confusional state. Two of the pilots reported similar symptoms and also complained of influenza-like symptoms during flight and felt incapable of landing the aircraft. In most cases symptoms have

persisted for many years following exposure and have been associated with a perceived heightened sensitivity to diverse sources of petrochemical inhalation in the majority of flight attendants and some of the pilots.

Respiratory investigations were rarely undertaken at initial presentation. During follow-up spirometry was found to be normal in all the flight attendants and two of the pilots. Pulmonary diffusing capacity was abnormal in three flight attendants and three pilots. Arterial blood gas analysis was performed in only three subjects and in all the oxygen tension was reduced (mid 80's mm Hg) and a widened alveolar-arterial oxygen gradient was observed. At follow-up one flight attendant and three pilots were found to have abnormal Chest X-Rays (for example, see Figure 1) and CT scans (for example, see Figure 2). These included non-specific inflammatory changes and a nodular infiltrate in one pilot.

Two pilots had abnormal DTPA lung clearance studies and in one, granulomata were observed in a trans-bronchial lung biopsy (see Figure 3). There were no extra-pulmonary features of sarcoidosis.

Figure 1: Chest X-Ray with a diffuse upper lobe infiltrate

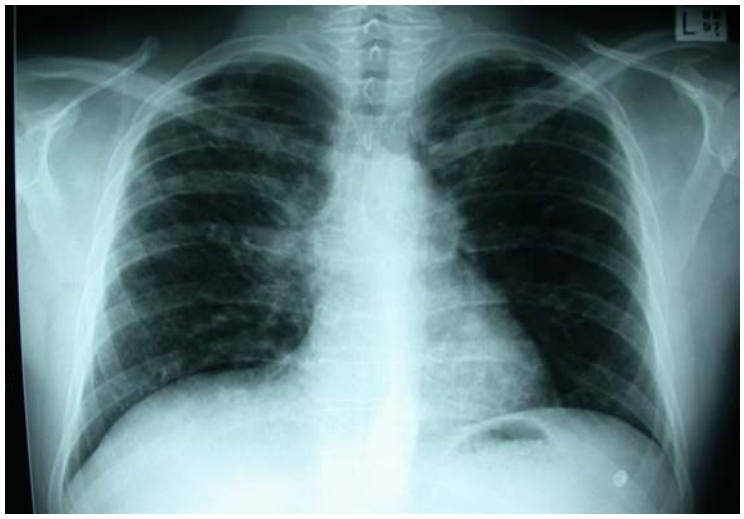


Figure 2: High Resolution CT scan confirms bilateral parenchymal infiltrates without mediastinal lymphadenopathy

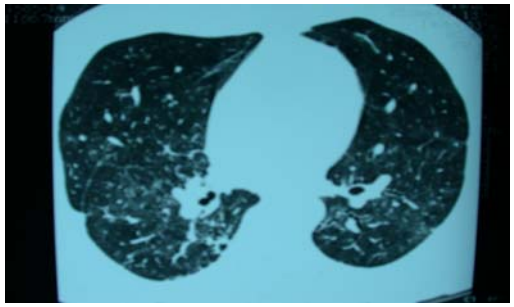
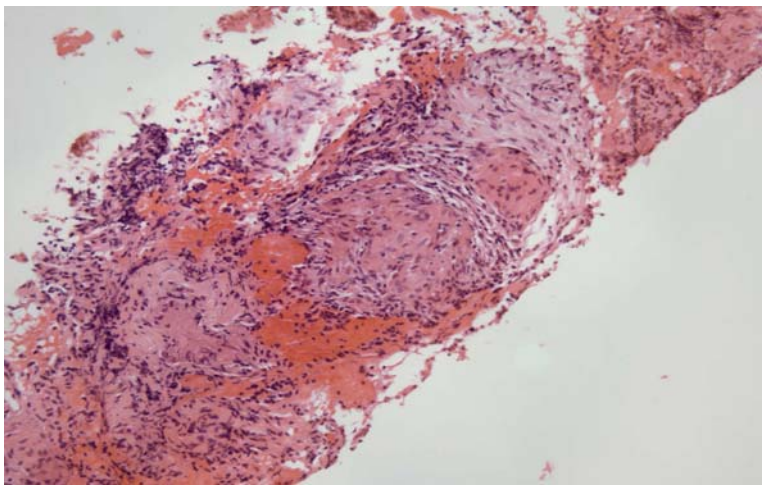


Figure 3: H&E stain of right upper lobe transbronchial lung biopsy showing granulomata. Special stains were negative for fungi and acid fast bacilli



DISCUSSION

This study reports the presence of respiratory disease in a small number of aircrew exposed to hydrocarbon aerosols in flight. Various diagnoses have been made including asthma, reactive airways dysfunction syndrome and multiple chemical sensitivity syndrome. In this study we have concentrated on the respiratory symptomatology, as this was the prime reason for referral to us. There is no doubt that in all cases reported here an injury to the respiratory system had been sustained. The long-term effects are difficult to demonstrate but in those cases where blood gas analysis has been performed abnormalities of gas exchange have been demonstrated with a widening of the alveolar-arterial oxygen gradient suggesting injury at the alveolar or interstitial level. All have continuing symptoms after ceasing exposure.

The strengths and weaknesses of this study can be debated but it is without argument that the presence of respiratory and neurocognitive complaints raises very serious concerns about the occupational health and safety of BAe 146 flight crew and ultimately, passengers. Weaknesses include the generic problems of retrospective analysis where other unknown and uncontrolled for factors may have influenced the observations. The absence of lung function data collected close to the time of discrete exposure limits the interpretation of the impact of the alleged exposure to largely subjective analysis.

Finally, all of the subjects were seen some time after exposure and it is therefore likely that the acute effects of the toxic fumes would have resolved. However, the uniformity of symptom reporting between subjects is impressive. It is noteworthy that the subjects were not co-workers and that the medical staff who collected the data were not employed by the airline industry. We also recognise an inability to continue working in the industry due to heightened sensitivity to petrochemical inhalation is a significant impost that may bias towards over-reporting.

Governments and the airlines need to recognise that a significant problem exists. There is an urgent need to undertake formal and detailed studies of flight crews considered to be at risk. Such studies need to include those already exposed and those without recognised complaints. It is very likely that the individuals reported here represent the tip of the iceberg as underreporting of symptoms is almost certainly occurring because of the fear of loss of career, employment, employer support and ostracism.

In order to confirm these preliminary findings it is recommended that symptomatic flight crews are studied prospectively and ideally before they develop permanent respiratory and other, for example, neurocognitive abnormalities. A detailed clinical and occupational history and complete physical examination with particular reference to whether the individual was symptomatic at the time of testing, the timing with respect to an acute incident and the frequency and length of exposure are mandatory. The following respiratory function tests are recommended

- Spirometry (pre- and post- bronchodilator);
- Methacholine (or histamine) provocation test;
- Diffusing capacity;
- Static lung volumes;
- Arterial blood gases (breathing air, at rest), alveolar-arterial oxygen gradient;
- Measurement of true shunt and venous admixture;
- Chest x-ray (or high resolution CT scan, if clinically indicated);

In conclusion, it is clear that respiratory complaints consistent with lung injury secondary to hydrocarbon inhalation have occurred in BAe 146 flight crews. In many cases these abnormalities are irreversible. Symptom patterns differ between flight attendants and pilots exposed to petrochemical inhalation perhaps reflecting episodic high-dose exposure versus chronic low-dose exposure.

It is, therefore, incumbent on all those involved to appreciate that early recognition of hazards and risks to health are of paramount importance, that prevention is better than cure and that lung injury may not be reversible. There is an urgent need for government and industry support to conduct further rigorous clinical studies.

From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 59-90.

ORGANOPHOSPHATE ESTER INDUCED CHRONIC NEUROTOXICITY (OPICN)

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BIOGRAPHICAL SKETCH

Professor Mohamed Abou-Donia has a 1961 Diploma from Alexandria University (Egypt); a 1967 PhD in Agricultural Chemistry from the University of California, (Berkeley, California). He is board certified with the American Board of Toxicology and the Academy of Toxicological Sciences. He has been a professor of Pharmacology and Cancer Biology, since 1985 and a professor of Neurobiology, since 1995, and a deputy Director, Duke University Marine Biomedical Center, Durham, North Carolina. He has published over 300 papers and is editor of Neurotoxicology, Published by CRC press in 1992.

ABSTRACT

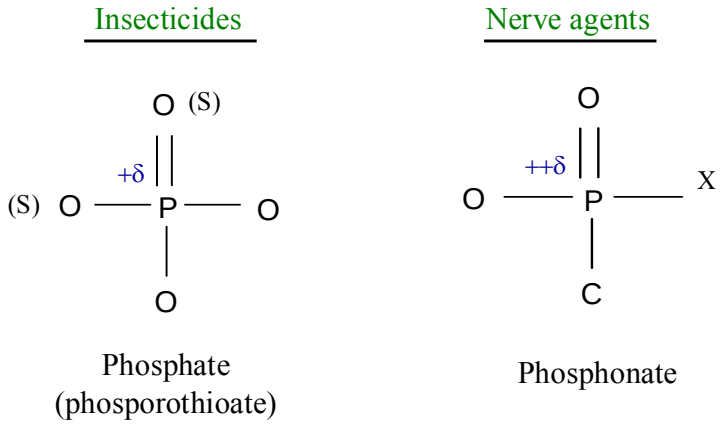
Organophosphorus compounds have been developed for use in medicine, industry, agriculture, as pesticides, and in warfare as nerve agents. Most of these chemicals are neurotoxic, and have three distinct neurotoxic actions. The primary action is the irreversible inhibition of acetylcholinesterase, resulting in the accumulation of acetylcholine and subsequent over stimulation of the nicotinic and muscarinic acetylcholine receptors leading to cholinergic effects. Following a single or repeated exposures, some of these compounds produce a delayed onset of ataxia, accompanied by a Wallerian-type degeneration of the axon and myelin in the most distal portion of the longest tracts in both the central and peripheral systems that is known as organophosphorus ester-induced delayed neurotoxicity (OPIDN). A third action that has been reported, since the introduction and extensive use of synthetic organophosphorus compounds in agriculture and industry half-a-century ago, has been recently termed organophosphorus ester-induced chronic neurotoxicity (OPICN), and is characterized by long-term, persistent, chronic neurotoxicity symptoms in individuals resulting from acute exposure to high doses that cause acute cholinergic toxicity, or from long-term, low-level, sub-clinical doses of these chemicals. Although the mechanisms of this neurodegenerative disorder are yet to be defined, available data suggest that large toxic doses of organophosphorus compounds cause acute necrotic neuronal cell death in the brain whereas sub-lethal or sub-clinical doses produce apoptotic neuronal cell death and involve oxidative stress.

INTRODUCTION

Phosphorus-containing organic compounds may be divided into two major subgroups; one has a trivalent phosphorus atom with a pyramidal

configuration and the other has a pentavalent phosphorus atom with a tetrahedral configuration. Because the trivalent phosphorus atom is electron-deficient in tri-substituted phosphorus acid (triaryl or trialkyl phosphites) such as triphenyl phosphite and tri-*iso*-propyl phosphite, are highly reactive and used as antioxidants, while *S,S,S*-tri-*n*-butyl phosphorotrithioite (merphos) is used as a cotton defoliant.[1] On the other hand, most synthetic organophosphorus compounds belong to the pentavalent group. These compounds are used in agricultural pesticides, nerve agents, pharmaceuticals, flame retardants and for industrial uses. While most organophosphorus esters are organophosphates or organophosphorothioates, nerve agents are phosphonate esters (see Figure 1).

Figure 1: Organophosphate molecules



Organophosphorus compounds have three distinctive neurotoxic actions:

1) Cholinergic neurotoxicity;

2) Organophosphorus ester-induced delayed neurotoxicity (OPIDN);

3) Organophosphorus ester-induced chronic neurotoxicity (OPICN).

CHOLINERGIC NEUROTOXICITY

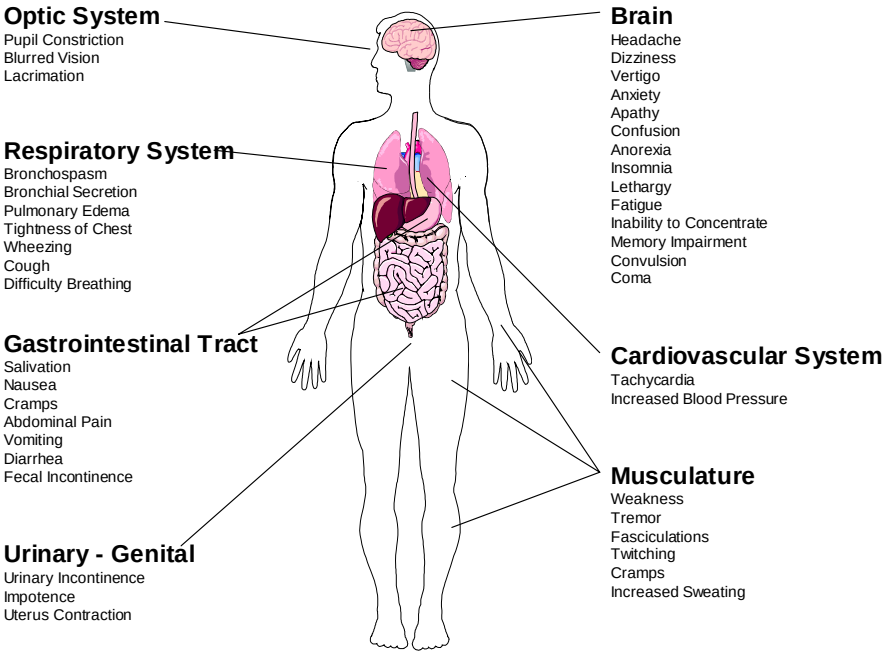
Acetylcholine (ACh) is a neurotransmitter involved in the functioning of the cholinergic nervous system. ACh is released in response to nerve stimulation and binds to post-synaptic acetylcholine receptors, resulting in a muscle contraction or a gland secretion. The action of ACh is rapidly terminated by hydrolysis with the enzyme acetylcholine esterase (AChE).[2,3] In the central nervous system (CNS), AChE is present in many areas, particularly in the cerebral cortex and striatum. In the peripheral nervous system, AChE is localized in the ganglia of the autonomic nervous system, in the parasympathetic nerve endings, and at the neuromuscular junction.[4]

Organophosphorus esters inhibit AChE by phosphorylating the serine hydroxyl group at the catalytic triad site.[3] The phosphoric or phosphonic acid ester formed with the enzyme is extremely stable and is hydrolyzed very slowly. Phosphorylated AChE also undergoes aging, a process that involves the loss of an alkyl group, resulting in a negatively charged monoalkyl

enzyme.[3] Organophosphorus compounds undergo detoxification by binding to other enzymes containing the amino acid serine. These enzymes include plasma butyrylcholinesterase,[5] and paraoxonase.[6] They are also dealkylated or dearylated by the cytochrome P450 mixed function oxidase system.

Inhibition of AChE results in the accumulation of acetylcholine (ACh) at both muscarinic and nicotinic receptors in central and peripheral nervous systems (see Figure 2).

Figure 2: Manifestations of Organophosphate Poisoning



Initially, excess ACh causes excitation, then paralysis of the cholinergic transmission, resulting in some or all of cholinergic symptoms, depending on the dose size, frequency of exposure, duration of exposure, route of exposure as well as other factors such as combined exposure to other chemicals, and individual sensitivity and susceptibility.

Symptoms of Cholinergic Toxicity Resulting from Organophosphate Poisoning

a. Central nervous system (brain and spinal cord)

Headache, dizziness, anxiety, apathy, confusion, restlessness, anorexia, insomnia, drowsiness, lethargy, fatigue, inability to concentrate, cognitive dysfunction, generalized weakness, tremors, depression of respiratory centers, depression of circulatory centers, convulsions and coma.[1]

b. Peripheral nervous system:

1 Parasympathetic autonomic postganglionic nerves (muscarinic symptoms):

a) *sweat glands:* increased sweating;

b) *salivation glands:* excessive salivation;

c) *lacrimation glands:* lacrimation (tearing);

d) *pupils:* constriction (pinpoint and miosis), spasm of accommodation;

e) *ciliary body:* blurred vision;

f) *respiratory tract:* bronchi constriction, increased bronchi secretion pulmonary edema, wheezing, tightness in chest, cough, difficult or labored breathing (dyspnea), and slow breathing (bradypnea);

g) *cardiovascular system:* bradycardia, decreased blood pressure;

h) *gastrointestinal system:* nausea, swelling and cramps, abdominal pain, vomiting, diarrhea, fecal incontinence;

i) *urinary bladder:* urinary frequency, urinary incontinence;

j) *uterus*: contraction.

2. Parasympathetic and sympathetic autonomic ganglia (nicotinic receptors):

   a) *cardiovascular system:* tachycardia, increased blood pressure;

   b) *skin:* pale skin (pallor).

3. Somatic motor neurons, neuromuscular junction (nicotinic receptors):

   Skeletal muscles: muscle fasciculations (eyelids, fine facial muscles), twitching, muscle weakness, cramps, tightness in chest, respiratory difficulty, tremors, paralysis, cyanosis, arrest.

Severity of Symptoms

In organophosphorus ester poisoning, not all symptoms are seen in any one patient. The frequency and severity of the symptoms depend on the compound used and level, frequency, duration, and route of exposure.

Mild Poisoning: Initial symptoms are usually fatigue, dizziness, and sweating. These symptoms may also be accompanied by headache, inability to concentrate, cognitive dysfunction, weakness, anxiety, tremors of the tongue and eyelids, miosis (pupil constriction), and tightness of the chest.

Moderate Poisoning: In addition to the initial symptoms, the following symptoms may result: salivation, lacrimation, abdominal cramps, nausea, vomiting, slow pulse, bradycardia, fall in blood pressure, and muscular tremors.

Severe Poisoning: Pinpoint and non-reactive pupils, muscular twitching, wheezing, increase in bronchial secretion, respiratory difficulty, cough,

pulmonary edema, cyanosis, diarrhea, loss of sphincter and urinary bladder control, tachycardia, elevated blood pressure, convulsions, coma, heart block, and possibly death.

Acute and Chronic Exposure: Generally, the interval between a single acute toxic exposure to organophosphorus ester and onset of symptoms is very short, usually ranging from 5 to 60 minutes. Some individuals, however, may not develop the symptoms of poisoning until 24 hours after exposure.

Repeated small exposures have cumulative effects. Early symptoms of chronic organophosphorus insecticide exposure are influenza-like symptoms. As exposure continues, clinical manifestations appear until a full picture develops.[1]

Effect of Route of Exposure

Organophosphorus compounds are efficiently absorbed by inhalation, ingestion, and skin exposure. The route of entry influences the development of symptoms. In mild cases, only some of the symptoms become evident, depending upon the route of absorption. In severe poisoning, however, most of the signs appear, irrespective of the route of entry.[1]

Inhalation: Inhalation of organophosphorus esters first affects respiratory system and eyes. These effects may include: tightness of the chest, wheezing, a bluish discoloration of the skin, salivation, constriction of the pupils, aching in and behind the eyes, blurring of vision, tearing of the eyes runny nose, headache, inability to concentrate, and cognitive dysfunction.

Ingestion: Ingesting organophosphorus esters causes loss of appetite, nausea, vomiting, abdominal cramps, and diarrhea may take place within two hour of exposure.

Skin: Skin absorption results in sweating and twitching of the area affected usually within fifteen minutes to one hours of exposure.

Severe intoxication by organophosphorus esters via all routes may produce in addition to the above symptoms, body weaknesses, generalized muscle twitching, paralysis, leading to asphyxia and death. Furthermore, the following symptoms may occur: dizziness, confusion, staggering, slurs speech, generalized sweating, irregular or slow heartbeat, convulsions, and coma.

Human Exposure

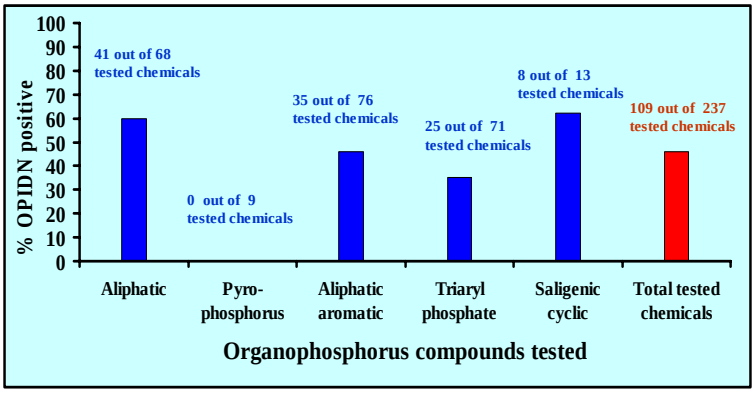
Recent human exposure, mostly via inhalation, to the organophosphorus nerve agent, Sarin has been documented in two terrorist incidents in Japan. Sarin was released at midnight in Matsumoto city on June 27, 1994.[7] Of the 600 persons who were exposed, 58 were admitted to hospitals, where seven died. While miosis was the most common symptom, severely poisoned patients developed CNS symptoms and cardiomyopathy. A few victims

complained of arrhythmia and showed cardiac contraction. Following a terrorist attack by Sarin in the Tokyo subway trains, at 8:05 am, on March 20, 1995, a total of 5,000 persons were hospitalized and 11 died.[8] Patients, with high exposure to Sarin in the Tokyo subway terrorist incident, exhibited the following symptoms: marked muscle fasciculation, tachycardia, high blood pressure (nicotinic responses), sneezing, rhenorrhea, miosis, reduced consciousness, respiratory compromise, seizures, and flaccid paralysis.[9] Patients with mild exposure complained of headaches, dizziness nausea, chest discomfort, abdominal cramps, and miosis. Interestingly, patients had pupillary constriction, even when their cholinesterase activity was normal. Furthermore, inhibition of red blood cell acetylcholinesterase activity was more sensitive than serum butrylcholinesterase activity.[10] The absence of bradycardia and excessive secretions, which are common in dermal or ingestion exposure, suggest that the major route of exposure to the Sarin gas was via inhalation. These patients were treated with atropine eye drops for marked miosis, and pralidoxime iodide (2-PAM).

ORGANOPHOSPHORUS PESTICIDE-INDUCED DELAYED NEUROTOXICITY (OPIDN)

Although many organophosphorus esters cause cholinergic neurotoxicity, only some of these compounds are capable of producing OPIDN. The results of studies that tested 237 organophosphorus compounds for the potential to produce OPIDN, showed that only 109 compounds were positive. Figure 3 shows these chemicals according to their chemical structure.

Figure 3: Percentage of Positive Organophosphorus Compounds Tested for OPIDN



Characteristics of OPIDN

OPIDN is a neurodegenerative disorder characterized by a delayed onset of prolonged ataxia and upper motor neuron spasticity from a single or repeated exposure to organophosphorus esters.[11,12,13,14] The neuropathological lesion is a central-peripheral distal axonopathy, caused by a chemical transection of the axon known as a Wallerian-type degeneration of the axon, followed by myelin degeneration of distal parts of long and of large-diameter tracts of the central and peripheral nervous systems.

Incidents of OPIDN have been documented for over a century (Table 1).

Table 1: Chronology of TOCP Induced OPIDN

Year	Country	Incidence	Cases
1899	France	Creosote	59
1930-31	USA	Contaminated Ginger Extract	Approx 50,000
1925-34	France, Germany, Switzerland	Apiol Abortifacient	200-500
1937	South Africa	Contaminated Cooking Oil	600
1940	Switzerland	Contaminated Cooking Oil	80
1942	United Kingdom	Manufacturing	3
1945	United Kingdom	Contaminated Cottonseed Oil	17
1943-47	Germany	Used as Cooking Oil	10-20
1947	Switzerland	Contaminated Food	73
1952	Switzerland	Contaminated Olive Oil	80
1955	South Africa	Contaminated Water	11
1955	Morocco	Used as Cooking Oil	10,000
1960	India	Contaminated Cooking Oil	58
1966	Rumania	Contaminated Alcohol	12
1967	Fiji	Contaminated Flour	56
1973	Morocco	Shoe Glue Exposure	40
1977-78	Sri Lanka	Contaminated Sesame Oil	23
1988	India	Contaminated Cooking Oil	2

The earliest recorded cases were attributed to the use of tri-*ortho*-cresyl phosphate (TOCP)-containing creosote oil for treatment of pulmonary tuberculosis in France in 1899.[13,14] In 1930, TOCP was identified as the chemical responsible for an estimated 50,000 cases of OPIDN in the Southern and Midwestern regions of the United States.[11-14] More recently, Himuro *et al*[15] reported that a 51-year old man who was exposed to Sarin during the Tokyo subway incident and survived its acute toxicity, died 15 months later. Neuropathological alterations and neurological deficits were consistent with dying back degeneration of the nervous system characteristic of OPIDN. This incident indicates that humans are more sensitive than experimental animals to Sarin-induced OPIDN, since it required 26-28 daily doses of LD_{50} (25 µg/kg, i.m.) Sarin to produce OPIDN in the hen.[16]

OPIDN has been classified into three classes: Type I caused by phosphates and phosphonates as well as their sulfur analogs, and Type II, produced by phosphites. Recently, previously unknown neurotoxicity produced by phosphines has been classified as Type III OPIDN.[13,14]

Factors Involved in the Development of OPIDN

To evaluate the potential for an organophosphorus compound to produce OPIDN, several factors should be considered (see Table 2).

Table 2: Threshold single and daily doses of organophosphorus compounds for the production of OPIDN in hens

Compound	Single Dose		Repeated Doses (mg/kg)			Single/ Daily	Single/ Total Repeated
	mg/kg	Route	Daily	Total	Route		
TOCP	250	Oral[17]	0.5	36	Oral[17]	500	6.9
Leptophos	200	Oral[18]	1.0	64	Oral[19]	200	3.1
Leptophos			0.5	25	Dermal[20]	400	4[8]
EPN	25	Oral[21]	0.1	1.9	Oral[22]	250	13
EPN			0.01	0.2	Dermal[23]	2,500	125
DEF	100	Dermal[24]	0.5	36	Dermal[25]	200	2.8

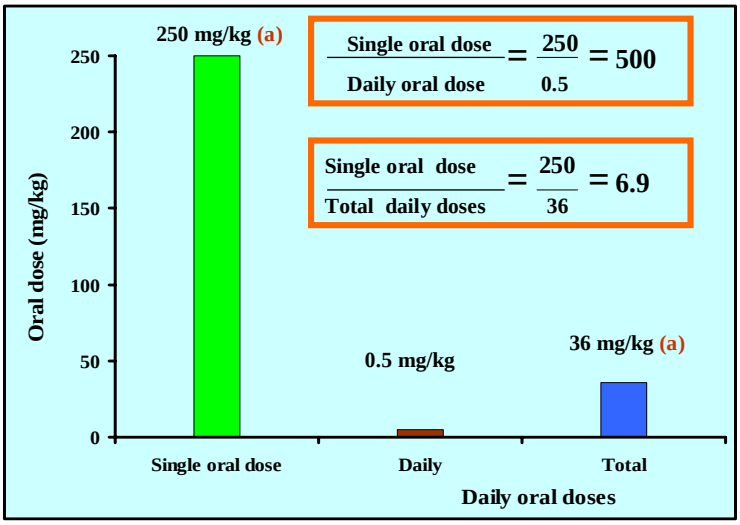
Species

Although humans are very susceptible to OPIDN, not all animal species are sensitive.[11,13] The susceptible species include cows, sheep, water buffaloes, dogs, cats, and chickens, while rodents are much less sensitive.[13] Also, since the young of susceptible species are not sensitive, the adult hen has become the animal model to study this disorder. Thus, a positive result that an organophosphorus insecticide can produce OPIDN in the hen is indicative that this compound is capable of causing this effect in humans. On the other hand, a negative result in the hen screening does not indicate that the test compound will not induce OPIDN in humans.[14] This conclusion is supported by several clinical reports indicating that some organophosphorus pesticides are capable of causing OPIDN in humans, despite the result that they did not produce it in the hen. These pesticides include: omethoate, trichloronate, trichlorfon, parathion, methamidophos, fenthion, and malathion. Subsequent studies have shown that malathion can produce OPIDN in hens and cats.[13,14]

Dose Size

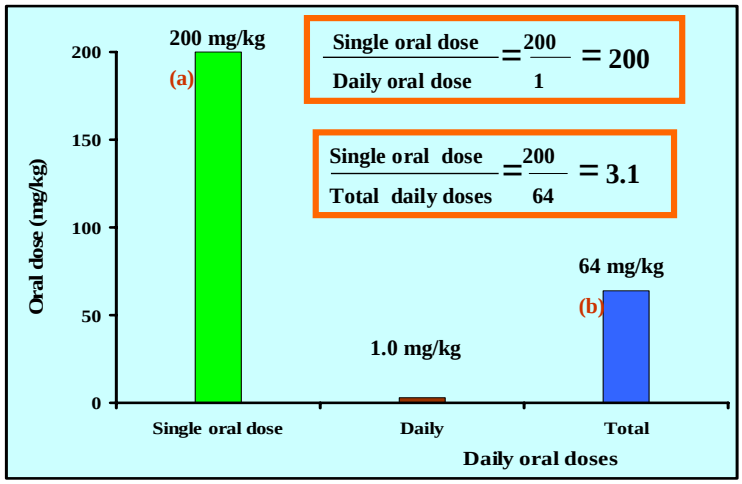
Chronic or subchronic exposures to small daily doses of organophosphorus compounds are more toxic and efficient in producing OPIDN than large single doses (Table 2, Figure 4). While the threshold for a single oral dose of the organophosphorus ester, TOCP that produced OPIDN in hens was 250 mg/kg,[19] a total of 36 daily 0.5 mg/kg doses induced OPIDN,[19] indicating that daily small doses were 7 times as effective as a single oral dose in producing OPIDN.

Figure 4: Threshold Single and Daily Oral Doses of TOCP for Producing OPIDN, (from [19])



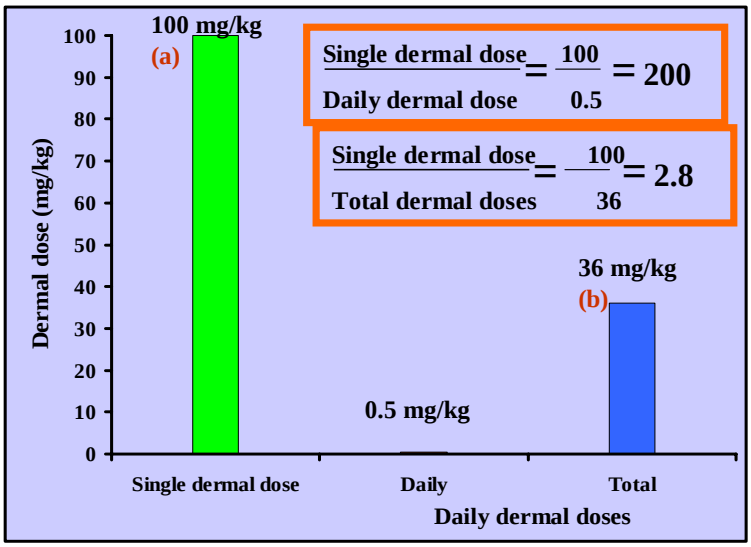
Also, while 200 mg/kg was the maximum oral dose of leptophos was the minimum single oral dose required to produce OPIDN,[24] it took 64 daily 1.0 mg/kg doses of leptophos, totaling 64 mg/kg to produce OPIDN (Table 2, Figure 5), demonstrating that daily small oral doses of leptophos were 3 times as effective as a single oral dose to produce OPIDN.[19]

Figure 5: Threshold Single and Daily Doses of Leptophos for Producing OPIDN (from[19,24])



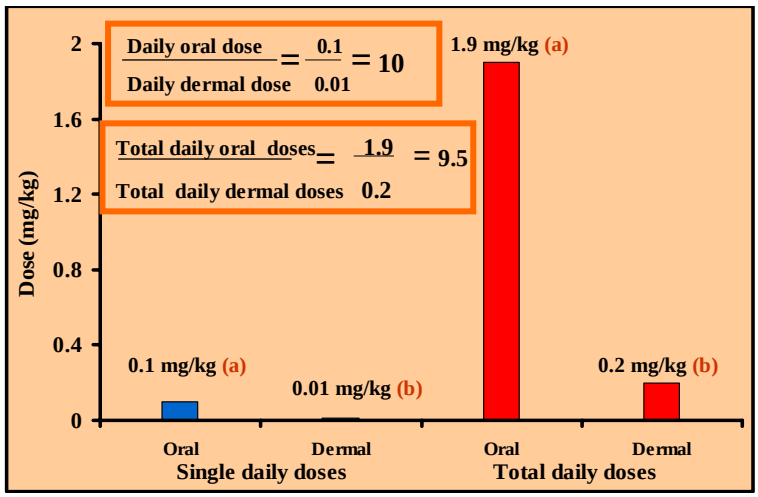
Similarly, daily dermal doses of small doses of the delayed neurotoxic organophosphorus compound DEF (Table 2, Figure 6) were three times as effective as a single dermal dose.[21,25]

Figure 6: Threshold Single and Daily Doses of DEF for Producing OPIDN (from [21,25])



While the threshold for a single oral dose of OP insecticide EPN to produce OPIDN in hens was 25 mg/kg,[21] it took 20 daily oral doses of 0.1 mg/kg to reach the same condition (Table 2, Figure 7).[22] Thus, the minimum daily oral dose and the cumulative total dose of EPN required to cause OPIDN are 250 and 13 times less than that of the single oral dose, respectively.

Figure 7: Threshold Daily Oral and Daily Dermal Doses of EPN for Producing OPIDN (from [22,23])

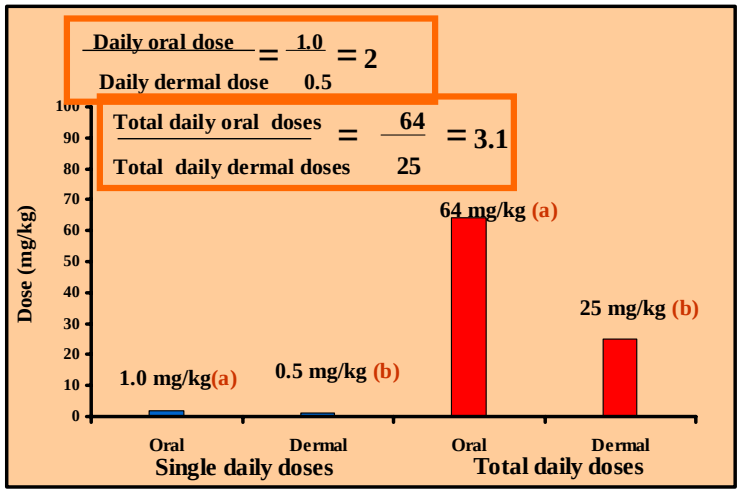


Route of Exposure

Organophosphorus compounds have more access to the neurotoxicity target through inhalation, and skin penetration than the gastrointestinal tract with inhalation being the most effective route of entry, preceded only by intravenous injection. The results of our studies show that dermal exposure to be a more effective route for the development of OPIDN (Table 2, Figure 8). Thus, while daily oral administration of 1.0 mg/kg leptophos for 64 days produced OPIDN in hens,[19] only 25 daily dermal applications of 0.5 mg/kg

caused OPIDN. The results indicate that dermal application was eight times as effective as oral administration in causing OPIDN.

Figure 8: Threshold Daily Oral and Daily Dermal Doses of Leptophos for Producing OPIDN (from [19,22])

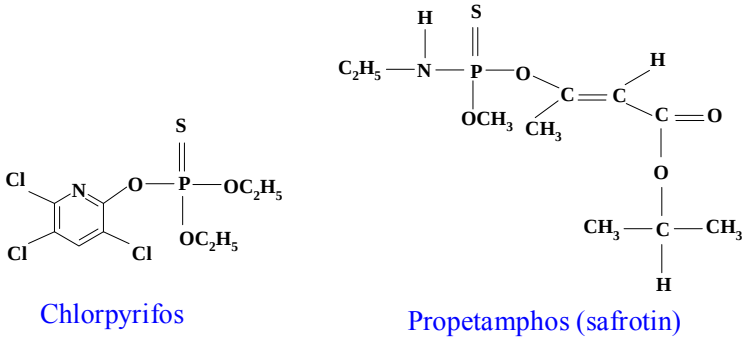


Also, the threshold daily oral administration of EPN that produced OPIDN was 0.1 mg/kg/day topical dose for 20 days.[23] These studies indicate that the minimum total daily dermal dose was 10 times as effective as daily oral administration in producing OPIDN.

Exposure to Other Chemicals

Concurrent exposure to organophosphorus compounds and other chemicals may increase their potency to induce OPIDN. The non-neurotoxicant solvent methyl isobutyl ketone given either via inhalation or dermal application, increased the severity of OPIDN induced by EPN.[26,27] Also, propetamphos, an OP that is capable of producing OPIDN (Figure 9), decreased the threshold oral dose of chlorpyrifos to induce the disorder.[28]

Figure 9: Factors involved in the Development of OPIDN: Combined Exposure with other Chemicals



Chlorpyrifos

Propetamphos (safrotin)

Oral LD_{50} in rats 150 mg/kg
Causes OPIDN at lethal doses

Oral LD_{50} in rats 119 mg/kg
Does not cause OPIDN

Other chemicals, such as the insect repellent DEET, may enhance the transdermal delivery of other pesticides[29] that compete with OPs for blood

and liver esterases such as arylesterases and aliesterases decrease the body's ability to detoxify these OPs, allowing larger concentrations of them reach in the neurotoxicity target. Recent studies have demonstrated that combined exposure to pyridostigmine bromide, DEET, and permethrin[30] DEET and permethrin,[31] and malathion, DEET, and permethrin[30] increased the neurotoxic action of individual compounds.

Neurological Dysfunction of OPIDN in Humans

OPIDN is characterized by a motor-sensory deficit resulting from Wallerian-type degeneration of the axon followed by demyelination of the central and peripheral nervous systems. Early changes in OPIDN result from degeneration of the peripheral nerves leading to flaccid paralysis. Long lasting effects are followed by degeneration of the central nervous system producing spasticity. The course of neurological deficits of OPIDN in humans may be divided into the following distinct phases.[13,14] Usually, not all the signs and symptoms are exhibited in one patient all the time.

Latent Period

Following exposure to organophosphorus compounds, there is a delay before onset of neurological deficits. The length of this latent period varies from a few days to weeks depending on the following factors:

1. The nature of the chemical
2. Route of exposure
3. Dose size and duration and frequency of exposure
4. Exposure to other chemicals
5. Individual differences

Progressive Phase

Early stage of OPIDN is a peripheral neuropathy and is characterized by:

1. Symmetric cramping, burning and/or stinging pain in the calves of the legs and less often in the ankles and feet.
2. Numbness and tingling in the feet and legs.
3. Bilateral dragging of the toes on the floor (foot-drop).
4. Next, the weakness spreads symmetrically to the hand.
5. "Glove-and-stocking" type decreased insensitivity.
6. Steppage gait
7. Positive Rhomberg
8. Absence of Achilles and ankle joint reflexes.
9. Neurological dysfunction may progress to flaccid paralysis.
10. Some patients exhibit urinary and bowel irregularities.

Stationary Phase

After early progression, symptoms, neurological deficits become stationary. During this phase, bilateral paraplegia or quadriplegia persists.

Improvement Phase

During this phase sensory symptoms disappear first followed by improvement of motor function, with hands and arms recovering before feet and legs. As improvement resulting from regeneration of the peripheral nervous system occurs, central nervous system damage becomes unmasked and are characterized by spasticity and exaggerated knee jerk.

Prognosis

The prognosis of patients with OPIDN depends on the severity of neurological deficits resulting from nervous system damage. Patients with mild cases of OPIDN will show clinical improvement and recovery in some cases, as peripheral nerves regenerate. In contrast, severe cases of OPIDN that involve damage to the central nervous system would persist as central nervous system does not regenerate. On the other hand, reversible changes in the central nervous system, such as edema, may subside with time. Also, other neurons may take over the function of damaged neurons, resulting in functional improvement. Patients with severe neurological dysfunction may suffer permanent neurological deficits despite the regeneration of their peripheral nerves.

Mechanisms of OPIDN

Previous studies eliminated the involvement of acetylcholinesterase[32] and butyrylcholinesterase[33] in the mechanisms of OPIDN.[34] The hypothesis that inhibition and ageing of neurotoxicity target esterase (NTE), an enzymatic activity preferentially inhibited by organophosphorus compounds, results in OPIDN has not been proven.[35] The most convincing evidence against this hypothesis is the recent finding that NTE-knockout mice are sensitive to the development OPIDN,[36,37] indicating that this enzyme is not involved in the mechanisms of OPIDN.

We hypothesized that the increased aberrant protein kinase mediated phosphorylation of cytoskeletal proteins could result in the destabilization of microtubules and neurofilaments (NF) leading to their aggregation and deregulation in the axon. Protein kinases are able to amplify and distribute signals, since a single protein kinase is able to phosphorylate many different target proteins. Several protein kinases are turned on by second messengers. For example, calcium/calmodulin-dependent protein kinase II (CaM kinase II) is inactive until it is bound by the calcium- calmodulin complex that induces conformational changes and causes the enzyme to unfold an inhibitory domain from its active site.[38]

We have demonstrated that aberrant hyperphosphorylation of cytoskeletal proteins is central to the pathogenesis of OPIDN. Our results showed that aggregated cytoskeletal proteins are not only a feature of OPIDN, but also a mediator of axonal dysfunction.[39,40,41,42,43,44,45,46,47,48,49,50,51] Sustained hyperphosphorylation of cytoskeletal proteins perturbs the dynamics of cytoskeleton and disrupts axonal functions and stability.

ORGANOPHOSPHATE-INDUCED CHRONIC NEUROTOXICITY (OPICN)

Numerous epidemiological studies have demonstrated that individuals who were exposed to a single large toxic dose or small sub-clinical doses of organophosphorus compounds have developed a long-term, neurological deficits that last for years after exposure, that was distinct from both cholinergic and OPIDN effects. These studies described a nervous system disorder induced by organophosphorus compounds, that involves neuronal degeneration and subsequent neurological, neurobehavioral, and neuropsychological consequences that has been referred to as "organophosphate ester-induced chronic neurotoxicity" or OPICN.[52]

Characteristics of OPICN

The concept of OPICN encompasses structural, functional, physiological, neurological, and neurobehavioral abnormalities, including neuropsychiatric alterations. OPICN has the following characteristics:

1. It is produced by exposure to large acutely toxic or small sub-clinical doses of organophosphorus compounds.
2. Clinical signs consist of neurological and neurobehavioral abnormalities.
3. Persistent, long-term clinical signs continue for a prolonged time, ranging from weeks to years after exposure.
4. Nervous system damage is present in the peripheral (PNS) and central nervous systems (CNS), with more involvement of the latter.
5. In the brain, neuropathological lesions are seen in various regions including the cortex, hippocampal formation, and cerebellum.
6. The lesion is characterized by neuronal cell death resulting from early necrosis or delayed apoptosis.
7. Neurological and neurobehavioral alterations are exacerbated by combining exposure with stress or other chemicals that cause neuronal cell death or oxidative stress.
8. Because CNS injury predominates, improvement is slow and complete recovery is unlikely.

Neurological and neurobehavioral alterations

Although the symptoms of OPICN are caused by damage to the peripheral (PNS) and central nervous systems (CNS) they are primarily related to injury

of the CNS system leading to neurological and neurobehavioral abnormalities. Studies on the effects of exposure to organophosphorus compounds over the past half-a-century have shown that chronic neurological and neurobehavioral symptoms include headache, drowsiness, dizziness, anxiety, apathy, mental confusion, restlessness, labile emotion, anorexia, insomnia, lethargy, fatigue, inability to concentrate, memory deficits, depression, irritability, confusion, generalized weakness and tremors.[53,54,55,56,57] Respiratory, circulatory and/or skin problems may be present as well in cases in chronic toxicity.[1] It should be noted that not every patient exhibits all of these symptoms. In 1997, Jamal carried out an extensive review of the health effects of organophosphorus compounds, and concluded that either acute or long-term, low-level exposure to these chemicals produce a number of chronic neurological and psychiatric abnormalities that he called organophosphate induced neuropsychiatric disorder, or COPIND.[58]

OPICN following large toxic exposures to organophosphorus compounds

Numerous studies have reported that some individuals who were exposed to large toxic doses of organophosphorus compounds and experienced severe acute poisoning but subsequent recovery, have eventually developed the long-term and persistent symptoms of OPICN that were not related to AChE inhibition.[59] Individuals with a history of acute organophosphate exposure reported an increased incidence of depression, irritability, confusion and social isolation.[60] Such exposure resulted in a decrease in verbal attention, visual memory, motoricity and affectivity.[61]

Exposure to Organophosphorus Pesticides

In 1991, Rosenstock et al reported that even a single exposure to organophosphates requiring medical treatment was associated with a persistent deficit in neuropsychological functions.[62] A study of the long-term effects in individuals who had acute toxicity with organophosphorus insecticides indicated a decrease in sustained visual attention and vibrotactile sensitivity that were dose-dependent.[63] In another study, one-fourth of the patients who were hospitalized following exposure to methamidophos exhibited an abnormal vibrotactile threshold between 10 and 34 months after hospitalization.[64] Callender et al,[65] have described a woman with chronic neurological sequelae after acute exposure to a combination of an organophosphorothioate insecticide, pyrethrin, piperonyl butoxide, and petroleum distillates and initial development of symptoms of acute, cholinergic toxicity. Twenty-eight months after exposure, she developed "delayed sequelae of gross neurological symptoms" consisting of coarse tremors, intermittent hemiballistic movements of the right arm and leg, flaccid fasciculations of muscle groups, muscle cramps, and sensory disturbances. Colosio et al,[66] reviewed the literature on the neurobehavioral toxicity of pesticides, and reported that some individuals who were acutely poisoned with organophosphorus compounds developed long-term impairment of their

neurobehavioral performance that was "an aspecific expression of damage and not of direct neurotoxicity". These results are consistent with neuronal necrosis induced by the organophosphorus insecticide, fenthion.[67]

Exposure to Organophosphorus Nerve agents

Organophosphorus nerve agents such as Sarin and Soman cause damage to the blood brain barrier leading to neuronal cell death with subsequent neurological deficits.[68,69] In the 1995 Tokyo subway Sarin incident, some victims of who developed acute cholinergic acute neurotoxicity, also developed long-term, chronic neurotoxicity characterized by CNS neurological deficits and neurobehavioral impairments.[70] Six to eight months after the Tokyo poisoning, some victims showed delayed effects on psychomotor performance, the visual nervous system, and the vestibule-cerebellar system.[71] Furthermore, females were more sensitive than males in exhibiting delayed effects on the vestibular-cerebellar system. Three years after the Matsumoto attack in Japan, some patients complained of fatigue, shoulder stiffness, weakness and blurred vision.[72] Others complained of insomnia, had bad dreams, husky voice, slight fever, and palpations.

Petras (1981) investigated the neuropathological alterations in rat brains, 15–28 days after intramuscular injections of large, acutely toxic doses (79.4–114.8 μg/kg) of the nerve agent Soman.[73] He reported that the brain damage in all four animals that developed seizures, was comparable to that present in three of the four animals that only exhibited limb tremor. Neuropathological lesions were characterized by axonal degeneration, seen in the cerebral cortex, basal ganglia, thalamus, subthalamic region, hypothalamus, hippocampus, fornix, septum, preoptic area, superior colliculus, pretectal area, basilar pontine nuclei, medullary tegmentum and corticospinal tracts. Although the mechanism of Soman-induced brain injury was not known, he noted that the lesions did not resemble those present in fetal hypoxia[74] or OPIDN.[75] These results are consistent with latter findings obtained after acute exposure to Soman[76,77] or Sarin.[78] Although Petras indicated that Soman-treated-animals did not need to have a seizure to develop lesions in rat brain lesions,[73] other investigators have recently reported that only mice exhibiting long-lasting convulsions developed neuropathological alterations in the brain.

Abdel-Rahamn et al,[69] demonstrated neuropathological alterations in rat brain 24 h after administration of an intramuscular LD_{50} dose (100 μg/kg) of Sarin. Neuronal degeneration was present in the cerebral cortex, dentate gyrus, CA1 and CA3 subfields of the hippocampal formation, and the Purkinje cells of the cerebellum. In these animals, both superficial (layers I-III) and deeper (IV-V) layers of the motor cortex and somatosensory cortex showed degenerating neurons. In the deeper layers of the cortex, degenerating neurons were seen in layer V. The layers III and IV neurons in the cortex are the source of axons of the corticospinal tract which is the largest descending fiber tract (or motor pathway) from the brain controlling movement of contralateral muscle group. Thus, Sarin-induced death of layer V neurons of the motor cortex could lead to considerable motor and sensory abnormalities, ataxia, weakness and loss

of strength. Furthermore, disruption of hippocampal circuitry because of the degeneration of neurons in different subfields can lead to learning and memory deficits.[79,80,81,82] Lesions in the cerebellum could result in gait and coordination abnormalities. Because the severely affected areas, such as the limbic system, corticofugal system and central motor system, are associated with mood, judgment, emotion, posture, locomotion, and skilled movements, humans exhibiting acute toxicity symptoms following exposure to large doses of organophosphates may develop psychiatric and motor deficits. Since the damaged areas of the brain do not regenerate, these symptoms are expected to be long-term effects.[68,83,84] The 0.50 × LD_{50} Sarin dose did not cause motor convulsions and only caused some Purkinje neuron loss. The dose 0.1 and 0.01 × LD_{50} Sarin did not cause any alterations at 24 hours after dosing. These results indicate that Sarin-induced acute brain injury is dose-dependent.

Shih et al,[85] have demonstrated that lethal doses (2 × LD_{50}) of all tested nerve agents (that is, Tabun, Sarin, Soman, Cyclosarin, VR and VX) induced seizures accompanied by neuropathological lesions in the brains of guinea pigs similar to those reported for Soman in other species.[86,87,88,89,90,91] Recent reports indicated that anticonvulsants protected guinea pigs against Sarin- and Soman-induced seizures and the development of neuropathological lesions.[92,93] Time-course studies also have reported that Sarin-induced brain lesions exacerbated over time and extended into brain areas that were not initially affected.[†,78] Similar results have been reported in a variety of species.[85,94,95] A subcutaneous dose of 104 µg/kg Soman, induced *status epileptus* in rats followed by degeneration of neuronal cells in piriform cortex and CA3 of the hippocampus.[91] Only mice treated with a subcutaneous dose of 90 µg/kg of Soman and developed long-lasting convulsive seizures exhibited neuropathological alterations.[96] Twenty-four hours after dosing, there were numerous eosinophilic cells and DNA fragmentation (TUNEL-positive) cells in the lateral septum, the endopiriform and entorhinal cortices, the dorsal thalamus, the hippocampus and amygdala. Animals that had only slight tremors and no convulsions did not show any lesions. Guinea pigs given a subcutaneous dose of 200 µg/kg Soman (2 × LD_{50}) developed seizures and exhibited neuropathological lesions between 24-48 h in surviving animals in the amygdale, the substantia nigra, the thalamus, the piriform, entorhinal and perirhinal cortices and hippocampus.[92] Male guinea pigs developed epileptiform seizure after receiving 2 × LD_{50} subcutaneous doses of the following nerve agents (µg/kg): Tabun 240, Sarin 84, Soman, 56, Cyclosarin 114, VX 16, or VR 22 accompanied by necrotic death of neuronal cells, with the amygdale having the most severe injury, followed by the cortex and caudate nucleus.[85]

† Unpublished results.

Exposure to Other Organophosphates

Kim et al,[97] reported that an intraperitoneal injection of 9 mg/kg (1.8 × LD_{50}) DFP in rats protected with pyridostigmine bromide and atropine nitrate, caused tonic-clonic seizures followed by prolonged mild clonic epilepsy, accompanied by early necrotic and delayed apoptotic neuronal degeneration. Early necrotic brain injury was seen between 1 and 12 hours after dosing, in the hippocampus and piriform/entorhinal cortices. On the other hand, typical apoptotic (TUNEL-positive) cell death began to appear at 12 hours in the thalamus. An intraperitoneal injection of 9 mg/kg (1.8 × LD_{50}) diisopropyl phosphorofluridate (DFP) caused severe early (15-90 min) tonic-clonic limbic seizures followed by prolonged mild clonic epilepsy.[97] Necrotic cell death was seen one hour after DFP administration mostly in the CA1 and CA3 subfields of the hippocampus and piriform/entorhinal cortices, which was exhibited as degeneration of neuronal cells and spongiform of neuropils. While the severity of hippocampal injury remained the same up to 12 hours, damage to piriform/entrohinal cortices, thalamus, and amygdala continued to increase up to 12 hours. Furthermore, apoptotic death (TUNEL-positive) of neuronal cells was seen in the thalamus at 12 h and peaked at 24 h. Rats that survived 1 × LD_{50} Sarin (95 µg/kg) exhibited persistent lesions mainly in the hippocampus, piriform cortex, and thalamus.[78] Furthermore, brain injury was exacerbated by time and three months after exposure, other areas that were not initially affected became damaged.

OPICN following Sub-clinical Exposures to Organophosphorus Compounds

Reports on OPICN in individuals following long-term, sub-clinical exposures, without previous acute poisoning have been documented in humans and animals.

Exposure to Low-level Organophosphorus Insecticides

Professional pesticide applicators and farmers who had been exposed to organophosphorus pesticides showed elevated levels of anxiety, impaired vigilance and reduced concentration.[98] A significant increase in hand vibration threshold was reported in a group of pesticide applicators.[99] Male fruit farmers who were chronically exposed to organophosphorus insecticides showed significant slowing of their reaction time.[100] Female pesticide applicators exhibited longer reaction times, reduced motor steadiness, and increased tension, depression, and fatigue compared to controls.[101] Workers exposed to the organophosphorus insecticide quinalphos during its manufacture exhibited alterations in the function of the central nervous system that were manifested as memory, learning, vigilance and motor deficits, despite having normal AChE activity.[102]

Kaplan et al,[103] reported persistent long-term cognitive dysfunction and defects in concentration, word finding, and short-term memory in individuals exposed to low sub-clinical levels of the organophosphorus insecticide

chlorpyrifos. These neurological deficits are in agreement with a recent study that evaluated the effects of chronic low-level exposure to the organophosphorus insecticide, chlorpyrifos in 22 patients for neurobehavioral impairments.[104] The study demonstrated, for the first time, the presence of an association between chlorpyrifos sprayed inside homes and offices and neurophysiological impairments of the body balance, visual fields, color discrimination, hearing, reaction time, and grip strength. Furthermore, these patients also had psychological impairments of verbal recall and cognitive function and two-thirds of them had been prescribed antidepressant drugs. The patients exhibited excessive respiratory symptoms that were accompanied by airway obstruction. Other chlorpyrifos-induced neurotoxicity incidents in humans have been reported.[105]

Published results of chlorpyrifos-induced OPICN in humans are consistent with a recent report that daily dermal application of 1.0 mg/kg chlorpyrifos to adult rats resulted in sensorimotor deficits.[106] Also, maternal exposure to 0.1 mg/kg chlorpyrifos during gestational days 4-20, caused an increased expression of glial fibrillary acidic protein (GFAP) in the cerebellum and hippocampus of offspring on postnatal day 30.[107] A major component of astrocytic intermediate neurofilament, GFAP is upregulated in response to reactive gliosis resulting from insults, such as trauma, neurodegenerative diseases, and exposure to neurotoxicants.[108] Also, daily dermal administration of $0.01 \times LD_{50}$ of malathion for 28 days caused neuronal degeneration in the rat brain that was exacerbated by combined exposure to the insect repellent DEET and/or the insecticide, permethrin.[109]

Exposure to "Sheep dip" Pesticides

A significant cognitive and neuropsychological deficits have been found in sheep dippers who had been exposed to organophosphorus insecticides.[110] Pilkington et al,[111] reported a strong association between chronic low-level exposure to organophosphate concentrates in sheep dips and neurological symptoms in sheep dippers, suggesting that long-term health effects may occur in at least some sheep dippers exposed to these insecticides over their working lives.

Exposure to Low-level Sarin

Rescue workers and some victims who did not develop any acute neurotoxicity symptoms nevertheless complained of a chronic decline of memory, three years and nine months after the Tokyo attack.[112] Upon their return from the Persian Gulf War, thousands of American and British veterans complained of a range of unexplained illnesses including chronic fatigue, muscle and joint pain, headaches, loss of concentration, forgetfulness, and irritability.[113] Many of the military personnel were exposed to low-level of the nerve agent Sarin that was released into the atmosphere in the region at Khamisiya, following the destruction of enemy's arsenal during the war.[114] Follow up studies in rats have established that large toxic doses of Sarin caused acute necrotic death of brain neurons,[69] whereas small doses resulted

in delayed apoptotic neuronal cell death.† Thus, OPICN can explain the report that Persian Gulf War Veterans are at an almost two-fold greater risk of developing ayotrophic lateral sclerosis (ALS) than other veterans.[115] This also is in agreement with the suggestion that the increase in ALS is "a war related environmental trigger".[116]

Exposure to Hydraulic Fluids and Jet Engine Lubricating Oils

Hydraulic fluids and Jet engine lubricating oils have been identified as possible contaminants in the recent incidents of smoke in the cabins of aircrafts.[117] For example, a total of 760 incidents involving 900 flight attendants subsequent to 1989, have been reported.[118] The components of these fluids, that include several organophosphates, have been identified and are listed in Table 3).

Table 3: Components of Some Jet Engine Oils and Hydraulic Fluids

Product	Components (wt%)
Engine lubricating oils	
Mobil Jet Oil 254	Tricresyl phosphate (TCP, 3%)
Mobil Jet Oil II	Tricresyl phosphate (TCP, 3%), N-Phenyl-1-naphthtylamine (PAN, 1%)
Hydraulic fluids	
Skydrol 5 (Solutia Inc.)	Triisobutyl phosphate, Triphenyl phosphate, Epoxy-modified alkyl ester
Skydrol 500B (Solutia Inc.)	Tributyl phosphate, Dibutyl phenyl phosphate, Butyl diphenyl phosphate, Epoxy-modified alkyl ester, 2,6-Di-tert-butyl-p-cresol
Skydrol LD-4 (Solutia Inc.)	Tributyl phosphate, Dibutyl phenyl phosphate, Epoxy-modified alkyl ester
Hyjet IV-A (Chevron)	Tributyl phosphate (79%), Cyclic aliphatic epoxide (<2.9%), Additives (<21%)

Although the main components of tri-cresyl phosphate (TCP) are approximately 15-25% tri-*meta*-cresyl phosphate, 5-10% tri-*para*-cresyl, 60-75% mixed *meta*- and *para*-cresyl phosphates, and small amounts of *ortho*-cresyl isomers (mainly in the mono-*ortho*-cresyl form with low amounts of di-*ortho*-cresyl isomers and minute amounts of the tri-*ortho*-cresyl isomer, resulting in more than ten cresyl isomers. Because jet oils contain up to 3% tri-cresyl phosphate as anti-wear agent, inhalation exposure to the chemical constituents in this product is likely. Although the cholinergic neurotoxicity of TCP isomers is low, six members of this group of chemicals contain one or more *ortho*-cresyl moiety and are capable of causing OPIDN (Table 4).

† Unpublished results.

Table 4: Isomers of Tri-cresyl phosphate (TCP)

There are ten possible TCP isomers:

***Ortho* content**	**Isomers**	**OPIDN**
Tri-*ortho*-TCP	o,o,o	✓
Di-*ortho*-TCP	o,o,m, o,o,p	✓
Mono-*ortho*-TCP	o,m,m, o,m,p, o,p,p	✓
Non-*ortho*-TCP	m,m,m, m,m,p, m,p,p, p,p,p	×

Consistent with this is the finding that inhalation exposure to it, in a manufacturing plant produced toxic polyneuritis.[119] Furthermore, jet engine lubrication oils contain up to 3% TCP, including 0.1% of TOCP,[120] the potent OPIDN producing isomer. Also, long-term inhalation exposure of chickens to concentrations between 23 and 110 mg/m^3 produced neurotoxic effects.[121] It has been suggested, also that humans are 10 to 100 times as susceptible to developing OPIDN as chickens.[122]

Available information suggest that inhalation of jet cabin contaminated air may be related to induction of organophosphate-induced chronic neurotoxicity. Air crew members including, pilots and flight attendants have consistently complained of neurological illnesses, such as headache, dizziness, cognitive dysfunction, difficulty concentrating, tremors and generalized weakness, lack of motor control, typical of OPICN. Although the neurotoxic effects of TCPs have been associated with the ortho isomer, results of experimental studies cannot be explained by the presence of the ortho isomer alone. A recent study reported an unexpected high neurotoxic potency of aviation engine lubricants containing 3% TCP levels and less than 0.02% of the ortho isomer.[123] In addition to the ortho isomer, the presence of TPCP has been confirmed in the two jet engine lubricating oils, Castrol 5000 and Exxon 2380.[124] Furthermore, our preliminary results showed that dermal exposure to each of the three isomers: that is, TOCP, TMCP, and TPCP caused sensorimotor deficits in rats and neuropathological lesions in the brain.[†] Although most of the investigations of cabin air-induced illnesses have focused on OPIDN, TCP and its constituent isomers, other components of the hydraulic fluids and engine lubricating oils should also be studied for their action in producing OPICN. These chemicals include: tributyl phosphate, tri-isobutyl phosphate, butyl diphenyl phosphate, dibutyl phenyl phosphate, and triphenyl phosphate. These chemicals may cause OPICN or contribute to its occurrence.

Neuronal and Glial Autoantibodies as Biomarkers for Neuronal Injury Induced by OPICN

Alterations of the cytoskeletal structure are prominent features in some neurological diseases and chemically induced neurological disorders. Neurofilament (NFP) and Tau proteins are major constituents of the axon and

[†] Unpublished results.

microtubule associated protein-2 (MAP-2) are mostly present in the dendrites. Increased autoantibodies of these proteins are indicative of axonal degeneration. Also, increased autoantibodies against myelin basic protein (MBP) are consistent with axonal demyelination. The increase of glial fibrillary acidic protein (GFAP) autoantibodies is suggestive of neuronal injury.

Sera obtained from eight flight crew members and from healthy adults (controls) were assayed for the presence of autoantibodies against proteins associated with neurogenesis, that is, high molecular weight neurofilament protein (NFP-200), MAP-2, and Tau proteins; myelinogensis, that is, MBP; and gliogenesis, that is, GFAP, that have been used as markers for injury to the central nervous system. Autoantibodies against tubulin, a protein present in all tissues, including the nervous system, have been determined as markers for global tissue damage. Finally, autoantibodies against the glial calcium-binding protein S-100 were determined as markers for acute traumatic brain injury. Autoantibodies against neuronal proteins, NFP-200, MAP-2, Tau proteins, and MBP and those against the protein associated with gliogenesis, GFAP, that were increased in some sera correlated with the neurological condition of the patients.[†] Autoantibodies against the global protein, tubulin, were not significantly higher than controls. Autoantibodies against S-100 protein are used as an internal standard to determine the precision of the assay. The results show that the level of these autoantibodies was low in the patient and controls. The results indicate the high precision of the results. They also suggest the absence of acute traumatic brain injury in the cases and controls.

Many neurotoxicants, such as organophosphorus esters, as well as other insecticides, solvents and heavy chemicals cause neuronal cell death and axonal degeneration and over-expression of GFAP, with subsequent release of neuronal, myelin, and glial proteins into circulation, followed by the formation of autoantibodies against these proteins. While not diagnostic for specific disease, the presence of circulating autoantibodies against neuronal and glial proteins, at higher levels in patients who had been exposed to neurotoxic chemicals and developed neurological deficits, over that of controls, can be used as further confirmation for chemical-induced nervous system injury. The low level of autoantibodies of S100 protein in the serum indicates that the neuronal condition is not related to an acute injury, but is rather a chronic condition.

The serum profile of increased autoantibodies against nervous system proteins in flight crew members, is consistent with neurological deficits and in the absence of other neurological diseases, it is concluded that it is consistent with chemical such as TCP-induced nervous system injury.

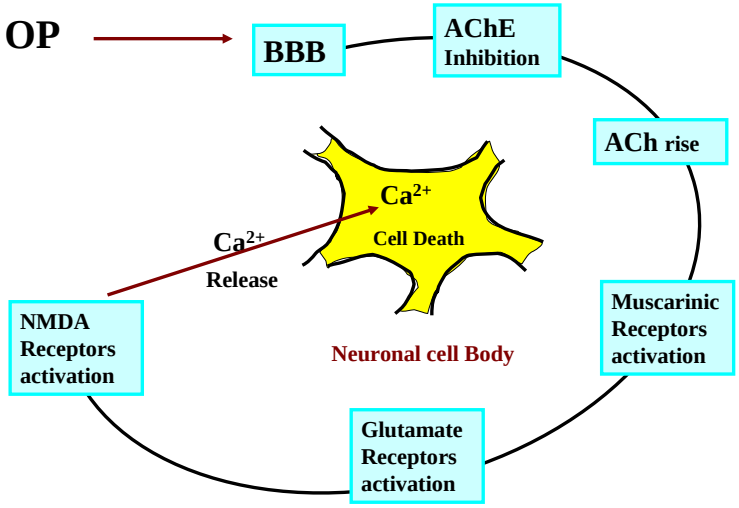
Mechanisms of OPICN

Recent studies have shown that large toxic doses of organophosphorus compounds cause early convulsive seizures and subsequent encephalopathy,

leading to the necrotic death of brain neuronal cells, whereas small doses produce delayed apoptotic death. Pazdernik et al,[91] have proposed the following five phases that result in organophosphorus compound-induced cholinergic seizures: initiation, limbic *status epilepticus*, motor convulsions, early excitotoxic damage, and delayed oxidative stress.

Necrosis: In addition to breaking down the blood brain barrier and producing early seizures, large toxic doses of organophosphorus compounds result in the activation of the glutamatergic system and the involvement of Ca^{2+}-related excitotoxic process,[119,120] possibly mediated by the *N*-methyl-*D*-aspartate (NMDA) sub-type of glutamate receptors.[125,126] Accumulated ACh, resulting from acute inhibition of AChE by organophosphorus compounds, leads to activation of glutamatergic neurons and the release of the excitatory L-glutamate amino acid neurotransmitter,[92] that is a major agonist of NMDA receptors and a major excitatory neurotransmitter in the CNS as well as being a potent excitotoxin.[127] This leads to increased depolarization and subsequent activation of the NMDA subtype of glutamate receptors, and the opening of NMDA ion channels, resulting in massive Ca^{2+} fluxes into the postsynaptic cell and the disruption of postsynaptic calcium homeostasis.[128] This results in the production of free radicals and degradation of intracellular components and mitochondrial damage, and causing neuronal degeneration (see Figure 10).[129]

Figure 10: Cholinergic Cascade Following a Large Toxic Dose of Organophosphate (OP)



Activation of nitric oxide synthase, following stimulation of NMDA receptor increases the level of nitric oxide, which functions as a signaling or cytotoxic molecule responsible for neuronal cell death.[130] As a retrograde messenger, nitric oxide induces the release of several neurotransmitters including excitatory amino acid L-glutamate (131) which alters neurotransmitter balance and affects neuronal excitability.[131] The production of nitric oxide is enhanced in AChE inhibitor-induced seizure.[132,133] Kim et al,[97] have demonstrated the involvement of nitric oxide in organophosphate-induced

seizures and the effectiveness of nitric oxide synthesis inhibitors in preventing such seizures.

Apoptosis: Small doses of organophosphorus compounds cause delayed neuronal cell death that involves free radical generation, that is, reactive oxygen species (ROS). Organophosphates that cause mitochondrial damage/dysfunction, cause depletion of ATP and increased generation of ROS, which results in oxidative stress.[134,135] ROS cause fatal depletion of mitochondrial energy (ATP), induction of proteolytic enzymes and DNA fragmentation, leading to apoptotic death.[131,136,137] These results are consistent with the DNA damage detected in the lymphocytes in peripheral blood in eight individuals, following residential exposure to the organophosphorus insecticides chlorpyrifos and diazinon.[138] The brain is highly susceptible to oxidative stress-induced injury for several reasons: its oxygen requirements are high; it has a high rate of glucose consumption; it contains large amounts of peroxidisable fatty acids; and it has relatively low antioxidant capacity.[136,137] A single sub-lethal dose of $0.5 \times LD_{50}$ Sarin, that did not induce seizures, nevertheless caused delayed apoptotic death of rat brain neurons in the cerebral cortex, hippocampus, and Purkinje cells of the cerebellum 24-h after dosing.[90,†] Furthermore, rats treated with a single $0.1 \times LD_{50}$ dose of Sarin which did not exhibit brain histopathological alterations 1, 7 or 30 days after dosing, nevertheless showed apoptotic death of brain neurons in the same areas mentioned above, one year after dosing.[69,†] These results are consistent with the sensorimotor deficits exhibited by Sarin-treated animals three months after exposure; the animals continued to deteriorate when tested six months after dosing.

Increased AChE gene expression: Recent studies suggested that AChE may play a role in the pathogenesis of OPICN, similar to that reported for Alzheimer disease.[139,140] We have demonstrated that Sarin induced AChE gene in the same regions of the brain that underwent neuronal degeneration.[141] AChE has been shown to be neurotoxic *in vivo* and *in vitro*, and accelerate assembly of amyloid peptide in Alzheimer's fibrils, leading to death through apoptosis.[142] Further studies demonstrated increased AChE expression in apoptotic neuroblastoma SK-N-SH cells after long-term culture.[142] These results support the association between AChE and neuronal apoptosis in Alzheimer's disease. Brain AChE was shown to be toxic to neuronal (Neuro 2a) and glial-like (B12) cells.[140] Also, transgenic mice over-expressing human AChE in brain neurons underwent progressive cognition deterioration.[143] The results suggest that Sarin provokes an endogenous cell suicide pathway in susceptible neurons such as caspase-3 pathway, resulting in the release of AChE into adjacent brain tissues. AChE aggregates and initiates more apoptotic neuronal death. Thus this cascade amplification results in the progressive neuronal loss that is the hallmark of Sarin-induced chronic neurotoxicity. It is noteworthy, that a common symptom of both OPICN and

† Unpublished results.

Alzheimer's disease is memory deficit, suggesting that OPICN accelerate aging process following exposure to organophosphorus compounds.

CONCLUSIONS

Previous reports have indicated that after exposure to organophosphorus compounds, an individual could develop acute cholinergic neurotoxicity, followed by OPICN. In a few cases, OPIDN may occur with or without the development of cholinergic neurotoxicity and then latter, OPICN ensues. Furthermore, OPICN may take place after long-term, low-level exposure to organophosphorus compounds and without the development of acute neurotoxicity. Because the long-term, persistent effects of OPICN result from neuronal degeneration of the peripheral and central nervous systems induced by organophosphates, it is unlikely that improvement is the consequence of the regeneration of brain neurons, since such repair phenomenon is not typical of the CNS. Clinical improvement may take place, however, through the repair of the PNS. Also, reversible changes in the CNS that might be initially present (for example, edema), could later subside, and result in the appearance of repair. Furthermore, if the damage is not too extensive, other neurons having the same function could meet the added demands and maintain normal activity. When the central nervous system is severely damaged, neither of these repair mechanisms is possible and some loss of function could occur.

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From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 91-98.

IN FLIGHT SMOKE AND FUMES

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BIOGRAPHICAL SKETCH

Dr Bhupinder Singh has a MB BS (1969), Diploma Aviation Medicine (1976), and MD in Aviation Medicine (1983). He is a qualified fighter pilot and has flown many types of jet fighters with the Indian Air Force. He has served with the Indian Air Force for 22 years, as an aviation medicine specialist; retired voluntarily as WGCDR in 1993. Dr Singh was an instructor at the IAF Institute of Aviation Medicine at Bangalore, and also Asst Professor of aviation medicine at Bangalore University. He was admitted to the International Academy of Aviation and Space Medicine in 2003. Subsequently, designated as a Senior Aviation Medical Examiner for the FAA and CASA and worked for two years as Chief Medical Officer for the civil aviation authority of Oman and as Head, Airport Clinic at Muscat, Oman. Dr Singh has been working as Senior Research Officer at the RAAF Institute of Aviation Medicine in Edinburg, South Australia for the last 6.5 years. He has a number of research papers, journal publications, and presentations to his credit.

INTRODUCTION

The occurrence of smoke and/or toxic fumes in the aircraft cockpit or cabin is more common than is generally realised, and it is a hazard which endangers the health and lives of aircrew and may limit their capability to deal with the source of the problem.

THE EXTENT OF THE PROBLEM

The reported incidence of in-flight smoke and fumes in Australian Defence Force (ADF) aircraft was calculated by reviewing the number of Aviation Safety Occurrence Reports (ASORs) raised for such incidents in last five years, and also determining the quantum of flying undertaken during that period. For every 2000 hours of flying operations conducted in the ADF, one incident of in flight smoke/fumes is being reported (or 0.5 per 1000 hrs). The incidence is very similar in the Air Force and the Navy, but is almost half as that of the Army (Table 1 below).

Table 1: Incidence (ASORs) of Smoke and Fumes per 1,000 flying hours

Service	Incidence
All ADF	0.523
Royal Australian Air Force	0.582
Australian Army	0.288
Royal Australian Navy	0.665

The incidence varies significantly from one aircraft type to the other, as seen in Table 2 below.

Table 2: Incidence (ASORs) of Smoke and Fumes per 1000 flying hours

Aircraft Type	Incidents
CL604 Challenger*	2.498
Sea King	1.599
P3C Orion	1.588
HS748	1.196
CT4B	1.012
F111	0.941
Hawk127	0.879
Caribou	0.813
Falcon900	0.726
King Air (AF)	0.671
Iroquois	0.668
B707	0.660
Squirrel	0.628
C130	0.521
DHC6 Twin Otter	0.431
PC9	0.428
Black Hawk	0.385
Sea Hawk	0.381
F/A18 Hornet	0.352
Chinook	0.162
Kiowa	0.113
King Air (Army)	0.077

* *CL604 Challenger data since 2002/2003*

SOURCE OF SMOKE AND FUMES

Smoke or fumes can originate from a variety of sources. The immediate cause is usually a leakage, over-heating, or burning of various materials. Some common sources are listed below.

- Aircraft materials (insulations, cables, composites etc)
- Batteries
- Radioactive substances
- Ordinance
- Fuels
- Hydraulic fluids
- Lubricants
- Fire extinguishing agents
- De-icing fluids
- Oxygen system impurities
- Ozone

In flight smoke/fumes may contain a variety of toxic substances. Some potential contaminants and their concentrations for situations where smoke protection equipment is required are listed in Table 3.

Table 3: Potential Contaminants and their Concentrations

Contaminant	Potential Level	
Carbon Dioxide (CO_2)	35,000 ppm	(3.5%)
Carbon Monoxide (CO)	10,000 ppm	(1.0%)
Hydrogen Chloride (HC1)	1,000 ppm	(0.1%)
Hydrogen Fluoride (HF)	1,000 ppm	(0.1%)
Hydrogen Cyanide (HCN)	400 ppm	(0.04%)
Oxides of Nitrogen (N_xO_x)	200 ppm	(0.02%)
Acrolein	50 ppm	(0.005%)
Ammonia (NH_3)	1,000 ppm	(0.1%)
Hydrogen Bromide	1,000 ppm	(0.1%)
Total Hydrocarbons	5,000 ppm	(0.5%)
Sulphur Dioxide	100 ppm	(0.01%)
Particulates (0.5-10 micron)	3.5 mg/Litre	

EFFECTS OF TOXIC SUBSTANCES

Most of the contaminants enter the body through inhalation, and many are highly toxic, even in extremely small amounts. Short-term exposure may cause irritation of the respiratory passage, cough, shortness of breath, light-headedness, dizziness, and confusion. Skin irritation, nausea, abdominal cramps, and vomiting may also occur.

There is some evidence that continued exposure to small amounts of certain contaminants may produce chronic, long term, and irreversible damage to humans. Blood disorders, and damage to lungs, liver and kidney may occur. Some toxins may be potentially carcinogenic, that is, cancer causing. Unfortunately, specific information relating to such effects is very limited, since by its very nature, no human research is possible due to ethical considerations. Animal research has its limitations when extrapolated to humans. Consequently, most of the evidence is presumptive.

The aircraft cockpit and cabin are unique workplaces that cannot be compared with industrial and other workplaces on the ground. Aircrew members are required to perform complex tasks requiring high level cognitive skills, which may be much more sensitive to insult by hazardous contaminants in the smoke/fumes, such as Tricresyl Phosphate (TCP). Therefore, the maximum permissible limits for safe exposure recommended by the US Occupational Safety and Health Administration (OSHA), the American Council of Governmental Industrial Hygienists (ACGIH) or the Australian National Occupational Health and Safety Commission (NOHSC) for industrial workers cannot be applied to aviation.

Various Australian Defence Force (ADF) agencies charged with that role are constantly working to eliminate, or minimise to the extent possible, exposure to all hazardous contaminants at workplace.

AIRCREW PROTECTIVE SYSTEMS

A system is required which can provide protection to aircrew while combating the emergency (of in flight smoke/fumes), and performing other essential duties at the same time. The requirement is for a device, or a system, to keep the contaminant(s) out of the breathing system, and also protect the eyes from exposure to toxic substances. Ideally, such a system would consist of a full-face mask to protect the eyes, the mouth, and the nose; and a closed-loop breathing system to prevent the inhalation of contaminated cabin air.

In addition, in all cases of in flight smoke and fumes, it is highly desirable that the cabin is flushed out to get rid of the contaminant(s) and avoid continued exposure, which means depressurising the aircraft if flying at altitude. If the incident occurs at an altitude of more than 10,000 feet, depressurising the aircraft will also bring in the problem of hypoxia, which will require supplemental oxygen for the aircrew. Therefore, unless the problem of smoke and fumes occurs at an altitude of less than 10,000 feet, provision of supplemental oxygen must form a necessary part of the solution.

Most national and international regulations mandate that 100% oxygen should be available for all aircrew for a period of 15-25 minutes. This is based on the time required to descend to a safe altitude of about 10,000 feet. However, the time required to descend may sometimes be much longer due to geographic or operational considerations, in which case a larger amount of oxygen will need to be made available. The cockpit crew will generally have a plumbed oxygen system, and the amount of oxygen is not a constraint. However, the backend and mobile aircrew need to carry a portable oxygen system, which limits the maximum amount of oxygen that can be provided. Detailed requirements for smoke protection breathing equipment for mobile aircrew have been specified by the Allied Nations interoperability agency, the Air Standards Coordinating Committee (ASCC), in Air Standard 61/101/15 (see Figure 1 below).

Figure 1: Smoke Breathing Requirement for Mobile Aircrew

Smoke Protection Breathing Equipment for Mobile Aircrew
(Ref: ASCC Air Standard 61/101/15)

- Man-mounted when in use.
- Provide both respiratory and eye protection
- Comfortable to wear
- Easy and functional donning within 10 seconds with minimal training.
- Hands free operation without restricting mobility or vision.
- Free of any features that may snag or entangle.
- Easily adjustable with a range of no more than 3 sizes to fit all.
- Compatible with the aircraft communication system and with spectacle use.
- Able to be stowed compactly and securely without causing an unacceptable hazard.
- Made of flame retardant, puncture-resistant, and tear-resistant materials.
- Able to withstand high thermal loads.
- Able to perform satisfactorily when donned at any time in the breath cycle.
- Able to be turned on and off, and prevent inadvertent activation/deactivation.
- Must include a gauge/indicator for the quantity of oxygen/air remaining and a device to indicate proper regulator operation.
- A demand system able to provide uncontaminated air/oxygen at high flow rates. Able to avoid significant inward leakage of contaminant gases.
- Able to provide a supply of breathing gas for 25 minutes for an active aircrew.

It is important not to confuse a smoke/fumes situation with incidents of loss of cabin pressure, wherein there is no need for a closed-loop oxygen system, and the aircrew can breathe a mixture of oxygen and air by selecting "airmix" on the regulator. Breathing on "airmix" increases the endurance of the oxygen system many-fold.

The only practical method of providing oxygen in a portable system is to carry gaseous oxygen under high pressure in metallic cylinders. Steel cylinders are heavier but can withstand higher pressures than most cylinders made of lighter materials. As a result, aircraft are able to carry greater amounts of oxygen in steel cylinders.

Oxygen hoods are commonly used in aviation. These devices provide oxygen from a small cylinder into a transparent hood sealed at the neck. The oxygen is re-breathed continuously from the hood, while a chemical scrubber absorbs the exhaled carbon dioxide. The major disadvantages of such a system are that it is incompatible with the aircraft communication systems, degrades the visibility, and produces heat around the neck (from CO_2 scrubbers) that may become intolerable at high workloads. Most importantly, the endurance of an oxygen hood is only a few minutes, especially at high workloads when it may last for not more than five minutes. However, oxygen hoods are useful for sedentary passengers waiting to be rescued.

Chemical oxygen generators are unsuitable for aircrew, as they can not be switched "off" once they are activated, and they also generate heat when in operation. Liquid oxygen and on-board oxygen generators (OBOGS, molecular sieve) are too complex and cumbersome for use in a portable system.

Air filters used by earth-bound fire fighters have a very limited role, if any, in the air. The number of potential contaminants in the air is large and varied, making it impossible to find a filter that will eliminate all contaminants.

Unfortunately, none of the portable oxygen systems currently available for mobile aircrew to deal with an in flight smoke/fumes situation is fully satisfactory. In such a situation, some compromises may have to be made, and a robust risk management plan needs to be put in place, based on the specific requirements and threat perceptions of each operation.

MANAGEMENT OF SMOKE/FUMES INCIDENT IN THE AIR

Flying units need to have their own Standing Instructions for dealing with incidents of smoke /fumes in the air. The strategy should be to immediately commence breathing 100% oxygen with the toggle down to prevent inboard leakage of cabin air into the mask and investigate the problem. If the problem persists, the aircraft should be descended to safe altitude as soon as possible, and then depressurised to ventilate the cabin, followed by a return to the base or landing at the nearest suitable airfield, if warranted. All cases are subject to reporting and investigation requirements. Each case needs to be evaluated on its merit, and decisions taken after considering all the factors, including operational imperatives, flight safety, and OHS guidelines.

Aircrew members who may have had a significant exposure to smoke or fumes need to consult a doctor for observation and further investigations. The determination as to whether the exposure is significant or not should be based on common sense and on factors such as the period of exposure and symptoms experienced. When in doubt, an exposure should be assumed, and medical/AVMED consulted. The protocol recommended by the RAAF Institute of Aviation Medicine (AVMED) for the medical management of exposure to smoke and fumes is given in Appendix 1 below. Further work is in progress to develop this policy.

Appendix 1: Institute of Aviation Medicine Royal Australian Air Force

GUIDELINES FOR THE MEDICAL MANAGEMENT OF AIRCREW EXPOSED TO SMOKE AND FUMES

Aircrew presents to medical section after a Smoke and Fumes incident.

1 **IF** patient is Asymptomatic **THEN**
- Observe for 20 minutes
- Go to Step 3 or 4.

2 **IF** patient is Symptomatic **THEN**
- Place patient on 100% oxygen for 20 minutes
- Obtain a brief history of the patient and the incident
- Perform a Clinical assessment
- Obtain Spirometry reading
- Determine blood Oxygen saturation
- Complete Physiological Incident Report
- Go to Step 5 or 6.

3 **IF** patient is Asymptomatic **THEN**
- Return to flying duties.

4 **IF** patient becomes Symptomatic **THEN**
- Go to Step 2.

5 **IF** patient becomes Asymptomatic **AND** the tests are normal **THEN**
- Return to flying duties.

6 **IF** patient remains Symptomatic **OR** the tests are abnormal **THEN**
- Perform a Clinical Review
- Admit patient for Observation
- Perform a Chest X-Ray
- Perform FBC, LFT, and Biochemistry tests
- Proceed to Step 7 or 8.

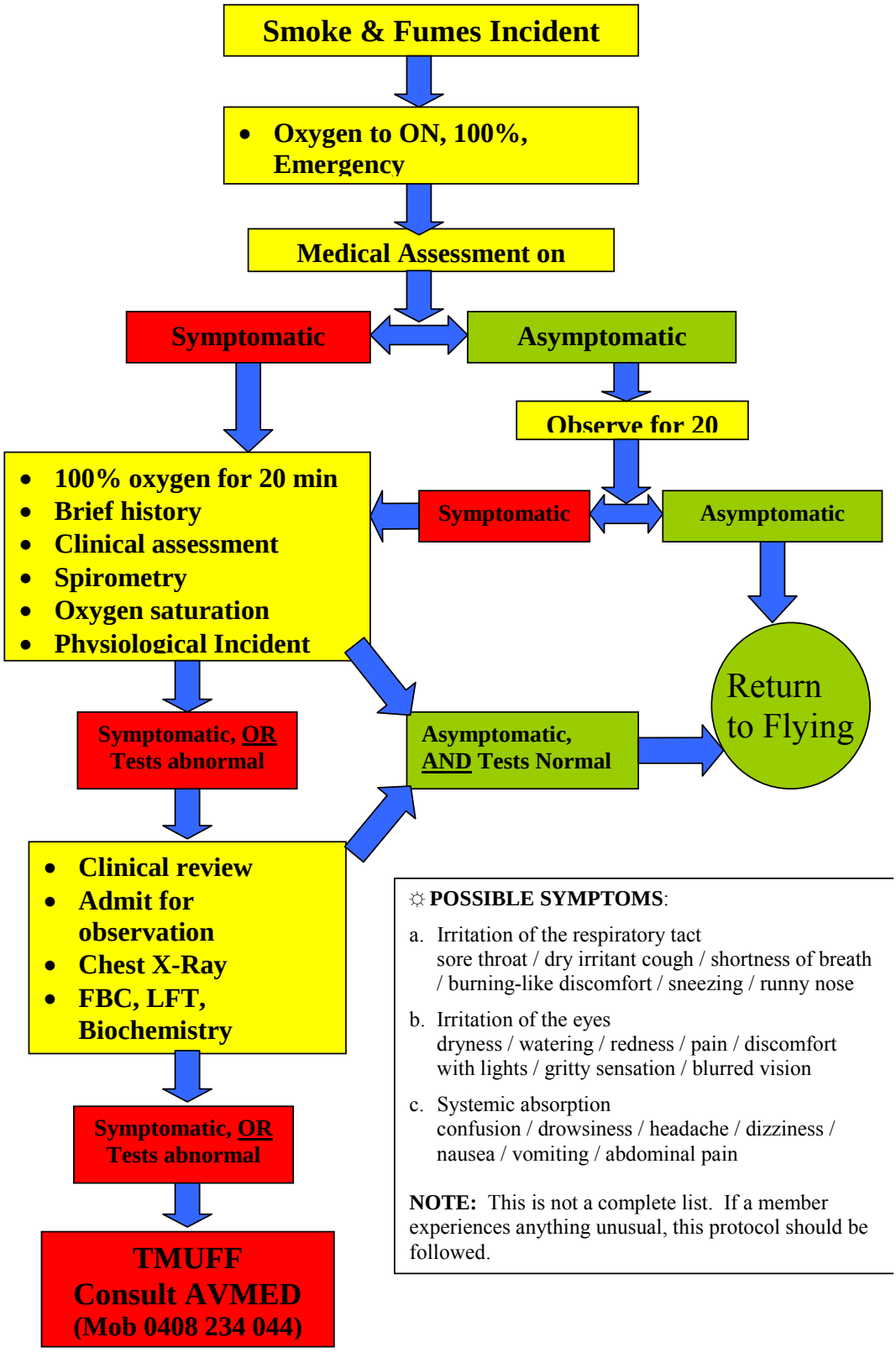
7 **IF** patient becomes Asymptomatic **AND** the tests are normal **THEN**
- Return to flying duties.

8 **IF** patient remains Symptomatic **OR** the tests are abnormal **THEN**
- Declare the patient TMUFF
- Consult AVMED for further disposition of the case.

NOTE: In **ALL** cases, a full record of all actions must be kept in the treating clinic and copies sent for the member's medical file.

Flow chart on next page

Figure 2: AVMED Flow Chart for the Medical Management of Aircrew Exposed to Smoke and Fumes w



From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 99-104.

ENGINE BLEED AIR CONTAMINATION IN MILITARY AIRCRAFT

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BIOGRAPHICAL SKETCH

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ABSTRACT

One of the most common and potentially hazardous sources of aircraft cockpit/cabin air contamination is the entry of jet engine oil into the engine bleed air supply. This is due to the presence of tricresyl phosphates (TCP), phenyl-α-naphthylamine (PAN) and dioctyldiphenylamine (DODPA) in modern jet engine oils. In addition, thermal decomposition of the oil can produce irritating and odorous products. On occasions there have been health problems amongst passengers and crew who have been exposed to smoke/fume incidents originating from engine bleed air. Although the effects have been attributed to these compounds, to date their presence has not been quantified.

Currently an attempt is being made to determine the cockpit air concentrations of TCPs in a survey of Australian military aircraft with a history of bleed air contamination (smoke/fumes). The results from three types of aircraft have indicated the presence of TCP in the bleed air heat exchangers and coalescer bags as well as low concentrations of TCP in the cockpit air. Recently PAN and DODPA have also been detected at similar concentrations.

INTRODUCTION

Cockpit/cabin air contamination in both military and commercial aircraft has a number of sources. In recent years contamination from the engine bleed air supply has been of foremost concern. This is due to the presence of potentially neurotoxic tricresyl phosphate (TCP) anti-wear additive in jet engine oil and amine anti-oxidants which are potential irritants.[1,2,3] Although there has been much speculation about the hazards of cabin air contamination from jet engine oil additives, there have been no reported measurements of these compounds in cockpit/cabin air. However, TCP had

been previously detected in the engine bleed air system of an Australian Defence Force (ADF) turbo-prop aircraft.[4]

A survey of ADF aircraft, by the Institute of Aviation Medicine (Royal Australian Air Force) over the past five years has catalogued the incidence (Aviation Safety Occurrence Reports) of smoke and fumes in the cockpit/cabin.[5] As a result of these occurrences, a survey of TCP air concentrations was conducted in three types of ADF aircraft. Amine concentrations were determined in one aircraft type.

In the turbo-prop and fighter aircraft, smoke and odour incidents were observed by crews to occur at high engine thrusts. These conditions were most likely to arise during take-off and ground engine runs at high power. The source of air contamination in the trainer aircraft was the auxiliary power unit (APU) which was used only on the ground.

Depending on the aircraft type, air contamination was perceived as smoke or fumes (odour). The fighter and trainer aircraft were associated with smoke contamination while the turbo-prop aircraft was reported to produce "smelly" bleed air. All aircraft used jet engine oils made to military specification MIL-PRF-23699. The oils are known to contain TCP and amine-oxidants.[1]

METHODS

Cockpit Air Sampling

Long Duration

Long duration air sampling was carried out using sorption tubes connected to a metering pump (for example, Aircheck™ model 2000) operating at 2 L/min. Glass-lined stainless-steel tubes (90mm x 6mm outside diameter) packed with approximately 0.06g Porapak Q™ and held in place with glass wool. The packed tubes were washed with iso-hexane (6 mL) and heated at 220°C in an oven while purged with helium (70 mL/min) for 2 hours. The tubes were then cooled and capped with in-house polymeric end-caps before and after air sampling.

The air sampling was carried out in the cockpit/flight deck, during operational flights with the sorbent tube located as close as possible to an air vent. The sampling was conducted by flight crew with the sampling period varying between 2-6 hours depending on the aircraft type and sortie.

Short Duration

High volume, short duration (below 20 min) air sampling was carried out using Pall Corporation Metricel™ membrane filters (0.8 μm) GN (glass filled nylon). These were conducive to the high flow rate required and the likelihood of aerosols being present. They were used in conjunction with a battery (12 V) powered diaphragm pump (Thomas 107 series), operated at 36 L/min. This protocol was used for static engine test runs with the aircraft in a

fixed location on the ground. Air samples were taken by the ground crew with the engines at high throttle (~80%).

Extraction of TCP and Amines from Sorbents and Filters

The sorbent tubes were washed with iso-hexane (7 mL) and the washings were evaporated to ~1 mL. The Metricel™n-filters were immersed in iso-hexane (20 mL) and sonicated for 5 min. The filters were then removed and the solution was evaporated to 1 mL.

Analyses of TCP Sorbent/Filter Extracts

Gas Chromatography

Samples containing organophosphate species were routinely analysed by gas chromatography using a Varian CP-3800 equipped with a pulsed flame photometric detector (PFPD), flame ionisation detector (FID) and CP-8400 autosampler. Separation was conducted with a Varian CP-Sil 8 MS (30 m × 0.32 mm × 0.25 μm) column with a carrier gas (high purity helium) flow rate of 1.2 mL/min. The injector temperature was set to 320°C and the injector operated in a splitless mode for 0.7 sec, then in a split (100:1) mode. The initial oven temperature was 120°C and held for 2 minutes, then ramped at 20°C/min to 300°C and held at this temperature for 5 min.

The PFPD was operated at 325°C with a phosphorous filter, a gate delay of 4.0 msec, a gate width of 10.0 msec and a trigger level of 200 mV. The Air 1 flow was set to 15.0 mL/min, the Air 2 flow at 10.0 mL/min and hydrogen flow at 14.0 mL/min.

Analysis of amines

DODPA and PAN were analysed by ms/ms using a Varian CP-3800 gas chromatograph coupled to a Varian Saturn 2000 ion trap mass detector. Gas chromatographic conditions were identical to those used for the analysis of TCPs.

The mass spectrometer was operated in the ms/ms mode. The scan range was 33-250 *m/z* (PAN), 33-330 *m/z* (DODPA) with a scan time of 0.38 sec/scan (PAN) and 0.40 sec/scan (DODPA). The emission currents were 50 μA, the excitation storage levels were 75 *m/z* and the excitation amplitudes were 52V for both compounds for both compounds. The parent ions occurred at 219 *m/z* (PAN) and 322 *m/z* (DODPA).

The trap temperature was 160°C, the transfer line temperature was 170°C and the manifold temperature was 80°C.

Chemical Reference Standards

PAN and TCP were purchased from Aldrich Chemicals. The RT Vanderbilt Company, Inc., (Norwalk, CN) kindly supplied a sample of DODPA (octylated diphenylamines, Vanlube™ 81).

RESULTS AND DISCUSSION

TCP

TCP was detected in all coalescer bags tested. They are used to condense water in the engine bleed air supply and represent the final stage in the engine bleed air treatment process after cooling through heat exchangers. Their contamination with TCP was indicative of likelihood of TCP entering the cockpit/cabin air. Approximately half of the aircraft tested had quantifiable concentrations of TCPs in the cockpit/cabin air.

The results of retrospective air monitoring for total TCPs in three types of ADF aircraft are shown in Table 1. The smoke and odour incidents reported were rare and did not correlate with elevated TCP concentrations.

Table 1: Organophosphorus Compound Concentrations in Cockpit Air

Aircraft Type	TCP Concentration (μg m³) (Sample Time)				Samples (In flight, Ground)
	In flight		Ground Engine Runs		
	Mean	Maximum	Mean	Maximum	
Jet Trainer†	-	-	2.1 (9-46 min)	22(10 min)	-, 14
Turbo-Prop	0.006 (2-8 h)	0.052 (5.2 h)	0.19 (2-6 h)	0.26 (2 h)	31, 2
Fighter	0.02 (1-2 h)	2.1 (25 min)	0.80 (10-20 min)	3.2 (20 min)	20, 12

† Air samples taken during the operation of the APU.

The highest TCP concentrations were found to occur in the jet trainer aircraft. One air sample was taken from each aircraft. The concentrations were below 4 μg/m³ with the exception of one aircraft (22 μg/m³).

The lowest TCP concentrations were found in the turbo-jet aircraft. This may be due to a number of factors including the lower operating engine temperatures, longer ducting and better engine oil seals.

The highest recorded TCP concentration was well below the time weighted average (TWA) exposure standard of 100 μg/m³ (based on tri-ortho-cresyl phosphate).[6,7] A recent study of the jet engine oil used in these aircraft has indicated a total TCP concentration of approximately 3% in the oils. The concentrations of ortho-cresyl TCP isomers in recent batches of oil are very low (1300-1600 ppm of the TCP).[8] At these low concentrations the ortho-cresyl isomers are present almost exclusively in the form of the mono-ortho-cresyl-di-meta/para-cresyl phosphate.

A total TCP concentration of 4 μg/m³ would correspond to 0.05-0.08 μg/m³ of the mono-ortho-di-meta/para-cresyl phosphate. Although these isomers are

considered to be ten times more toxic than tri-ortho-cresyl phosphate the levels are still very low.

PAN and DODPA

The jet engine oils contained approximately 1% of both PAN and DODPA amine antioxidants.[8] The concentrations of PAN and DODPA sampled from the flight deck air of the turbo-prop aircraft are presented in Table 2 and are of the same order as the TCP concentrations for the same aircraft type reflecting the low volatility of these compounds. The absence of an established exposure limit for the two amines is indicative of their relatively low toxicity. The concentrations measured are low and hence unlikely to be a health concern.

Table 2: PAN and DODPA Concentrations in the Flight Deck Air of a Turbo-Prop Aircraft

Amine	Amine Concentrations (μg/m^3) (Sample Time)				Samples (In flight, Ground)
	In flight		Ground Engine Starts		
	Mean	Maximum	Mean	Maximum	
PAN	0.043 (2-7h)	0.081 (5h)	0.029 (2-6h)	0.055 (2h)	-
DODPA	0.006 (2-7h)	0.040 (5h)	0.026 (2-6h)	0.039 (2h)	7, 2

According to a review published in 1993 by the German Chemical Society, the acute toxicity of PAN is low as shown by tests conducted on laboratory animals. It has been stated that PAN is not regarded as a skin irritant in humans, although it has been associated with cases of allergic contact dermatitis.[9]

DODPA is also regarded as being of low acute toxicity as indicated by studies with laboratory animals. There have been no reports of adverse health effects on humans and neither DODPA nor PAN is registered on the NOHSC *Designated List of Hazardous Substances*.[7]

CONCLUSIONS

The concentrations of the jet engine additives, TCP, PAN and DODPA were measured in ADF aircraft cockpit air. The concentrations of total TCP isomers were found to be less than 4 μg/m^3 (with the exception of one air sample) and significantly less than the maximum allowable time weighted average (TWA) exposure level of 100 μg/m^3. The concentrations of the two amine anti-oxidants (PAN and DODPA) were also low (below 0.1 μg/m^3) and with no exposure limit for comparison it is assumed that they do not pose a health risk at these concentrations.

Under these circumstances those airline workers at a greater risk from TCP exposure are the engine maintenance mechanics who come into skin contact with the jet engine oil containing 3% TCP rather than the flight crews.

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From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 105-110.

CLINICAL EVALUATION OF FLIGHT ATTENDANTS AFTER EXPOSURE TO FUMES IN CABIN AIR

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BIOGRAPHICAL SKETCH

Dr Gunnar Heuser (contributing author) was born in Germany and obtained his MD degree at the University of Cologne in Germany. Shortly after this he emigrated to Canada where he obtained a PhD degree (in experimental medicine) at the University of Montreal and a Diploma in Internal Medicine at McGill University. While in Montreal, Dr Heuser developed a special interest in the effects of hormones on the brain and described seizures, anesthesia, and natural sleep as conditions which can be induced by certain steroid hormones. He then accepted an offer from UCLA and became a fulltime member in the Division of Endocrinology, Department of Medicine. In addition, he became a member of the Brain Research Institute at UCLA and functioned as a Clinical Neurophysiologist, advising neurologists and neurosurgeons in the latest techniques of studying the electrical activity of the brain. On the medical side, he participated in a number of clinics and taught in the Neuro-endocrine Clinic, Neurology Clinic and later on the Pain Clinic at UCLA as an attending physician. Eventually, Dr Heuser transferred to a clinical position at UCLA and started in private practice in which clinical toxicology developed into a sub-speciality. Dr Heuser has coauthored several books and written numerous scientific papers and abstracts. He has been an invited speaker all over the United States and Canada as well as Europe, South America, and Australia. He is in essence an "in the trenches" physician who has used his experience as much as possible to inform the public and his colleagues of the potentially devastating effects of toxic exposure. His motto is … "healing with science and compassion".

ABSTRACT

Twenty six flight attendants were carefully examined after an in flight neurotoxic injury. Our examination included a physical examination, a neuropsychological examination, and a Positron Emission Tomography (PET) functional brain scan. Significant abnormalities were found and combined to arrive at a diagnosis of toxic encephalopathy in our subject population. There is an urgent need to establish a protocol so that flight personnel can be properly examined when developing complaints following a potentially neurotoxic injury.

INTRODUCTION

Pilots, flight attendants and passengers travel in an artificially controlled environment which may become toxic. This happened to twenty six flight attendants flying in a North American airline that we saw after toxic exposure

incidents. In this case fumes emanated from the Auxiliary Power Unit [APU] and found their way into the cabin air.

Flight attendants developed multisystem, often disabling complaints for which they were carefully evaluated. Many of these complaints were neurotoxic in nature and were therefore addressed whenever possible, not only with a neuropsychological evaluation, but also with a Positron Emission Tomography (PET) functional brain scan and a careful neurological examination. It should be noted that their complaints had not always been properly and thoroughly evaluated by their workers' compensation physicians and were therefore often trivialized.

We have had a special interest in functional (as opposed to structural MRI) brain scans in the past and have published a detailed analysis of SPECT (Single Photon Emission Computed Tomography) brain scans[1] and PET brain scans[2] in subjects after neurotoxic exposure.

In view of the above, we undertook a careful evaluation of all twenty six flight attendants. Not published here are additional evaluations of other flight personnel we have also seen in recent years.

METHODS

Experimental Subjects

All subjects agreed in writing to publication of their data following deletion of their names. All had experienced exposure to cabin fumes on one or multiple occasions. This exposure was often documented with flight interruption, emergency room visits, sick leave and visits to personal or workers' comp physicians.

Relevant details of the subject population are shown in Table 1. For confidentiality and ethical reasons, the names of our subjects were omitted. We have also omitted the ages so that subjects or others do not easily recognize our subjects by name. In the PET column: Only a limited number of PET scans have been conducted. However, all scans carried out in this group were abnormal. Blank spaces indicate that no PET scan was done on a given subject.

Positron Emission Tomography (PET)

The methodology has been published previously.[2] PET scans were conducted at the University of California at Irvine (UCI) and under the direction of Dr JC Wu, who interpreted the results. A PET scan consists of the intravenous administration of radioactive F-18 deoxyglucose (FDG) to the subject following which the radioactivity in different regions of the brain is assessed. Uptake of FDG is a measure of the metabolism of the brain cells.

The scans were conducted after the subject had been engaged in a continuous performance task. This was used to alert the subjects.

Neuropsychological Evaluation

This was conducted by a board certified neuropsychologist with experience in the evaluation of subjects after neurotoxic exposure.

Physical Examination

This included a neurological exam which was done by the senior author [GH] who over the years had examined several thousand subjects after neurotoxic exposure.

RESULTS

Description of subjects and results of neuropsychological and neurological/physical examinations are shown in Table 1.

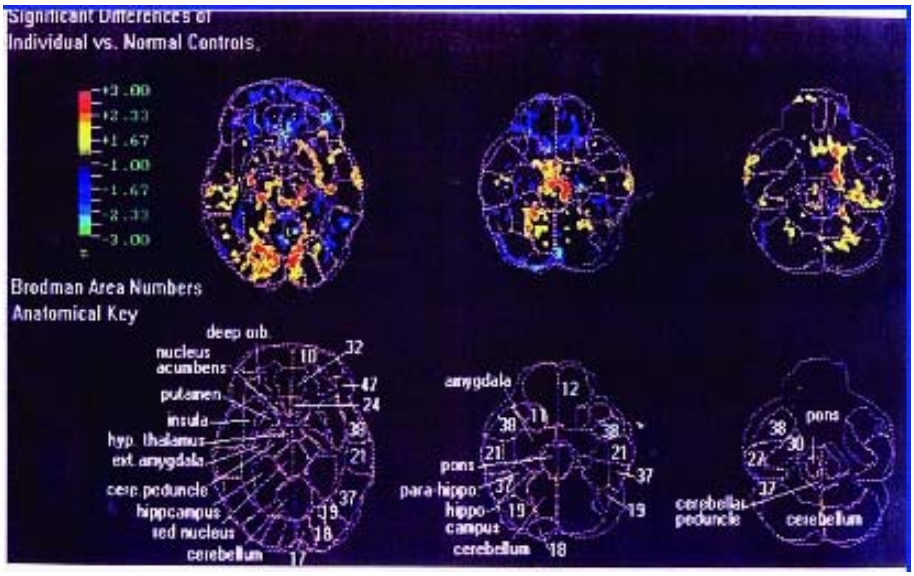
Table 1: Description of Subjects and Results of Examinations

Case No	Gender	PET	Neuropsychological evaluation	Neurological/ Physical Examination
1	F		TE, LDM	Abnormal
2	F	Abnormal	TE, LD, RD	Abnormal
3	F	Abnormal	TE	Abnormal
4	F		TE. LDM	Mildly abnormal
5	F		TE, LDM	Within normal limits
6	F		TE, LD, RD, DST	Mildly abnormal
7	M	Abnormal	TE	Abnormal
8	F		TE, LD, DST	Within normal limits
9	F	Abnormal	TE	Abnormal
10	F		TE, LDM	Mildly abnormal
11	F	Abnormal	TE, LD Reading	Within normal limits
12	F		TE, DST	Within normal limits
13	F	Abnormal	TE, LD	Abnormal
14	F		TE, LD, Depression	Within normal limits
15	F	Abnormal	TE, LDM, DST	Abnormal
16	F	Abnormal	TE. LDM	Mildly abnormal
17	F		TE, LDM	Within normal limits
18	M		TE, LD, Depression	Within normal limits
19	F		TE, LD, DST	Within normal limits
20	F	Abnormal	TE	Abnormal
21	F	Abnormal	TE, LDM	Within normal limits
22	F		TE, Depression	Within normal limits
23	F		TE, DST, Depression	Mildly abnormal
24	M	Abnormal	TE, LDM	Abnormal
25	F		TE, DST, LDM	Within normal limits
26	F	Abnormal	TE, DST, Depression	Mildly abnormal

Abbreviations
TE: Toxic encephalopathy
LD: Learning disabilities
RD: Reading disorder
DST: Disturbances × smell and taste
LDM: Learning disability in mathematics

Abnormalities were found in all subjects who had a PET functional brain scan. Most striking was the frequent occurrence of hypofrontality (decreased frontal and increased posterior brain function), and increased function in some limbic areas, especially the extended amygdala region (see Figure 1).

Figure 1: PET Scan Showing Functional Abnormalities



Section through the brain of one of our subjects illustrate abnormalities in a PET scan. Blue areas show where there is impairment of function. Yellow and red areas show where there is above normal function. Note the preponderance of blue in the anterior brain and the preponderance of yellow and red in the posterior brain. Also note that increased activity is seen in the extended amygdala region.

All subjects who underwent a neuropsychological evaluation were diagnosed with toxic encephalopathy. Many had learning disabilities of one sort or another (18/26) and some had disturbances of smell or taste (8/26).

Table 1 also shows that the physical/neurological examination was abnormal in 9/26, mildly abnormal in 6/26 and within normal limits for the remainder 11/26 of the subjects.

DISCUSSION

Many of our subjects developed cognitive and memory impairment. Their impairment was objectively documented with our test results.

The neuropsychological evaluations showed many abnormalities and deficits which combined to arrive at a diagnosis of toxic encephalopathy.

PET brain scans showed abnormalities in various areas, often with imbalance of function between cortical [decrease] and subcortical [increase] and frontal [decrease] and occipital [increase] functions. This imbalance was observed in other subjects of ours after neurotoxic exposure and included asymmetry between the left and right hemispheres. This asymmetry was statistically significant in our SPECT data.[1]

Many subjects had impaired balance and impaired coordination. Some had developed a movement disorder. Many showed a postural bilateral tremor.

Airline regulations require that a sick flight attendant be seen by special referral to a clinic or physician who has contracted with the airline. In this setting, physicians are not highly specialized, especially when it comes to evaluation of a neurotoxicological insult. This is why most flight attendants were told that they would quickly recover and should therefore be able to return to work within a few weeks if not within a few days. The examination was usually limited and therefore often normal. Sophisticated approaches were typically not used.

When examined for neurotoxic injury with a sophisticated approach (SPECT, PET, neuropsychological evaluation, and so on) profound impairment can be documented and was in many of our subjects. This impairment was severe enough in some subjects to eventually result in disability.

Our experience shows that flight attendants deserve more medical and certainly more sophisticated attention to their complaints than is routine. This statement of course also applies to pilots and other personnel who are potentially exposed to fumes.

Cabin air in the situations described in this paper was not analyzed. Therefore, we cannot assign certain symptoms to certain chemicals. However, subjects are typically exposed to a mix of toxic chemicals. In addition, flight personnel are also exposed to electro-magnetic fields, ozone, and other potentially toxic components which may contribute to their impairment. It should be noted however that our subject group was functioning normally and well prior to the incidents described above. Therefore it was almost certainly the chemical fume exposure which caused their neurological problems.

A careful evaluation of immune function in flight personnel would shed light on the potential presence of impairment of immune function. Some immune parameters (for example, natural killer cell function) respond rather quickly, sometimes within hours, to a given toxic insult. This is why measurements of immune function may well be helpful in the future.

While correlation between abnormalities in brain scan and neuropsychological function is now possible, it was not attempted in our population. However, a rough correlation was found in that neuropsychological function and SPECT were specifically impaired in frontal lobes, temporal lobes, and limbic system in a predictable way.

In addition to correlating localized impairment (neuropsychological evaluation versus brain scan findings), the consequences of the imbalance we found in our subjects on PET scanning deserves further examination. This imbalance between frontal and occipital areas of brain function and between cortical and subcortical areas is certainly intriguing and would be expected to contribute to further impairment in our subject population.

In view of the above, we strongly suggest that a protocol be created which outlines the evaluations that flight personnel should undergo when evaluated for incidents such as the ones described in this paper.

ACKNOWLEDGEMENTS

The authors would like to thank Dr JC Wu who reported on the PET scans of our subjects; Dr Guiterrez who performed the neuropsychological evaluations, and Ms Chantal Quirk for secretarial and related services.

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From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 111-127.

BIOMARKERS FOR EXPOSURE AND OF SENSITIVITY TO ORGANOPHOSPHORUS (OP) COMPOUNDS

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BIOGRAPHICAL SKETCH

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Key words: OP sensitivity, OP exposure, organophosphate, protein adducts

ABSTRACT

The questions of whether an individual has been exposed to a given toxicant, what consequence they may have experienced and the role their genetics may have played in modulating the exposure are usually difficult to answer. Often, the individual is not aware of having been exposed at the time of the exposure and may not have become aware of the exposure until symptoms appear some time afterwards. The contribution of their genetic make-up with respect to modulating the exposure may or may not be ascertainable. Genetic variability of the human PON1 gene provides an excellent example of one system where something is known about genetic and developmental variability and the role of this variability in modulating exposures to specific organophosphorus (OP) compounds. Exposure to various toxicants is often estimated from urinary metabolites. These often drop to low or undetectable levels within a short time following exposure. Analysis of proteins modified by specific xenobiotics provides an approach for examining the nature of an exposure over a much longer time frame. We describe as an example the use of multidimensional protein identification technology (MudPIT) to identify tricresyl phosphate modifications to serine residues in the liver enzyme, carboxylesterase. Depending on the specific exposure, this approach may be especially useful for identifying the toxicant(s) involved in the exposure.

[†] The contents of this paper are solely the responsibility of the authors and do not necessarily represent official views of the US NIH or the US EPA.

INTRODUCTION

In assessing exposures, four elements of information are required:

1) the nature of the exposure; that is, the compound(s) to which the individual was exposed;

2) the level and duration of the exposure;

3) the consequences of the exposure; and

4) the genetic capacity of the individual to modulate the exposure(s).

Biomarkers of exposure

One of the traditional means of assessing exposures has been to measure the quantities of metabolites of the toxicant in the urine. For example, the presence of diethyl or dimethyl phosphate in the urine may indicate exposure to an organophosphorus (OP) insecticide. However, this analysis will not provide information about the specific insecticide to which the individual may have been exposed. Determining the presence of other specific metabolites can provide information about the specific compound to which the individual was exposed. For example the presence of 3,5,6 trichloro-2-pyridinol in the urine would indicate an exposure to chlorpyrifos (Dursban®).[1] Exposure to many different toxicants can be determined by the presence in the urine of metabolites specific to the particular toxicant.

As noted above, however, urinary metabolites are generally cleared after a few days. Denghardt et al[2] noted in their search for longer-lived biomarkers of exposure that "they should be specific for the agent, detectable at low concentrations and persist in the body for a significant time period following exposure, allowing ample time for sample collection". In 1997, Polhuijs et al[3] reported a new procedure for detecting exposure to OPs retrospectively. They found that several nerve agents could be regenerated or released from target proteins by exposure of exposed sera to high levels of fluoride to yield the respective phosphofluoridate compounds. They examined sera from a total of 18 victims of the two incidents of Sarin release in Japan (Tokyo and Matsumoto), demonstrated the regeneration of Sarin in twelve of the samples.[4] These methods have the advantage that they can detect agent that is attached to target proteins for weeks or even months following exposure,[5] depending on factors that decrease the levels of modified protein in the plasma such as metabolism of the protein, reactivation (loss of the OP from the protein), and aging (loss of part of the OP molecule from the target protein).[6] Degenhardt et al,[2] reported improvements in the original procedure that increased the sensitivity of the method to a detection limit of approximately 10 pg/ml plasma, corresponding to only 0.09% inhibition of butyrylcholinesterase (BuChE). Peeples et al,[7] used a biotinylated OP compound coupled with quadripole time-of-flight mass spectrometry to identify albumin and ES1 carboxylesterase as major targets for OP binding in mouse plasma. While carboxylesterase has not been considered a useful biomarker in man due to the reputed lack of carboxylesterase in human blood,[8] the characterization of modified albumin as a marker of OP exposure illustrates the potential of these

types of methods. A macrophage specific serine esterase-1 has been reported in humans,[9,10] and a membrane-bound carboxylesterase has been purified from human peripheral monocytes.[9] The latter was apparently inhibited in vitro by several OP compounds, including diisopropylfluorophosphate, paraoxon, and triphenyl phosphate.[9,11] A monocyte esterase had previously been shown to be decreased in process workers exposed to OPs.[12,13] While these esterases may serve as markers of exposure, the more abundant plasma proteins such as albumin modified by the agent of exposure would be more convenient and more sensitive. It might also be possible by analyzing modified plasma proteins with different half-lives to estimate the time or date of exposure.

The level and duration of exposure are more difficult to assess. The levels of metabolites present in the urine may provide some information about the level of the exposure. The duration of the exposure and in some cases the estimated levels of exposure may rely on analyzing the levels of toxicant present in the individual's environment.[14]

The consequence(s) of the exposure has been analyzed by examining the inhibition of enzymes that are inactivated by a specific toxicant, as quantifiable endpoints. Since the primary action of the OP class of insecticides is inhibition of acetylcholinesterase, ascertaining the level of an OP exposure often relies on comparing an individual's serum or red blood cell (RBC) cholinesterase values, or both, with their established baseline levels, since these activities vary somewhat from individual to individual.[15]

In some US states (for example, California and Washington), basal cholinesterase levels are determined prior to the beginning of the spraying season, then the levels are checked periodically through out the spraying season.[16] If an individual's plasma or RBC cholinesterase level falls to 80% of their baseline level, the work practices of the employee must be reviewed. If their level of RBC cholinesterase falls to 70% of their baseline level or their plasma cholinesterase to 60% of their baseline level, they should be removed from the risk of further exposure until their cholinesterase levels return to 80% of their baseline levels. Additional details of each state's monitoring programs are listed on the states' respective web sites noted above. This type of monitoring program should be adaptable to other exposures, once appropriate biomarkers of exposure are identified. There are also many other targets of OPs and other endpoints of toxicity that may need to be evaluated, such as effects on cognition, motor coordination, gene expression and other physiological phenomena.[17]

Biomarkers of Sensitivity

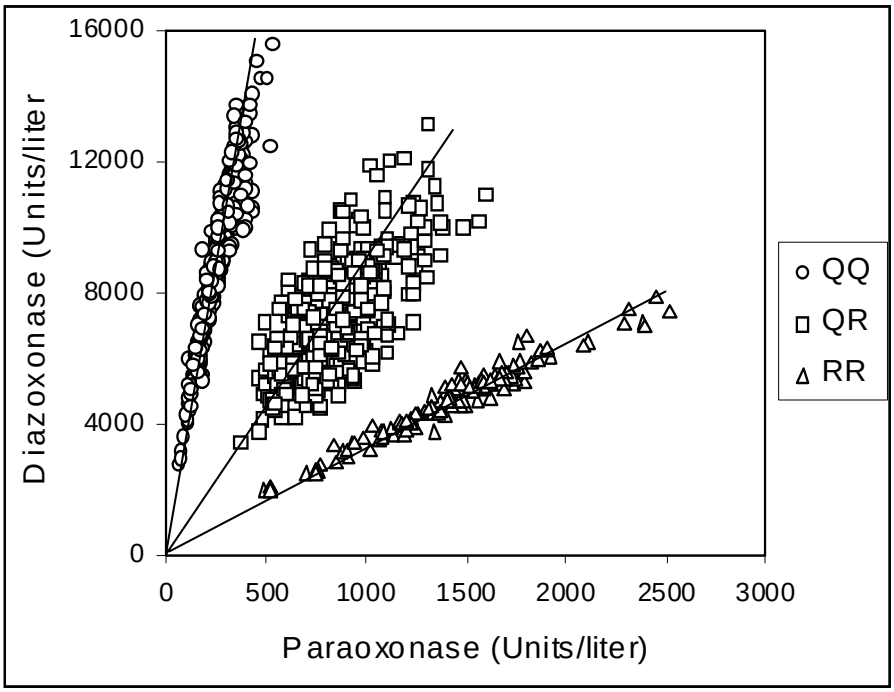
The effect of genetic variability in susceptibility is known for relatively few compounds. One classic example of variability in susceptibility is that associated with metabolism of the anesthetic, succinylcholine. Individuals who are unable to metabolize this compound due to an atypical esterase will not recover readily from anesthesia following surgery and will require some time on a respirator.[18]

One of the better characterized examples of variability in sensitivity to OP compounds is provided by the genetic variability in the human *PON1* gene. Genetic variability in the quantity and quality of the plasma enzyme paraoxonase (PON1) affects the sensitivity of exposure to the OP compounds chlorpyrifos/chlorpyrifos oxon and diazinon/diazoxon. In humans, this enzyme is encoded as a 355 amino acid protein. The N-terminal methionine is removed after synthesis;[19] however, the rest of the secretion signal is retained and used to anchor PON1 into HDL particles.[20] A polymorphism at position 192 results in the presence of an amino acid substitution so that some individuals have the amino acid glutamine at this position ($PON1_{Q192}$) and others arginine ($PON1_{R192}$).[21,22] Heterozygous individuals have variable levels of each PON_{192} alloform in their plasma. The Q192R polymorphism affects the catalytic efficiency of hydrolysis of a number of PON1 substrates.[23] The available data indicate that individuals with low plasma PON1 levels will have increased sensitivity to diazinon/diazoxon and chlorpyrifos oxon/chlorpyrifos exposures.[24] Individuals with $PON1_{Q192}$ will have an additional increase in sensitivity to chlorpyrifos/chlorpyrifos oxon exposures, since $PON1_{Q192}$ does not detoxify chlorpyrifos oxon nearly as well as $PON1_{R192}$. $PON1_{Q192}$ homozygotes with low plasma PON1 levels are predicted to be the most sensitive to chlorpyrifos/chlorpyrifos oxon exposure, while individuals with high levels of $PON1_{R192}$ are predicted to be the most resistant to exposure.

The PON1 status of an individual can be determined by measuring the rates at which their plasma hydrolyzes two different pesticide metabolites, diazoxon and paraoxon.[25] Plotting these rates for a population provides a distribution where the status of each individual is clearly evident (see Figure 1). The plot separates the population into three separate groups, individuals homozygous for $PON1_{Q192}$, heterozygotes, and individuals homozygous for $PON1_{R192}$, and at the same time provides the plasma level of PON1 for each individual.

While it has become popular to simply characterize the DNA polymorphisms in a given gene by PCR analysis, this analysis provides only information about a given base in the DNA sequence and provides no information about the level of PON1 in plasma, which, for PON1, is at least as important as the amino acid present at position 192. The plot shown in Figure 1 provides both the functional position 192 genotype as well as the level of PON1 in individuals' plasma.

Figure 1: Determination of the functional genomics of plasma PON1 (PON1 status) using citrate stored plasma



Plotting the rates of hydrolysis of diazoxon versus paraoxon for plasma (or serum) samples from a population divides the population into 3 distinct groups, individuals functionally homozygous for $PON1_{Q192,}$ heterozygotes ($PON1_{Q/R192}$) and individuals homozygous for $PON1_{R192}$. While PCR analysis of the position 192 polymorphism may reveal that an individual possesses one copy of each allele, this analysis will pick up alleles in heterozygotes that are inactivated by any number of mutations (Jarvik et al, 2003), that is, the analysis provides the functional status of an individual's *PON1* genomics (From[26], with permission).

The term "PON1 status" has been introduced to include PON1 levels and functional position 192 genotype.[24] It has also been referred to as the *PON1* functional position 192 genotype, since we have recently found 4 cases where the PCR analysis indicated that the individual was heterozygous for the position 192 polymorphism (Q/R) whereas their PON1 status indicated that they produced only one active alloform of PON1 (Q- or R-192).[27] The reason for this was shown to be the presence of an inactivating mutation on one of the individual's two *PON1* genes. Thus, these individuals had only one functional *PON1* gene, even though PCR analysis in the region that encodes amino acid 192 indicated the presence of two copies of *PON1*. While this is one of the rare or early cases where the functional status of a specific gene in an individual can be analyzed in a simple high throughput assay, it points out the importance of doing such functional analyses where possible. There are a lot of things that can happen between the gene and final protein product that would render PCR analysis uninformative. This simple two substrate functional genomic analysis points out the importance of analyzing both the quantity and functional quality of a specific gene product.

The demonstration that PON1 genetic variability is important in modulating exposures to specific organophosphorus insecticides comes from several lines of evidence. Early research showed that species with high plasma levels of

PON1 were resistant to exposure to specific OP insecticides.[28,29] More direct evidence was provided in an experiment by Main where he injected partially purified rabbit PON1 into rats and found them to be more resistant to paraoxon exposure.[30] These observations were verified and extended by experiments in our laboratory. We repeated his observation and showed that injection of purified rabbit PON1 also provided a very significant increase in resistance to exposure to chlorpyrifos oxon.[31] We subsequently switched to the mouse as a model system since much less purified PON1 was required to increase their plasma levels by injection and it was becoming clear that genetic manipulations were much easier to carry out in mice. Subsequent experiments in mice showed that injection of purified rabbit PON1 provided very good protection of brain and diaphragm cholinesterase from chlorpyrifos oxon exposure.[32,33] These results provided convincing evidence that high plasma PON1 levels provided protection against exposure to CPO.

The consequences of low PON1 levels were examined in mice that were missing the PON1 gene and had no PON1 in their plasma or livers [PON1 knockout mice ($PON1^{-/-}$)]. These mice exhibited dramatically increased sensitivity to both CPO,[34] and diazoxon (DZO) exposure. Doses that caused no symptoms in wild type mice and only low levels of cholinesterase inhibition killed the PON1 knockout mice. These mice exhibited less dramatically increased sensitivity to the respective organophosphorus parent compounds, suggesting that other detoxification pathways such as the cytochrome P450 systems are important in the overall detoxification of the parent compounds. Interestingly, Usami et al,[35] have shown that CPY3A4 is inactivated by the sulfur atom during the oxidative replacement of the sulfur atom with oxygen. Since CYP3A4 is important in testosterone metabolism, the effects of exposure on reproductive health outcomes raises important issues.

Since the PON1 null mice were devoid of plasma PON1, they could have their plasma PON1 restored by injection of exogenous PON1. Purification of each human $PON1_{192}$ alloform from pooled plasma samples of Q/Q or R/R homozygotes allowed for the determination of the efficacy of each alloform in providing protection against specific OP exposures. It was found that both alloforms provided equivalent protection against diazoxon exposure when injected into the PON1 null mice. However, the $PON1_{R192}$ alloform provided significantly better protection against chlorpyrifos oxon exposure than the $PON1_{Q192}$ alloform.[24] Further, experiments with transgenic mice that express either $PON1_{R192}$ or $PON1_{Q192}$ at equivalent levels in their plasma and livers, in absence of native mouse PON1, also showed that $PON1_{R192}$ provided better protection against CPO/CPS exposure.[36]

In addition to causing acute cholinergic effects, exposure to some OP compounds can result in delayed or chronic neurological syndromes, including a delayed neurological syndrome called organophosphate induced delayed neuropathy (OPIDN).[37,38,39] In a notorious poisoning incident in 1930, thousands of people in the southern USA were paralyzed with OPIDN as a result of exposure to tri-*ortho*-cresyl phosphate (TOCP),[40] an OP compound now used as a lubricant in jet oil.[41] OPIDN is characterized by progressive

neurological signs occurring 10-14 days following exposure, including weakness, ataxia, paralysis of the lower limbs and degeneration of long axons in the peripheral nervous system and spinal cord.[37,42] The primary molecular target of neuropathic OPs is neuropathy target esterase (NTE), an integral membrane protein expressed in neurons.[43,44] In the case of tri-*ortho*-cresyl phosphate (TOCP), it is first metabolized to the neuropathic OP, cresyl saligenin phosphate.[45] OPs that cause OPIDN react covalently with NTE, inhibiting the enzyme by attaching to the active-site serine residue and forming a covalent enzyme intermediate with a rate of hydrolysis slow enough to result essentially in permanent inhibition. In addition, the OP undergoes a second reaction termed aging, which entails loss of one of the R-groups from the bound OP compound, leaving a negatively-charged species attached to the active site serine. The aged, OP-modified NTE then causes a chemical transection of the neuron, calcium entry and Wallerian-type neuronal degeneration as a result of what is thought to be a toxic gain-of-function in its activity.[37,46,47,48] Evidence from NTE-deficient mice suggests that some of the action of OPs is due to direct inhibition of NTE, rather than a gain-of-function.[49] Generation of the negatively-charged group at the active site is essential for initiation of OPIDN.[37,50]

In addition to NTE, there are likely to be multiple other targets of the neuropathic OPs that cause OPIDN, including proteins that could serve as biomarkers of exposure due to their presence in blood. Richards et al,[51] identified a number of novel protein targets for OP compounds in neural tissue.

Because of the potential power of mass spectrometry for identification of proteins modified by exposure, as a proof of principle we used this method to detect tricresyl phosphate modified serine residues in the liver enzyme, carboxylesterase (CE). Using micro liquid chromatography (LC), mass spectrometry, and multidimensional protein identification technology (MudPIT), we were able to obtain greater than five times coverage for a majority of the protein, and detected a number of modifications to serine residues in CE, including modification of the nucleophilic Ser222 in the active site of this enzyme (see results below). These methods have the advantage that they can detect agent that is attached to target proteins for weeks or even months following exposure, depending on factors that decrease the levels of modified protein in the plasma such as metabolism of the protein, reactivation (loss of the OP from the protein), and aging (loss of part of the OP molecule from the target protein).

MATERIALS AND METHODS

In vitro *Inhibition of Carboxylesterase by Tricresyl phosphate*

A 1 mg/ml solution of porcine carboxylesterase (pCE) in 50 mM Tris HCl pH 8.0 was made from a 10 mg/ml ammonium sulfate suspension of the enzyme (Sigma E-2884). CE inhibition was conducted by mixing 1 mg (1 ml) of pCE with a 2.5 mM solution of tricresyl phosphate (TCP, 90%, mixture of isomers; Aldrich) in methanol, for a final concentration of 25 µM (i.e., ~10 ng/ml) TCP.

The solution was incubated at 25˚ C for 20 minutes and then diluted 1:100 in the assay buffer, 100 mM Tris HCl pH 8.0.

CE activity was assayed by a modification of the method described by Munger et al,[52] using *p*-nitrophenyl valerate as a substrate**.** Aliquots (5 and 10 µl) of the pCE-TCP solution were placed in a 96-well visible microplate and combined with 200 µl of 1 mM *p*-nitrophenyl valerate in 100 mM Tris HCl pH 8.0. The controls used were 5 and 10 µl of a 0.01 mg/ml uninhibited pCE solution combined with 200 µl of the enzyme substrate. The resulting colorimetric product, *p*-nitrophenol, was detected by measuring absorbance at 405 nm against blanks that consisted only of the assay buffer.

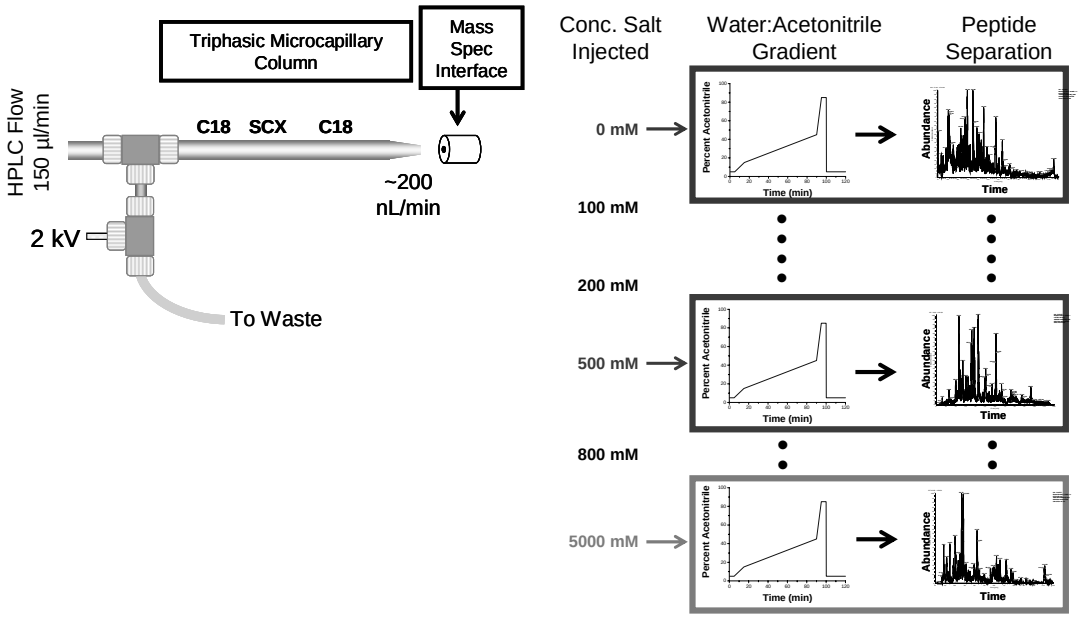
Protein Sample Preparation for Mass Spectrometry

Inhibited pCE (1 µg) was added to three separate microcentrifuge tubes. The protein was denatured with 0.1% Rapigest, reduced with 5 mM DTT, and alkylated with 15 mM iodoacetamide. Each of the three different fractions was digested with either trypsin, chymotrypsin, or elastase. The protease was added at a 1:100 enzyme:substrate ratio and incubated with mixing at 37˚C for 4 hours. At the end of the 4 hours, the digest was quenched and the Rapigest hydrolyzed with 200 mM HCl. The hydrolyzed Rapigest was pelleted by centrifugation and the supernatant from the three digests were pooled and analyzed by tandem mass spectrometry.

Identification of Organophosphorous Modifications on Carboxylesterase by µLC/µLC/MS/MS

The protein digests were loaded directly onto a fused silica capillary column (100-µm internal diameter) packed with packed with 7 cm of 5 µm Luna C18 material (Phenomenex, Ventura, CA) at the tip, 3 cm of 5 µm Partisphere strong cation exchanger (Whatman, Clifton, NJ) second, followed by an additional 3 cm of 5 µm Luna C18 material as described previously.[53] After loading the peptide digests, the column was placed inline with an Agilent 1100 HPLC/Autosampler (Figure 3) and analyzed using a 6-step multidimensional separation similar to the approach described previously.[53] The HPLC was run at 150 µL/min and split to ~200 nL/min immediately upstream of the capillary column. The peptides were displaced from the strong cation exchange (SCX) resin onto the reversed phase material using 6 separate salt fractions consisting of 50 µL injections of ammonium acetate from the autosampler (0 mM, 100 mM, 200 mM, 500 mM, 800 mM, and 5000 mM). Each salt injection was followed by a 2h water:acetonitrile gradient (Figure 2).

Figure 2: Experimental setup for Multidimensional Protein Identification Technology (MudPIT)



A) A 100 µm I.D. fused silica capillary is pulled to a 5 µm I.D. tip using a CO_2 laser based micropipette puller and packed first with C18 chromatography material, then with strong cation exchange material (SCX), and followed with an additional phase of C18 material. The column is placed in-line between an HPLC system and the interface to the vacuum system of the mass spectrometer. The HPLC flow is split down to ~200 nl/min and the effluent from the column is electrosprayed into the mass spectrometer with the application of a distal 2 kV voltage.

B) The multidimensional separation is performed using step gradients of ammonium acetate from the HPLC autosampler. Each salt step displaces a fraction of peptides from the SCX material onto the proximal C18 material and is eluted from the column using a water:acetonitrile reversed phase gradient. The tandem mass spectrometer acquires fragmentation spectra on all molecular species above a predetermined threshold continuously during the entire multidimensional separation. Our separation used six salt steps and acquired data in an automated fashion over a 12 hour period.

As peptides eluted from the microcapillary column, they were electrosprayed directly into an LTQ linear ion-trap mass spectrometer (ThermoFinnigan, San Jose, CA) with the application of a distal 2 kV spray voltage. A cycle of one full-scan mass spectrum (400-1400 m/z) followed by 5 data-dependent MS/MS spectra at a 25% normalized collision energy was repeated continuously throughout each step of the multidimensional separation. The application of all mass spectrometer scan functions and HPLC solvent gradients were controlled by the Xcaliber datasystem.

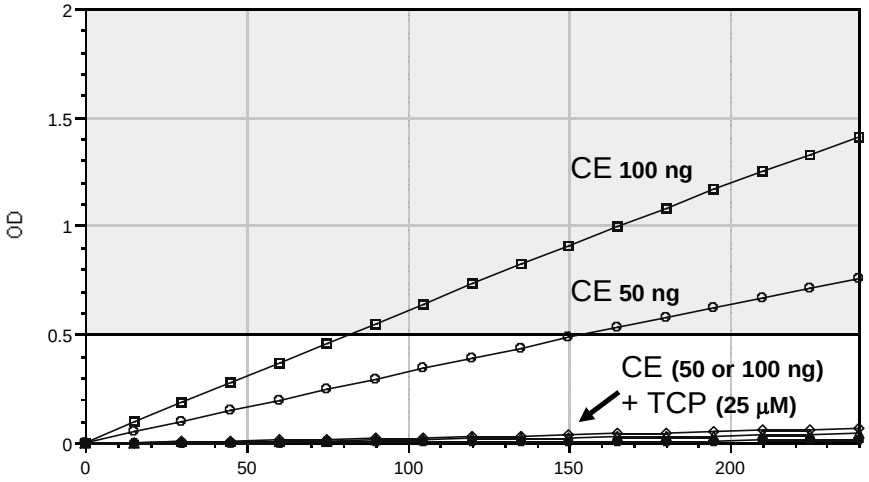
The acquired tandem mass spectra were searched against a fasta database containing the bovine and human protein sequences using a parallelized implementation of SEQUEST-NORM,[53] with no enzyme specificity selected in the parameter file. Spectra were searched with a static +57 modification on Cys, a dynamic +16 modification on Met, and a dynamic +170 modification on Ser and Tyr to search for the aged TCP modification. The data were also searched with a dynamic +260 modification on Ser and Tyr to search for the unaged modification. The program DTASelect,[54] was used to filter the peptide identifications and assemble the peptides into proteins. Peptide

identifications matching human protein sequences, with normalized Xcorr < 0.3, and with Cn < 0.1 were omitted from the final output list.

RESULTS AND DISCUSSION

While biomarkers of sensitivity for exposure to diazinon/diazoxon and chlorpyrifos/chlorpyrifos oxon have been identified, none have yet been identified for TCP exposure. As a proof of principle for the use of mass spectrometry for OP biomarker identification, we used MudPIT to identify the residues in purified porcine carboxylesterase (pCE) that are modified by exposure to TCP. TCP, at a concentration (10 ng/ml) relevant for human exposure, was mixed with 1 mg/ml pCE for 20 min at RT, resulting in greater than 94% inhibition of pCE activity (Figure 3), measured using p-nitrophenyl valerate as a substrate.

Figure 3: In vitro Inhibition of Porcine Liver Carboxylesterase (CE) by Tricresyl phosphate (TCP)

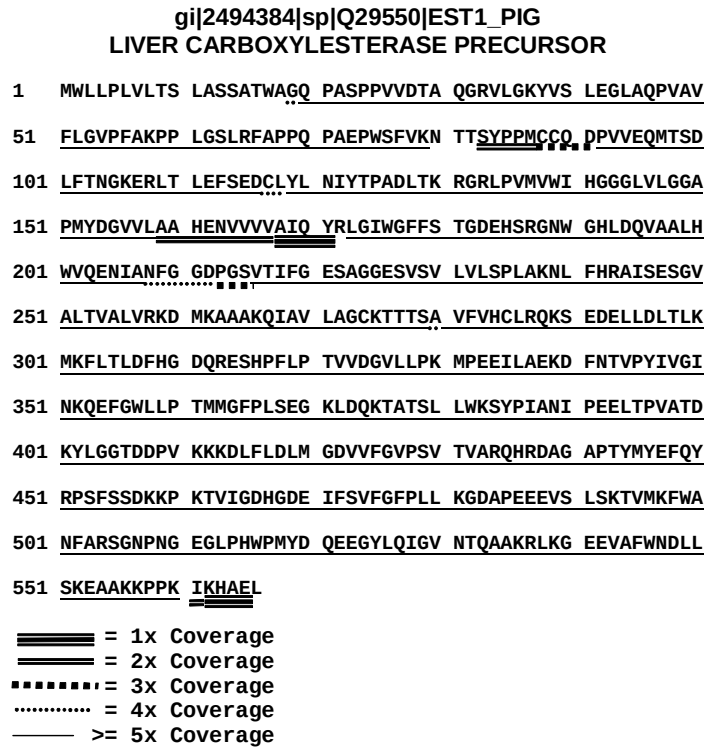


CE, 1 mg/ml, was incubated with 25 µM (~10 ng/ml) TCP (mixture of isomers) for 20 min, then diluted 1:100 in 100 mM Tris HCl pH 8.0. CE activity of the diluted mixture (5 l, open squares or 10 l, open circles) was measured in a kinetic assay using 1 mM *p*-nitrophenyl valerate as the substrate. TCP, at the same concentration used for detection of modified serine residues by MudPIT, inhibited CE by about 96% after a 20 min incubation *in vitro*.

For more direct relevance to human exposures, a mixture of TCP isomers was used for the inhibition of pCE. Following denaturation, reduction, and alkylation of the TCP-inhibited protein, fractions were digested with trypsin, chymotrypsin, or elastase as described in Materials and Methods, and the samples were hydrolyzed and pelleted, with the supernatant from the three digests pooled for analysis by tandem mass spectrometry.

TCP modifications on specific amino acid residues of CE were identified by LC and multidimensional separation in an approach similar to that described in MacCoss et al.[53] The experimental setup for MudPIT analysis is shown in Figure 2. From the fragmentation spectra of overlapping peptides by MudPIT, more than 95% of the precursor sequence of pCE was identified, with a majority of the protein sequence represented by greater than 5x coverage (see Figure 4).

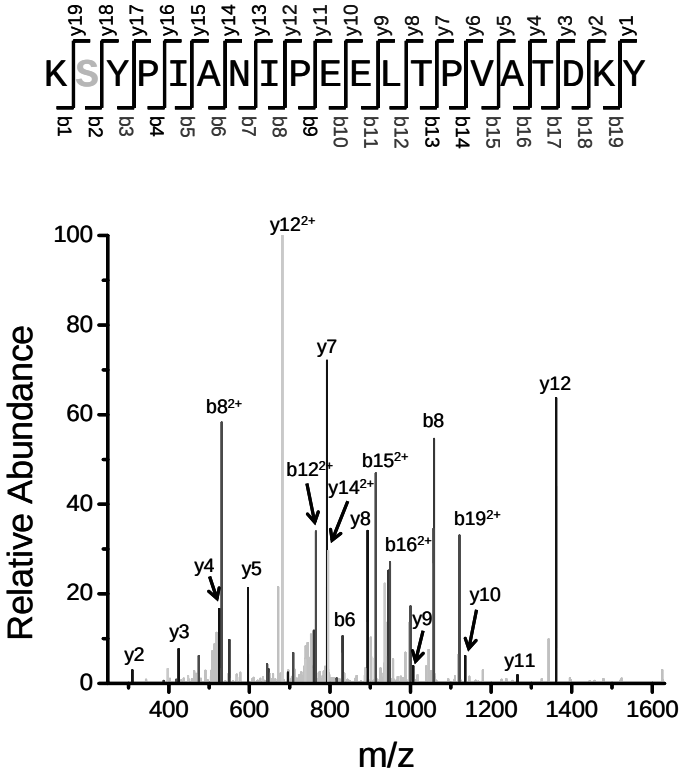
Figure 4: Coverage of Porcine Liver Carboxylesterase Obtained from Fragmentation Spectra of Peptides by MudPIT



More than 95% of the precursor sequence was identified and a majority of the protein sequence was represented by >5x coverage from overlapping peptides produced by the multienzyme digest.

Figure 5 shows a typical chymotryptic peptide fragmentation spectrum, in this case identifying a 170 Da mass shift on Ser384.

Figure 5: Chymotryptic Peptide Fragmentation Spectrum



An example of a chymotryptic peptide fragmentation spectrum identifying a mass shift of 170 Da on Ser384 of carboxylesterase. The fragment ion series containing the C-terminus and N-terminus are labeled as y-ions and b-ions respectively. This tandem mass spectrum confidently localizes a shift of 170 Da to the N-terminus of the peptide sequence – mostly likely to the serine residue highlighted in gray. Unfortunately, neither the b2 nor y18 was present to indisputably distinguish the exact localization of the modification between the Ser384 and Tyr385.

Figure 6 shows the TCP-modified peptides detected by MudPIT.

Figure 6: Modified peptides identified by MudPIT

A.

```
Ser63     AVFLGVPFAKPPLGS*LRFAP
            FLGVPFAKPPLGS*L

Ser222    GGDPGSVTIFGES*AGGESVSVL
                 TIFGES*AGGESV
                 TIFGES*AGGESVS
                  IFGES*AGGESVSV
                  IFGES*AGGESVSVL

Ser368    IVGINKQEFGWLLPTM@M@GFPLS*EG
                QEFGWLLPTM@M@GFPLS*E

Ser384    KS*YPIANIPEELTPVATDKY

Ser473    SSDKKPKTVIGDHGDEIFS*VFGFPLLKGDA
                     GDHGDEIFS*VFGFPLLKGDAPEEEV
                     GDHGDEIFS*VFGFPLLKGDAPEEEVS
                     GDHGDEIFS*VFGFPLLKGDAPEEEVSLS
                      DHGDEIFS*VFGFPLLKGDAPEEEV
                      DHGDEIFS*VFGFPLLKGDAPEEEVS
                      DHGDEIFS*VFGFPLLKGDAPEEEVSLS
                            FS*VFGFPLLKGDAPEEEVSLSK
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B.

```
Ser379    SEGKLDQKTATS#LLWK
                    ATS#LLWKSYPIANIPEELTPVATDKY
Ser384               TS#LLWKS#YPIANIPEELTPVATDKY
                         LWKS#YPIANIPEELTPVATDKY

Ser473    SSDKKPKTVIGDHGDEIFS#VFGFPLLKGD
                     IGDHGDEIFS#VFGFPLLKGDAPEEEVSLSK
                              S#VFGFPLLKGDAPEEEVSL
```

A) Peptides identified with a mass shift of 170 Da on serine (indicated by S*). This mass shift is most likely a result of an aged tricresyl phosphate modification. M@ indicates an oxidized methionine residue. Ser222 is the catalytic serine located in the active site of carboxylesterase and this modification is likely responsible for the inhibition of the esterase activity. Ser368, Ser384 and Ser473 are located near the active site, with Ser473 only 6 residues from the active site His467 residue. **B)** Peptides identified with a mass shift of 260 Da on serine (indicated by S#). This mass shift is most likely explained by a tricresyl phosphate modification. Interestingly, two of these modification sites, Ser384 and Ser473, are also identified as aged modification sites.

A mass shift of 170 Da, most likely a result of an aged TCP modification, was evident on Ser63, Ser222, Ser368, Ser384, and Ser473 (Figure 6A). The modification to Ser222, the nucleophilic serine that comprises part of the catalytic triad in the active site of CE, is most likely responsible for the inhibition of pCE enzyme activity. In addition, 3 residues (Ser379, Ser384, and Ser473) were identified with a mass shift of 260 Da on their respective peptides (Figure 6B), which is most likely explained by a TCP modification. Two of these sites, Ser384 and Ser473, were also identified as aged modification sites, with mass shifts of 170 Da (Figure 6A). Based on the crystal structure of rabbit liver CE,[55] Ser63 and Ser473 of porcine CE would presumably be located in the catalytic domain, between 3- 4 and 14- 15, respectively, with Ser473 only 6 residues from the active-site histidine. Ser384 and Ser379 would be located in 10 of the regulatory domain, and Ser368 would be located between 16 of the catalytic domain and 10 of the

regulatory domain. These results demonstrate the possibility that TCP modifications to individual residues within a protein can be detected using MudPIT. This type of approach should make the identification of modified proteins in a complex mixture or biological sample more feasible, providing a powerful and thorough screening approach for identification of novel biomarkers of OP exposure.

The polymorphic protein PON1 that is important in modulating exposure to the OP insecticides also appears to hydrolyze TCP (Richter et al, unpublished results), however, there is not yet any evidence one way or the other that that the genetic variability in PON1 status is important in determining differential sensitivity to TCP exposures.

Another useful approach for measuring the presence of toxicant in the air is the miniature personal air collector system developed by Prof Chris van Netten.[†,56] Coupling data from the collector system that monitors airborne contaminants with an assessment of proteins modified by the exposure will provide the necessary data for assessing exposures.

CONCLUSIONS

Increasing numbers of reports of genetic variability in levels and quality (catalytic efficiency) of enzymes involved in detoxication as well as developmental differences in detoxication capabilities, particularly in the very young or during fetal life, emphasize the importance of considering these factors when assessing exposure risks. As shown here and in other cited reports, current proteomic technology allows for the identification of specific protein targets and at the same time provides new approaches for examining biomarkers of exposure to specific compounds or classes of compounds. The technology is available for establishing whether an exposure to TCP has occurred. There are already significant data available on the health effects of TCP exposure. Additional research needs to be carried out to make use of proteomics technology in assessing exposures to TCP and other toxicants.

ACKNOWLEDGEMENTS

This work was supported by the following grants: R01ES09883; 2P01ES009601/EPA-RD83170901; P42ES04696; P30ES07033; U19ES11387, and DK069386.

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† van Netten, C. Self Contained Personal Air Sampling System, US Patent 6945127, issued, 20 September 2005, US Patent and Trademark Office.

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ASSESSING OVER THIRTY FLIGHT CREW WHO HAVE PRESENTED AS A RESULT OF BEING UNWELL AFTER EXPOSURE TO FUMES ON THE BAE 146 JETS

Moira Somers
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BIOGRAPHICAL SKETCH

Dr Moira Somers has a MBBS from the University of Western Australia 1979 and has further professional education in Theoretical and Practical Training Course in Acupuncture (Acupuncture Academy of Australia, 1992); Basic Postgraduate Course in Nutritional and Environmental Medicine; Australian College of Nutritional and Environmental Medicine, 1993); Basic Underwater Medicine (Australian Sports Medicine Federation, WA, 1986); Approved Medical Practitioner for the purpose of the Noise Abatement Act (Health Department of WA, 1984). From 1979 to 1981 Moira worked at Royal Perth Hospital and then Princess Margaret Hospital for Children. She then moved into general practice and since 1983 has been established in her own general practice in association with Dr G P Deleuil. The Practice is a broad based general practice with special interests in underwater medicine; asbestos related disease and occupational medicine. In particular, she has special interests in women's health, chronic fatigue syndrome and chemical injury. In relation to her experience with chemical injury Moira first became involved in the management of patients with chronic fatigue syndrome (CFS) in 1988 and since that time have seen a large number a patients for assessment of this condition. As a flow on from this area of interest patients with chemical injuries presented and over the past ten years she has seen many patients with this type of injury. Since 1999 Moira has seen 39 flight crew, including both flight attendants and pilots, who have been affected by fumes while working on the BAE146 jets.

PERSONAL BACKGROUND

My background is that I am a general practitioner and have been established in general practice for 22 years. I work with one other doctor and we have several areas of special interest between us including diving medicine and occupational medicine. Since 1988 I have developed a special interest in chronic fatigue syndrome and over time this has expanded to include chemical injury.

First Contact with Air Cabin Quality Problems

The first flight attendant presented to me after seeing a couple of doctors. She had an existing workers compensation claim and was thought to have a primary anxiety disorder by her current GP and had been commenced on Ativan.

Experience to Date

Since 1999 I have seen 39 flight crew and 1 passenger who have reported symptoms in relation to exposure to fumes in the cabin space of the BAE146 jet. Some have also reported incidents on other aircraft including the A320 and B737.

PROCESS OF ASSESSMENT

Typical Approach

Many times each day General Practitioners are presented with problems that require defining, for example, what is the nature of the patient's chest pain.

- We operate in a set framework or context that is our understanding of disease and follow a set routine of questioning and decision making in attempt to determine the underlying cause.
- We ask questions, a lot of questions one after the other.
- It is a relatively objective process.
- This type of process presents to us frequently every day and often in a standard consult of 10 -15 minutes and with a waiting room full of other patients.
- We work under pressure.

The Challenge

The challenge in general practice is stop ourselves from operating in this manner at all times. When a new patient with an obviously complex problem comes along it is important to recognise they need time to express themselves and we need time to be able to listen to their story. Then we can begin to understand the context of their presentation and we can identify the problem and make decisions about diagnosis and management. We must let the patient tell his/her story and resist the temptation to constantly interrupt and ask questions.

To do this we have to make some decisions about our way of practicing medicine such as:

- Am I going to be available for longer consults, often outside of my normal GP sessions?

My usual practice is to book such patients outside of my general practice sessions so that I can spend the time necessary to obtain a very detailed history and after the initial consult further consults are arranged as necessary.

- Am I willing to get involved in difficult and complex medical problems and be prepared to think about areas of medicine that are not familiar to me? If necessary am I prepared to operate out of my current framework of understanding of disease.

- In the case of this issue am I prepared to get involved in the worker's compensation process which is very demanding on my time and energy.
- When necessary am I prepared to maintain independence and not be swayed by vested interests.

So with this background and general approach I was presented with my first flight attendant in 1999. As mentioned she already had a diagnosis of primary anxiety disorder and was on worker's compensation. After listening to her story one of the things that was clear to me was that there was definitely some relationship between her exposures and her symptoms.

My Approach to Patient Assessment

My approach has been to objectively assess the patient by

(i) taking a very detailed history,

(ii) examination,

(iii) standard investigations, as necessary, to eliminate any condition that may be causing their reported symptoms and

(iv) referral to independent specialist physicians where necessary.

With regards to history, questions have to be open-ended and allow the patient to tell their story. As well as allowing me to listen to the patient this also prevents me from biasing the consult in favour of my framework of understanding of disease.

Then direct questions are asked and specific enquiry of each system completed.

Once examination is completed symptoms and signs may point to differential diagnoses and then specific investigations are performed to rule out any other condition that may possibly explain the findings.

Referrals to specialist physicians were made for two reasons, firstly to assist with the diagnosis and secondly in some cases to provide a double check on my assessment.

I was very aware of my responsibility to the patient and as well my responsibility to the employer. As no definitive tests were available I consulted with practitioner experienced in this area and as a result referred some patients for AERP testing and chromosome analysis. I also referred some patients for SPECT scanning.

One important role was that of education. Many of the air crew were concerned about what was happening to them. They wondered where they were on the continuum of this experience and what they could do to improve their health and prevent deterioration.

DATA

This data has been collected by reviewing the files of 36 flight crew. Not all statistics total to 36 as information was collected by open questioning and not by use of a template.

Number of Air Crew Seen

Over the past six years I have seen 40 people over 275 consults regarding this issue including:

- 7 pilots
- 32 flight attendants*
- 1 passenger

* In one case the flight attendant presented to me because of exposure events, but the final diagnosis was not related to fume incidents.

My impression was that air crew presented independently of each other and often without discussing their situation with others. It seemed they were careful not to be identified in the workplace as taking any position regarding this issue. There was a remarkable consistency in their reporting of events and symptoms and definite temporal relationship of symptoms to exposure events.

Reasons for Presentation

The main reasons why these individuals came to see me was:

14 expressed concern over poor health

2 presented to obtain chromosome analysis (no detailed history was taken other than history of exposure events)

1 presented expressing concern for his future health and to assist in making a decision about future work-he was symptomatic from exposure events

1 presented expressing concern over future pregnancy

6 presented to obtain exemption to fly on the BAE146 - all were unwell with significant history of exposure events and one had a miscarriage while flying on the 146

5 requested general information about their symptoms and future health - all had been symptomatic with exposure events

Prior Education

It was of interest to me to note the high academic achievement of many of the air crew and the success several had achieved in business and at high levels of management in the corporate world. Prior to their employment they were well and psychologically robust as evidenced by their selection into the company and the pre-employment selection process.

7 Pilots - No other educational history was obtained

Of the flight attendants:

2 reported completing high school

1 studied at TAFE (Technical and Further Education College)

7 had completed university degrees and of these two had completed two degrees

5 had run their own business prior to becoming flight attendants.

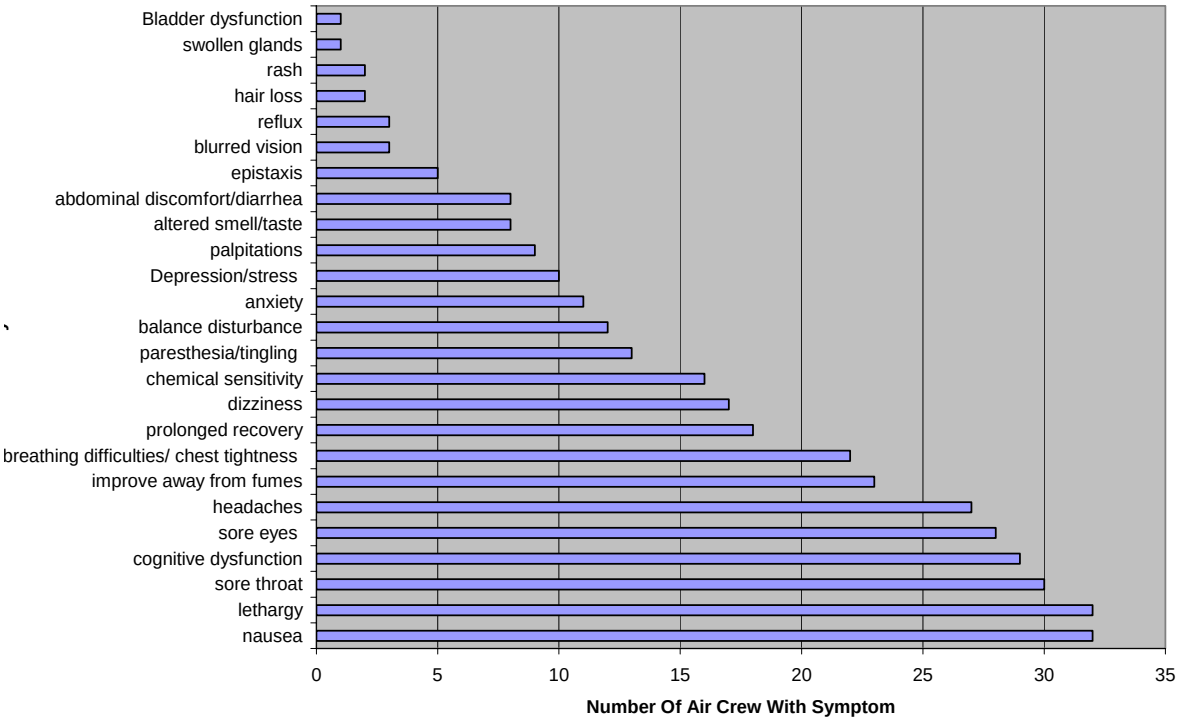
Symptoms

A spreadsheet of symptoms recorded for each flight crew is provided in Table 8.

Table 8: Raw Data of Symptoms

| | | Case Number | | |

Figure 5: Frequency of Symptoms recorded for 36 Air Crew



The most common symptoms were:

- nausea;
- headaches;
- mucous membrane irritation;
- lethargy; and
- cognitive dysfunction.

Reports of Other Crew Involved

From information provided by presenting crew the following reports of other members of the air crew being affected were made:

4	Entire crew (2 reports made by Flight Crew)
1	Entire crew and 1 Passenger
1	Captain, 3 Flight Attendants and 1 Passenger
1	1 Flight Attendant and 1st Officer (Report made by Captain)
9	1 other Flight Attendant
4	2 other Flight Attendants
1	3 other Flight Attendants
1	Child had an asthma attack
2	2 Passengers
1	3 Passengers

1 9 Passengers and 2 Flight Attendants

1 First Officer

Aircraft

The Ansett Australia BAe 146 aircraft JJW, JJP, NJD, NJL, NJA, NJZ were frequently reported by flight crew as having exposure events.

In addition to incidents on the BAe 146 jets, nine crew also reported fume incidents on the A320 and one reported an incident on the B737.

Timing of Symptoms

Fume incidents were reported as having occurred at the following stages of the flight:

7 Push back and Taxiing

6 Take off

5 Climb

4 Top of Descent

6 Descent

2 Landing

Correlation Of Fume Incidents With Documented Technical Faults

- Twelve flight crew reported that they were involved in fume incidents that correlated with documented technical faults.
- Some reported more than one incident that correlated with a technical fault.
- On one occasion a technical fault was documented with Engine No.1 and the flight attendant reported that she was informed by management that no cause had been found.
- Also in the case of one pilot the employer has provided to me extensive documentation outlining several fume incident reports and the documentation confirming the technical faults correlating with each report.

Alternative Diagnoses

The following diagnoses have been given to flight crew, generally by company medical personal and insurance medical personal or by medical personal who had seen only the isolated case.

- Infection
- Primary anxiety disorder
- Hyperventilation
- PTSD

- Depression
- Dehydration
- Gastro-Oesophageal Reflux Disease
- Mass Psychogenic Illness
- "All in the Head"
- "Just flying"
- Stress
- Bronchitis
- Viral illness
- No diagnosis - fit to fly

Descriptions of Cognitive Impairment

- Unable to write report post flight
- Unable to speak
- Poor memory
- Poor co-ordination
- Felt drugged
- Unable to remember passenger requests
- Can't think clearly
- Can't think of words
- Trips over words
- Loses train of thought
- Disorientation
- Working in slow motion as if drunk or stoned
- Couldn't put dates in order
- Conversation with other flight attendants bizarre-in case of an emergency wouldn't function
- Slurred speech
- Had to close own business - too unwell with lack of energy and poor co-ordination
- Can't handle multiple pieces of information
- Can't do simple calculations
- Concentration span very poor
- Has to follow the PA script with her finger
- Difficulty negotiating simple program on home computer
- Difficulty doing simple personal tax return - previously had read and implemented complex changes to the tax laws relating to a multimillion dollar business
- Has to constantly re-learn simple task

CASE STUDIES

Four case studies are outlined below that illustrate common characterise these cases.

Case Study 1

Background

A 34 year old female flight attendant presented with the history of being unwell after several incidents on the BAe 146. Nine months prior to presentation she had been involved in an incident with misting in the cabin. She reported nausea and disorientation. Three days later she reported another incident on the same aircraft with nausea, flushing and problems with her speech. She had further symptoms on the return leg at take-off, with heavy limbs, breathing difficulty and clouded mental function. She was unable to write her trip report and on the way home she drove off the side of the road. She was extremely tired after the incident and for the next five days had headache and nausea and felt as though she was in a trance.

She experienced further incidents over following months with increasing symptoms. She particularly noted difficulty with her memory and inability to express herself. She reported that she felt as though her vocabulary was locked in her brain and she would frequently lose her train of thought. She was unable to negotiate simple computer packages and her memory was poor.

Like others, she was reluctant to present for medical advice as she saw herself as a company person and also was fearful of reprisal from the company. She reported that the final straw and reason for her to seek exemption from the BAe 146 was when she could not perform simple addition. She was very distressed by this. She had an outstanding academic record for both school and university, graduating with honours in the top few percent of her class.

She was given an exemption from the BAe 146 but unfortunately also had recurrence of symptoms flying on the A320. She developed sensitivities to other agents such as petrol and household cleaning agents.

She did not feel depressed, and still loved her job, though she was angry with her employer. She was very stressed by the whole process and said “I love my job and don't want this to be happening to me”. She has been very distressed she learnt of private investigators calling other flight attendants to talk to them about her and as well she had great difficulty dealing with the company administration.

Neuropsychometric testing demonstrated cognitive impairment and as well AERP confirmed attention abnormality that would have detrimental impact on psychomotor function and memory. She also had chromosome analysis performed and she was referred to a specialist physician who confirmed no other medical condition was present to explain her symptoms.

Points of interest

- Repeated incidents of exposure events on the same aircraft putting crew at risk of illness.
- Breakdown of communication between employer and worker.
- Staff reluctant/fearful to present for health assessment.
- Major symptoms were nausea, headache and cognitive impairment lasting several days.
- Eventual development of sensitivities to broader range of products.

Case Study 2

Background

A 39-year male pilot who flew commercial passenger jets for several years before deciding to return to Perth. He flew BAe 146 jets approximately 75 flying hours per month and did not notice any problems in the first 1-2 years. He started to notice problems in 1998 and over the next two years symptoms became more problematic causing him to hand over controls to his co pilot on several occasions.

He reported a noxious, acrid smell and at times noted misting. Symptoms included mucous in the back of the throat, tingling in the head and low back, sensitive skin as though sun burnt, pressure headache over the temples and bridge of the nose followed by nausea and constriction of the throat. He reported he felt as though he was going to vomit and also noted he was light and sound sensitive, had lethargy and fatigue and reported some deterioration in memory. Symptoms settled over days and completely resolved with longer breaks.

Symptoms occurred at take off, at times of maximum mass air flow-through 1000 ft, at change over from the APU to the engines and then again on descent. He described the high levels of activity in the cockpit up to 1500 ft with these critical operational times corresponding to the times of highest fume exposure. He also related the difficulties preventing the use of oxygen at these times and therefore that when oxygen was used it was well after the onset of symptoms and at 10,000 ft when critical operations were completed.

In January 2002 he was suspended from flying duties as he had submitted a number of Operating Crew Reports and had been required to use crew oxygen. Copies of his incident reports were provided to me by his employer with the corresponding technical reports of oil leaks and the maintenance performed. There was remarkable consistency between the incident reports and documented leaks. His case came before the Australian Industrial Relations Commission in 2003. He was not prepared to take the lower position flying on the Dash8 and despite his employer admitting that they could not provide a safe working environment his employment was terminated.

Points of interest

- Short term health effects.
- Fit to fly as a pilot as long as safe working environment provided.
- Certain aircraft are consistently reported to have problems with cabin air quality. It maybe then, that there are certain BAe 146 aircraft that do not have a history of cabin air contamination and could possibly have been considered safe for him to operate.
- If assurances cannot be given regarding a safe working environment then it raises serious air safety issues for both crew and passengers.
- Given the correlation with documented technical faults it is highly unlikely that he is alone, as a pilot, in his experience of the ill effects of leaked fumes. It is of concern that there may be under-reporting of such incidents by pilots for a number of reasons. He has, in fact, demonstrated integrity and courage in objectively recording incidents and as a result has significantly contributed to air safety.
- It is the legal obligation of the Captain and First officer to report exposure events to CASA and the company. There have been incidents where the First Officer has been over-ridden and prevented from submitting such a report and therefore prevented from performing his legal duty.
- There needs to be some system of reporting events that provides for air safety at the same time as protecting crew from fear of reprisal.

Case Study 3

Background

A 30 year old flight attendant presented with the history of being unwell after several incidents on the BAE146. She had been involved in a very significant incident and required oxygen. Symptoms experienced were nose and throat irritation and inability to understand and complete the occurrence report. Her arms were weak and her chest and throat felt closed up. She reported that she was confused and disorientated. She was unable to stand and was hospitalised after landing. After the incident she experienced a pounding headache and tiredness. On the return flight home she was very tired and reported that she felt confused and could not remember drink orders. She was unable to drive herself home and when she did get home she could not remember the name of a family member and could not remember what she wanted to say. Words came out in the wrong order and she had slurred speech. Symptoms persisted for weeks and when she did return to work she requested the company doctor contact her. He eventually did and reassured her that the aircraft had been pulled apart and no problem found. That same day she signed onto the aircraft involved and checked the log book only to find the No. 1 engine had been replaced after her incident due to a major oil leak. To that point in time she had no idea of the health effects associated with the BAe 146. Her managers contacted her and advised her to see a counselor.

She continued to work over the next five months with frequent incidents and moderately severe symptoms. Other symptoms included nausea, epigastric discomfort, myalgia, arthralgia, hair loss, flushing and difficulty with temperature control, lethargy and fatigue, cough and wheeze. She developed sensitivities to a broad range of other chemicals and with exposure experienced recurrence and or aggravation of symptoms.

When I first saw her she was being treated for anxiety disorder. I certified her unfit for work. She had also had incidents on the A320. Eventually she attempted return to work and had a further incident on the B737. She then attempted work as ground crew but was unable to sustain that work due to extreme tiredness and chemical sensitivities. Similarly she attempted return to work outside the aviation industry and has not been able to work due to the persistence of symptoms. Her memory has deteriorated and she has difficulty learning new tasks. She has developed progressive muscle weakness in her arms and legs and paresthesia in a stocking and glove distribution. She reports that she is clumsy and tends to drop things and fall. She also has difficulty with co-ordination and balance.

Injuries sustained include asthma, neurotoxic injury with both central and peripheral nervous system damage, multiple chemical sensitivity, and psychological injury which may be related to the neurotoxic agent itself or secondary to the impact of the injuries sustained.

She has had extensive investigation and seen numerous specialists from several disciplines and no other cause has been found to explain her symptoms.

Points of interest

- Employee put at further risk of injury with lack of adequate information about the nature of the injury and further exposure over several months.
- Symptoms have persisted over six years.
- Central and peripheral neurotoxic injury.

Case Study 4

Background

A 40 year old male passenger who frequently flew on the 146 jet from Perth to Karratha, Broome and Port Hedland. He flew approximately twice weekly with additional other small range flights.

Presented September 2000 and had been unwell on and off over the previous 3½ years. He reported gradual deterioration in health since commencing flights to Karratha.

Symptoms included lethargy and fatigue, slowed mental function and skin irritations. Symptoms were always worse immediately after the flight. He

could not work effectively on the day of the flight and noted poor memory and inability to link jobs with numbers on the day of the flight. He was able to work more effectively on the day after the flight.

He had attended his regular GP and was referred to a Rheumatologist and given a diagnosis of Chronic Fatigue Syndrome.

Six months prior to presenting to me he had decreased his flying and had noted a marked improvement in his health.

As he did not fit the diagnostic criteria for chronic fatigue syndrome, a letter was provided to his insurance company outlining his history and the reasons why his diagnosis was incorrect.

Points of interest

- Wide reaching impacts when explanation of illness not apparent.
- Temporal relationship between the onset of his symptoms and exposure was clear.
- Improvement was noted with decrease in flying.

DISCUSSION

Overview

After seeing the first patient it was clear that there was a definite relationship between her symptoms and events in the workplace. That association has been further confirmed after seeing the many air crew that have presented. In addition over 300 reports of fume incidents can be found in Appendix Four of the Senate Inquiry report on Cabin Air Quality.[1] I have no doubt that they are very genuine and that their problem is very significant both for themselves and for the wider community.

Several factors point to this phenomenon being a genuine illness.

- The temporal relationship of symptoms to exposure events.
- The frequent correlation of exposure events with technical faults.
- The consistency of reporting of symptoms and events.
- The symptom complex reported by aircrew. The pattern of nausea, headaches, mucous membrane irritation, lethargy and cognitive dysfunction are consistently reported by crew.

In addition to all of the above the fact that this illness occurs in previously physically, intellectually and psychologically robust individuals makes suggestions of primary psychiatric illness and mass psychogenic illness less plausible.

Of particular note, there were five reports of incidents involving both the Captain and the First Officer. Given the apparent level of under-reporting this must raise serious concerns for safety.

From a General Practitioner perspective the main point to make is that history is without doubt the most important component of what we do. Without a detailed history taken in a manner that allows the patient to tell their story we cannot ever begin to address such problems. Context is also important, not only the context in which the patient presents, but also we need to be able to appreciate not everything fits into our understanding of disease. Every so often a new phenomenon presents itself and just because I don't fully understand it doesn't mean it is not real or genuine. First the phenomenon has to be recognised and only then the pathophysiology can be determined.

Response by All Parties

Response by all parties including Air Crew, Ground staff, Management and Medical profession will be mentioned. Differences exist in the way various parties respond to this issue. It is important to note that at times the responses have been less than adequate and we need to recognise this because it engenders fear and antagonism and adds to the burden of illness and impacts on safety. Working in this type of environment is not going to achieve the best outcome for all. The problem needs to be clearly defined then all parties will be better able to understand the challenge and plan appropriate and effective responses.

Future Needs

- The most obvious is for a reporting system that is totally objective and independent of the operator so as to protect both air safety and the employee from fear of reprisal.
- The true incidence and the spectrum of symptoms needs to be determined and can only be achieved with reliable reporting.
- We need to determine why certain individuals are affected. Is it basic toxicological principles or some individual susceptibility that is operating?
- Research into the pathophysiology is important to define the illness.
- An area of concern expressed by aircrew is the need to understand the impact, if any, of this type of injury on offspring.

CONCLUSION

- After very extensive clinical assessment I consider that what is being reported by flight crew is very genuine and has wide reaching consequences on their health, finances, future work capacity and relationships.
- There are real concerns regarding safety of both flight crew and the public.
- From the medical point of view history is vitally important. It is the cornerstone to diagnosis.
- It is important to consider the context in which illness occurs, and also the context of the communication between the practitioner and the patient.

- Somewhere in the whole story there is truth. Reliable reporting will allow us to understand that truth.

REFERENCE

[1] Parliament of Australia. Appendix Four: List of Incidents Reported to Flight Attendants Association of Australia Involving Fumes on BAe 146 Aircraft (to Date), between 5/8/92 and 29/12/99. *Air Safety and Cabin Air Quality in the BAE146 Aircraft.* Report by the Senate Rural and Regional Affairs and Transport References Committee. Parliament of Australia, Canberra, October 2000.

From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 145-160.

THE EFFECTS OF NEUROTOXIC EMISSIONS ON THE COGNITIVE FUNCTIONING OF WORKERS IN MEDICAL, INDUSTRIAL AND AVIATION SETTINGS

Leonie Coxon
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BIOGRAPHICAL SKETCH

Leonie Coxon is a Clinical and Forensic Psychologist from Perth, Western Australia who has a keen interest in Neurotoxicity. She has a Bachelor of Arts Degree with Honours in Psychology, a Masters Degree in Applied Psychology (Clinical and Educational) and is currently completing her Doctorate in Clinical Psychology at Murdoch University. Leonie also participated in a postgraduate course in Forensic Psychology at Edith Cowan University to obtain her forensic qualifications and registration. Leonie has worked with many head injured populations as a Clinical Psychologist at the Royal Perth Rehabilitation Hospital and the Melville Rehabilitation Centre's Head Injury Unit. She has been in Private Practice for 20 years as a Clinical and Forensic Psychologist and the bulk of her work involves the assessment of clients for Medicolegal purposes. Leonie is the Australian Secretary and also the State President of the Australian Psychological Society's Division of Independently Practising Psychologists and the State Secretary of the College of Forensic Psychologists. She belongs to many other professional psychological and medical associations and has held office on a number of their committees. Leonie is currently working as a consultant Clinical Psychologist for the Royal Australian Air Force on a project involving aircraft engineers who have been exposed to neurotoxins in the course of their work and the impact on their families. Her doctoral thesis addresses the effect of the chemical Glutaraldehyde on the cognitive functioning of health care workers.

ABSTRACT

Many industrial and pharmacological substances have been found to be neurotoxic to the human central nervous system. Impairments can range from subtle neurological and behavioural disturbances such as headache and mild confusion to overt encephalopathy, total incapacity, and peripheral nerve disease. In general, of the over 40,000 occupational chemicals available globally, there are five broad groups that are potentially neurotoxic including: solvents, pesticides, metals and metalloids, gases, and miscellaneous compounds such as glutaraldehyde. However, the impact that such neurotoxic emissions have on the workforce is likely to be severely underestimated. This is because there may be many other common chemicals which have neurotoxic properties that have not as yet been identified or recognised, as well as the differentia; effects of acute versus chronic exposure. Neurotoxicity is therefore a problem of major concern for many workplaces. Neuropsychological test results and their implications for

individuals exposed to neurotoxic substances from medical, industrial and aviation settings are discussed in this paper.

INTRODUCTION

There are many chemical compounds present in a variety of work settings which can produce a range of impairments in the human nervous system. The condition which arises from exposure to such compounds is called neurotoxicity. Neurotoxic substances may be chemically manufactured (neurotoxicants) or they may be naturally occurring (neurotoxins).

The neurotoxic impairments to workers can range from subtle neurological and behavioural disturbances to more severe encephalopathy and peripheral nerve disease.[1,2,3,4,5]

Although the toxic effects of certain substances on the human body and nervous system have been documented for centuries, Singer notes that it has only been since the 1970's that occupational neurotoxicity has emerged as a specialised area of study.[6,7] This is due to the more frequent use of chemicals in industrial and agricultural settings.

However, the impact that such neurotoxic emissions have on workforces is likely to be severely underestimated as there may be many other common chemicals which have neurotoxic properties that have not yet been identified or recognised. There are also the differential effects of acute versus chronic exposure, and the synergistic effects of combinations of chemicals. In addition, there is the impact of temperature, wind direction and atmosphere, which may render many chemical components more toxic. These issues are problems of major concern to many work environments.

Toxic chemicals have been divided into five general groups:

- Solvents
- Pesticides
- Metals and metalloids and their compounds
- Gases
- Miscellaneous compounds (formaldehyde and glutaraldehyde)

Occupations at Risk

Occupations at risk include those in Table 1, (from[3]).

Table 1: Occupations at Risk

Occupations at Risk	*Neurotoxic Substances*
Agriculture and farm workers	Pesticides, herbicides, insecticides, solvents
Aviation	Jet oil fumes, sealants, organophosphates, Avgas
Chemical and Pharmaceutical workers	Industrial and pharmaceutical substances
Degreasers	Trichlorethylene
Dentists and dental hygienists	Mercury, Anaesthetic gases, Glutaraldehyde
Dry cleaners	Perchloroethylene, Trichloroethylene, other solvents

Occupations at Risk	*Neurotoxic Substances*
Electronic workers	Lead, Methyl ethyl ketone, Methylene chloride, Tin, Trichloroethylene, Glycol ethers, Xylene, Chloroform, Freon, Arsine
Hospital personnel	Alcohols, Anaesthetic gases, Ethylene oxide, Glutaraldehyde (cold sterilisation)
Industrial workers	Solvents, Lead, lacquers, Toluene
Laboratory workers	Solvents, Mercury, Ethylene oxide, Glutaraldehyde
Painters	Lead, Toluene, Xylene, other solvents
Plastic workers	Formaldehyde, Styrene, PVC
Printers	Lead, Methanol, Methylene chloride, Toluene, Trichloroethylene, other solvents
Rayon workers	Carbon disulfide
Steel workers	Lead, other metals, Phenol
Transportation workers	Lead (in gasoline), Carbon monoxide, solvents
Hobbyists	Lead, Toluene, glues, solvents
Office workers	Solvents

The Effects of These Neurotoxicants and Neurotoxins on Workers

As outlined below, neurotoxic symptoms fall into three categories:[3]

1. Motor and sensory (see Table 2)
2. Cognitive
3. Affective/Personality (see Table 3)

Table 2: Effects on General Motor and Sensory Functions

General Motor	**Abnormal Movement**	**Sensory**
Activity changes Paralysis Performance changes Pupil constrictions Rigidity Weakness	Ataxia Chorea Convulsions/spasms Gait, spastic Movement disorders Tremor	Auditory disorders Equilibrium disorders/vertigo/dizziness Gustatory changes Olfactory changes Pain disorders Tactile disorders Vision disorders Visual sense organ pathology

Cognitive effects include:

- Intellectual decline
- Alertness loss
- Impaired judgement
- Memory loss
- Slurred speech
- Slowed reaction time

Table 3: Affective/Personality Effects

Effect	Symptom
Substance abuse	Inebriation
Anxiety	Insomnia
Asthenia/neurasthenia	Irritability
Belligerence	Lassitude/lethargy
Delirium	Laughter
Delusions	Malaise
Depression	Nervousness/nervous disorders
Disorientation	Psychological/mental disorders
Excitability	Psychosis
Exhilaration	Restlessness
Giddiness	Sleepiness
Hallucinations	Viciousness

How is Neuropsychological Performance Affected?

The most common neuropsychological symptoms of neurotoxicity are:

- General intellectual impairments
- Intelligence (lowered IQ with more severe exposures)
- Attention
- Concentration
- Abstract reasoning
- Cognitive efficiency and flexibility
- Global impairments (dementias)
- Motor impairments
- Fine motor speed
- Fine motor coordination
- Gross motor coordination
- Gross motor strength
- Sensory impairments
- Visual disturbances
- Auditory disturbances
- Paraesthesias/anaesthesias
- Tactile disturbances (PNS or CNS disorders)
- Memory and learning impairments
- Short term memory (verbal and non verbal information)
- Learning (encoding of new information – verbal and non verbal)
- Long term memory (verbal and non verbal)
- Visuospatial impairments
- Constructional apraxias

What Methods of Neuropsychological Assessment are used to Verify these Deficits?

There are numerous neuropsychological batteries available using either traditional neuropsychological tests or micro computer based tests or both.[8] A comprehensive neuropsychological battery of tests assesses:

- Intellectual functioning
- Memory skills
- New learning skills
- Fine motor skills
- Verbal fluency
- Dominance
- Higher order functioning
- Reaction times
- Sensory functions

NEUROTOXICITY PROBLEMS IN MEDICAL SETTINGS

Glutaraldehyde Exposure

Glutaraldehyde is a chemical used extensively in hospitals as a convenient disinfectant for optic fibre endoscopes and other delicate medical instruments. It is effective against viruses and bacteria and is used as a 1% or 2% solution in instrument disinfecting. It is also used as a biocide in cooling towers and as a fixative in microbiology and histopathology laboratories. It is a tanning agent for leather and is also used as a component of the developer solutions which are used in x-ray film processing.[9]

Prior to the 1980's glutaraldehyde had been used mainly as a fixative in histology laboratories, and as such was used by only a limited number of workers. However, with the advent of the HIV problem in the 1980's there was a re-evaluation of the efficacy of cold sterilization agents in use at the time. Some agents were not considered adequate to destroy the AIDS virus, so glutaraldehyde was suggested as a more effective alternative in hospitals and surgeries. This meant that the risks of glutaraldehyde poisoning rose as:

- Greater volumes of glutaraldehyde were being used
- More workers were exposed to glutaraldehyde
- The controls for glutaraldehyde were poor in terms of ventilation, protective clothing and storage methods.

There is evidence in the literature that health care workers in endoscopy units, veterinary surgeries, dental surgeries and hospital operating theatres have experienced concentration and memory difficulties, and slowed speed of information processing.[10,11] Complaints of these above mentioned problems have been made by workers who were regularly exposed to 1% and 2% solutions of glutaraldehyde over prolonged periods of time. Sometimes

up to twenty years of accumulated exposure to glutaraldehyde were experienced.

In the course of clinical practice during 1995 and 1996, two endoscopy unit nurses, one dental technician and one x-ray assistant, who were exposed to glutaraldehyde in the course of their work, were interviewed and assessed psychometrically. The dental technician and one of the endoscopy unit nurses had the most intense and direct exposure to glutaraldehyde, as they experienced both skin contact and inhalation of the chemical. They were exposed to glutaraldehyde for periods of 18 months and 15 months respectively. As well as cognitive deficits, they were found to have EEG changes and both had experienced seizures. The other endoscopy unit nurse and the x-ray assistant were exposed to glutaraldehyde for longer periods, (8 and 9 years, respectively), but their exposure was less intense and their deficits were less severe.[11,12]

All four individuals were administered components of the Halstead Reitan Battery of neuropsychological tests, the Spielberger Anxiety Inventory and the Beck Depression Inventory. The most commonly occurring neuropsychological deficits found among these four health care workers were:

- Lowered attention span (Digit Span Subtest of the WAIS-R)
- Short term memory problems (Wechsler Memory Scale)
- Slowed speed of information processing (Digit Symbol and Trail Making tests)
- Lowered manual speed (Reitan Finger Tapping test)
- Lowered manual dexterity (Grooved Pegboard test)
- Significant levels of anxiety and depression were found (Spielberger Anxiety Inventory and Beck Depression Inventory)

Complaints such as these from several workers, led to the decision to conduct a more thorough investigation of the problem.

Glutaraldehyde Research Project

The proposed study investigates the effects of Glutaraldehyde on attention span, short term memory, speed of information processing, reaction time to stimuli, manual speed and manual dexterity of groups of health care workers. The first of the experimental groups will have been exposed to glutaraldehyde for one to twenty years and will be still working with the chemical. The second group will have been exposed to glutaraldehyde in the past but will no longer be working with the chemical. The third group of control subjects will never have been exposed to glutaraldehyde in the course of their work.

The effects of the exposure of glutaraldehyde on these two groups of workers will be measured in terms of:

- Attention span and concentration
- Fine motor skills

- Speed of information processing
- Reaction time
- Emotional state

Purpose of the study

The purpose of the study was to determine the extent of cognitive impairment if any, experienced by health care workers exposed to glutaraldehyde. The study also aims to verify the findings of Teo and Naido,[13] that health care workers exposed to low doses of glutaraldehyde solutions have impairments in their rate of response to stimuli.

Hypothesis

The research hypothesis is that occupational exposure of health care workers to the chemical glutaraldehyde results in impairments in cognitive functioning.

Method

Three groups of health care workers who were recruited via the Australian Nursing Federation were tested before and after exposure to glutaraldehyde. A group of control subjects was tested before and after commencing work.

The first group comprised health care workers who are currently exposed to glutaraldehyde. They were tested immediately after their exposure to glutaraldehyde and tested again at least twelve hours after they had left their workplace.

The second group comprised those who worked with glutaraldehyde over the past twenty years, but no longer do so. They were tested immediately after their work day and again at least twelve hours after they had completed their work day.

The third group, the control group, comprised health care workers who had never been exposed to glutaraldehyde. They followed the same procedure of testing as the second group.

Outcome

Although the data has not yet been fully analysed, initial review suggests that those most adversely affected by Glutaraldehyde are those who were exposed to the chemical long ago, without protective measures such as gloves, aprons, respirators, masks, extractor fans, ventilation systems and closed sterilization units.

These individuals were exposed regularly to stronger solutions of Glutaraldehyde, had skin contact with the chemical, as well as direct inhalation.

NEUROTOXICITY PROBLEMS IN INDUSTRIAL SETTINGS

Two workers in different settings were both exposed to solvents and lead. One was also exposed to lacquers and mercury vapours, the other to chromium.

1. A female factor worker from the UK who was exposed to lead, lacquers and mercury vapours for ten years in a canning factory. Poor protective measures were used and ventilation was poor.
2. A male spray painter, who worked in a heavy duty machinery factory for three years, was exposed to lead, solvents and chromium. Inappropriate protective measures were used in his work environment.

Reported symptoms common to both workers included:

- Fatigue
- Headaches
- Speech changes
- Loss of sense of taste and smell
- Lowered grip
- Lowered manual speed

The factory worker also complained of body tremors and severe tics, and the spray painter complained of psychomotor slowness and slow reaction time. Both workers were assessed using the above mentioned battery of neuropsychological tests. Their neuropsychological deficits are shown in Table 4.

Table 4: Neuropsychological Deficits

Factory Worker	Spray Painter
Memory problems	Processing speed deficits
New learning deficits	New learning difficulties
Problem solving difficulties	Problem solving deficits
Loss of grip strength	Loss of grip strength
Loss of manual speed	Loss of manual speed

These individuals had similar test results except for the memory deficits in the factory worker and the processing speed deficits in the spray painter.

NEUROTOXICITY PROBLEMS IN AVIATION SETTINGS

Over the past ten or more years, reports have been made by airline pilots, cabin crew and passengers, of an array of symptoms arising from travel on BAe-146 aircraft.[14] The BAe-146 is a small jet aircraft that operates on short domestic flights within Australia, Britain, Canada, Alaska and Sweden. In Australia, it is used predominantly in the less populated states of Western Australia, Queensland and South Australia, as a means of transporting small numbers of passengers to the more remote areas.

The most common complaints which have been made by individuals exposed to engine oil emissions while flying on the BAe-146 aircraft are: breathing difficulties; chest pain; nausea; fatigue; chronic headaches; dizziness; light headedness; confusion; concentration problems; memory difficulties and hypersensitivity to a range of chemicals.[15,16]

Complaints are generally made when the crew and passengers are exposed to jet oil emissions through the air conditioning system of the aircraft, at take off and landing.

The oil escapes through faulty oil seals and into the compressor bleed air, which is used to ventilate and pressurise the BAe-146 aircraft cabins.[17] The concentration of these emissions is considered to peak at take off and landing of the planes, or at other times when the engine is under load. Reports of foul smelling gases and the subsequent development of symptoms of nausea, breathing difficulties, chest pain, confusion and dizziness are most common at times when the air conditioning systems are on full volume.

The jet oil used by the BAe-146 aircraft is synthetic phosphate ester oil in which tricresyl phosphates are constituents. One of these tricresyl phosphates, tri-ortho-cresyl phosphate (TOCP), is said to be a highly neurotoxic contaminant.[18] However, other ortho-cresyl phosphates in the oil are present in higher concentrations and are known to be even more neurotoxic than TOCP.[19]

This oil also contains naphthylalamine and a broad range of other chemicals, many of which are considered hazardous to human health.[18,19,20]

On the International scene, the BAe-146, the MD80, the B737 and the A300 aircraft have been the cause of over 90% of the world wide cabin contamination problems identified. It is considered that this is due to the fact that the above mentioned aircraft are more prone to leakages of oil emissions, due to their particular design. The BAe-146 engine was reported to have been designed for use in combat helicopters during the Vietnam War. Post war these engines have been modified to fit small jet aircraft operating on short domestic flights. Statistically, the BAe-146 aircraft operating in Australia, Canada, Alaska and Sweden are the highest ranking aircraft for cabin air problems.[21,22]

Several case reports and epidemiological studies suggest that chronic central nervous system effects may occur in solvent-exposed workers, such as workers exposed to jet oils. Headaches, dizziness, concentration difficulties, memory impairment, fatigue, irritability, depression, alcohol intolerance and personality changes are the most frequently reported symptoms. Psychometric testing has revealed disturbances in memory and perception, also prolonged reaction times and some loss of coordination.[5]

Hartman cites studies demonstrating acute neuropsychological effects on jet oil workers, which include; dizziness, headaches and fatigue. Chronic exposure produces symptoms of neuroaesthesia, anxiety, depression and

increased reaction time to stimuli. Of the most severely affected, 50% were considered to have mild organic brain syndrome.[3]

Flight safety is a major issue, when one considers the effects on crew who are exposed to jet engine oil emissions as described above.[16,23] A pilot with disorientation, altered memory, concentration difficulties, blurred vision, slurred speech, and loss of balance and co-ordination could not be expected to operate and land an airplane safely, nor could cabin crew be expected to carry out their duties adequately when experiencing the above mentioned problems.

Despite numerous complaints of cognitive problems following exposure to BAe-146 jet oil emissions, very few psychometric assessments have been conducted to determine the nature and magnitude of the reported problems.

However, one study by Teo in which he assessed five airline crew, including two pilots and three flight attendants, who were exposed to jet oil emissions, demonstrated significant findings.[24]

Teo assessed each of the five individuals using Auditory Evoked Response Potentials (AERP). He reported that the AERP test is a useful tool for the detection of chemical exposure effects, as it can detect the depressant effects of organophosphates and other chemicals, even at sub clinical levels. The resultant effects of organophosphates and solvents are that the ability to attend and respond to stimuli is decreased.[25] The results of Teo's 1999 study revealed that in each case, there was a significant deficit in the individual's capacity to process information efficiently. This dysfunction impacted on the individuals' performances on cognitive and psychomotor tasks. This was considered by Teo to be an air safety risk factor.[24]

Despite the above mentioned AERP findings, there do not appear to be any comprehensive neuropsychological studies carried out in Australia on groups of individuals exposed to these jet oil emissions.

According to Lezak, the lack of thorough investigation of reported cognitive problems among chemically exposed workers generally occurs because of the similarity between some of the reported complaints and those of both depression and neuroticism. This confusion, often coupled with the absence of distinct neurological symptoms, can lead naïve investigators into discounting chemically exposed workers' complaints of cognitive deficits.[26]

However, Lezak reports that when neuropsychological evidence is presented, individuals' symptoms are often supported by positive objective findings.[26]

The health problems of cabin staff exposed to BAe-146 jet oil emissions were considered to be of such significant concern as to warrant an inquiry by the Australian Senate. The Journal of the Senate, No 24, dated 22 March 1999 stated that; "the following matter be referred to the Rural and Regional Affairs and Transport References Committee for Inquiry and Report." This matter

was; "(d) The examination of air safety, with particular reference to cabin air quality in BAe-146 aircraft".

Six senators representing five states of Australia subsequently met in 1999 and 2000 to investigate the 24 public submissions and a number of other private submissions on air quality in BAe-146 aircraft. A report was tabled in the Australian Parliament in October 2000.[27]

Preliminary BAe-146 Study in Western Australia

The aim of this small case study was to determine the presence of any neuropsychological deficits among a small group of airline employees, exposed to jet engine oil emissions from the BAe-146 aircraft in the course of their work.

Participants

A medical practitioner, who treated many of the flight crew affected by BAe-146 emissions, considered that neuropsychological assessment was important in determining the nature and extent of the problems which were being reported. She therefore referred five flight attendants for neuropsychological assessment. Another flight attendant and two pilots were referred by their own medical practitioners in the other states of Australia.

In total, eight air crew exposed to BAe-146 oil emissions were referred by their medical practitioners for neuropsychological assessment. These individuals reported cognitive difficulties, such as; mental confusion; concentration difficulties and memory problems following their exposure to jet oil emissions.

The eight individuals assessed were all females. Six were cabin crew members and two were pilots. Their ages ranged from 24 to 56 years and they had worked in their respective positions on the BAe-146 aircraft from two years to twelve years. All had completed twelve years of secondary school education and most had studied at a tertiary level. All participants were right side dominant.

Mean age of participants was 36.1 years and the mean education level in years was 13.7 years.

Measures

Each of the eight participants was administered a battery of neuropsychological tests, which had been used in previous research studies on neurotoxicants.[12,28 29,30]

The test battery included:

- WAIS-III Subtests
- Wechsler Memory Scale - Russell Adaptation

- Rey Complex Figure
- Controlled Oral Word Association test (FAS Test)
- Symbol Digit Modalities test
- Trail Making tests "A" and "B"
- Card Version of Category test
- Rey 15 Item Test
- Dynamometer Grip Test
- Reitan Finger Tapping Test
- Grooved Pegboard Test
- National Adult Reading Test
- California Computer Assessment Package

The tests which demonstrated greatest sensitivity to neurotoxic exposure were the CALCAP Reaction Time tests. Of the participants, 7 demonstrated impairments in the choice and sequential reaction time tasks. Interestingly, the simpler tests demonstrated the most severe impairments.

Test scores of grip strength were also impaired among all of participants on the dominant side and 7 of the 8 on the non dominant side, although the bulk of these were of a mild nature.

Impairments were found on the Digit Symbol Subtest of the WAIS-III and the Symbol Digit Modalities Test in 7 of the 8 participants. These are similar tasks of processing speed. However only 5 of the 8 of participants demonstrated impairments on the oral version of the SDMT. Among other subtests of the WAIS-III, 5 showed impairments on the Picture Arrangement test of sequencing while 4 were impaired on the Letter Number Sequencing test and the Digit Span test, both of which are tests of concentration and attention span. All other subtests of the WAIS-III showed impairments in none, one or only two individuals, so were not considered to be of great significance.

The National Adult Reading Test results of all 8 individuals suggested that all pre-morbid IQ's would have been in the average to high average range (from 108 to 116; Mean = 113), and their academic records supported these findings. Of the 8 participants, 5 demonstrated losses in Full Scale, Verbal and Performance IQ's.

Although memory deficits, as measured by the Wechsler Memory Scale - Russell Adaptation, were only mild, 7 of the 8 participants demonstrated impairments in both short and longer term verbal recall. Only one of the 8 demonstrated a mild to moderate impairment in short term non verbal recall, but 4 demonstrated mild to moderate impairments in longer term non verbal recall.

The Trail Making test of processing speed demonstrated only mild impairments in performance among three of the participants in both the "A" and "B" versions. Mean scores were slightly below average.

The tests which were least sensitive to neurotoxic exposure were the fine motor skills tests of manual speed and manual dexterity. Only two of the participants showed impairments in tapping speed and manual dexterity on their dominant hand. Although two showed impairments in manual dexterity on the dominant side, none showed impairments in tapping speed on their non dominant side.

Discussion

Although a statistical analysis has not been carried out on these test results and there is no control group of individuals working in the same field but not exposed to BAe-146 jet engine oil emissions, there are sufficient grounds to warrant further investigation of flight crew on BAe-146 aircraft.

The pattern of test results reflect studies carried out in other occupational settings, where workers were exposed to organophosphates and solvents.[31] According to Lezak, most chronic solvent toxicity occurs in the workplace as a result of long term exposure to fumes from such substances as paints, glues, cleaning fluids, petroleum fuel and lubricating and degreasing agents. The most prominent cognitive deficits found among these groups involve many aspects of attention and memory and also response slowing.[26]

The outcome of the Senate Inquiry, which was tabled in Parliament in October 2000 was that eight recommendations were made with the aim of ensuring that appropriate assessments were carried out on the BAe-146 and other passenger aircraft, to ensure that proper standards of air quality are made mandatory for Australian aircraft, bearing in mind Australian operational activities. The recommendations made by the Senate Inquiry were particularly addressed to CASA as the Australian air safety agency, and the administrator of aircraft operating regulations and standards. In addition, the Committee recommended that the Commonwealth initiate a number of responses to ensure that occupational health issues are addressed.[27]

Bearing in mind the above neuropsychological findings, coupled with the outcome of the Senate Inquiry, it would be of considerable interest to conduct a wider scale study of BAe-146 aircraft flight crew via a comprehensive research study.

If the data gathered from this project, were conclusive, then the information gathered could be utilised as evidence to initiate the introduction of better working conditions for employees in the airline industry.

NEUROTOXICITY PROBLEMS AMONG AIRCRAFT ENGINEERS

An alarming situation has arisen in Australia over the past 25 years among RAAF aircraft maintenance engineers who were exposed to jet fuels and toxic

sealants as part of the F111 Deseal/Reseal Project. This project took place over a 25 year period from early 1975 to late 1999.

Magnitude of the Problem

Approximately 700 RAAF aircraft maintenance workers were involved in the Deseal/Reseal Program over 25 years, which resulted in significant health problems. When these health problems were identified the program was terminated. The RAAF has accepted liability and conducted a wide scale assessment of the health effects of the workers involved in the program. This wide scale health study resulted in the publication of "Study of Health Outcomes in Aircraft Maintenance Personnel" in September 2004.[32]

Details of the Study

There were 659 workers exposed and 1095 controls in the study: They were all assessed on a number of measures for:

- General health and wellbeing
- Cardiovascular health
- Respiratory health
- Dermatological abnormalities
- Neurological problems
- Sexual dysfunction
- Mental health problems
- Neuropsychological deficits

Many health outcomes emerged from this study, but those related to neuropsychology which were of significance were; Lowered performance on tests of executive functioning or problem solving, processing speed, memory capacity; and new learning skills.

It was found that the most toxic component of the desealing agent used was a chemical known as SR51. In all the analyses carried out, this particular chemical agent demonstrated the most wide spread symptoms and health effects.

Common Deficits Among All Three Groups

Among the three groups of workers in medical, industrial, and aviation industries, there were some common areas of neuropsychological deficit. These deficits were in; memory functioning; processing speed; reaction time; attention span and some aspects of fine motor skills.

CONCLUSIONS

Industrialisation is a necessary feature of economic growth, but it brings with it occupational health and safety problems.

The increasing incidence of occupational neurotoxic diseases calls for a demand for safer working conditions, better occupational health services and a broader coverage of health education.

Although multi-disciplinary research efforts are to be encouraged to investigate the pathogenesis, diagnosis and treatment of neurotoxic disorders, it is multi-sectoral collaboration that is urgently needed if we are to prevent the growth of occupational neurotoxic disorders world wide (Fengsheng He 1998).[33]

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MULTI-SYSTEM AND MULTI-ORGAN ILLNESSES IN THE UK: GULF WAR SYNDROME ME-CFS, PESTICIDE POISONING, MCS AND FIBROMYALGIA

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BIOGRAPHICAL SKETCH

Malcolm Hooper obtained his degrees from the Faculty of Medicine University of London and took up an appointment at Sunderland Technical College in 1959. Successively promoted to become the Professor of Medicinal Chemistry before retiring in 1992 from the new University of Sunderland, when he was appointed Emeritus Professor of Medicinal Chemistry. A life time of research and teaching in medicinal chemistry particularly into drugs for tropical diseases, leprosy, malaria, trypanosomiasis with a special interest in drug design and development. He was Chairman of the Society for Drug Research for two years and served on its main committee for many years. In 1997 he became involved with the 1990-01 UK Gulf War Veterans and has served on their behalf on two major committees established by Government, Vaccine Interactions Panel, and the Depleted Uranium Oversight Board. He is also a member of the Gulf War Group established by the Royal British Legion that brings together scientists, politicians, service charities and Gulf War Veterans. He has presented evidence to the Select Defence Committee on behalf of the veterans and brought major UK scientists together for a joint Parliamentary and USA Congress presentation in June 2002. He gave evidence to the Lloyd Inquiry that concluded in November 2004 that Gulf War Syndrome is a legitimate illness following deployment of many troops in the Gulf War 1990-01. Following his involvement with the Gulf War Veterans he has become very much involved with other groups fighting for recognition of pervading chronic illnesses, ME-CFS [myalgic encephalomyelitis-chronic fatigue syndrome], MCS [multiple chemical sensitivity], OP poisoned farmers. Tests carried out at the Autism Research Unit in Sunderland have proved useful in helping many people suffering from these 20th/21st Century illnesses. Many of these illnesses are being denied and sufferers have lost benefits, supports and care due to attempts by the medical establishment supporting the insurance industry to label these illnesses as psychiatric. His latest concerns are with the World Wildlife Fund, WWF, studies that have shown widespread contamination of people, including some political leaders in the EU, with a whole range of chemicals used in contemporary society that are now the feature of national and international legislation.

SUMMARY

Gulf War Syndrome, GWS, has now been recognized and is a consequence of multiple biological and chemical exposures which include

organophosphates, OPs, and other pesticides. The effects of OP exposure is of interest to this conference and is considered in detail especially in regard to the experiences of Gulf War Veterans (GWVs), who were exposed to nerve agents and pesticides which affect the same target enzyme systems in the body. Organophosphate poisoned farmers provide another group whose exposures will provide important information about the adverse health effects of OPs. Synergistic effects are known to enhance the toxicity of pesticides. In addition the newly recognized toxic effects of man-made chemicals in the wider environment all add to the total toxic burden of most people today. Although a common array of symptoms of ill-health, that affect many systems and organs in the body, are found in many chronic ill-health conditions these symptoms are often disregarded and labeled non-specific. Somatisation has been proposed as an explanation of these symptoms but some psychiatrists regard this as an abuse of psychiatry. In addition to these symptoms there is an excess of some sell defined illnesses among Gulf War Veterans and OP poisoned farmers including motor neurone disease, Parkinson's disease, autoimmune diseases, some cancers, heart defects, and birth defects in children. Extensive and detailed clinical and scientific studies have identified organic damage as a result of Sarin and OP exposures. Such studies are briefly summarised and conclusions drawn with regard to addressing the welfare of air and cabin crews.

INTRODUCTION

The Gulf War 1990-91 was the first major conflict in which UK troops were engaged that deployed a comprehensive defence measures aimed at protecting our troops against the possible deployment of chemical and biological weapons known to be possessed by the armies of Saddam Hussein, the leader of Iraq. The description of this war as the "most toxic war in western military history", accurately describes the battlefield situation.[1] Regrettably many of the measures taken were unproven in any theatre of warfare and represented experimental use of troops to validate the use of these measures.

The most important biological and chemical exposures were:

- **vaccines** which included both established "health and hygiene" vaccines and those aimed at counteracting possible biological agents such as anthrax and plague and an antitoxin against botulinum toxin;
- **pyridostigmine bromide**, a carbamate, used in nerve agent protection sets (NAPS) that were taken in the field as a possible protective agent against the nerve agent Soman;
- **pesticides**, especially organophosphate pesticides, OPs, and related carbamates, but including also, lindane, an organochlorine, and pyrethroids such as permethrin and related compounds, thought to be less toxic to humans than the OPs and DEET a widely used insect repellent, all to avoid insect transmission of tropical diseases known to be associated with sandflies and mosquitoes;

- **depleted uranium** weapons used for the first time in warfare but only by the UK and USA forces. A wide range of these weapons that contain solid cores of depleted uranium distributed large quantities of radioactive uranium oxide dust over the battlefield; oil and smoke from buring oil fields through which the advancing troops had to pass;
- **oil and smoke** from burning oil wells

Some forty four other toxins were identified in a report from the Institute of Medicine in America,[2] and included vapours from oils and fuels – including jet propulsion fuels and additives, heavy metals from burning fuels and the oil wells and also heavy electromagnetic radiation from the intense communications deployed over the battlefield.

For the purposes and interests of this paper the most important were:

- Pesticide exposures of which organophosphates, OPs, are a major concern.
- Nerve agent exposure, Sarin, detections reported from the opening air war, 16 Jan 1991 and from demolition of storage dumps for nerve agent shells after hostilities had ceased.
- Pyridostigmine taken as a prophylactic against the nerve agent Soman that was never identified unambiguously.

These three different groups of toxins all act similarly by inhibiting the enzyme acetylcholinesterase and thereby extensively disturb and damage the cholinergic nervous system that has a key role in every nervous system, central, peripheral and autonomic. Together they constitute a "triple whammy" on the cholinergic nervous system and the many interactions between other nerves, organs, and glands. Whilst the acute effects of exposure to these agents are well known, it is increasingly becoming clear that long term and often delayed effects can also follow exposure to these agents.[3,4]

Table 1: Critical Exposures shared by GWVs and Air/Cabin Crews

Type of exposure		Comment
A	Organophosphates and Carbamates	Potent anticholinesterase inhibitors
B	Pyrethroids	Pesticides replacing OPs but now found to have cause neurological damage
C	Jet fuels and additives	Volatile organic compounds, JP8 – jet fuel
D	Combustion products	Carbon monoxide, heavy metals such as lead, cadmium etc., other toxicants such as naphthylamines
E	Radiation	From communication systems.

In addition it is becoming clear that there is a major toxic load in nearly everyone that involves, particularly, persistent and bioaccumulative chemicals in every day use and endocrine disrupting chemicals. Extensive studies by the World Wildlife Foundation (WWF) have identified the most important, (see Table 2).[5,6,7]

Table 2: Persistent Bioaccumulative and Endocrine Disrupting Contaminants found in nearly all Members of Western Society

a	Persistent bioaccumulative chemicals	
	i	Organochlorine Compounds – pesticides eg. DDT, lindane, hexchlorobenzene, PCBs
	ii	Organobromo Compounds – Flame retardants, polybromodiphenyl ethers
	iii	Organofluoro Compounds – stain repellents, non-stick cooking implements
b	Endocrine Disrupters	
	i	Includes some of above, such as DDT, lindane, some PCBs
	ii	Phthalates – the commonest plasticizers used to provide flexibility in plastic materials, such as film wraps for food, children's toys etc
	iii	Bisphenol-A - widely used as a protective film plastic food containers, cans and dental sealants

Many of these are present in cabins through carpets and fabrics and electrical equipment. The consequences of these exposures are only now becoming apparent in major effects on:

- babies *in utero*.
- children in their early development, especially male children
- young men and reduced sperm counts and infertility
- the elderly with a massive escalation of degenerative diseases.[8]

SHARED SYMPTOMS OF CHRONIC ILLNESSES

The symptoms commonly reported by sick Gulf War Veterans are extensive and involve every major system and organ in the body they also have much in common with symptoms reported by other groups of people with a variety of chronic illnesses that have been little investigated and often denied. Table 3 lists some characteristic symptoms and the different groups that share this constellation of symptoms.

Table 3: Shared Symptoms involving Multi-systems and Multi-Organs in emerging Chronic Illnesses, Multiple Sclerosis and HIV/AIDS

Adapted from Jackie Burkead

Symptoms	OPs	GWS	MCS	FMS	CFIDS	MS	AIDS
Joint pain	✓	✓	✓	around joint area	✓	✓	✓
Fatigue	✓	✓	✓	✓	✓	✓	✓
Headache	✓	✓	✓	✓	✓	✓	✓
Memory Problems	✓	✓	✓	✓	✓	✓	✓
Sleep disturbed	✓	✓	✓	✓	✓	due to medicines?	✓
Skin problems	✓	✓	✓	✓	✓	burning skin	✓
Problems in Concentration	✓	✓	✓	✓	✓	✓	✓
Depression	✓	✓	✓	✓	✓	✓	✓
Dizziness	✓	✓	✓	✓	✓	✓	✓
Gastrointestinal – Irritant bowel	✓	✓	✓	✓	✓	✓	✓
Chemical/Environmental sensitivity	✓	✓	✓	✓	✓	Reported	–
Eye problems	✓	✓	✓	✓	✓	✓	✓

Symptoms	OPs	GWS	MCS	FMS	CFIDS	MS	AIDS
Anxiety	✓	✓	✓	✓	✓	✓	✓
Tachy and/or chest pain	✓	✓	✓	✓	✓	✓	✓
Breathing problems	✓	✓	✓	**Reported**	✓	✓	-
Light sensitivity	✓/-	✓	✓	**Reported**	✓	✓	-

Abbreviations

✓	Reported in the literature **Reported** Anecdotal evidence
AIDS	Autoimmune Deficiency Syndrome
CFIDS	Chronic fatigue immune dysregulation syndrome
FMS	Fibromyalgia syndromes
GWS	Gulf war Syndrome
MCS	Multiple Chemical Sensitivity
MS	Multiple schlerosis
OPs	Organophosphorus compounds

The first five columns list symptoms associated with illnesses that are often hotly debated and frequently dismissed, namely Organophosphate poisoning, OPs, Gulf War Syndrome, GWS, multiple chemical sensitivity, MCS, fibromyalgia syndrome, FMS, chronic fatigue immune dysregulation syndrome, CFIDS, which is the terminology used in the USA for myalgic encephalomyelitis – chronic fatigue syndrome, ME-CFS. Many of theses symptoms are described by air and cabin crews who have become ill following fume and smoke events that are thought to involve OPs and other toxins. What is striking is the inclusion of the symptoms of multiple sclerosis, MS, and acquired immune deficiency syndrome, AIDS, or more accurately AIDS-HIV (human immunodeficiency virus). MS is now a well characterised neurological illness with an immunological basis that was earlier defined as hysteria.[9] AIDS-HIV is a specific immune disease resulting from a viral infection. From this table it can reasonably be concluded that the first five disorders may be expected to involve dysregulation and disorders of both the central nervous system and the immune system.

Despite the controversial nature of some of these illnesses there is increasing recognition of some of them. GWS is now authenticated in both Lloyd Report, 2004,[3] and the RACGWI, 2004.[4] The USA Government has recognised the real organic nature of Gulf War Illness and the presumption now is that sickness among Gulf War Veterans is a consequence of service in the Gulf.

MCS is recognised in Germany where it has been classified under allergy of unknown origin. In the USA official recognition of MCS has come in the form of reports from the Department of Justice, the Department of Housing and Urban Development, and the Department of Education. Medical resistance to MCS has begun to evaporate among the American College of Physicians. The American Medical Association and American Lung Association and Environmental Protection Agency state that, "Claimants should not be dismissed as psychogenic and a thorough workup is essential …" large population surveys report from 16-33% of people being sensitive to every day chemicals.

Ashford and Miller, 1998, describe the direct entry of inhaled chemicals into the limbic system of the brain through intraneuronal transport that bypasses the protective blood brain barrier.[10]

Literature available from Pesticides Action Network, PAN, 2005, emphasizes the multi-organ and multi-system damage identified in people with pesticide poisoning,[11] and the Merck Manual, 1999, places GWS, MCS and ME-CFS in the category of Syndromes of Unknown Origin.[12] The Merck report also draws attention to the multi-system and multi-organ effects found in these syndromes. Table 4 summarises the cumulative assessment of the situation to date.

Table 4: Summary of Multi-System Damage and Dysfunction

System	Reported Effects
Neurological	affecting the peripheral, autonomic and central nervous system
Cardiovascular	affecting heart function especially
Immune system	damage with the emergence of autoimmune disorders
Gastrointestinal	often with food intolerances
Respiratory	with asthma and breathlessness
Endocrine problems	especially concerning libido, sexual dysfunction and frequently thyroid and stress responses
Urinary system	
Reproductive system	
Liver and metabolic problems	
Musculoskeletal	
Skin	

Despite all these problems it is clearly stated that, Merck 1999:[12]

> *"Considering the extent of the patients' complaints and disability, the results of routine laboratory tests were strikingly normal"*

Such a statement emphasises the inadequacy of the current tests used to assess general ill-health and the need for better and different tests to address the damage arising from exposures to pesticides and other environmental toxins.

Inquests in the UK into the deaths of Major Ian Hill, a 1991 Gulf War Veteran in November 2003, and Mrs Kathleen Sullivan of Honiton, Devon, in July 2003, who was a pig farmer repeatedly exposed to OP pesticides during her work, describe the effects of their illnesses and final demise as involving global illness syndrome (Ian Hill) and multi-system atrophy (Mrs Sullivan). Both clinical assessments confirm the multi-system and multi-organ effects of the exposures suffered by them.

SOMATISATION AND ILLNESSES INVOLVING NONSPECIFIC SYMPTOMS

The constellations of symptoms found in all these syndromes, as shown in Table 3, are often belittled by referring to the symptoms as non-specific and therefore of little value in understanding the complaints and disabilities of those exposed to the various environmental agents. It is failure to engage

with evident sickness of patients that has lead to a concerted attempt to construct a whole new series of mental illnesses that have come to be termed psychosomatic illnesses which have arisen as a result of somatisation. In essence this means that these illnesses are driven by a disturbed psyche and not by any organic causes - they are functional somatic syndromes. This theory that was especially developed to offer an explanation of Gulf War Syndrome has now been extended to cover illnesses that cover all the major systems of the body, as shown in Table 5.[13,14]

Table 5: Functional Somatic Syndromes- One or Many?

Specialisation	**Diagnosis**
Gastroenterology	Irritant Bowel Syndrome, non-ulcer dyspepsia
Gynaecology	Pre-menstrual Syndrome, chronic pelvic pain
Rheumatology	Fibromyalgia
Cardiology	Atypical or non- cardiac pain
Respiratory medicine	Hyperventilation
Infectious Disease	Postviral fatigue syndrome, chronic fatigue syndrome myeloencephalitis,
Neurology	Tension headache
Dentistry	Temporomandibular joint (TMJ) dysfunction, atypical facial pain
Ear Nose Throat	Globus syndrome (sensation of lump(s) in the throat)
Allergy	MCS

What these syndromes share in common are:

- They cannot be explained by conventional medical paradigms.
- Conventional therapies are ineffective.
- They are more common in women than in men.
- Shared "non-specific symptoms.

It is telling that Globus syndrome is named globus hystericus in Oxford Concise Medical Dictionary.

There is considerable pecuniary advantage for Governments, the insurance industry, and the chemical industry in the designation of these unexplained illnesses as psychiatric disorders in that payments and benefits to help and support sufferers are considerably less those for identifiable organic illnesses. Further it is possible to compel people to undergo psychiatric therapies such as CBT (cognitive behavioural therapy) and/or GET (graded exercise therapy) before any payments are made to them.

Associated with the concept of somatisation and CBT phrases such as, " false illness beliefs" that blame the sufferer for their illness and insist that only by changing their beliefs will they find any resolution to their chronic illnesses or receive any financial help in their commonly straitened circumstances.

The following extract from a letter to a General Practitioner by a Medical Assessment Panel physician, 2001, about a Gulf War Veteran states:

> *"He has a psychiatric illness. I hope he will not waste his time, energy, and aspirations chasing after non-existent organic explanations that will never be found".*

An MCS sufferer is described in her medical notes.

> *"She has a psychosomatic illness with false illness beliefs."*

The same GP refused to consider a report from a clinical psychologist that he had commissioned.

Studies have often been constructed to combine very disparate groups that have fatigue as a major symptom of their illness. Such terminology disguises and belittles the crippling and destructive fatigue shared by sufferers from the syndromes listed in Table 3, where it is recovery from exercise and effort that is compromised not simply an expression of tiredness. Fatigue is also allied to many other established illnesses such as asthma, chronic obstructive pulmonary disease, cancer and so forth. This has best been exemplified in the recent clinical criteria for the diagnosis of ME-CFS published by a group of physicians in North America, and known as the Canadian Consensus, 2003.[15]

The deception has been extended to challenge the International Classification of Diseases, ICD-10, which classifies ME (G 93.3) under neurological disorders. Quite unprincipled totally unacceptable behaviour tried to reclassify this illness as a behavioural and mental disorder (F 48.0). The outcome was a debate in the House of Lords in which the Secretary for Health, Lord Warner eventually conceded that ME is a neurological condition and the UK Government will correct the official information distributed to GPs and others that suggests otherwise.[16,17]

All this means for organophosphate poisoned sufferers that they face entrenched attitudes in Government and the industry concerning any recognition of their pervasive and chronic illnesses.

For this reason it is essential to meet this challenge head on and expose it for the sham that it is. Much of the evidence has accumulated as a result of studies on Gulf War Veterans who form a large, coherent cohort of chronically ill military personnel. Much of this work can be fairly applied to those who suffer from organophosphate poisoning.

The recent reports on Gulf War Illness, following extensive independent medical and scientific research (see below for a summary) in the USA, vehemently conclude that the psychosomatic theory is dead. In the words of the report "the stress theory is dead", RACGWI 2004.[4] This view has now prevailed in Congress and Government in the USA but is still being resisted in the UK where no reasoned arguments against the conclusions of the Lloyd Report have been presented, but only specious grounds for denial are put forward. Australia has also remained obdurate in the mounting evidence of organic damage found among Gulf War Veterans and people exposed to pesticides and other environmental chemicals.

Wessely who is a principal architect of somatisation has published an important paper in 2002, that demonstrates:

- GWVs do not have an excess of formal psychiatric illnesses.
- Do not have an excess of PTSD (post traumatic stress disorder)

These conclusions lead him into "the thicket of somatisation",[17] rather than to the acceptance of organic damage as a result of environmental exposures.

A major two-phase study of a population with MCS produced the information that in a sample of 1582, the prevalence of emotional problems before exposure was 1.4% but after this had risen to 37.7%, Caress and Steinmann, 2003.[18] The authors conclude that this "suggests MCS has a physiological not psychological etiology."

A number of psychiatrists, doctors, and scientists reject the somatisation theory as applied by Wessely and those who support his views. An article by the psychiatrist, Per Dalen, lists the following in an extensive and important paper entitled "Somatic Medicine abuses Psychiatry and neglects Causes."[19]

- There is almost total lack of scientific support.
- Bodily symptoms are being reclassified as mental problems where conventional medicine is at a loss for an explanation.
- Lack of firm knowledge is converted into speculative asseretions without any critical voices being heard.
- Causal explanation for illnesses …. go with predominantly somatic symptoms [that] lack any basic similarity to known mental disorders.
- Somatic medicine offers an evasive argument with a lamentably poor record of research into causes, particularly where environmental factors are concerned.
- Industrial interests are actively influencing the course of what is ostensibly a scientific discussion.
- What makes an individual human being ill cannot be determined by statistics.
- Lack of knowledge is a considerable handicap in the treatment of chronic diseases.

Martin Walker recounts the psychiatric hegemony that seeks to label all chronic illnesses as having a psychiatric rather than an organic origin.[20]

Dr John Diamond a former psychiatrist makes the astonishing confession, Facets of Diamond, quoted in Hooper et al, 2003:[1]

> *"I am no longer a psychiatrist. I renounce it because I believe cruelty is at the core of the profession (and) I believe that there is something inherent in the profession that tends to bring out any cruelty lurking within. I have long wondered why this profession … which ought to be so compassionate … has it seems to me, turned its back on humanity."*

SUMMARY OF EVIDENCE IN SUPPORT OF ORGANIC DAMAGE IN CHRONIC ILLNESSES

Other presenters at this symposium will be providing more detailed information, including Professor Haley, Dr Abou-Donia, Dr Goran Jamal, Dr Peter Julu, and Dr Sarah McKenzie Ross.

Haley's work with Gulf War Veterans is consistent with damage to the deep brain structures, the basal ganglia and brain stem, identified with magnetic resonance spectroscopy.[21,22,23,24] Exposure to nerve agents is the most likely cause of this damage. Both OPs and pyridostigmine bromide would be expected to cause similar damage. The signs and symptoms are those associated with early signs of Parkinson's disease, Huntingdon's chorea and other diseases known to involve damage and deficits in theses structures. Subtle adverse changes in autonomic cholinergic control of heart rate and Q/T intervals involving the electrical control of heart function.

Independent research groups have confirmed the neurological observations,[25] and extended them to other areas of the brain particularly the hippocampus.[4,26] None of these tests have yet been used to investigate sick Gulf War Veterans, OP farmers or air/cabin crews. They are urgently needed

Furthermore and very worryingly, it is now clear that very low doses of Sarin can lead to delayed toxic effects many years after the original symptom-free exposure.[4]

Professor Abou-Donia describes his own work in his paper to this Conference. He has concentrated on delayed effects of OPs and also identified autoantibodies to intracellular neural proteins following OP exposure. Such antibodies are clear indicators of profound damage to the nervous system. Another major piece of work identified synergistic toxicity involving OPs and pyrethroids in laboratory animals. Since cabin crew may well be exposed to OPs through inhaling cabin air that contains bleed air from the engines and pyrethroids used to spray the cabin at various locations enhanced toxicity may well result.

Dr Goran Jamal was among the first to identify peripheral neuropathy in OP poisoned farmers and Gulf War Veterans,[27,28] whilst Dr Julu has developed a complementary battery of tests of autonomic system function that show clear deficits particularly in regard to the heart and cold sensitivity.[29]

Dr McKenzie Ross has developed a battery of psychological tests that make possible a detailed analysis of deficits in the higher brain functions and found these to be present in OP poisoned farmers.

Important studies on both Gulf War Veterans s and OP poisoned farmers have identified very low levels of paraoxonase an enzyme that has an important detoxifying role with regard to OPs.[30,31,32,33] This enzyme protects against atherosclerosis and diabetes.

Osteoporosis has been identified in young male Gulf War Veterans and in OP poisoned farmers.[34,35]

Detoxification methods are available to address the health problems of exposed personnel, see Myhill[36] in the UK and Rea in the USA.[37]

DISCUSSION AND CONCLUSIONS

In the light of the foregoing comments and information several conclusions can be drawn.

Air and cabin crews are exposed to a wide variety of toxins including organophosphates. The latter as a consequence of the use of bleed air from the engines in the ventilation system of modern aircraft.

Bleed air contains tricresyl phosphates used as anti-wear agents in modern jet engines.

There is abundant evidence in both humans and animals to show that every major system of the body can be damaged by OPs. They cause multi-system and multi-organ damage.

Disturbing new evidence is now emerging to show that other man-made chemicals in the environment have extensively contaminated most people in our society and exert serious and far reaching adverse health effects.

Any psychosomatic claims lack credibility and cannot be sustained on scientific and medical grounds.

Currently clinical tests are available that will allow a full assessment of the damage to the brain, autonomic nervous system, and the immune system.

Delayed effects of exposures to OPs are known and monitoring of air/cabin crews is essential to identify any early signs and symptoms of multi-system and multi-organ damage.

The most effective way to prevent poisoning of air/cabin crews and passengers is to remove as many toxins as possible.

All cabin air must be thoroughly filtered to remove all possible toxins. Such action is possible now.

Treatment of personnel reporting ill must include much longer compulsory breaks from flying in any atmosphere that contains these toxins.

Other treatments to detoxify affected personnel are available and should be investigated as a matter of urgency.

It is arguable that flying in the current environment provided in nearly all commercial aircraft could give rise to serious and long term health effects particularly to babies *in utero* and their pregnant mothers. Male foetuses

appear to be especially at risk. The toxins discussed are known to cause disruptions in the developmental neurobiology and the sexual organs of the foetus and baby.

Children especially in connection with the later developments of the brain and central nervous system.

Elderly people may also be particularly susceptible to enhanced damage and chronic illness from flying.

The commercial and health cost of such events would be catastrophic and every step should be taken to reduce these risks to a minimum – much more needs to be done.

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CLINICAL DIAGNOSIS OF CHRONIC FATIGUE-PAIN-COGNITIVE ILLNESS: LESSONS AND APPROACHES FROM GULF WAR ILLNESS RESEARCH

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BIOGRAPHICAL SKETCH

Robert W Haley, MD, is Professor of Internal Medicine and Director of the Division of Epidemiology in the Internal Medicine Department at the University of Texas (UT) Southwestern Medical Center at Dallas and holder of the US Armed Forces Veterans Distinguished Chair for Medical Research Honoring America's Gulf War Veterans. He received his MD degree from UT Southwestern Medical School and served a residency in internal medicine at Dallas Parkland Memorial Hospital. He spent 10 years (1973-1983) at the US Centers for Disease Control and Prevention (CDC), where he investigated nosocomial infection epidemics, served as director of the Hospital Infections Program, and performed epidemiologic research in nationwide samples of US hospitals. His primary research at CDC was the Study on the Efficacy of Nosocomial Infection Control (SENIC Project), a nationwide epidemiologic study that demonstrated the efficacy of infection surveillance and control programs and the feedback of risk-stratified nosocomial infection rates to hospital personnel in reducing rates of hospital-acquired infections. In 1983, Dr Haley founded the Division of Epidemiology and Preventive Medicine at UT Southwestern Medical Center in Dallas. He was an attending physician at the Dallas VA Medical Center for 10 years (1985-1995) and has been an attending physician at Parkland Memorial Hospital since then, where he serves on the Infection Control Committee. Dr Haley has conducted extensive research on the epidemiology and prevention of hospital-acquired infections, Hepatitis C and Gulf War syndrome. He teaches epidemiology and clinical research study design to medical students and research faculty and for fifteen years lectured in the nationwide training course for hospital epidemiologists sponsored by CDC and the Society for Healthcare Epidemiology of America. He is a fellow of the American College of Epidemiology and the American College of Physicians, a member of the Association of American Physicians, and is listed in *The Best Doctors in America*.

ABSTRACT

Research to understand the nature and causes of obscure fatigue-pain-cognitive syndromes is a difficult undertaking that will require great understanding and organization to accomplish. Obstacles to successful research include pervasive prejudice and skepticism in the medical field and active obstruction by financial and political interests. A decade of research to

understand the chronic fatigue-pain-cognitive illness in Gulf War veterans, called Gulf War syndrome, has taught several lessons that could inform interests designing research on similar illnesses. The approach that has developed to address the Gulf War syndrome involves formulation of a case definition, epidemiologic surveys with risk factor analysis, nested clinical case-control studies to identify biomarkers (objective biologic measures) of the illness, particularly focusing on the brain, experimental studies in animal models, and replication of the major findings by several research institutions. A serious threat to successful research is the outpouring of poorly designed research that confuses the literature and usurpation of the research funding stream by financial and political interests with counterproductive incentives. Science is ultimately self-correcting if those representing the patients' interests can raise substantial research funding, select researchers and approaches well, and maintain a long-term view of the research enterprise.

INTRODUCTION

Chronic conditions characterized by fatigue, pain and cognitive disturbances and other symptoms, but no objective signs or laboratory abnormalities are, and always have been, common in medical practice. In some specialties such as primary care, rheumatology and neurology such conditions often account for half of new patient evaluations. While standard medical evaluations may identify a diagnosable disease underlying the symptoms, which may be curable or controllable with standard medical treatments, a high proportion of such patients turn out to have no detectable basis for their symptoms, leaving both patient and physician in a quandary on what to call the illness and how to treat it. Usually such patients are given diagnostic labels such as chronic fatigue syndrome, fibromyalgia, or irritable bowel syndrome, even though these labels convey little more than that no basis for the illness was identified. Or worse, physicians subtly blame the patient with labels such as "crock" and "malingerer" and attribute the complaints to psychological or financial "secondary gain." Unfortunately, sometimes such blame is justified.

The fact that this problem has been so deeply and negatively ingrained in medicine for so long presents serious difficulties to groups of workers who think they may have developed such an illness as a result of some work-related exposure. When presenting to a physician for evaluation, they often are surprised and shocked to meet what appears to be a prejudged skepticism of their illness, a strong tendency to treat the symptoms as psychological in etiology, and a resistance to the possibility that the illness could be work-related. Add to this the resistance that is generated by the businesses, corporations, government agencies or congressional bodies that would incur huge costs if found to be responsible for the condition in a large class of workers. It is no wonder then that workers with these conditions encounter so much difficulty in getting their problem recognized, treated and compensated.

In early 1994, I was asked to examine a high rate of a fatigue-pain-cognitive illness in US veterans of the 1991 Persian Gulf War, known as Gulf War syndrome. Predictably my initial reaction was that this was just another manifestation of the age-old problem familiar to all physicians or, worse, an organized effort to obtain undeserved pension support. Coming to this problem fresh in an era in which diagnostic technology and epidemiologic research methods had substantially advanced, I and my collaborators at the University of Texas Southwestern Medical Center set out on a set of studies that may not only have shed new light on Gulf War syndrome but also have defined a novel strategy for attacking the puzzle of fatigue-pain-cognitive illnesses and their potential etiologic relationship with environmental or workplace exposures.

THE LESSONS

Ten years of virtually full-time research on Gulf War syndrome has imparted several lessons that underlie our approach and may prove useful to those meeting the problem of fatigue-pain-cognitive illnesses in airline flight crews and other contexts.

First, the affected workers must understand the considerable opposition to their concerns about an association of their illness with work-related exposures. The opposition is coming both from well meaning, objective physicians motivated by nothing more than their past clinical experience with this type of problem and from other vested interests motivated by strong financial stakes. They must realize that the only way to overcome both sources of resistance is the development of scientific research that produces clear biological insights into the nature (pathogenetic mechanisms) of the illness, the causal links with work-related environmental exposures, objective diagnostic markers of the illness than can be measured in routine clinical practice, and treatment for the illness. Armed with this insight, the affected workers can organize and ensure that the research takes place.

Second, they should realize that until the research is done, there is no test or treatment available in standard clinical practice that can give them a reputable diagnosis, pension funding, or relief from symptoms. This realization is important both to motivate the pressure to get research done and to avoid the potentially large expense and disappointment of ineffective treatments widely promoted by charlatans, who prey upon the desperate victims of these vague illnesses. On the other hand, the most useful thing sufferers of these illnesses can do is to find a reputable physician who is interested in their problem and will experiment with a wide array of available medications until helpful regimens are found. For example, clinical depression is a common companion of chronic illness, and thus, standard treatments for depression such as antidepressant medications and cognitive behavior therapy can be helpful to treat accompanying depression. At the same time, medications that do not provide clear relief of one or more symptoms should be discontinued to avoid worsening of the illness from unintended interactions among medications.

Third, they should become acquainted with the research approaches that are likely to contribute toward understanding the illness and its diagnosis and treatment and to differentiate these from approaches that are likely not to contribute or even to retard progress. I will outline below some elements of productive research approaches. Unfortunately, because of the natural skepticism and resistance to fatigue-pain-cognitive illnesses discussed above, research on this problem is far more likely to prove counterproductive. This is because it is highly likely to be undertaken by researchers with strong biases against an organic etiology, a similar bias toward a neo-Freudian psychological explanation, or worse, a financial conflict of interest from the ease of obtaining generous grant funding, or outright bribes, from business or governmental entities bent on maintaining a state of ignorance to protect financial interests. Just as problematic is the high probability of encountering research by scientists who gravitate to controversial illness problems because they are too inexperienced or too inept to obtain research funding for more mainstream research objectives. Above all, beware of any self-styled scientist who claims to have "the answer" but cannot produce confirmatory papers published in well regarded scientific journals. Such groundless claims are common in subject areas like this and are to be eschewed. Always ask, "Can you show me the scientific publications where you proved this?"

THE APPROACH

If sufferers of fatigue-pain-cognitive illnesses face such a difficult time getting productive research done, they certainly need to know what type of research might be worthwhile and how to recognize it. The following are the steps that I think should be taken.

Defining Epidemiologic Studies

Clearly the first priority is epidemiological studies to establish a case definition for the illness, define subtypes (or variants), and estimate their prevalence. These are needed to move beyond the state where the illness is a diffuse "multi-symptom illness," which breeds contempt among even reputable researchers. A proper study should begin with informal clinical interviews with typical cases of the illness from which a provisional case definition is formulated. A case definition is a simple statement of seminal combinations of symptoms, signs or laboratory findings that seem to characterize the typical illness and differentiate its typical sufferers from all who do not have the illness.

When objective signs and laboratory findings are available, the case definition can be simple, straightforward and widely agreed upon. For example, in the initial epidemiologic investigations of toxic shock syndrome, a case was defined essentially as a woman with high fever, dangerously low blood pressure and red skin. For investigations of fatigue-pain-cognitive syndromes, however, one has only subjective symptom reports with which to build a case definition. In this case, more complex mathematical methods may be necessary. For example, in the Gulf War syndrome investigation we

applied a technique called factor analysis to symptoms measured on a special questionnaire developed for this approach. This ultimately identified three syndrome variants, which turned out to differ widely on objective tests of biological function. Without the distinction among the syndrome variants, the later studies would have been far less enlightening.

The symptoms needed to formulate the case definition must then be incorporated into a questionnaire along with questions to document possibly relevant exposures and used to survey the target population in which the illness is thought to have occurred. The survey should include representative samples of both the ill and well segments of the target population, not just the ill as less thoughtful researchers are often tempted to do. The analysis measures the prevalence of the syndrome variants and their associations with risk factors that reflect relevant exposures. If the survey was designed insightfully, these risk factor associations provide strong clues to the etiology of the syndrome variants that can be followed with experimental studies in animal models.

Certain types of epidemiological findings provide stronger evidence for a causal link than others. For example, finding very strong statistical associations (high relative risks), evidence that a higher level of exposure is associated with a higher risk of disease (dose-response effect), and demonstration of the absence of alternative explanations, such as confounding, all strengthen the causal inference. Survey methodology and epidemiological analysis are quite complex, and to get a useful result the surveys should be done by highly experienced survey and epidemiologic researchers.

Unfortunately, the great majority of studies on Gulf War syndrome proceeded without first deriving a case definition at all or using a nonspecific case definition, such as those for post-traumatic stress disorder and chronic fatigue syndrome, which did not truly reflect the patterns of symptoms reported by the ill veterans. Much of it was also performed by clinical psychologists and psychiatrists with little survey and epidemiological research expertise. As a result, these studies were poorly designed and ineptly analyzed, severely confused the early scientific literature on the illness, and led to misconceptions and false directions in the research.

Nested Clinical Case-Control Studies of Biomarkers

Once a case definition is formulated, applied in a sophisticated epidemiologic survey of the ill population, and the analysis identifies strong risk factor associations, the next step is to perform follow-up case-control studies in small subsamples of the ill and well subjects identified in the survey. Ideally one selects a random subsample of each of the syndrome variants and a control group of well survey subjects matched for age, sex and education level to the ill subjects. Ideally ten to twenty subjects are chosen from each group. Narrowing down the sample size to these small numbers is critical because the types of research tests required to elucidate so complex

an illness are too expensive to apply to larger groups. If the case definition was insightfully formulated, the groups identified by the survey should have relatively homogeneous manifestations of the disease, thus allowing the illness groups to be well represented by small numbers of subjects.

The types of tests to do on the cases and controls are where the real creativity comes. Fortunately, we are living in a time of rapid innovation in testing methodology, and most physiological processes in the body can now be measured insightfully. Since most of the modern testing methods are expensive, however, it is important to select the tests that are squarely aimed at body processes that might plausibly underlie the troubling symptoms of the illness. Selecting the right tests can lead to highly insightful breakthroughs; whereas, picking the wrong tests can lead to negative results that waste valuable resources and aggravate the already rampant skepticism.

It is my current impression that most of the symptoms of fatigue-pain-cognitive illnesses are due to damage to, or at least dysfunction of, the brain and not the peripheral nerves, the immune system, or the muscles and joints. Moreover, the damage probably involves either receptor proteins or biochemical processes in brain cells, not the death of collections of brain tissue that might be visible on a simple CT or MRI picture of the brain. Consequently, the highest yield tests are most likely to be those that measure the biochemical composition of small brain regions, the level of function of brain cells in small regions, or other bodily functions that are controlled by the brain.

Examples of these include magnetic resonance spectroscopy (MRS) scans that measure brain chemistry, positron-emission tomography (PET) or single photon-emission computed tomography (SPECT) scans that measure the rate of brain metabolism in small regions, and objective tests of brain reflexes including audiovestibular tests, autonomic tests, quantitative sensory tests, and some neuropsychological tests. Such objective tests, if positive, would constitute biomarkers of the nature of the illness. Finding biomarkers is the single most important goal—the scientific Holy Grail—for turning a disreputable fatigue-pain-cognitive syndrome into a respectable illness that researchers and physicians would enthusiastically address.

Laboratory Studies in Experimental Animal Models

While clinical case-control studies address the nature of the illness, linking the illness to work-related or other environmental exposures requires a combination of epidemiological studies, described above, and experimental animal studies. The epidemiological studies suggest links with exposures but, since such associations are subject to many alternative explanations, they cannot be relied upon entirely. When particularly strong epidemiological links are found, it is usual to follow these up with laboratory experiments in animal models to confirm the biological plausibility of the epidemiologically identified link. It should be emphasized that both epidemiologically identified links without animal studies and animal studies without

epidemiological links are less than convincing to skeptical scientists and physicians. A strong epidemiological link and supportive results from animal experiments, however, is the combination that eventually brings consensus on causal links.

Studies of Genetic Susceptibility

An emerging new strategy for establishing the causal link between a fatigue-pain-cognitive illness and a specific environmental exposure is finding that most individuals with the illness share a genetic trait that makes them more susceptible to brain damage from the particular environmental exposure; whereas well individuals (controls) do not have the susceptibility trait. This is a very clever way of coming at the causal link from the reverse direction.

For example, in the Gulf War investigation we had strong epidemiologic evidence that syndrome variant 2 was strongly associated with war zone exposure to low-level sarin nerve gas liberated by Allied bombing of Iraqi chemical weapon stores, and animal experiments established the biological plausibility of the link. From a literature review I found that the blood enzyme paraoxonase destroys Sarin in the blood before it can get to the brain, and its activity level remains constant throughout adult life. Moreover, the enzyme has two subtypes, the Q and R isoenzymes. The Q form protects against sarin but the R form does not.

I hypothesized that the Q form, but not the R form, would be low from birth in most of the veterans with Gulf War syndrome variant 2 and normal in most of the well veterans. To test this I contacted the world's expert on paraoxonase, he measured the two isoenzyme activity levels in the cases and controls, and the results were as hypothesized. If sarin had not caused syndrome variant 2, there is no reason for the Q isoenzyme activity to be lower in the ill veterans than in the well ones. Since the paraoxonase measurements were an objective biological marker, the finding added immense support to the causal link with Sarin.

Replication of Findings

The final essential ingredient in bringing understanding and respect to a fatigue-pain-cognitive illness is replication of findings by different research groups. A finding by a single research group, no matter how well conceived and powerful the results, ultimately does not generate consensus in science until it can be replicated by researchers at other institutions. Theoretically, if the studies of one researcher discover the truth, the studies of other researchers should find the same thing. When this happens and there is no reason to expect collusion or conflict of interest, news of the replication usually brings scientific consensus.

There is a serious danger in research on fatigue-pain-cognitive illnesses, however, that replication will not occur for several reasons. If most researchers or scientific funding agencies are skeptical or contemptuous of

the illness, none will want to invest the time, money and effort to replicate a finding. If financial or political interests are working aggressively to retard research progress, they might block funding for replication studies or even threaten to punish researchers who attempt to replicate promising findings. And perhaps most likely, incompetent researchers seem to obtain funding more readily for these fatigue-pain-cognitive illnesses, and they fill the scientific journals with reports of poorly designed studies with confusing and conflicting findings that may hopelessly confuse the literature. One marker of such lesser lights is a high ratio of the number of scientific journal papers presenting pure commentaries and editorials to the number reporting original research findings by the same author or group. Fortunately, the scientific process tends to be self-correcting over a long period of time, but the correction ultimately requires sound scientific studies by good scientists to override the chaff.

CONCLUSION

In Texas (and perhaps elsewhere) we have an old expression that should guide groups wanting to bring understanding to fatigue-pain-cognitive illnesses, "Ya' pays ya' money and ya' takes ya' shot." The interests wanting progress must obtain access to *substantial* research funding and then pick researchers and research strategies carefully. If the initial picks misfire, they must reload with more funding and pick again. Expect interference from competing financial and political interests that will attempt to gain control of the funding stream and sew confusion. But keep the ultimate goal in mind over a long period of time despite all the poor science that will emerge to confuse the process. The problem is an exceedingly difficult one fraught with legion pitfalls, but a successful model for approaching the problem has arisen in the past decade, and research methods are rapidly becoming more powerful.

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From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 184-188.

COGNITIVE DEFICITS ASSOCIATED WITH LONG TERM, LOW LEVEL EXPOSURE TO ORGANOPHOSPHATE PESTICIDES: A SMALL GROUP STUDY

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BIOGRAPHICAL SKETCH

Sarah Mackenzie Ross is a Consultant Clinical Neuropsychologist and Chartered Clinical Psychologist with twelve years experience in clinical practice. She holds several posts at present: (1) She is employed by University College London as a senior clinical tutor on the doctoral programme in clinical psychology; (2) She holds a major research grant from DEFRA and is investigating whether low level exposure to OPs causes disabling psychiatric and neurological disease; and (3) She is a medical expert witness and provides medico-legal reports for solicitors involved in personal injury litigation. Prior to these appointments she had several clinical and research positions within the NHS working as both a clinical neuropsychologist and a clinical psychologist in adult mental health.

INTRODUCTION

Organophosphate (OP's) pesticides were derived from World War II nerve gas agents and are used for a variety of agricultural, industrial and domestic purposes.[1] They are potentially toxic to human beings, although the effects vary widely according to the compound, route, frequency and duration of exposure.[2] The immediate effects of OP poisoning which occur within hours of exposure have been well documented.[3,4,] OP's disrupt neural transmission, by inhibiting the enzyme acetylcholinesterase causing changes in peripheral, autonomic and central nervous system function (cholinergic crisis).

It is possible to recover from an episode of acute poisoning and as a result, it is widely believed that OP's do not cause lasting damage. However, recent research suggests there may be long-term changes in nervous system function following cessation of the cholinergic crisis and even in the absence of a previous episode of acute poisoning.[3,4,5,6] The mechanism by which OP's might cause these delayed effects is unclear and the focus of current research. Three types of delayed neurotoxic effect have been described, (1) the intermediate syndrome, (2) OPIDN and (3) neurobehavioural problems, such as impaired memory, processing speed and mood disturbance. The cholinergic effect, intermediate syndrome, and OPIDN are well recognised, but opinion is divided as to whether neurobehavioural problems constitute long term effects of low level exposure.

PRESENT STUDY

In order to highlight methodological and clinical issues inherent in conducting research in this area, Sarah Mackenzie Ross (SMR) presented the results of a case-series analysis of 25 agricultural workers (mean age 48 years) who complained of a variety of physical and psychological symptoms, which they attribute to OP poisoning. Many individuals had stopped working because of disabling levels of cognitive impairment. All participants underwent detailed neuropsychological testing and a lengthy interview concerning work, exposure, medical and psychosocial history.

METHODOLOGICAL AND CLINICAL ISSUES RAISED

Differentiating Acute versus Low Level Exposure

The vast majority of previous research studies have examined individuals with a history of acute poisoning,[7,8,9,10,11,12,13,14,15,16] and it is now generally accepted that individuals with such a history may report persistent health effects. Few studies have looked at the effects of low level exposure and many which claim to do so fail to provide sufficient information about exposure history to reassure the reader that individuals with a history of acute poisoning have been excluded.[17,18,19,20,21] The definition of low level exposure is rudimentary and unsophisticated. It is usually defined as that which "does not give rise to clinical signs and symptoms of acute toxicity of sufficient severity to require medical intervention."[4]

However, many agricultural workers complain of repeated episodes of flu-like symptoms (for example, fatigue, muscle pain, headaches and general malaise) following exposure to OPs, which may reflect mild cholinergic toxicity. Few seek medical help, so the possibility that they may have suffered from acute exposure was not documented. Many factors, other than severity of illness, determine whether individuals seek medical help including beliefs about the likely value of medical intervention, fears about the consequence on employment of reporting ill health and stoicism. Therefore, the health effects of exposure to OPs may be underestimated. As an occupational group, agricultural workers are thought to have low level exposure to OPs, yet the pattern of deficits identified in SMR's cohort has more in common with that seen in individuals who have a history of acute OP poisoning. It is possible that occupational groups, thought to be at risk of low level exposure only, actually have an unrecognized history of acute exposure. This needs to be considered by future research. Under reporting of problems is likely to be an issue in the aviation industry.

Quantifying and Characterising Exposure

Exposure history can differ enormously, despite the fact that individuals may appear to have similar jobs. This is an important finding which has not been commented on before because previous studies seldom describe exposure history in much detail. However, this factor needs to be taken into account

by future research as it may account for some of the discrepancies noted in previous work. Given the shear number of factors which can influence toxicity, it is important to obtain detailed information about exposure history and to obtain large enough samples of participants to allow meaningful comparisons between homogeneous sub-groups.

Comparisons between studies

The literature on the effects of exposure to OPs is beset with difficulties as studies have employed different methodologies and population samples (pest control operators, fruit tree sprayers, farmers and so on). These individuals may not be comparable since the level, frequency and duration of exposure varies considerably in these groups. Some individuals may have been exposed dermally, some by inhalation and certain groups wear more protective clothing than others. This makes it difficult to draw any firm conclusions about the long term effects of exposure to OPs from a review of the literature.

Vulnerable Sub-Groups

The possibility that there may be sub-groups of individuals who are more at risk than others of developing problems following exposure to OPs needs to be explored. Possible sources of susceptibility include genetic differences in relevant aspects of metabolism;[22,23] developmental issues (for example, unborn children, infants, the elderly and infirm may be at greater risk); previous exposure history; psychological profile and medical history.

Sensitivity of Measures used in Assessment

Future studies should employ internationally accepted, comparable and detailed medical tests and psychological test batteries, as opposed to less well known or brief screening measures. A reasonable number and variety of psychometric tests are required to detect, potentially quite varied, patterns of impairment, and to elucidate the nature and extent of any damage. Large scale studies tend to be limited by time constraints to studying only a few cognitive functions.

Impact of mood disorder

Many agricultural workers report high levels of anxiety and depression which could reflect (1) direct neurological damage (2) adjustment to ill health (3) stress which is unrelated to exposure. This issue needs to be explored by future studies.

Clinical Issues

The long-term prognosis for individuals reporting ill health following exposure to OPs is unknown and there is little work on the impact of ill health on everyday functioning and capacity to work. There are no agreed medical treatment protocols and many health care workers have limited

knowledge of toxicology. This results in affected individuals receiving a range of medical opinion, diagnoses and treatment options. Consequently, it is impossible to devise effective policies and recommendations regarding health and safety issues and future capacity to work. These issues need urgent attention.

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DEVELOPMENT OF A STANDARD FOR AIRCRAFT AIR QUALITY

Dr Byron Jones
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BIOGRAPHICAL SKETCH

Dr Byron W Jones received his BS degree in Mechanical Engineering from Kansas State University in 1971 and his MS and PhD degrees in Mechanical Engineering from Oklahoma State University in 1973 and 1975, respectively. He served as a Senior Systems Analyst at the Montana Energy and MHD Research and Development Institute before joining the Engineering Faculty at Kansas State University. Dr Jones currently holds the positions of Associate Dean for Research and Director of the Engineering Experiment Station at KSU. He is also Professor of Mechanical Engineering. He previously served as Director of the Institute for Environmental Research and as Head of Mechanical and Nuclear Engineering at KSU. Dr Jones is a Fellow of the American Society of Heating Refrigerating and Air-Conditioning Engineers (ASHRAE) and has conducted research in the field of human environmental engineering for over 25 years. He chaired the ASHRAE Transportation Air-Conditioning technical committee at the time it initiated the development of an aircraft air quality standard and currently serves as chair of ASHRAE SPC 161P, Air Quality in Commercial Aircraft, which is writing the standard. Dr Jones served on the US National Research Council committee which reviewed the status of aircraft air quality and which generated the report "The Airliner Cabin Environment and the Health of Passengers and Crew" to Congress that is being used as the US guideline for aircraft cabin air quality research. Kansas State University is a member of the recently formed FAA Center of Excellence for Aircraft Cabin Environment Research (ACER) this is expected to play the leading role for US research in this field. Dr Jones is the principal investigator for KSU's activities in this center.

INTRODUCTION

The mission of the American Society of Heating, Refrigeration and Air-conditioning Engineers (ASHRAE) is to advance the arts and sciences of heating, ventilation, air conditioning, refrigeration and related human factors to serve the evolving needs of the public and ASHRAE members.[1] Similarly, the mission of the American National Standards Institute (ANSI) is to enhance … the quality of life by promoting and facilitating voluntary consensus standards and conformity assessment systems, and by safeguarding their

† The statements made in this paper are those of the author and do not necessarily represent the views, opinions, or policies of the American Society of Heating Refrigerating and Air-conditioning Engineers (ASHRAE). ASHRAE has not issued any official drafts of an aircraft air quality standard. Any reference to the content of such a standard are strictly the observations of the author that may or may not be reflected in any document ASHRAE eventually issues.

integrity.[2] Both ASHRAE and ANSI prepare standards and guidelines in their fields of expertise to guide industry in the delivery of goods and services to the public.

DUE PROCESS IN STANDARDS SETTING

Elements of the ASHRAE/ANSI standard development process are that it should be open, balanced and follow due process.

Openness includes

- allowing participation to all persons who are materially affected by the activity in question;
- there must be no undue financial barriers to participation; and
- standards development activities (such as committee meetings) do not operate behind closed doors.

Due process is intended to allow equity and fair play, and allows any person, organization, government agency or other entity with a direct material interest a right to participate by:

- expressing a position and its basis;
- having that position considered; and
- appealing if adversely affected.

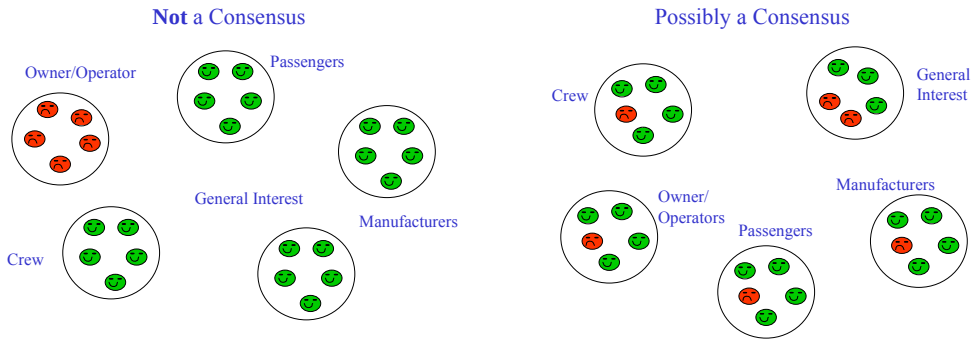
Each standards setting committee must include a balance of interests, although balance does not imply equal membership in all categories. However, not one category of membership may dominate the membership. For example, membership of an ASHRAE Standard Project Committees (SPC) is subject to a number of requirements:

- Initial membership proposed by a technical committee.
- Membership changes proposed by SPC once it is established.
- All membership is approved by oversight committees.
- Members are selected for knowledge and experience.
- Members act independently and not as representatives of their employer.
- Only one member per employer.
- No terms of appointment but membership may change.
- No set number of seats on the committee.
- No person has a right to a seat on the committee.
- No deadline for completion; work until it is done or the committee is hopelessly deadlocked.

Of course, **participation** in the process is not necessarily the same as membership in, or a right to vote on, a standard project committee (SPC). Further, the right to participation does not automatically imply the right to committee membership. For example, participation can be as simple as submitting a public review comment.

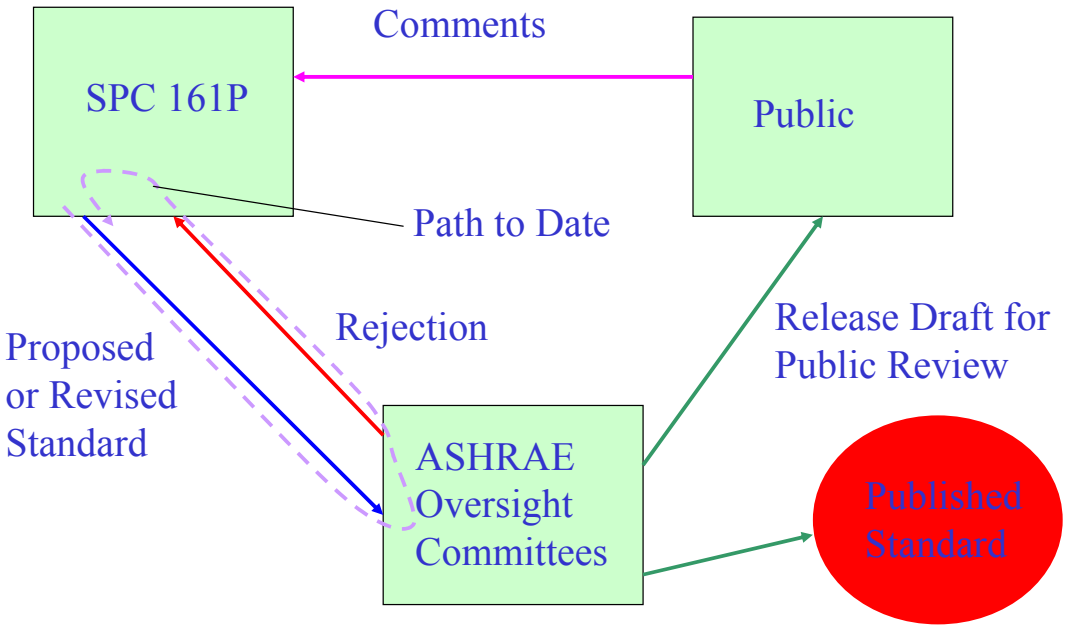
While standard rules of parliamentary procedure apply to committee deliberations members should participate openly and strive to reach **consensus** on an SPC for any standard document developed. Establishing consensus may be problematic in some situations. For example, consensus does not require unanimous agreement but a majority vote does not represent a consensus (see Figure 1).

Figure 1: Consensus in Standard Setting



Once the work of the committee is complete, a draft standard is subject to oversight requirements. Normally, these involve release of the draft subject for public review, consideration of public comments by the SPC, and ultimately, finalization and publication of the standard (see Figure 2).

Figure 2: Standard Approval Process



STANDARD 161 AIR QUALITY IN COMMERCIAL AIRCRAFT

The purpose of this standard is to define the requirements for air quality in air-carrier aircraft and to specify methods for measurement and testing in order to establish compliance with the standard

The scope of the standard is to:

1) Apply to commercial passenger air-carrier aircraft carrying twenty or more passengers and certified under Title 14 CFR Part 25.

2) Considers chemical, physical, and biological contaminants as well as, but not limited to, factors such as moisture, temperature and pressure that may affect air quality.

3) Because this standard cannot take into account every variable, especially those relating to safe operation of the aircraft, the diversity of sources and types of contaminants in aircraft cabin air, and the range of susceptibility in the population, compliance with this standard will not necessarily ensure acceptable aircraft cabin air quality for everyone.

The standard applies any time crew or passengers are on board an aircraft, either in the air or on the ground. The current working draft of the standard includes requirements for:

- Cabin Pressure
  - Maximum cabin altitude – not specified
  - Rate of change of cabin pressure –
    - Ascent – 1.8 kPa/min (0.27 psi/min); 150 m/min (500 ft/min) at sea level (0.27 psi/min)
    - Descent – 1.1 kPa/min (0.16 psi/min); 90 m/min (300 ft/min) at sea level
- Temperature
  - Operative temperature at occupied locations –
    - Target – 18.3°C to 23.9°C (65°F to 75°F)
    - Limit – 26.7/29.4°C (80/85°F)
  - Horizontal variations in the cabin – 4.4°C (8°F)
  - Vertical variations at any seat – 2.8°C (5°F)
  - Sidewall and floor surface temperatures –
    - Seats: – 5.6°C (10°F) of mean local operational temperature
    - Galleys – 8.4°C (15°F) of mean local operational temperature
- Air Speed
  - Applies to seated passengers and crew –
    - Below 0.36 m/s (70 ft/min)
    - Below 0.30 m/s (60 ft/min) on draft sensitive body areas
  - Head level minimum velocity –
    - Above 1.0 m/s (200 ft/min) with PAO on
    - Above 0.1 m/s (20 ft/min) with no PAO present
- Ventilation - Flight
  - Cabin ventilation (applies to each section) –
    - Outdoor air - above 3.5 l/s-p (7.5 cu ft/min)/Ve VE<1

- Total air above 7.1 l/s-p (15 cu ft/min)
- Local airflow –
  - 0.9 l/s (2 cu ft/min) PAO ta each seat or
  - Below 0.1 m/s (20 ft/min) in upper body area
- Galleys –
  - 3.5 l/s-p (7.5 cu ft/min) outside air
  - 7.1 l/s-p (15 cu ft/min) Total air, exhaust
- Jump seats –
  - 2.4 l/s (5 cu ft/min) PAO with 1.2 l/s (2.5 cu ft/min) outside air
- Crew rest areas –
  - 3.5 l/s-p (7.5 cu ft/min) outside air, 9.4 l/s-p (20 cu ft/min) total air
- Lavatories –
  - 9.4 l/s-p (20 cu ft/min) total, exhaust

- Ventilation – on the ground
  - Air source from onboard systems –
    - 3.5 l/s-p (7.5 cu ft/min) outside air
    - 7.1 l/s-p (15 cu ft/min) total air
  - Air source not from onboard systems –
    - 9.4 l/s (20 cu ft/min) total air
- Ventilation – other requirements
  - Recirculation air – HEPA filtration required
  - Quality of outside air – Defers to actions required related to contamination events
  - Quality of building air source – building sources must meet requirements of ASHRAE 62.1-2004
  - Ventilation shutdown may be allowed for temporary needs (such as de-icing), but these should be minimized and not allowed for periods over 30 minutes
- Specific Contaminants
  - Ozone –
    - Below 0.25 ppm as a peak concentration
    - Below 0.1 ppm as a three hour average
  - Carbon monoxide –
    - Below 9 ppm as a ten minute average (exceedances require immediate action)
- Addressing Contamination Events
  - Deicing fluid
  - Exhaust fumes
  - Fuel
  - Hydraulic fluid
  - Engine oil

- Ozone
- Bacteria and viruses
- Pesticides
- Lavatory fluids/odors
- Carry on baggage/cargo
- Anti-corrosion spray and paint
- Human bioeffluents
- Galley odors
- Solvents
- Electrical odors
- Dry ice

- Measurements for Specific Variables
  - Monitoring for air temperature, surface temperature, operative temperature, relative humidity, and air speed measurements are specified in ASHRAE 55 2004[3]
  - Continuous monitoring is not mandated for any environmental variables other than Carbon monoxide
  - Specific methods not defined for airflows or contaminants other than Carbon monoxide

REVISION OF STANDARD 161

Standard 161 has been under development for a number of years. The current working draft contains only the requirements and necessary explanatory information to comply with these requirements. This draft document has been completed, approved by SPC 161P, and is ready to submit to oversight committees.

The SPC has also been working on a guideline that will serve as a companion to the standard. This current working draft of the guideline contains extensive background material on aircraft air quality, explanatory material useful in applying Standard 161, and other information useful for attaining good air quality in aircraft. This guideline is essential completed and ready to submit to oversight committees, but the formation of the guideline committee has not been approved.

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THE POLITICS OF AIRCRAFT HEALTH AND SAFETY – SENATE INQUIRY, AUSTRALIAN PARLIAMENT – OCTOBER 2000

The Reverend John Woodley
Former Australian Senator

BIOGRAPHICAL SKETCH

The Reverend John Woodley has a LTh from the Melbourne College of Divinity, and a BTh from the Brisbane College of Theology. In 1967 John was ordained in the Methodist Church; from 1962-2005 and was Minister of the Methodist Church which became Uniting Church in 1977; with service at parishes in Queensland: Mitchell, Gympie, Cloncurry, Sandgate, Gladstone, Wynnum. John was also Director of Department for Social Responsibility, Queensland Synod; and Chaplain at the Queensland University of Technology. In 1993, John was elected Senator for Queensland in the Australian Senate retiring in 2001. While in the Senate, John was Joint Chair of Senate Rural and Regional Affairs and Transport Committee; Member of Joint Statutory Committee on Native Title; Member of Senate Committee on Community Affairs; Spokesman for Australian Democrats on Native Title, Family Services, Regional Development and Agriculture. John has continued public service since retiring, being Chair of the Committee, Uniting Care Centre for Social Justice; President of Pacific Peace Building Initiatives Inc; National President of Australian Progressive Alliance. The Reverend John Woodley, 27 Railway Parade, Caboolture, Queensland 4510, Australia.

INTRODUCTION

I was elected to the Senate of the Australian Parliament in 1993. So, from then until I retired in 2001, I traveled from Brisbane to Canberra around 20 to 30 times per year – a distance of between 1200 to 1400 kms. For the first few years I always traveled with Airlink, a subsidiary of Qantas and these direct flights were in the BAe 146 aircraft.

For the first couple of years a Flight Attendant, Lesley, was regularly on these Brisbane to Canberra and return flights. Lesley was always bright, attentive, chatty, knew regular passengers by name, busy (almost fussy), always ready with a word of greeting and always helpful and quick-witted. An example of her brightness and other qualities was a private joke which developed between us. On these flights I often wore an old brown sports coat which I had bought in a second hand charity shop. When she saw me wearing this coat, Lesley would comment: "Senator Woodley – not that old brown jacket again."

After a couple of years I didn't see Lesley again for quite some time – I assumed she was flying different routes or with another airline. That is, until late in 1999 when she attempted to appear before the Senate Rural, Regional Affairs and Transport Committee in Canberra as a witness in the Inquiry into

fumes in the BAe 146 aircraft. Unfortunately, to get to the Senate Committee room where we were holding the hearing, she had to pass along a Parliament House corridor which was being repainted. When she arrived at the Senate hearing she, clearly, was very sick and had to lie down before she could give her evidence. Subsequently, we learned that she was hypersensitive to chemical odours and had long term, chronic health problems. She gave her evidence in private but obviously was not capable of sustained conversation. Fortunately, we had her written submission. Lesley was pale (very white), withdrawn, halting in her speech, at times vague and clearly, very unwell.

LESLEY IS WHAT THIS CONFERENCE IS ALL ABOUT.

- That she was very sick, there is no doubt.
- That she was a different person with a radically altered personality was painfully obvious to me.
- That she had been affected by her career as a flight attendant we soon learned from her evidence.

So, Lesley represented the human face of the debate which has raged around her condition and that of hundreds of other pilots and flight attendants world wide since the early 1980s. Consequently, this debate is about the answers to a number of questions:

- What has caused this debilitating illness of Lesley and her colleagues?
- Was it caused by toxic fumes fed from the aircraft engines through the air conditioning system?
- Do such fumes cause only temporary discomfort and minor health problems, or is there a cumulative effect which, not only results in some flight crew having to have time off work, but in some cases the result has been permanent incapacity and the inability to fly in aircraft either as crew or as passengers, without getting sick?
- If fumes in aircraft do cause health problems, is this due to a sensitivity to these fumes alone, or does the person affected develop a sensitivity to other chemical odours as well?
- Is this simply an occupational health problem, or does it also impact on aircraft safety ?

In this regard (the issue of safety) I trust that representatives of the aircraft regulators and industry are present at this Conference and that they are not asleep. Our Senate Committee was very critical of the casual attitude of the Australian regulator, the Civil Aviation Safety Authority, and of their reliance on what airlines, British Aerospace and Mobil Oil told them. It was these questions which led to:

THE DECISION OF THE AUSTRALIAN SENATE TO INVESTIGATE AIR SAFETY AND CABIN AIR QUALITY IN BAe 146 AIRCRAFT.

THE AUSTRALIAN SENATE INQUIRY INTO AIR SAFETY AND CABIN AIR QUALITY IN BAE 146 AIRCRAFT

First of all I should explain a **peculiarity of the Australian Federal system**: For about the last twenty-five years, the Party forming Government by having a majority in the House of Representatives has not had a majority in the Senate. This is due to the two Houses having different ways of electing representatives and the sophistication of the Australian voting public which, when it elects a Government, also elects a curb on Government by changing its vote in the Senate.

This situation led in 1999 to a decision by the Senate to conduct the Inquiry, because the Government did not have the numbers to prevent it going ahead; could not control the terms of reference; and could not predetermine what the final Report would recommend. In any case, the Report and its conclusions and recommendations was accepted by all the members of the Committee, including Government members, who were able to sort through the mass of written and oral evidence and to express their strong concern about the failure of the industry to solve this serious health and safety issue.

Our Report was tabled in the Senate in October 2000 and I retired in July 2001. I have tried to remain informed about the issues involved but I'm sure there will be some developments of which I am not aware. This Conference has certainly revealed how much more advanced the medical science is since 2001. The disappointing thing, however, is that those who should be more aware than I am, such as representatives of the airlines, manufacturers, regulators and government are not present except for a few exceptions. We are grateful to those who have come.

THE EVIDENCE SUBMITTED TO THE INQUIRY

Now I want to give you an idea of how we handled **the submissions we received:**

- I have been told that the written submissions when stacked on top of each other reached almost 1 metre high but, because of the amount of material, the Senators were not able to read every submission. However, the permanent staff of the Committee did.
- From the written submissions a representative sample was selected and the authors invited to support their submission with oral evidence.
- We did read and cross examine all the evidence presented by the airlines, British Aerospace, Mobil Oil, the regulators and the unions.
- Public hearings were held between November 1999 and August 2000.
- We also conducted a number of private hearings because, either the witnesses were in the process of making claims for compensation, or they feared their jobs would be under threat if their evidence to the Committee was made public. (We learned their fears were well founded.)

- By means of video conferencing we interviewed Dr Jean-Christophe Balouet from France and Dr Christian van Netten from Canada as well as a flight attendant from Perth.
- Ansett Airlines arranged for us to inspect modifications they were making to improve the airflow in the cabin of the BAe 146 at their workshops in Brisbane. Of all the airlines they were the most co-operative. Qantas did not go to the same lengths in presenting their evidence and National Jet System's presentation was quite hostile at some points.

Although most witnesses were willing to co-operate with the Committee (they had little choice as the Senate has the powers of a court), there were a couple of occasions when attempts were made to mislead our members. On those occasions we learned to **beware of the bureaucrats** – both public servants and bureaucrats in private enterprise. On a few occasions Sir Humphrey Appleby from "Yes Minister" appeared to be alive and well! I will give you some examples in a minute.

LISTENING TO THE EVIDENCE

The Senate Committee system in Australia is well established and effective, although it remains to be seen what will happen after July this year when, for the first time in 25 years, the Government will have a majority in both Houses of the Australian Parliament. It should be said that none of our Committee members were experts in the subject matter of many of the Inquiries we conducted, but all the members were skilled at sifting through the masses of often contradictory evidence we received.

We rejected the proposition put to us by some that the Committee should not make any findings unless we had 100% proof of our conclusion. This proposition is nonsense, as there is nothing in this life of which we can be 100% sure and, as responsible parliamentarians, we had often to choose between conflicting evidence in the Inquiries we conducted. In any case there were **some things about which the experts did agree:**

- They agreed that occasionally fumes enter all jet aircraft through the air conditioning system.
- They agreed that these fumes may cause temporary discomfort.
- They agreed that a number of air crew had experienced short-term health problems.
- They agreed that perhaps, occasionally, oil leaks in the engines and hydraulics were the source of discomfort and maybe health problems.

However, there were many issues about which they did not agree: These included the long-term health effects; whether there is such a thing as aerotoxic syndrome/multiple chemical sensitivity; whether toxic particles from Mobil Jet Oil II could enter aircraft through the air conditioning system and whether we are dealing with a health issue or a safety issue as well?

In the course of the Inquiry the members of the Committee noted a number of anomalies in the evidence given:

- The airlines, especially Ansett Australia, went to great lengths to modify the aircraft (they spent about Aus$7 million) if it was only a minor problem.
- A significant number of air crew have had to give up flying altogether with long-term and chronic health problems. We were dealing with more than short-term irritation and temporary discomfort.
- The aircraft regulators appeared to play down safety aspects of the problem in the face of their own regulatory regimes which clearly indicate safety issues are involved.

Indeed, with regard to safety, one only has to read some of the evidence to be amazed about the casual attitude towards safety which was, at times, expressed. The following is an extract from the evidence of Captain Frank Kolver who, in 1997, was involved in a serious incident during a night descent into Melbourne having piloted a freight flight from Sydney. The flight crew at the time was Captain Kolver, a co-pilot and a Senior Captain in the jump seat who was carrying out crew monitoring:

> *During the latter stage of the descent shortly after passing 10,000 feet I smelt strong oily odours and fumes in the cockpit. Some 3 to 4 minutes later after making a directional change of 25 degrees it was necessary to make another directional change in the opposite direction of about 10 degrees. I had great difficulty trying to do this because I felt it would roll the aircraft to an excessive angle towards becoming inverted. This was followed by considerable difficulty in flying the aircraft and concentrating on making the approach to land. I became confused and was not quite sure what was going on at the time but realized I was having some sort of difficulty so I asked the first officer to take over flying the aircraft. He did so and continued to land safely.*

With regard to health, the evidence given by Captain Kolver at the hearing was also significant and his evidence is similar to that of many others:

> *For the next ten days or so I felt as if I was having a continuous hangover with a constant headache. This was accompanied with a feeling of strong pressure on the top of my head. At night if I got out of bed I had difficulty in standing upright. When I traveled in a motor vehicle the headache would get worse and after 20 minutes I would get nauseous and had to stop and get out for some relief.*
>
> *During this period I was on sick leave and for the next two months my health slowly improved to moderate continuous headaches and later mild headaches with a constant pain in the left or right temple area. Several medical examinations, blood tests and a CT scan gave no indication of any medical disorder or problem. At the time and prior to this incident I was medically and physically fit and had no sickness or virus of any kind.*

The worrying thing about this evidence of Captain Kolver is the way in which the airlines, manufacturers and regulator went to great lengths to try to discredit the evidence and a subsequent report done by the Bureau of Air Safety Investigation (BASI): Captain Siebert of National Jet Systems (NJS), the aircraft operator, told the inquiry that Captain Kolver ….

> *…. became dizzy and recognized he had some vertigo, but he certainly was not incapacitated. He formally handed control across to the first officer, which is a standard operating procedure between the crew, and the first officer went ahead and landed the airplane….The first officer never smelt anything and was not affected. The supernumerary pilot, in his first report to the company, said that, yes, he could smell it and felt a bit nauseous but was unaffected generally. There is a slightly different interpretation put on it in the final report from BASI.*[†]

I am sure that the flying public, if they could read the evidence from Captain Kolver, would not agree that he was "not incapacitated" and would be concerned about the attitude of the operator! The assertion by Captain Siebert that BASI in its report gave "…a slightly different interpretation" is, I believe, grossly misleading. BASI, in fact, referred its report to the Civil Aviation Safety Authority (CASA) for urgent attention and the "implementation of suitable counter measures".

The Committee was deeply concerned that CASA also did not treat the incident or BASI's report seriously and we concluded:

> *The Committee believes that CASA erred in rejecting the finding of Occurrence Brief No. 199702276 dealing with the incident involving Captain Kolver published in September 1999. The Committee was not provided with a substantive reason for this action by CASA. The Committee believes that CASA should now accept the BASI/ATSB recommendations and develop an action plan for implementing them.*

Subsequently, we translated our criticism of CASA into Recommendation 1 and expanded our conclusion into a comprehensive series of actions we believed CASA should take.

However, this was not the only time that the Committee was concerned about what, we regarded, as attempts to mislead us. The evidence of one medical expert, a Dr Robert Loblay, was **dubious in the extreme**.

Dr Loblay did not make a written submission to the Inquiry but simply phoned a Committee staff person and offered to attend the public hearing in Sydney. His rather irregular offer was accepted without reference to me as chairman and he turned up in Sydney and gave his "evidence" which

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[†] BASI is the Bureau of Air Safety Investigations, whose functions were transferred to the Australian Transport Safety Board (ATSB) in 2000.

consisted mostly of scandalous attacks on the other medical experts who gave, or were to give, evidence.

He attacked the qualifications of a Dr Mark Donohue as bogus, which was untrue. He inferred that Dr Donohue's evidence should be viewed with suspicion because he practiced what Dr Loblay called "alternative medicine" which, in fact, is main stream medicine, even if some consider it "alternative". He attacked the testing done by a Dr Richard Teo in the area of neurobehavioural toxicology as unreliable and useless. He dismissed the work done by Associate Professor Chris Winder because he "frequently leaps" to conclusions about the symptoms of neurotoxicity in those affected. He inferred that air crew who had linked their health problems to toxic fumes in the BAe 146 were caught up in a kind of "mass hysteria". Dr Loblay's assertion about the above medical experts may be summed up in the following quote:

> *I think the sort of misinformation that has been circulating amongst staff, as a result of the activities of Dr Donohue and colleagues, is endangering the situation more than would have been the case if people had a more sensible, down-to-earth approach*.

If Dr Loblay was seeking to reassure the Committee that there were no problems with fumes in the BAe 146 (and other jet aircraft) then his testimony had the opposite effect. The members of the Committee became convinced that it was not Dr Loblay who had a "sensible, down-to-earth approach" but that the evidence presented by all the other medical experts we interviewed was much more credible.

This was especially so when the Committee discovered after his appearance (he did not reveal it at the time of giving his evidence), that he had been a witness on behalf of Insurance Companies in a number of court cases dealing with compensation for affected air crew. However, he did place on record that he had invited himself onto the Ansett Committee investigating the problem of fumes in BAe 146 aircraft.

I'm sure it won't surprise this audience either if I tell you that the reluctance to settle claims for compensation by **the Insurance Industry has also influenced this debate**.

The Committee received evidence from former flight attendant, Ms Alysia Chew, including a transcript of the judge's findings in her case. Ms Chew was awarded compensation on the basis that her career as a flight attendant had aggravated a pre-existing condition of glandular fever or a viral infection. However, the judge rejected any suggestion of multiple chemical sensitivity caused by toxic fumes from the aircraft in which she had worked. It interested the Committee members that the judge relied heavily on the evidence of Dr Loblay and a Dr Carroll. I have described to you how Dr Loblay operates but I should also explain our expressed concern about Dr Carroll, because of a possible conflict of interest. We learned that Dr Carroll

was the doctor to whom another claimant in Queensland was referred for assessment and treatment. He was also a witness in the hearing before the Queensland Compensation Tribunal where he gave a negative report about the claimant. The Committee's concern was raised most of all, however, when we learned that Dr Carroll was a consultant to Ansett Australia, the defendant in the case before the Tribunal!

As a consequence of this case, and many others which were brought to our attention, the Committee recommended that the (Federal) Minister for Transport, in consultation with State Ministers, should appoint a retired judge to review unsuccessful or inordinately delayed employees' compensation cases and report to Parliament.

I think you can understand now why the title of this address is: **The Politics of Aircraft Health and Safety**. It is more about politics, power and money in the Australian industry than it is about medical evidence, medical treatment or medical science. From my meetings with delegates to this Conference I understand that air crew and their supporters in other countries have been subjected to the same harassment, denigration and demotion as those in Australia. An almost standard response these days is that as soon as someone complains of fumes in aircraft, they are sent to a psychiatrist for "assessment". One report about an Australian pilot compared her condition to reports of witchcraft in the fifteenth century.

TWO REPORTS

At the same time as our Inquiry was underway, the UK House of Lords was also conducting an Inquiry into various aspects of aircraft health and safety. I met in London with the Chair of the Committee and also with the public servant who was the Secretary to her Committee, a most charming gentleman, who never left her side apart from a few minutes during lunch when he went to the toilet. While he was away she confided in me that she felt she was being "conned" by the bureaucrats and, having read the **House of Lord's Report**, I believe she was!

The first draft of the **Senate Report**, which is called the Chairman's draft, was written by a public servant from the staff of the Committee. I had to approve this first draft before it was considered and debated by the other members of the Committee. When I read it I was horrified to read the conclusions and recommendations for they seemed to me to be an apology for all those who wanted to prove there was no real problem. I had to rewrite parts of the Report to express views which I knew the members of the Committee held about the evidence they had received. The Report was then debated in great detail by the Committee and every conclusion and recommendation approved by every member.

I can't give you the detail of the **Conclusions and Recommendations** because that would take too long but I will give you a summary of the recommendations:

- We recommended further research be done in those areas where it was felt further information was needed. (If we had had the information which has been made available at this Conference we would have been able to recommend far less research was needed than in October 2000.)
- We recommended that all modifications which were found to reduce fumes in the aircraft should be made compulsory for all BAe 146 aircraft.
- We recommended that CASA rewrite regulations concerning maintenance, air quality standards, monitoring, reporting and the grounding of affected aircraft, if necessary, to take account of the problem of fumes in aircraft.
- We recommended that CASA reassess its dismissal of the BASI Report into the Frank Kolver incident and take action to fulfill the BASI recommendations.
- We recommended a judicial review or all unsuccessful and inordinately delayed insurance claims.
- We recommended a review of the standards for Mobil Jet Oil II.
- We recommended that new high grade filters being developed at the time be fitted to all commercial jet aircraft flying in Australia and that this be made mandatory.

CONCLUSION

It is almost four years since I retired from the Senate and I continue to be concerned about this issue. That's why I responded positively when I was invited to the Conference. However, the Australian Government and CASA have never responded properly or adequately to our Report. One wonders, **"Who cares?"** I certainly do and so do most of the people at this Conference. The inaction of Government and the Industry reminds me of a golf story and this is my **conclusion**:

One day Moses and God were playing golf and God said to Moses at the number one tee, "You can hit off first." So Moses lined up the ball and hit it 300 metres, straight down the middle of the fairway. God turned to Moses and said, "Not bad for a mortal!" Then Moses said, "Your turn." So God lined up the ball, gave it an Almighty swipe and sliced it into a group of trees at the edge of the fairway. The ball bounced off half a dozen tree trunks and then dribbled to the margin of the fairway next to a bank of sand where there was a rabbit warren. Before the ball stopped a rabbit hopped out of a hole, picked up the ball in its mouth and began to hop towards the green. Just then a large eagle flew over and, spotting the rabbit, flew down and picked it up in its talons but, as it flew over the green, a bolt of lightning struck the eagle: The eagle dropped the rabbit; the rabbit dropped the ball and the ball fell into the hole. God turned to Moses with a large grin on his face and said, "What did you think of that?" Moses replied, "Are you going to play golf or ARE YOU GOING TO MUCK AROUND ALL DAY?"

The moral of this story is: Some people in the industry and some of the regulators seem to think they are God and so can take risks with the lives of their employees and customers, but they are not God and this is not a joke. It is time they got serious, stopped mucking around and started to play the game seriously.

From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 205-216.

THE UNITED STATES JURY SYSTEM: A MUCH MALIGNED BUT EFFECTIVE REGULATOR OF CORPORATE MISCONDUCT – THE DANGEROUS COCKPIT, A CASE IN POINT

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BIOGRAPHICAL SKETCH

Stuart Calwell is the founder and owner of The Calwell Practice, PLLC. The firm has offices in Charleston and Morgantown, West Virginia, and the firm has offices in New York City, New York, as well. For the last 25 years, Mr Calwell's firm has limited its practice to complex cases involving the adverse effects of toxic substances on the environment and man. Most notably the firm has prosecuted cases involving the adverse effects of dioxins and organophosphates. Mr Calwell is a member of the West Virginia and New York bar associations and holds the degree of Doctor of Jurisprudence from the West Virginia University College of Law. Additional information is available on the firm's web site at: www.calwelllaw.com.

INTRODUCTION

During the last twelve years or so, I have had the privilege of working with a number of experts who have been invited to participate in this Conference concerning unsafe cockpit and cabin air.[†] They have provided invaluable assistance in court cases I have prosecuted on behalf of seriously injured persons exposed to organophosphate compounds. But my experience in suing large corporations on behalf of persons injured by toxins goes back even further in time. In 1979 I began a series of lawsuits on behalf of workers injured by dioxin in a chemical plant in Nitro, WV, USA, where Agent Orange was manufactured. We sued Monsanto and in 1984-1985 spent eleven months in a jury trial. Throughout these experiences, I have become accustomed to the sing song mantra of the large corporation's response to those bold enough to complain of injuries caused by exposure to toxins: "Well you might feel sick now, but it won't hurt you in the long run"; and, "You've probably been eating too many tomatoes, they're full of acid"; and, "We see a lot of this, but it's mostly in your head, you feel a little sick, someone suggests it's caused by something or other and pretty soon you think you're sick."; and, "You just can't get exposed (in an airplane for example) to enough of this stuff to hurt you. You'd have to drink a gallon of it"; and, my personal favorite, "Look, we've studied and studied this chemical. It's safe.

[†] Prof Abou-Donia, Dr Howard, Prof Furlong, Dr Jamal and others have been most patient and extraordinarily instructive in preparing me to present cases involving nervous system injuries and exposures to organophosphates. Without their expertise and guidance through the difficult scientific issues I would have enjoyed little or no success in my endeavors on behalf of persons injured by these toxins.

There's no reason for you to be worried about a little bit of this stuff leaking out into the air. It just won't cause any long term or permanent injury or disease. We've studied it."

I call statements like these: "the flying saucer defense". Here's how it works. The company creates its own junk science (they call them internal studies), takes advantage of its position as an important business providing jobs and convinces people that chemical diseases don't exist. Then when someone claims to have a chemically related disease he's made to feel as though he or she is crazy. The injured person begins to feel as though he or she is trying to convince "sane" people that a flying saucer really did land in the back garden. The more insistent the injured person becomes, the crazier he or she is made to feel or seem by "proper persons" who know there are no flying saucers. In point of fact, the injuries and illnesses that people suffer from these toxins in the workplace are real. They actually do land in the back garden, and I've spent the better part of my career successfully proving it. You who fly the skies in these large contraptions full of contaminated air can prove it also.

AOPIS and others have provided me with an astonishing amount of information regarding the how, why and makeup of contaminated air in the cockpit. Given the life altering health risks presented by contaminated cockpit air, the continued exposure of crewmembers to these dangerous toxins is an injustice bordering on the outrageous. Upon reading the materials, it seems obvious that any sensible reading and plain interpretation of JAR/FAR 25.831 and proper enforcement thereof would lay the matter to rest. However, this has not been the case. CAA's interpretation of JAR/FAR 25.831, as a matter of law, good sense, and common decency is clearly wrong and indefensible.[†] To hold that poisonous cockpit air is not an issue of an aircraft's continuing air worthiness is absolutely astonishing. So, while the struggle over the interpretation of JAR/FAR 25.831 goes on, I have been asked to explain how the American Jury System may help solve the problem of the contaminated cockpit. Put more simply, I intend to explain how one might sue various parts of the air transportation industry to recover money damages.

[†] JAR/FAR 25.831 part (a) provides in pertinent part: "Under normal operating conditions and in the event of any probable failure conditions of any system which would adversely affect the ventilating air, the ventilation system must be designed to provide a sufficient amount of uncontaminated air to enable the crew members to perform their duties without undue discomfort or fatigue and to provide reasonable passenger comfort…."

Part (b) provides in pertinent part: "Crew and passenger compartment air must be free from harmful or hazardous concentrations of gases or vapors." In spite of the fact that these two parts of 25.831 are now incorporated into the Annex to EU Reg 2042/2003 which expressly refers to "continuing airworthiness" in its title and elsewhere in its text, the SRG section of the CAA state: "We do not agree with the interpretation that events "leading to discomfort" should be considered as a failure of JAR 25.831 unless there has been an adverse impact on safe flight and landing." (For this footnote I rely on correspondence from the Simpson Millar Law Firm).

In turn, the prospect of paying money damages may influence the industry to address and solve this serious problem.

By way of this introduction, I also point out that one must be sensitive to the "politics" of lawsuits. My law firm and I represent a number of trade unions. It is most always in the best interest of the union to promote, protect and work for the success of the industry in which its members work. Destroying the industry the union serves is obviously "killing the goose that lays the golden egg". With that overriding principle in mind, however, it is necessary from time to time to find ways of protecting the membership from the industry it serves. The art in this is to find ways of achieving justice without shooting one's self in the foot. As will be shown below, I believe a strategy of suing certain of the manufacturers of the component parts of airplanes and the producers of certain lubricants used in airplanes may present a reasonable approach to effecting the needed changes. This approach avoids suing the airline employer and it also avoids suing the airplane manufacturer. I think it achieves a rough balance between the need to promote the industry and the equally important need to protect the crew.

HAS ANYONE EVER PROVEN THAT THE TOXIC MOLECULES IN COCKPIT AIR ACTUALLY INJURES HUMANS?

The answer is yes. My firm and I represented a man name Joey Walker. Mr Walker was exposed to organophosphate molecules formulated as a pesticide he was spreading on his lawn. At first there were general symptoms of weakness, nausea and flu like complaints. Then he developed cognitive problems. He was a parts manager in an automobile dealership which required him to memorize multi-digit identification numbers. His previous uncanny abilities in this regard disappeared. He became confused and developed a dementia like demeanor. Seizures followed, requiring him to be confined to a nursing home approximately eighteen months after exposure. We sued the manufacturer of the pesticide. The experts we retained, some of whom are participating in this conference, predicted that Mr Walker's brain and spinal chord had been damaged. Unfortunately, Mr Walker died of breathing complications during the case. We flew our neuro-pathologist to the hospital in Texas so that he could perform an autopsy. What he found was described as a "Swiss cheese brain". Axons in brain and spinal chord had dissolved, leaving axonal spheroids or holes in his nervous system. These lesions were responsible for his seizures, his Parkinson like symptoms, his dementia symptoms and the other manifestations of a toxic encephalopathy. The findings were a text book picture of what one would expect to find as a consequence of organophosphate exposure. In fact the defendants own experts agreed. To my knowledge, Mr Walker's autopsy was the first performed on a person known to be environmentally exposed to organophosphates and where injuries from these molecules were specifically looked for.

BUT HAVE LAWSUITS EVER BROUGHT ABOUT REGULATORY CHANGES WHERE ORGANOPHOSPHATES ARE CONCERNED?

Once again, the answer is yes. In the early 1990s my law firm and I sued a chemical manufacturer on behalf of a new born infant. At age five days, Joshua Herb, was brought home to a house that had been treated with organophosphate pesticides. The molecules are in the same family as the organophosphates in Mobil II Jet Oil. The pesticide had gotten in the fresh air system in the house. Within weeks Joshua became inconsolable. He developed breathing problems and finally right phrenic nerve paralysis resulting in diaphragmatic paralysis. Soon he developed a flaccid quadriplegia. It was determined that Joshua's peripheral nervous system had been "knocked out". The doctors first ignored, and then ridiculed the suggestion that organophosphates were the cause. Instead a diagnosis of spinal muscular atrophy was made (a genetic condition involving non-functioning anterior horn cells). Our experts prevailed, however, when the world's leading expert in spinal muscular atrophy disagreed. The final proof is that Joshua is now 17 years old. Spinal muscular atrophy children do not survive, most dying before their third year of life. During the case we discovered that the manufacturer had not reported to the government, as required by law, approximately 200 other complaints about children being exposed to this product. When the judge in our case ordered the reports released they were turned over to the authorities. An investigation ensued, and the product was taken off the market and is no longer registered for residential use in the United States. Incidentally, this case was the subject of a Granada Television special on World In Action some years ago. Lawsuits can be effective regulators of corporate conduct.

A FEW WORDS ABOUT POWER

We are born. As we come to awareness, the need to be effective assumes greater and greater significance. To protect ourselves and advance our interests in life, effectiveness becomes dearer, metamorphosing often to the need to be powerful. In democratic societies, individual effectiveness and individual power generally derives from some legal construct that at once provides for protection of individual rights and at the same time provides a mechanism permitting the individual to enforce those rights against perceived transgressors.

The foregoing paragraph is all well and good and very high minded, in addition to being astonishingly broad in its sweep. But what does it really mean? What does it have to do with something as arcane as JAR/FAR 25.831? More to the point, what does it have to do with spritzing the cockpits of huge commercial airliners with organophosphate containing jet oil fumes? In actuality, in spite of its sheen of pomposity, it has everything to do with the risks to crew members of the unsafe cockpit. The unsafe cockpit is a real, present and palpable threat to the safety and well-being of aircraft crews and passengers. We know this. Then how does one become effective enough and powerful enough to do something about it? That is to say, how

does one become effective enough to do something more than simply identify the problem and quantify the risk? How does one FIX the unsafe cockpit? Where is the source of power sufficient to force a resolution of the risk and restore a safe cockpit to crew and passenger? How does one become so effective?

Certainly, the answer is complex, has many parts, and embodies a variety of actions that could be taken. Undoubtedly, political, economic, and educational efforts will be necessary to completely resolve the issue. The purpose here is to put the power of litigation on the planning table. Litigation within the context of the American jury system is an effective tool to bring economic pressure to bear on the status quo. In turn, success in this regard will add to the wave of political pressure necessary to bring about a final resolution.

This paper, then, is about the American Jury System and how it empowers the individual to be effective within the larger context of government and society. To understand this, a brief explanation of the opening paragraph is necessary. Democratic governments, however one may choose to define them, have as one important purpose to provide rules which govern conduct. These rules are allocators of advantages and disadvantages. This simply means that those in power and those with influence seek rules which at the very least allow them to pursue their goals with as little interference as possible. Indeed, once rules are established those with influence seek favorable interpretations of the rules to the same end.

An important element of "influence" is money. In the vernacular we say "money talks". In America, political influence, that is to say influence over rule making and rule enforcement, is a direct function of the power of money. Because it is permissible to make direct contributions of money through various lawful devices to those in power, law making and rule enforcement become predictable for those who "contribute" and whose interests are sought to be governed.

Multi-national and national corporations, in the eyes of the law are legal "persons". Because they control vast sums of money they are for the most part very effective at influencing rule making and influencing rule interpretation to their advantage. In fact, they are tireless in these efforts to build absolute predictability into this process so that the end is controlled and their interests are advanced. How does a mere mortal compete with the immortal corporation for influence with the rule makers and enforcers? Failing that, how does an individual regulate the conduct of these corporations to protect body and soul?

In America, mere mortals turn to the American Jury System.

THE JURY SYSTEM: WHAT IS IT AND HOW DOES IT WORK?

Juries are vested with enormous power. Properly instructed on the applicable law, jurors decide whether a corporation's conduct is acceptable or not. That is to say a jury may decide that a corporation's conduct in producing a product or in a myriad other endeavors falls below acceptable standards. If some person is injured as a result of such conduct, then the jury may require the wrongdoer to pay compensatory damages. If the conduct is deliberate or particularly loathsome, the jury may require the wrongdoer to pay punitive damages sufficient to deter future bad conduct.

Individual jurors are selected randomly from the community. They are immune from direct contact by the parties to litigation. There are no lawful channels through which a powerful corporation or other entity can utilize money to directly influence a juror to "fix" the out come (other than, of course, hiring high priced lawyers). On the whole, when viewed through the eyes of a corporation accustomed to directly influencing regulators in a predictable way, the idea of a group of average citizens deciding the corporation's fate in such an unpredictable way is terrifying in its contemplation.

The jury's job is to decided issues of fact. The forum for this activity is a court room presided over by a judge. Lawyers for each side of a conflict present evidence (competing facts) to the jury. For example, two automobiles collide in the center of an intersection, and each driver claims the benefit of a green light. Each is supported by witnesses. Clearly, one driver is guilty of wrongdoing – running a red light. On the other hand, perhaps the traffic signal malfunctioned and each driver in fact had a green light. In the latter event, perhaps the manufacturer of the traffic signal is at fault. Or perhaps the power company permitted a momentary surge of electricity. Or maybe the town or council is at fault for not maintaining the signal in good working order. These are imponderables that must be left to the good judgment of the citizen juror to decide after hearing all the relevant evidence. The absolute truth may never be known and indeed the absolute truth may not be knowable in this circumstance, but at least justice will have been done. An independent body, the jury, will have spoken.

Let's say the jury hears evidence that the manufacturer of the traffic signal used a timer that was susceptible to moisture. In all respects the timer conformed to government regulations where traffic signals are concerned, but under certain circumstances moisture could cause a malfunction that gave a green light in both directions at the same time. The problem of moisture in timers had been the subject of much regulatory debate. Administrative hearings and intense industry lobbying however had prevented any change in the regulations which would require a moisture proof seal on the timer. Upon hearing evidence of the moisture defect and upon hearing evidence of an increase in intersection accidents, the jury found the traffic signal to be defective and ordered the manufacturer to pay an enormous sum in both compensatory and punitive damages.

Faced with the prospect of paying future damage awards for moisture related intersection accidents, the manufacturer decided that investing an additional two cents for a moisture proof seal in each timer was preferable to paying repeated damage awards.

At this juncture, it is my fervent hope that the pertinence of all this to JAR/FAR 25.831 is beginning to emerge from the murk. As one can see, the economic pressure from the threat of damage awards brought about a reformation in the manufacturer's conduct - a reformation that had been resisted by the industry as well as the regulators who were influenced by the industry for the "good of the industry".

Juries, then, are independent regulators of corporate conduct. The jury's will is enforced through the requirement that corporations must pay money in an amount decided by the jury to compensate persons injured by corporate wrongdoing. Importantly, the jury decides what constitutes wrongdoing,[1] and the jury decides whether wrongdoing has occurred. It is the jury that defines the nature of the conduct and decides whether it is acceptable to the community. The jury is the conscience of the community.

BUT ISN'T THE AMERICAN JURY SYSTEM A RIP-OFF?

And besides, what impact would a jury have on jar/far 25.831?

For reasons which should be obvious to anyone with a pulse, the American Jury System is much maligned. Consider the identity of the maligners. Yes, it's the business community. Yes, it's the insurance industry. Yes, it's all those "powerful" entities and persons with access to the media where the evils of the crazy juries and greedy lawyers are exposed. And yes, it's the politician who has benefited from the largess of those seeking to influence rule making and enforcement. And why, you may ask, do they feel compelled to malign such an egalitarian institution? Because the jury has the power to take their money away from them.

What is it about the jury system that makes it so effective that it is able to take money from powerful corporations? Basically it is the contingent fee system. Few mortals have the financial resources to hire a law firm and pay hourly rates of up to $500 per hour. Of course corporations are able to do this. They and their insurance companies have vast resources to hire extraordinarily powerful private law firms to defend them against claims. Additionally, complex cases like those which would address the concerns raised in JAR/FAR 25.831 require the services of a host of highly skilled experts in a variety of fields. These experts command fees that range in the hundreds of dollars per hour. Further, often scientific studies are required to

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[1] The jury is instructed by a judge as to the nature of any duty owed by the corporation to the person claiming injury. The jury then decides whether the corporation's conduct has breached that duty. In general corporations owe all reasonably foreseeable persons the duty to put only safe products into the stream of commerce.

be carried out. These costs can run to the millions of dollars. So how, do you ask, does an out of work airline pilot afford to file a lawsuit under such circumstances with any hope of success? Doesn't the price of admission make the promise of the power of the jury simply an illusion for all but the richest of rich? In America, the answer is no.

Here's how it works. The claimant (called a plaintiff) enters into an arrangement with a plaintiff's law firm. These are private firms just like the corporate law firms except plaintiffs firms represent mortals and not the immortal. The plaintiffs firm then agrees to perform all work and to advance all expenses, hire all the experts, and pay for all the necessary testing in exchange for a percentage of any moneys received by way of settlement or jury verdict. The plaintiff, then, upon winning a settlement or jury award pays to the plaintiffs firm a percentage ranging from 33-40%. In addition the plaintiff pays back, out of winnings, whatever monies were advanced to pay experts and expenses during the course of the litigation. In no event does the plaintiff walk away with less than 50% of the award.[†] By the way, should you lose your case and should there be no settlement monies, the individual plaintiff pays nothing to the plaintiffs' lawyer. Nothing. Basically, the lawyer and the plaintiff are in a fifty/fifty deal. The lawyer risks his time and money and the plaintiff risks his case. Both lose if the case is not successful. Both win if it is. Think of it this way, would you lend a total stranger, say, $500,000 without any security whatsoever on the gambit that you could win a contest with no hope of getting your money back if you lost? That is the nature of the risk. Whether the gamble is a good one or not depends on the skill of the lawyer in sizing up the case in the first instance. Viewed in this light, 50/50 doesn't sound too badly, now does it?

By the way, among the chorus of those maligning the American Jury System you will find precious few plaintiffs. Those who have been injured and have had their rights vindicated in court, by all accounts, seem to be quite satisfied.

Without the ability of the plaintiff to find a lawyer willing to gamble his time and money, few cases would ever be brought. The American Jury System provides the opportunity for plaintiffs to hire powerful and rich plaintiffs' law firms. The individual person, the mere mortal, then, is able to level the playing field with the rich and powerful immortal corporation. It's the money, dear hearts. It's the money. Without it your effectiveness is limited and without it there is no power.

[†] The exception to this is in what is called a class action. In such cases sometimes tens of thousands of plaintiffs are grouped together. The award of fees and expenses in these cases is set by a judge. It is in these cases that the complaint is often heard that the lawyers got it all and I didn't get much of anything. But this is the exception. Usually it occurs in cases where the individual damages for each person is small, but the risk to the lawyer for bringing tens of thousands of these small claims is high. It is truly a myth that in the American Jury System the lawyer gets it all and the injured person gets little or nothing.

SO WHAT COULD THIS AMERICAN JURY SYSTEM DO ABOUT THE UNSAFE COCKPIT?

At long last we get to the heart of the topic. From what I have learned, the interpretation of JAR/FAR 25.831 portends significant consequences for the airline industry. If the regulation is interpreted as a "continuing airworthiness" requirement, then an aircraft may not be airworthy because of bad air and crew condition. Obviously, the impact of such an interpretation and the enforcement thereof would be of some significance to the airline industry. On the other hand, if the regulation is interpreted as a "design standard" or that it only applies if it directly impacts takeoffs and landings; the consequences to the airline industry are minimal. So how does one become effective enough, indeed powerful enough, to achieve the regulatory interpretation, and importantly, the enforcement of an interpretation that will protect the health and well-being of the crew and passenger and result in a safe cockpit? The answer may lie in the indirect attack, aimed at certain elements making up the airline industry rather than at the regulatory process itself and rather than at the airplane manufacturer or the airplane owner.

At the outset we must ask what is it that focuses attention on the interpretation of JAR/FAR 25.831? I have been provided with information from AOPIS establishing that certain configurations of an aircraft's fresh air and pressurization systems contribute to an unhealthy and outright dangerous breathing atmosphere by allowing the air to become contaminated with toxins emitting from the jet engines. Three toxic molecules finding their way into cockpit and passenger air are TOCP, MOCPs and DOCPs. As many of you already know each of these is an organophosphate. There are other toxins of course, but for our purposes these particular molecules will suffice. Organophosphate molecules are purposefully added to Mobil Jet Oil II by the manufacturer Mobil Oil Company. Inadequate seals associated with jet engines permit volatilized oil to enter the air systems carrying with it these molecules as well as other toxins. Once there, the crew and passengers are primarily exposed to these toxins by inhalation and skin exposure. Because the environment is sealed, there is no escaping exposure.

Based on my firm's fifteen years of experience in litigating injury cases involving organophosphate compounds and based on the information amassed by AOPIS we know that TOCP, DOCPs and MOCPs and the other toxins are dangerous and hazardous to human health. We know that these particular molecules are neurotoxic, capable of causing both central and peripheral nervous system damage. Symptoms of central nervous system damage include cognitive impairment, memory problems, difficulty concentrating, loss of spatial appreciation, tremors, seizures and Parkinson like conditions as well as numerous other manifestations. We know also, that these molecules bring on both short and long term effects. While the initial symptoms of flu like symptoms, coughing, shortness of breath, nausea and others often pass within hours if not days after exposure, the long term effects appear more subtly. Insidious, these long term conditions begin often with slowly developing loss of short term memory. Simple, familiar tasks become

more difficult. Confusion arising from the familiar often leads to dementia like manifestations. Tremors and Parkinson-like symptoms often appear. Because a temporal relationship to exposure is often not obvious, few medical professionals recognize a causal connection to these toxins. None of these conditions is compatible with the execution of the complex activities required to safely fly an airplane.

Against this scenario we see that JAR/FAR 25.831 is not really the issue or, in fact, the problem. Rather, it has been seized upon on as a solution to the real problem which is dangerous exposure to toxins in the aircraft during flight. But by focusing on this regulation as a solution another problem has been created: what does the regulation mean? What legal effect does it have? Who will enforce the interpretation? If the official interpretation does not achieve an end to cockpit contamination, how does one change the official interpretation to one that will bring about a change in the industry such that toxins are no longer spritzed into the cockpit? In other words how many legal opinions will fit on the head of a pin? This is a debate well suited to regulators and well paid corporate lawyers. All the while, of course, toxic molecules continue to dance in cockpit air.[†]

So, whilst the regulatory debate goes on, what if another front is opened? As in the case of the traffic signal timer, what if the costs of maintaining the unsafe cockpit exceeded the costs of maintaining a safe cockpit? Of course this is an oversimplification, but what if the costs of replacing inadequate seals and the costs of a jet oil devoid of organophosphates were less than continuing the use of leaking seals and TOCP laced jet oil?

A MODEST PROPOSAL FOR ACTION

Crewmembers and passengers injured as a result of bad air in the cockpit and cabin have an extraordinarily good case. In my judgment, the engine manufacturers, the seal manufacturers and the oil formulators should be sued in an appropriate American jurisdiction. Such a lawsuit would allege these components of the aircraft and the fluids necessary for the aircraft's operation are defective. Because the manufacturers and producers of the defective products are located in the United States or have extensive business connections with the United States, such a lawsuit could be brought in one or more courts in the United States. Where the injured crew or passenger lives on this planet generally does not preclude their filing such a case in the US Further, many injured crew and or passenger will have either flown over the US or landed in the US. All of these factors support the right to bring such a case in the courts of the United States.

[†] This paragraph is not intended to suggest or imply that focusing on the regulation is wrong or a waste of time. In fact it is all together appropriate and necessary as a means to draw attention to the problem and to create yet another pressure point to bring about the result. All efforts in this regard should continue unabated. My observations are merely to put these efforts in the context of the overall resolution of the problem.

In the event a case or cases are filed in the United States, their impact on cases already filed in other countries should not be negative. In fact simultaneous lawsuits in different countries against different defendants should not matter. For example, if we identify the issues making up the problem, certain types of defendants are clearly suggested. For example:

- Oil leaking from aircraft engines/APU into aircraft air supply.
- Oil, such as Mobil Jet Oil II, and other brands, containing neurotoxins such as TOCP, MOCPs, and DOCPs as well as sensitizers and carcinogens.
- Problems specific to certain aircraft such as the Boeing MD80 with its hydraulic fluid leakage issues.
- Aircraft oil bearing seals failing to perform during transient operations such as acceleration, deceleration, and warm up.
- Effectiveness of filters for cockpit air and their ability to filter toxic molecules from air supply.

From these problems it is easy to begin to identify target defendants. For example engine manufactures may be responsible for defective designs of leaking engines. Alternative designs for jet oils may make Mobil and others liable for injuries caused by exposure to the toxins in their products. Specific parts or components of particular aircraft, such as the MD80, may make the manufacturers of those components liable. The manufactures of seals and filters likewise may be targets. If the airlines themselves or the aircraft manufacturers are the target of litigation outside the United States, lawsuits against the component manufacturers are not inconsistent.

Because under the best of circumstances court proceedings move slowly, preparation of the lawsuit should begin quickly. Prior to filing, the case should be ready to launch: experts retained, medical examinations done, careful investigation of target companies and marshalling of adequate resources for the campaign. Such preparation permits the plaintiffs to push the case and resist delays due to lack of preparation. Delay is the strategy of the defendants in every case I have litigated. It draws the proceedings out. It causes the plaintiffs to spend all their money. It wears the injured person down. And it desensitizes the Judge.

To get started the following should be considered:

- Identify crew members with serious health problems related to contaminated cockpit air willing to be “test plaintiffs”.
- Assemble the complete medical and life history of test plaintiffs including their close blood relatives.
- Retain experts to review all collected records, perform diagnostic tests, rule out alternative causes and reach firm diagnosis and cause.
- Identify discreet components of the aircraft, such as particular seals or fittings, which permit the escape of toxic molecules to cockpit air.
- Identify substances, such as jet oil, which contain the toxic molecules.
- Identify the manufacturers of these products.

- Select a US jurisdiction or court in which to file a test products liability lawsuit against the identified manufacturers.[†]
- Retain a specialty public relations firm to manage the "court of public opinion" so that the progress of the lawsuit is accurately reported in the popular press, the financial press, and the medical press. This step is extraordinarily important to counter act the negative public relations that the corporate defendants will generate right from the beginning.

Such a lawsuit carries with it the prospect of a very large damage award. Damage awards are divided into two general categories. First, compensatory damages are meant to compensate for individual loss. The elements of compensatory awards include cost of medical care and lost wages, both past and future. Compensatory damages also include pain and suffering, loss of enjoyment of life, and mental suffering. Second, if the defendants' conduct is proven to be knowing and intentional, punitive damages may also be awarded. A punitive award is to be calculated as an amount that bears some relation to the compensatory award but also in an amount sufficient to deter future misconduct by the defendant. Additionally, negative publicity about the airline industry itself would invariably ensue. All of this would bring economic pressure to bear on the problem of the unsafe cockpit. Indeed, this circumstance is one of the salutary purposes of the American Jury System: to reform conduct to minimize injury and loss in the comings and goings of commerce and the world.

[†] In the US manufacturers are under a duty not to put products into the stream of commerce that are not reasonably safe for their intended use. Here, the identified products are defective because when used as intended reasonably foreseeable persons become injured. Hence, the manufacturers, under the American Jury System, could be found strictly liable for any injuries proximately caused by any such defect in their products.

From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 217-238.

PATTERN OF AUTONOMIC LESIONS AND NEUROPHYSIOLOGICAL FEATURES OF LONG-TERM EXPOSURE TO THE ORGANOPHOSPHATES IN SHEEP-DIP

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BIOGRAPHICAL SKETCH

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ABSTRACT

To establish the neurological sequelae of chronic exposure to organophosphates (OP) in sheep dip, the integrity of peripheral nerves was tested in two groups of farmers who regularly use OP based sheep-dip and a group of healthy controls of similar age range (n = 16 in each group). Group 1 farmers had episodes of acute but mild OP poisoning while Group 2 farmers had no previous symptoms of poisoning. Target-organ specific examination of the autonomic nerves was done in Group 3 farmers (n = 40) who developed chronic neurological symptoms following acute OP poisoning to establish the pattern of autonomic dysfunctions.

Functions of the distal somatosensory nerves sub serving cold, warm and vibration sensations were abnormal in both Groups 1 and 2 farmers. Peripheral motor nerve axonal dysfunctions were also found in both groups of farmers but were more pronounced in those with symptoms. More than 90% of group-three farmers had abnormal cutaneous thermoregulation and paradoxical resting bradycardia associated with very low cardiac vagal tone. There were also failures of the cardioaccelerator and baroreflex functions in over 70% of these farmers. However, sudomotor function and Respiratory modulation of cardiac vagal tone were preserved.

Our results show that a unique pattern of autonomic dysfunction is part of long-term neurological sequelae of acute OP intoxication or repetitive low-level exposure to the compounds. Target organs in the skin, in large blood vessels including the heart and in the brain are most vulnerable. There was selective preservation of cholinergic but deterioration of monoaminergic functions in the skin and the brain. Such imbalance in the brain can explain cognitive and memory dysfunctions in the neurological disorders associated with OP exposure. It is also evident that distal somatosensory neuropathy is

the main outcome of somatic nerve damage in long-term exposure to OP in sheep-dip.

Preliminary results from investigations in air crew suggest a similar pattern of autonomic dysfunction consistent with organophosphate exposed (Group 3) farmers but different from Carbon monoxide exposed miners. This is a compelling reason for further investigation, first to confirm the findings in the aircrew and then to investigate possible common toxic agents among group-three farmers and aircrews.

Keywords: Organophosphates, Sheep dip, Brainstem, Autonomic nervous system, Neurophysiology, Peripheral nerves

INTRODUCTION

Organophosphate (OP) based compounds are thought to be the most effective way of treating sheep scab and other parasites. Sheep farmers in the United Kingdom were required by law to treat their flocks regularly with OP compounds. Toxic effects of these substances have been reported before and were categorised as acute, intermediate or delayed effects.[1] The acute cholinergic effects occurring within 24 hours are well documented.[2] An intermediate neurotoxic syndrome of OP poisoning has also been described.[3] This may have a different underlying pathophysiological mechanism. It tends to involve only the proximal parts of limbs associated with neck flexor muscle weaknesses. It is also known that some OP compounds may induce a "delayed" polyneuropathy unrelated to inhibition of acetylcholinesterase.[4] This may often pass unrecognised in humans since the clinical features can be easily overlooked.[5] This delayed neuropathy is associated with phosphorylation of serum neuropathy target esterase leading to "ageing" of the enzyme complex.[5] Organophosphate induced delayed neuropathy is known to be caused by many different OP compounds.[6,7,8] There is additional evidence of central neurotoxicity too in experimental animals,[4,9,10] in animals with accidental poisoning[4] and in humans.[5] These effects may be reversible but can persist for many years.[11] There is evidence from epidemiological and other studies that OP pesticides can have other chronic effects in both the peripheral and central nervous system either after acute intoxication or following low-level long-term exposure.[1,12] There is therefore sufficient published evidence to suggest that the OP in pesticides are neurotoxic.

However, there is no evidence to date of any detailed study of the autonomic effects of chronic exposure to the OP compounds. This is a big gap in our knowledge considering that the OP poisons the cholinergic system of neurotransmission, the major form of neurotransmission in the autonomic nervous system, both in the sympathetic and parasympathetic systems. Moreover, the autonomic nervous system controls the function of every organ in the body and therefore will be a major influence in any form of ill health. We have therefore studied the pattern of autonomic dysfunctions in farmers with ill health who regularly used sheep-dip in the United Kingdom to try and

establish if some of their symptoms can be explained by autonomic dysfunction.

SUBJECTS, MATERIALS AND METHODS

Although we designed this current study to include the establishment of the functional integrity of peripheral and central nervous system in farmers who regularly use OP in sheep dip, our main aim was to elucidate the pattern of autonomic lesions in farmers with clear histories of chronic OP poisoning. We have also measured biochemical markers of recent exposure to OP in group-one and group-two farmers. All sheep farmers had been involved in dipping sheep regularly over a period of four or more years using OP compounds. At the time we examined these farmers, the time lapse since they were last exposed to sheep-dip was in excess of four months in all of them. The OP compounds used were diazinon, propetamphos or clorfenvinphos. None of our farmers had a previous history of exposure to other toxic chemicals apart from compounds in the sheep dip, other than occasional spraying of weed or treating livestock with other drugs or chemicals. None of the farmers had history of excessive alcohol intake and none were on any medication with neurotoxic effects. Other potential causes of peripheral neuropathy such as diabetes, thyroid disease and others were carefully excluded through appropriate investigations.

Investigation of functional integrity of peripheral and central nervous system

Two groups of farmers and one group of healthy controls were used for the study of somatic nerve functions. Group-one farmers were fifteen male and one female (mean age 44.5 years; SD 11.4; range 23-67 years) randomly selected from a list of 200 that was made available to us by a voluntary organisation. All had three or more symptomatic episodes consistent with mild to moderate acute OP poisoning in the course of their occupation. All subjects in this group claimed to have developed chronic illness following exposure to OP in sheep dip. Group-two farmers were all male (mean age 42.3 years; SD 11.2; range 25-62 years). They were selected at random using a standard computer program (Microsoft's Excel employing a congruential multiplicative random number generator). The target population was those who were still working among a total of 1907 farms listed in the Yellow Pages of Glasgow North and South. This covers an area in West of Scotland within a 60 miles radius from Glasgow. Group-two farmers were asymptomatic and had no history of episodes of acute poisoning with OP in sheep dips in the course of their occupation. A list of numbers between one and 1907 were generated and the first 16 sheep farmers contacted who fulfilled the criteria and agreed to take part in the study were included. The response rate was 85.6%. Group-four (n=16) consisted of age and sex matched healthy volunteers (mean age 44.9; SD 11.7 years) to serve as a control population for these farmers. The neurophysiological techniques we used in this study were sufficiently sensitive to detect early or sub-clinical signs of neurotoxicity in humans.[13,14]

Clinical tests for peripheral Neuropathy

Clinical symptoms were scored as follows: zero for absent and 1 for present without further elaborate quantification. The set of symptoms scored as present were fatigability, weakness, paraesthesiae, numbness, spontaneous sensation of burning heat, cold and pain with an overall symptom score between 0-6 for each subject. Five reflexes on the right side of the body were scored as follows. Each tendon reflex was graded as 0 for normal, 1for diminished and 2 for absent thereby providing an overall tendon reflex score between 0-10 for each subject. Power in the distal, intermediate and proximal groups of muscles in the upper and lower right limbs was assessed and scored using a scale ranging from 0 for normal to 5 for complete paralysis similar to the criteria in the MRC scale. The combined overall muscle power score was between 0-30 for each subject. Sensations of pinprick, vibration, touch and joint-position on the right side of the body were assessed and scored separately for each of these clinical sign as follows. Zero for normal, 1 for reduced below the ankle, 2 for reduced below the knee, 3 for reduced in the hand and below the knee, and finally 4 for reduced below the elbow and below the knee. The combined score for the clinical signs was between 0-16 for each subject.

Motor nerve conduction studies in the right median and common peroneal nerves together with sensory nerve conduction studies in the right median and sural nerves were carried out using well established standard techniques.[15] The shortest distal motor latencies, fastest motor nerve conduction velocities, amplitudes of compound muscle action potentials, F-wave latencies, sensory latencies and sensory nerve amplitudes were all measured. Needle electromyogram (EMG) was performed in groups -one and -two farmers using the right tibialis anterior and extensor digitorum brevis muscles. The results were scored as follows: zero for normal, 1for 30%-50% polyphasic motor units and/or occasional spontaneous activity and 2 for more than 50% polyphasia and/or frequent spontaneous activity. These EMG scores were combined to a total between 0-4 in each subject.

Quantitative sensory testing were performed by measuring thermal thresholds (both heat and cold) on the dorsum of the right foot[16] and vibration perception threshold over the right first metatarsal bone.[17]

Peripheral somatic nerves were examined as described above by three different teams each of which were unaware of the outcomes of the tests carried out by the other two teams. Each team performed the same set of investigations in all the subjects.

Examination of the central conduction pathway of the nervous system

We recorded Pattern reversal of visual evoked potentials, brainstem auditory evoked potentials and somatosensory evoked potentials in responses to stimulation of the right median nerve at the wrist to examine the integrity of

the central conduction pathways of these nerve signals. Only the latencies of these signals were measured.

Investigation of the pattern of autonomic lesions

Group-three farmers (n=40) who were all male (mean age 48.9 years, SD 13.4, range 22-75 years) and were from all over Great Britain were used to study the pattern of the autonomic dysfunctions. These sheep farmers had signs and symptoms suggestive of Chronic OP Induced Neuropsychological Disorders or COPIND in short.[18] The group was subjected to target-organ orientated examination of the autonomic nervous system as described below.

Target-organs Orientated Examination of the Autonomic Nervous System

A detailed examination of the following autonomic functions was carried out in the 40 farmers in group-three. These were farmers who developed chronic neurological dysfunction following clear histories of several episodes of mild to moderate acute OP poisoning.

Examination of Cardiovascular reflexes and cardiac parasympathetic function

The resting cardiac parasympathetic activity (Resting CVT in Figure 2), or cardiac vagal tone (CVT) was measured in a quiet laboratory with subdued light and room temperature was maintained at 24±1°C. Analogue electrocardiogram (ECG) from the patient was fed into the NeuroScope™ (MediFit Diagnostics Ltd, London, UK) for measurement of beat-to-beat intervals between consecutive ECG R-waves (R-R intervals) and the evaluation of CVT as previously described by Julu.[19] We used the effect of baroreceptor stimulation on the sino-atrial node, which is mediated through the vagal tone and although this effect is theoretically detectable in the ECG P-P intervals,[20] in practice the R-R intervals can be used to measure the CVT. The NeuroScope™ quantifies this baroreflex function using arbitrary clinical units of a linear vagal scale (LVS). The LVS was first derived by Julu[19] and is now validated for clinical use in humans[21] and in animals.[22] Arterial blood pressure (BP) was recorded continuously and non-invasively using the Finapres (Ohmeda, Eagleswood, USA). The systolic (SBP), mean arterial (MAP) and diastolic (DBP) BP in the digital artery of one finger in the non-dominant hand were measured with the help of the MedullaLab (MediFit Diagnostics Ltd, London, UK). The hand was held at the level of the heart during BP measurement. All data was recorded using a computer and displayed in real-time on the computer screen using VaguSoft© software (MediFit Diagnostics Ltd, London, UK). The NeuroScope™ system quantifies the output of the arterial baroreceptors and this was validated in real-time by mechanical stretching of the walls of empty carotid sinuses during carotid endarterectomy surgery.[23]

Baseline data was collected in supine position for about 4 minutes during which MAP was measured. The carotid sinus was massaged to test for cardiodepressor and vasodepressor functions (Figure 2) and then the patient

was asked to perform a 10 second cycle of deep breathing to examine the respiratory modulation of CVT. Phenylephrine injections (25, 50, 100,200 and 300 μg, bolus doses) were given through a venflon catheter in the brachial vein to measure the baroreflex slopes (Figure 2) using the Oxford methods.[24] The threshold of the response to phenylephrine injection (Baroreflex Threshold, Figure 2) is usually at 50 μg bolus dose, the 25 μg was used to test for denervation hypersensitivity to the drug, which would indicate significant damage to the sympathetic postganglionic nerve fibres.

The cardiac response to orthostasis (HR in Orthostasis, Figure 2) was quantified using the 30:15 ratio test.[25] In our modification of the test, the patients sat on a low stool from where they could stand up easily during the test to minimise electromyographic (EMG) noise.[26] After a brief training session, a short record of the R-R intervals (60 cardiac cycles) was collected while the subjects were seated, they were then allowed to rise and data collection was continued in the upright position for a further 100 cardiac cycles. The longest R-R interval occurring at around the 30th cardiac cycle following a data marker indicating an upright stance was divided by the shortest R-R interval occurring at around the 15th cardiac cycle after the marker to obtain the 30:15 ratio.

The response of arterial BP to orthostasis was assessed continuously using the Finapres. The readings of BP within 1-2 minutes of a change in posture are important for the assessment of the neural control of BP.[27,28] Dysfunctions in BP regulation were identified as follows: Variation of MAP by more than 25 mm Hg would suggest orthostatic instability, while a sustained fall in DBP by 10 mm Hg or more within three minutes of assuming an erect posture compared with supine position (BP in Orthostasis, Figure 2) was an indication of orthostatic hypotension.[29]

Cardiac baroreflex responsiveness during isometric exercise (BRR) indicating central baroreflex gain was assessed as follows. The responses of R-R intervals and BP to a pressor effect of 3-minute isometric contraction of the muscles of the dominant forearm were quantified while the patient remained connected to the NeuroScope™ and Finapres™. The subject applied 50% of his or her maximum sustainable grip force to a special machine and maintained the force for 3 minutes. A visual feedback through a pointer enabled the subject to maintain isometric contraction of the muscles. We defined BRR as the overall change in pulse intervals at the end of the 3 minutes per unit change in blood pressure in the same period during isometric exercise, which is the absolute value of the quantity $|\Delta R\text{-}R/\Delta SBP|$. Where: $\Delta R\text{-}R$ is the change in R-R interval in the third minute of isometric exercise in association with a corresponding change in systolic BP (ΔSBP) measured from baseline levels.[30]

The heart rate (HR) response to Valsalva's manoeuvre (HR in Valsalva, Figure 2) was assessed while the subject blew into a vitalograph tube connected to the MedullaLab™ through a leaky passage in order to maintain an intrathoracic pressure of 40 mm Hg actively for 15 seconds. A visual

feedback through a pointer enabled the subject to maintain the intrathoracic pressure at 40 mm Hg throughout the 15 seconds. The ratio of the longest R-R interval immediately following the cessation of positive intrathoracic pressure to the shortest R-R interval during the positive intrathoracic pressure is known as Valsalva's ratio. The average value of Valsalva's ratio in three manoeuvres was used to represent the overall response of the subject's HR to Valsalva's manoeuvre.

Examination of Sympathetic functions

In the skin

Emotional Sudomotor Function (ESF) (Skin Sudomotor, Figure 2) was assessed by measuring the Galvanic skin responses to emotional (or mental) sweating in the palms of the hands and soles of the feet and recorded using silver/silver chloride disc surface electrodes connected to a MS 25 five-channel EMG machine (Medelec Ltd, Old Woking, UK). The Galvanic skin response was evoked by a single inspiratory gasp and recorded simultaneously in each limb to avoid dissimilarities of responses caused by habituation. The responses were recorded at a sweep speed of 1 second/division, sensitivity of 5 mV/division and bandwidth between 0.01 Hz and 20 Hz. Elaborate quantification of the Galvanic skin response was not necessary. The EMG machine was used simply as a diagnostic aid for eliciting ESF in order to compare the presence or absence of responses on the two sides of the body and for the detection of response failure in any of the four limbs. A positive Galvanic response is 1 mV and above in amplitude.

Thermoregulatory Vasomotor Function (TVF) in the skin (Skin Vasomotor, Figure 2) was assessed as follows. The baseline skin blood flow was measured simultaneously from the dorsum of each limb for three minutes using a four channel laser Doppler flow meter (Moor Instruments, Axminster, UK) and then a cold challenge was applied to one hand while recording the skin blood flow in the contralateral limbs. The challenge was achieved by first immersing the hand in warm water (40^{o}C) for two minutes to maximise vasodilatation before transferring it into cold water (10^{o}C) for another two minutes to evoke vasoconstriction. The cooled hand was then re-immersed in warm water for a further two minutes. The laser Doppler flow meter was again used as a simple diagnostic aid to elicit TVF for comparing the presence or absence of responses in the two sides of the body, and for detection of response failure in the individual limbs. Normal responses were indicated by decreased blood flow in both contralateral limbs during cold challenge and a return to baseline levels in response to re-warming. Failure of TVF was indicated either by no effect of cold challenge on the skin blood flow, or a paradoxical increase of blood flow in the contralateral limbs.

In the heart and the skeletal muscles

Sympathetic cardioaccelerator function (Cardiac Sympathetic, Figure 2) and sympathetic tone in the skeletal muscles during isometric exercise (Muscle

Sympathetic, Figure 2) were assessed by measuring the change in heart rate (HR) and DBP respectively, in the third minute of isometric exercise compared with the basal level just before the onset of the exercise (see cardiac baroreflex responsiveness for details of the isometric exercise). The change in the vascular resistance that determines DBP during isometric exercise is linearly related to the muscle sympathetic activity measured by microneurography.[31] On the other hand, the increase in HR during isometric exercise measured continuously in our laboratory is closely related to the change in DBP, thereby proving the sympathetic origin of this cardioacceleration.[32,33] By the third minute of isometric exercise, the withdrawal of both vagal and baroreflex regulation of the cardiovascular system would be complete,[33] leaving only the sympathetic effects on the system.

In the splanchnic bed

The sympathetic adrenergic function in the splanchnic bed (Splanchnic Sympathetic, Figure 2) was assessed during Valsalva's manoeuvre as follows. If an active intrathoracic pressure of 40 mm Hg is maintained for 15 s, the SBP will change in five phases represented by Roman numerals as I, IIe, IIi, III and IV.[34] Phase I is the initial rise in BP due to pressure on the great vessels in the thorax, Phase IIe is a sharp drop in SBP and pulse pressure due to the sustained reduction in venous return caused by the positive intrathoracic pressure. Phase IIi is the recovery of both the SBP and the pulse pressure against the positive intrathoracic pressure and is due to sympathetic mobilisation of a reserved volume of blood from the splanchnic vascular bed stimulated by the blood volume crisis in the heart. It is a physiological process called "auto-transfusion".[35] The inferior vena cava carries more than two-third of the venous return,[35] but venous return from the lower limbs depends largely on the muscle pump effect. Our subjects carried out the Valsalva's manoeuvre in a sitting position without moving the lower limbs to exclude any contribution from the muscle pump effect to the recovery of pulse pressure and the SBP, allowing us to assess the splanchnic sympathetic adrenergic function selectively using Phase IIi.

Normal values for all our tests used in this target-organ-orientated examination of the autonomic nervous system are published elsewhere.[36]

Tests to exclude recent exposure to organophosphates

Blood was withdrawn from an antecubital vein of eleven of the sixteen farmers in group-one and from fourteen of the sixteen farmers in group-two for measurement of the activities of red blood cell acetylcholinesterase and serum cholinesterase using methods published elsewhere.[37]

Statistical analyses

Statistically significant differences between the various groups of farmers and the controls were assessed using analysis of variance (ANOVA) for parameters with normal (Gaussian) distribution, and Kruskal-Wallis ANOVA by Rank was

used in non-Gaussian data. Comparison of control subjects with the groups of farmers was carried out using Student's t-test for parameters with normal distribution and Mann-Whitney U-test for non-Gaussian data.

RESULTS

Evidence of Peripheral Neuropathy in Groups –one and –two Farmers

Clinical examination

The mean clinical scores for symptoms, reflexes and sensation are shown in Table 1, and were all significantly abnormal in group-one farmers ($P < 0.0001$, $P < 0.001$, $P < 0.0001$ respectively) and, to a lesser extent, in group-two farmers ($P < 0.025$, $P < 0.015$, $P < 0.0005$ respectively).

Table 1: Results of Clinical Scores and Quantitative Sensory Tests

	Controls (n = 16)			Group-two Farmers (n = 16)		Group-one Farmers (n = 16)	
	Median	Quartiles		Median	P values	Median	P value
		Ist	3rd				
Clinical scores							
Symptoms	0.0	0.0	0.0	1.0	0.02151	3.5	0.00000
Reflexes	0.0	0.0	0.0	1.0	0.01430	1.5	0.00053
Muscle power examination	0.0	0.0	0.0	0.0	0.76303	0.0	0.07045
Sensory examination	0.0	0.0	0.0	1.0	0.00030	6.0	0.00002
Quantitative sensory testing							
Vibration (μm)	0.38	0.17	1.09	2.3	0.0037	2.1	0.0039
Hot threshold (°C)	1.65	0.9	2.73	1.7	0.806	5.9	0.0017
Cold threshold (°C)	0.25	0.15	0.35	1.6	0.0003	0.7	0.0007

P values: Statistical probabilities calculated using the non-parametric Mann-Whitney test (see text for methodology).

Quantitative sensory tests

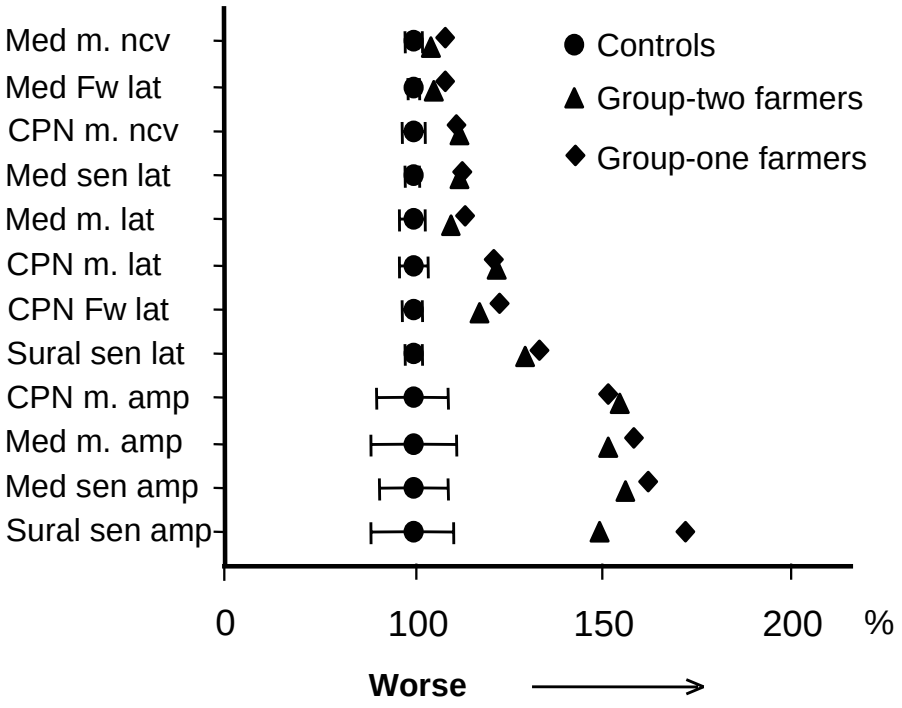
The increases in mean vibration threshold ($P < 0.005$) and cold perception threshold ($P < 0.001$) were significant in the two groups of farmers compared with controls (see Figure 1). Mean heat perception threshold was increased significantly in group-one farmers compared with farmers in group-two ($P < 0.002$).

Nerve conduction and needle-EMG studies

The mean values for distal motor, shortest F-wave and sensory latencies were significantly increased in both upper and lower limbs in farmers in groups -one and -two (see Figure 1). Abnormalities were more pronounced in sensory nerves and were worst in those nerves farthest away from the spinal cord (see Figure 1). The amplitudes of sensory nerve action potentials were most affected (Figure 1). Fourteen farmers in group-one (88%) and 11 farmers in group-two (69%) showed abnormalities of needle-EMG. Nerve conduction abnormalities were more notable in the distal muscles (Table 2). The changes were much more pronounced in farmer of group-one compared to those

farmers in group-two. Mean latencies of the evoked potentials were not significantly increased (Table 2).

Figure 1: Relative Neurophysiological Abnormalities in Sheep Farmers and Controls



Graphical illustration of relative neurophysiological abnormalities (percentages of control values) in two groups of sheep farmers compared with the control population.
Med m. ncv: median motor nerve conduction velocity.
Med Fw lat: shortest median motor nerve F-wave latency.
CPN m. ncv: common peroneal motor nerve conduction velocity.
Med sen lat: median nerve sensory latency.
Med m. lat: median nerve distal motor latency.
CPN m. lat: Common peroneal nerve distal motor latency.
Sural sen. Lat: Sural nerve sensory latency.
CPN m. amp: Amplitude of common peroneal nerve motor action potential.
Med m. amp: Amplitude of median nerve motor action potential.
Med sen amp: Amplitude of median nerve sensory action potential.
Sural sen amp: Amplitude of sural nerve sensory action potential.
Error bars in the control values represent one standard deviation. The largest deviations from normal were amplitudes of both sensory and motor nerve action potentials, but the very long sensory nerves of the lower limbs were most affected in these sheep farmers.

Table 2: Results of Neurophysiological Studies of the Somatic Nerves

	Controls (n = 16)				Group-two Farmers (n=16)			Group-one Farmers (n = 16)		
	Mean	± S.E.	Confidence interval (95%)		Mean	± S.E.	P value (2-tailed)	Mean	± S.E.	P value (2-tailed)
Lower limb (motor)										
SDML (ms)	3.97	0.15	3.36	4.58	4.87	0.22	0.0023	4.84	0.25	0.0068
FMNCV ($m \cdot s^{-1}$)	51.6	1.54	48.4	54.7	45.2	1.30	0.0038	45.5	1.32	0.0053
Amplitude (mV)	6.09	0.58	4.19	7.98	2.75	0.31	0.00004	2.91	0.55	0.0004
F-wave latency (ms)	48.0	1.20	44.9	51.1	56.5	1.23	0.00003	59.0	1.14	0.00000
Lower limb (sensory)										
Sural nerve latency (ms)	3.05	0.07	2.59	3.51	3.96	0.08	0.00000	4.09	0.20	0.0001
Sural nerve amplitude (μV)	12.0	1.32	10.6	13.3	6.0	0.51	0.00046	3.3	0.56	0.00001
Upper limb (motor)										
SDML (ms)	3.43	0.12	2.77	4.09	3.78	0.10	0.0283	3.92	0.08	0.0019
FMNCV ($m \cdot s^{-1}$)	59.2	1.40	56.6	61.9	56.5	1.23	0.1526	54.1	0.88	0.0049
Amplitude (mV)	10.9	1.23	8.24	13.5	5.23	0.42	0.0004	4.47	0.75	0.0002
F-wave latency (ms)	27.6	0.44	26.1	29.2	29.1	0.43	0.0197	30.1	0.37	0.0002
Upper limb (sensory)										
Median nerve latency (ms)	2.71	0.05	2.23	3.19	3.04	0.10	0.0062	3.07	0.06	0.0001
Median nerve amplitude (μV)	22.5	2.09	19.9	25.2	9.8	0.68	0.00002	8.3	1.40	0.00001
Evoked potential latencies										
Visual - P100 (ms)	97.4	1.31	94.5	100.2	103.1	1.23	0.0031	97.7	1.26	0.877
Brainstem Auditory										
I (ms)	1.65	0.04	1.28	2.02	1.70	0.02	0.247	1.64	0.04	0.847
I - III (ms)	2.24	0.04	2.08	2.39	2.20	0.05	0.587	2.08	0.07	0.074
III - V (ms)	1.86	0.09	1.65	2.06	1.65	0.07	0.076	1.96	0.08	0.384
Somato sensory Erb (ms)	10.2	0.15	9.59	10.76	10.8	0.25	0.036	10.7	0.24	0.058
Spine (ms)	13.9	0.25	13.2	14.6	14.6	0.25	0.069	14.5	0.26	0.092
Cortex (ms)	19.6	0.23	18.8	20.5	20.2	0.33	0.196	20.2	0.30	0.132

P values = Statistical probabilities calculated using the parametric Student's t-test. SDML = Shortest distal motor latency. FMNCV = Fastest motor nerve conduction velocity (see text for Methodology).

Evidence of recent exposure to organophosphates

Activities of red cell and serum acetylcholinesterase assessed in the samples of farmers in group-one and group-two were all normal. There were no statistically significant differences between the activities of these enzymes in these farmers compared with previously published values in normal controls.[38]

Evidence of autonomic neuropathy in group-three farmers

Sympathetic Functions

All subjects in group-three (100%) had one or more signs of sympathetic failure. Nearly 30% of the patients had evidence of denervation hypersensitivity to phenylephrine suggestive of significant damage of sympathetic postganglionic nerve fibres. The sympathetic dysfunctions were distributed as follows:

In the skin

There was extensive failure of the cutaneous thermoregulatory vasomotor function in 38 (95%) of group-three farmers. The lower limbs together with the dominant arm were often affected in majority of subjects. This was the commonest sympathetic abnormality in group-three farmers (Figure 2). The emotional sudomotor function was abnormal in only 8 (20%) of group-three farmers (Skin Sudomotor, Figure 2).

In the heart

Failure of cardioaccelerator function was elicited in 29 (73%) of the subjects in group-three. These patients have lost the ability to increase their heart rates effectively during isometric exercise (Cardiac Sympathetic, Figure 2).

In the skeletal muscles

Failure of the sympathetic regulated increase of arterial blood pressure during isometric exercise, achieved through vasoconstriction in the skeletal muscles,[31] was found in 27 (67%) of farmers in group-three. These are the farmers who could not increase their DBP effectively and were fewer than those who had failure of skin thermoregulatory function (Muscle Sympathetic, Figure 2).

In the splanchnic vascular bed

Failure of the sympathetic regulated auto-transfusion from the splanchnic vascular bed during the blood volume crisis created by Valsalva's manoeuvre was observed in 27 (67%) of patients in group-three (Splanchnic Sympathetic, Figure 2). Most of these farmers had positive histories of accidental oral ingestion of organophosphates.

Parasympathetic functions

Peripheral baroreflex function

There were disturbances in peripheral baroreflex functions in group-three farmers causing either increased or decreased sensitivities to the baroreflex measured from the slope of the response curve to phenylephrine injection. This indicates lesions in the walls of large blood vessels where the arterial baroreceptors are situated. Up to 33 (83%) of group-three farmers had either increased or decreased baroreflex sensitivity. The majority, 25 (63%) had decreased baroreflex sensitivity (Baroreflex Slope, Figure 2). Disturbances in the baroreflex thresholds were observed in 31 (78%) of group-three farmers (Figure 2), most of these were increased rather than low thresholds to phenylephrine injections.

The cardiodepressor function of the carotid reflex was abnormally low in 21 (53%) while the vasodepressor function was lower than normal in 16 (40%) of group-three farmers (Figure 2).

Central cardiac parasympathetic function

Resting cardiac vagal tone (or CVT) was lower than normal in all the patients in group-three (100%). It was the most frequent autonomic abnormality in group-three farmers (Resting CVT, Figure 2). However, the respiratory modulation of CVT during deep breathing was abnormally low in only 11 (27%) of group-three farmers. The resting heart rate was lower than normal in 37 (93%) of group-three farmers (Paradoxical HR, Figure 2).

Central baroreflex function

Disturbance in the central baroreflex gain was observed in the form of excessively high CBR in 16 (40%) of the group-three farmers.

Non-specific mixed autonomic functions

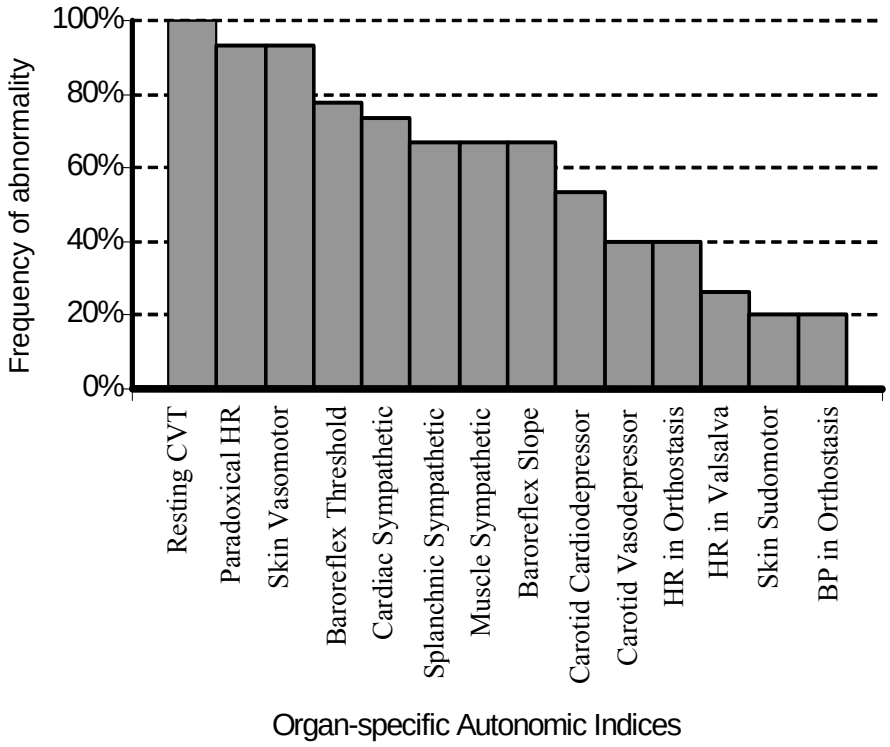
Autonomic responses to orthostasis

There was abnormal heart rate response to orthostasis in 16 (40%) of group-three farmers (HR in Orthostasis, Figure 2). These patients had no effective changes in their heart rates during orthostasis. Postural hypotension was observed in only 8 (20%) of group-three farmers (BP in Orthostasis, Figure 2). These patients had decreases of more than 10 mm Hg in their diastolic blood pressures when they stood upright.

Autonomic responses to Valsalva's manoeuvre

Heart rate response to Valsalva's manoeuvre was abnormal in 11 (27%) of group-three farmers (HR in Valsalva, Figure 2).

Figure 2: Abnormal Autonomic Functions in Group-three Farmers



A Bar-chart showing the frequency of abnormal autonomic functions in group-three farmers arranged in a descending order.
CVT: Cardiac vagal tone.
HR**:** Heart rate.
Skin vasomotor: Thermoregulatory vasoconstrictor reflex function in the skin.
Baroreflex threshold: Threshold of combined bradycardia/rise in systolic blood pressure in response to phenylephrine injection.
Cardiac Sympathetic**:** Cardioaccelerator function of the sympathetic nervous system.
Splanchnic Sympathetic: Sympathetic auto-transfusion function in the splanchnic bed.

Muscle Sympathetic**:** Vasoconstrictor function of the sympathetic nervous system in skeletal muscles.
Baroreflex slope: Gradient of the pulse intervals in relation to the increasing systolic blood pressure following intravenous injection of phenylephrine.
Carotid cardiodepressor: Increase in CVT following carotid massage.
Carotid vasodepressor: Decrease in systolic blood pressure following carotid massage.
HR in orthostasis: Cardiac response to orthostasis measure in the 30:15 test (see text).
HR in Valsalva: Cardiac response to a standard Valsalva's manoeuvre measured as the Valsalva's ratio (see text).
Skin sudomotor: Emotional sudomotor function in the soles and palms measured as sympathetic Galvanic responses to an inspiratory gasp.
BP in orthostasis: Postural hypotension (see text for Methodology).
The central cardiac parasympathetic function in the brainstem was most frequently affected in group-three farmers.

DISCUSSION

This is a unique, broadly based study designed to elicit any long-term neurological abnormality prevalent in farmers with clear histories of exposure to OP in sheep dip. It was necessary to examine a wide range of nerve functions in order to identify if there was any group of abnormalities that were more frequent in farmers exposed to OP in sheep dip. It was also necessary to examine autonomic functions in details among farmers exposed to OP in sheep dip using the new target-organ orientated method. The orthodox tests relying on wildcat stimulations of the autonomic nervous system during orthostasis or Valsalva's manoeuvre cannot achieve specific examination of a given target organ. We have therefore used autonomic target-organ specific examination methods to achieve the diversity and specificity required in this study.[39] These tests successfully identified occult autonomic lesions that presented as clinical puzzles.[36,39] The batteries of neurological tests we used have all been clinically validated and all the tests have been used before in previous un-related neurological studies published in the literature as cited in the Methods section. These tests are in current use in many neurological centres for routine clinical evaluation of nerve functions in normal medical practice. Some of the neurophysiological results presented here have already been published in phase I of the study[40] but are included here for the sake of clarity to the current readers.

Specific and Unique Pattern of Autonomic Dysfunction

Abnormality of the central cardiac parasympathetic activity was universal in group-three farmers. They all had low resting cardiac vagal tone (CVT) and a unique type too. In other diseases like diabetes mellitus,[41] hypertension,[42] chronic heart failure[43] and Rett syndrome,[44] low resting CVT is associated with resting tachycardia. This is the expected normal physiological outcome of low resting CVT. In group-three farmers, the low resting CVT was associated with bradycardia, which we called "paradoxical heart rate". Only one of group-three farmers had tachycardia with low CVT. It means that "paradoxical heart rate" was the second commonest abnormality in these farmers. It was clear from our results that the autonomic target organs in the skin, in large blood vessels including the heart and in the brain were very

vulnerable because the frequencies of abnormalities here were greater than 90%. Furthermore, the vulnerability of the target organs was relatively specific within all of the anatomical sites.

Vasomotor and sudomotor functions were affected independently within the skin, but the abnormality of vasomotor function was much more frequent. Independent involvement of the cardiodepressor and vasodepressor effects of carotid sinus massage in the farmers is further evidence of a relatively specific central parasympathetic lesion. Carotid sinus baroreflex initiated by massaging the wall of the artery usually causes bradycardia, known as the cardiodepressor effect, and hypotension, known as the vasodepressor effect. These two effects are often linked due their common origin. However, the central connections of the two reflex pathways are different.[45] These two central pathways can be affected independently by disease.[36] Abnormality of the cardiodepressor effect of the carotid reflex was more frequent in the farmers than the vasodepressor effect suggesting a relatively higher vulnerability of the central cardiodepressor pathway to chronic OP poisoning. This cardiodepressor pathway from the carotid sinus to the brainstem uses a monoaminergic neurotransmitter[46] and does not respond to a very low dose of atropine[47] while the less vulnerable vasodepressor pathway is cholinergic and responds to very low dose of atropine.[47]

Important Negative Results from Examination of Autonomic Functions

Useful inferences can be deduced from the negative results too. Sudomotor function in the skin was largely normal in group-three farmers and this is a cholinergic sympathetic function. Respiratory modulation of CVT was also preserved in the majority of group-three farmers. This is also a cholinergic function of the inspiratory neurones in the brainstem.[48] Respiratory sinus arrhythmia is caused by central inspiratory neurones as they modulate the activity of cardiovagal motor neurones[48] and to a minor extent by the inhibitory effects of slowly adapting pulmonary receptors.[46] This arrhythmia is often used to assess CVT by other authors.[49,50] In other diseases like diabetes mellitus, respiratory sinus arrhythmia is reduced to a similar extent as CVT.[51] The clear independent preservation of respiratory modulations of the CVT in association with very low resting CVT in group-three farmers suggests a unique type of central parasympathetic lesion in which the low resting CVT can respond to deep breathing and this is contrary to what happens in other diseases. This is also further proof that the lesion in these farmers was central, because had it been a peripheral end-organ failure, there would be no response to any form of central perturbation.

Moreover, only 30% of group-three farmers had detectable damage of sympathetic postganglionic nerve fibres indicated by the hypersensitivity to phenylephrine injection. It suggests that disintegration of the small unmyelinated peripheral nerve fibres is not a frequent feature in these farmers, but nevertheless it does occur. This is consistent with our other results here too, which show that the thermal threshold for hot sensation mediated by the small unmyelinated peripheral nerve fibres was not

significantly affected in group-two farmers who had no acute episodes of OP poisoning. However, small unmyelinated nerve fibres were significantly affected in group-one farmers who had acute episodes of OP poisoning similar to group-three farmers. It is possible that acute episode is a sign of subsequent more severe neurological sequelae, which may involve damage of the small unmyelinated peripheral nerve fibres.

The common orthodox tests of autonomic functions were not helpful in our investigation. Postural hypotension was found in only 20% of group-three farmers. This together with the very low frequencies of abnormalities of other orthodox tests like Valsalva's and 30:15 ratios implies that the popular clinical practice of looking for postural hypotension and wildcat stimulations of the autonomic nervous system in search of sympathetic failure is not appropriate in the examination of autonomic function in patients with chronic exposure to OP in sheep dip.

What could cause Paradoxical Heart Rates in Group-three Farmers?

Stimulation of sub-endocardial chemoreceptors can cause bradycardia that is independent of cardiac vagal tone.[52] Myocardial damage can also cause slowing of heart rate in association with low cardiac vagal tone.[53] The low heart rate in myocardial damage is thought to be due to stimulation of unmyelinated C-fibres in the walls of the heart.[52,54] It is uncertain if chronic exposure to OP in sheep dip may just alter the properties of either the sub-endocardial chemoreceptors, or the C-fibres in the cardiac wall thereby causing reduction of heart rate and, or prevent the heart from responding to a low cardiac vagal tone.

Distal Somatosensory Neuropathy in Farmers who Regularly Use OP in Sheep Dip

Abnormalities in the peripheral somatic nerves were more pronounced in group-one farmers compared to those in group-two, although the pattern and profile of the changes observed were similar in the two groups. These results are consistent with those previously reported in the literatures for the following reasons. Farmers in group-one were randomly selected from a population of sheep farmers who had a history suggestive of repeated episodes of acute, mild to moderate OP poisoning in the course of their occupations. They also claim to have developed symptoms of long-term ill health from exposure to OP compounds similar to previous reports.[12] However, group-two farmers were randomly selected from a farming community in the West of Scotland. They had no history of previous acute effects of OP poisoning although they were using it for at least a period of five years. Distal axonal degeneration is the principal and earliest feature of OP induced delayed neuropathy in both experimental animals[4] and in humans.[5] In toxic neuropathies, including those related to OP compounds, the vulnerability of somatic nerve fibres has been assumed to be related to axonal length where long axons, both motor and sensory, are more susceptible than shorter axons.[55] This assumption has been primarily based on earlier

morphological data and our results here seem to corroborate this hypothesis. However, recent electrophysiological, clinical and morphological data suggest that all populations of nerve fibres are equally vulnerable[56] and that sensory abnormalities are invariably present upon careful clinical examination.[57] We have found a predominantly distal somatosensory neuropathy in both groups –one and –two farmers. Current practice of combining several agents in a given product means complicated biological interactions and synergistic toxic effects may play a role. Moreover, many of OP compounds could have breakdown products of unknown toxicity during storage. Some OP compounds regarded as innocuous, may produce peripheral neuropathy of the axonopathy type after short term[58] or prolonged exposure under suitable conditions.[59,60] The precise biochemical abnormality responsible for the development of OP induced delayed neuropathy has not been clarified[60] but a selective metabolic lesion of the neurone, possibly involving phosphorylation of cellular components, has been postulated.[4] Chronic toxic effects of OP compounds are believed to be a consequence of cumulative damage from repeated exposure to non-lethal doses.[59] Furthermore, a few authors now believe that some OP compounds previously regarded as innocuous may produce axonopathy after prolonged exposure in some circumstances.[60] The mechanism by which chronic neurological effects are caused by OP compounds is still unknown.[12] Our results show clearly that distal somatosensory nerves are most vulnerable, but the central somatic conduction pathways including cranial nerves are resistant to the disease processes associated with exposure to OP in sheep dip. It is possible this could be another selective deterioration of monoaminergic functions in the Rexed's laminae of the spinal cord where sensory thresholds are pre-processed before being passed to the higher centres.[61,62]

Possible Diagnostic Markers of OP Neurotoxicity

The unique pattern of autonomic lesions could have a diagnostic value in suspected cases of OP neurotoxicity if it can be proven that other common toxic agents like acrylamide, organic solvents like trichloroethylene, heavy metals like arsenic, lead and thallium do not have similar autonomic patterns. Toxic heavy metals are stored in the body and can be identified using biochemical methods. Therefore, it is easy to rule them out. It is clear from our results that there are vulnerable anatomical sites where autonomic target-organs are most frequently damaged in chronic exposure to OP in sheep dip. It is also clear from our results that the damages caused at these sites are selective and appear to be specific. Chronic long-term exposure to low levels of OP appears to protect cholinergic nerves while injuring others and monoaminergic nerves are particularly affected according to our results here. This differential effect is true in all the vulnerable sites therefore can form the bases of diagnostic markers of chronic exposure to OP. The consequences of selective preservation of cholinergic functions accompanied by deterioration of monoaminergic functions in the brain will be diverse, depending on the area of the brain. The well-known effect of such an imbalance in the basal ganglia and substantia nigra is Parkinsonism.[63] The effects of the imbalances of cholinergic/monoaminergic functions on baroreflex and cardiac

parasympathetic functions in the brainstem are clearly shown here and we were also able to quantify these effects using our methods. Short-term memory is processed in the hippocampus through a physiological phenomenon called long-term, or "long-lasting" potentiation of action potentials in neurones.[64] Long-term potentiation can be elicited in the hippocampus by administration of metabotropic glutamatergic receptor agonists.[65] This is a clear indication that the metabotropic glutamatergic receptors in the hippocampus, which are monoaminergic, are in deed important and are used in the process of short-term memory. A battery of neuropsychological tests of short-term memory and cognitive functions can be used to assess the monoaminergic effects of chronic exposure to OP in this area of the brain. It is therefore apparent from this discussion that a combination of target-organ specific examination of autonomic functions at known vulnerable anatomical sites to demonstrate the differential cholinergic/monoaminergic effects and a battery of neuropsychological tests for short-term memory and cognitive functions can be a useful diagnostic tool for suspected cases of chronic exposure to OP. The somatic nerve lesions are not specific to OP neurotoxicity, but it is useful to demonstrate the predominantly somatosensory neuropathy in which the central conduction pathways and cranial nerves are preserved.

POTENTIAL DIAGNOSTIC VALUES OF THESE NEUROLOGICAL MARKERS IN AIRCREWS

We have interesting preliminary and unpublished data from the few aircrew we have so far subjected to our target-organ specific examination of the autonomic nervous system. These crew were referred to us following complains of chronic ill health. All of these individuals have a similar pattern of autonomic dysfunction similar to group-three farmers in this current study. We are aware of the argument that aircrews could be repeatedly exposed to toxic levels of carbon monoxide in their confined environment during flights. Interestingly, we have also obtained unpublished data from a group of miners from Wales in Great Britain. It is fully certified that the miners were all exposed to toxic levels of carbon monoxide in a confined underground environment. These miners were referred to us following complaints of chronic ill health and we carried out target-organ specific examination of their autonomic nervous system. The pattern of autonomic dysfunctions in the miners is remarkably different from that in group-three farmers and the aircrews. For yet unknown reason, the pattern of autonomic dysfunction in our group of aircrews is similar to that in group-three farmers, but different from the pattern in the group of miners. This is a compelling reason for further investigation, first to confirm the findings in the aircrew and then to investigate possible common toxic agents among group-three farmers and aircrew.

CONCLUSION

Neurological sequelae of long-term exposure to OP consist of a patchy pattern of dysfunctions of the autonomic target organs situated in the skin, in large blood vessels and in the brain. Cholinergic functions are selectively

preserved while monoaminergic functions deteriorate in the brain and the skin. Distal somatosensory neuropathy is the predominant somatic nerve dysfunction associated with chronic exposure to OP. The central somatic conduction pathways and the cranial nerves are resistant to the neurotoxic effects of chronic exposure to OP. These neurological sequelae can explain the symptoms and ill health in patients with chronic exposure to OP.

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From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 239-242.

CABIN AIR FILTRATION – PRESENT AND FUTURE

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BIOGRAPHICAL SKETCH

Karen Bull graduated from Southampton University with BEng (Hons) in Aeronautics and Astronautics. As part of the university degree course, she also completed a four year engineering sponsorship with BAE Systems, Space and Communications Division. Her previous work experience includes 14 years experience with Pall Aerospace (a division of Pall Europe Ltd) in the sales and marketing department, including seven years providing technical support to the airline aftermarket.

INTRODUCTION

Pall Aerospace has been involved in cabin air quality filtration since the Airbus A300-600/A310 program in the 1980's. Between 2001 and 2004, Pall Aerospace participated in the EU "CabinAir" project, and was the coordinator for work package three, focusing on aircraft filtration systems. This research work was divided into two main sections: (a) current filtration capabilities, including all types of transport vehicles; and (b) future filtration solutions and new technologies for improving cabin air quality on board commercial aircraft.

SECTION 1 - LATEST TECHNOLOGIES FOR COMMERCIAL AIRCRAFT

The initial research activities included a detailed review of the current technologies that are used on modern commercial aircraft, combined with a review of alternative technologies that are available and used on other transport systems, for example, automotive and marine. The main objective of this activity was to establish the in-service performance of current aircraft filtration systems.

Current technologies which can be installed on the aircraft cabin air recirculation system include:

- "True HEPA" disposable filter elements for removal of particulate contamination, including bacteria and viruses.[†]
- Disposable filter elements using adsorbent technology for volatile organic compounds (VOCs)/odour removal.

The current particulate filters used on modern aircraft are located in the Environmental Control Systems (ECS) recirculation loop only and are rated at 99.99% sodium flame efficiency or the equivalent 99.97% di-octyl phthalate

[†] "True HEPA" is a microbially tested High Efficiency Particulate Air Filter

(D.O.P.) efficiency. In certain cases a lower level of filtration may be in use, but generally there is an option of upgrading to HEPA filtration. Filters manufactured to this "true HEPA" specification provide excellent standards of particulate contaminant removal and control of micro-organisms from the recirculated cabin air.

Prior to the EU CabinAir project, although there existed several recommendations regarding the levels of filtration for commercial aircraft, there were no published standards. One of the outputs from the CabinAir project was a European pre-standard, "Aerospace series - Aircraft Internal Air Quality Standards, Criteria and Determination Methods", Reference prEN 4618.

SECTION 2 - FUTURE FILTRATION SOLUTIONS/NEW TECHNOLOGIES FOR MODERN COMMERCIAL AIRCRAFT

The main objective of this section of the research was to identify and develop new or enhanced features for filtration systems in order to improve the air quality in passenger aircraft cabins

The information that was gathered during the first part of the project provided some conclusions and recommendations on possible improvements that could be offered to the existing aircraft filtration systems. There were nine areas of improvement that were identified. In order to review the feasibility of each of these technologies, they were measured against various performance factors and given a numerical rating which was then used to prioritise the technologies worth pursuing.

Using this method, two new areas of technology were identified that could improve the cabin air quality on board aircraft:

- Regenerable VOC removal systems; and
- Filtration of outside air.

These are described below.

Regenerable VOC Systems

For aircraft cabin air and other industrial transport systems, VOC removal is currently performed using adsorption devices, which usually consist of a disposable filter element. However, due to the maintenance costs involved with this type of device, alternative, regenerable systems are being considered.

For aerospace applications, the three most suitable regenerable systems are:

- Temperature Swing Adsorption (TSA);
- Non thermal Plasma Oxidation; and
- Photo-catalytic oxidation (PCO).

After further analysis, the PCO technology was chosen to be investigated further within the research project. The PCO is a simple device with no moving parts, minimal pressure drop across the panels and low power consumption. UV lights and titanium dioxide coated surfaces are both established technologies and many units have been produced for industrial and domestic use and some of these have been tested at low VOC concentrations with good results.

During the final year of the project, a laboratory scale technology demonstrator was manufactured and tested at Cetiat, a research facility in France, with the assistance of BRE, a consultancy company in the UK. The test results were in line with expectations but further work is needed to develop a small, lightweight unit for the high flow rates encountered in the aircraft ECS.

Outside Air Filtration Systems

Most aircraft have the filters or adsorbers located in the recirculation loop but for future and existing aircraft, consideration needs to be given to providing adequate purification of both recirculated and outside air. There are various possible locations for an outside air filtration system and in all of these locations the main contaminants to be removed are particulate, odours/VOCS and sometimes, oil mist.

To remove these contaminants, and improve the quality of the outside air, Pall have researched and developed three suitable technologies:

- low temperature carbon adsorption;
- high temperature media for particulate removal;
- high temperature catalysts for VOC/odour removal.

The carbon adsorption devices (disposable filter elements) are only suitable for low temperature applications and they also require removal and replacement at regular maintenance intervals.

In comparison, the high temperature media for removal of carbon/soot particulate contamination is capable of withstanding temperatures up to 280°C. This product has undergone an in-service evaluation and is now qualified and OEM approved.

Finally, in order to remove VOCs/odours from the high temperature zones of the aircraft ECS, Pall have developed a catalyst filtration solution and the results from the laboratory tests show that the unit is very effective at reducing the level of VOCs and perceived odours. This unit is currently waiting an aircraft in-service evaluation

CONCLUSIONS

The removal of particulate contamination, bacteria, fungi and virus micro-organisms from recirculated air may be achieved by the installation of HEPA

filter elements (equal to or greater than EU grade H13) on the recirculation air line within the environmental control system.

This level of filter element removal efficiency must significantly reduce the risk of transmission of diseases through the recirculation system by stopping airborne microbes (microbes include bacteria and viruses) and particulate contamination on the first pass.

For the recirculation air and outside air systems, photocatalytic oxidation, adsorbent technologies and catalyst technologies have been shown to provide good VOC removal efficiencies in demonstrator tests and will continue to be investigated further.

From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 243-253.

AIRCRAFT AIR QUALITY INCIDENTS, SYMPTOMS, EXPOSURES AND POSSIBLE SOLUTIONS

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BIOGRAPHICAL SKETCH

Professor Christiaan van Netten, has a 1969 MSc in Electrophysiology, and a 1973 PhD in Membrane Physiology, both from Simon Fraser University. Chris is presently Professor, Division of Public, Occupational, and Environmental Health, Department of Health Care and Epidemiology, Faculty of Medicine and School of Occupational and Environmental Health, Faculty of Graduate Studies, University of British Columbia, Vancouver BC, Canada. Chris has written over 125 publications, book chapters, and reports in areas including: membrane physiology, neurology, cancer research, cancer research epidemiology, Indoor air quality, radiation exposure and health effects, occupational and environmental health including seven articles on aircraft air quality and was a member of the NRC Committee on Aircraft Air Quality, Washington DC 2001-02.

INTRODUCTION

Aircraft air quality problems have been experienced by pilots, flight attendants, as well as passengers over the years. In many instances the complaints of these individuals are often dismissed as anecdotal since the available information is incomplete preventing these incidents to be written up in a scientifically accepted format. In 1998 and article by van Netten and Hilliard, entitled "Air quality and Health Effects Associated with the operation of BAe 146-200 Aircraft" was published in the peer reviewed literature.[1] This article appeared to spark the interest, not only of pilots and flight attendants, but also of the industry and their lawyers. Although the authors of the above article submitted the manuscript for publication in good faith, meaning that identifying the problem would benefit the industry and thus work towards improving the air quality within aircraft, they did not expect to be legally challenged and instructed not to publish the article. Nevertheless, after some negotiation between the lawyers and one of the authors, the lawyers agreed that publication of the article was in the best interest of the industry and gave their permission. Although the upset conditions described in the article were nothing new, one can appreciate why very few, if any, of these events have been published.

THE AIRCRAFT CABIN ENVIRONMENT

A previous 1986 NRC publication identified a number of problems in the general cabin air environment and made numerous recommendations some of which were acted upon such as a ban on smoking on all domestic aircraft.[2] In spite of some of the changes made, the complaints by flight crew members

and passengers did not disappear and the NRC was instructed to revisit this area of research,[3] including the sporadic air quality incidents, or upset conditions that were addressed in the 1998 article mentioned above.[1]

Since 1998 a number of new inquiries have been conducted including one in Australia on BAe 146 aircraft,[4] and a report by the House of Lords in London.[5] Although the former inquiry was very extensive, and in depth, the latter was not. It is therefore no surprise that the final conclusions reached by each of these inquiries were not consistent.

Numerous air quality incidents have since been reported in local and regional newspapers some of which narrowly escaped accidents. These include the 13 March 2004 incident when an MD80 bound for Las Vegas made an emergency return to Santa Barbara Airport after smoke began filling its cabin, frightening passengers;[6] the 5 November 2000 Birmingham incident (on a BAe 146): Oil smell in cabin, Pilot felt "dreadful", "seeing double when landing";[7] and the 12 November 1999, Braathens Malmo incident (on an BAe 146): Oil leak in engine #2, "Poisoned pilots almost crashed", "Pilots close to blacking out", "Passengers seemed 'passivated'".[8]

The frequency of these air quality incidents has been reported by van Netten et al based on information obtained from three North American Air carriers.[9] The results have been summarised in Table 1.

Table 1: Air Quality Incident Frequencies, Based on Flight Incident Reports Submitted to Three North American Air carriers by Flight Crew Members

Aircraft type	Average number of incidents per aircraft	
	Per year	per 1000 cycles*
BAe-146	6.4	3.88**
MD-80	1.01**	1.02**
A-320	1.67	1.29
B-747	0.34	1.25
DC-10	0.38	1.04
B-767	0.21	0.63
B-737	0.07	0.09

* A cycle is defined as: a take-off, flight, and landing sequence.
** Based on incomplete data and estimates.

It should be emphasized that the reported frequencies are highly dependent on local maintenance and operating procedures, which can differ substantially from operator to operator. Nevertheless some trends can be observed specifically with BAe-146, MD-80 and A-320 aircraft.

The reported symptoms associated with these incidents[9] have also been summarized and are displayed in Table 2 below.

Table 2: Symptoms Associated with Air Quality Incident Reports

Symptom	Air Carrier		
	X	Y	Z
Any symptom	58%	78%	82%
Eye, ear, nose, and throat	38%	16%	25%
Central Nervous System	45%	72%	64%
Intoxication	45%	70%	63%
Neuropsychological	3%	3%	2%
Other	6%	19%	8%
Respiratory	9%	16%	28%
Gastro intestinal	16%	30%	21%
Skin	7%	10%	3%
Cardio vascular	2%	3%	2%
Total incident reports	128	598	299

It can be observed that the majority of symptoms were associated with the central nervous system in all three carriers whereas symptoms associated with the respiratory system ranked relatively low and were in two of the carriers, even less frequent than those associated with the gastrointestinal tract.

Since the central nervous system appears to be affected most often, it becomes necessary to ask whether any agent or agents are present in the aircraft that have a known neurotoxic effect. As identified in the 1998 article by van Netten in the BAe-146,[1] jet engine oil can enter the aircraft ventilation system when oil seals are wearing out, allowing jet engine oil to leak oil into the air.

MD-80 aircraft have an additional source of oil contamination into their air supply. This additional route involves the Auxiliary Power Unit or APU. The APU is also a jet engine which is used to supply power and air to the aircraft when the main engines are not running or when full power is required during certain phases of flight and bleed air cannot be spared from the main engines. Although all aircraft have an APU and are also vulnerable to potential jet engine oil leaking into the ventilation system, MD-80 aircraft have an additional problem. In this aircraft there appears to be a small orifice in the rear of the aircraft that allows hydraulic fluids and spilled oils that accumulate in the bilge of the aircraft to be dumped overboard. The location of this orifice happens to be directly in front of the air intake of the APU, which will ingest it and release it at high temperature into the ventilation system of the aircraft. For these reasons a number of engine oils and hydraulic fluids have been investigated for constituents that might be released into the cabin air environment. In addition, since bleed air is extremely hot when it leaves the engine and enters the ventilation system of the aircraft the possibility of pyrolysis of oil constituents also has to be addressed.

This was investigated and reported on by van Netten et al in a number of articles.[10,11,12,13] Aside from the finding that the organophosphate, tri-cresylphosphate (TCP) was present as an undisclosed ingredient in one of the hydraulic fluids investigated, the main findings were that CO is produced when oils and fluids are subjected to these temperatures and TCPs are

released into the air, remain airborne, and consequently can be captured from the air at room temperature.

The acute toxicology of CO is well known,[14,15,16] and exposure to this agent in the aircraft could very well explain the acute neurological symptoms experienced by the pilots of the Birmingham and Malmo incidents. The chronic toxicity of CO is coming into focus and this agent appears to damage central nervous system resulting in symptoms that have been compared to Parkinson's disease.[17] This is not surprising as it has been recently recognized that CO is a neurotransmitter.[18]

The toxicity of TCP is also well known,[14,16,19] and has centered on the ortho-isomer (TOCP). This agent has been linked to delayed chronic neurotoxicity symptoms. For this reason there is a clear statement on the back of some jet engine oil cans that warns that the oil contains an organophosphate esters belonging to a group known as tricresyl phosphates which, upon exposure, can cause nervous system disorders.

The symptoms associated with, and the toxicity of organophosphate esters has recently been reviewed by Abou-Donia,[20] and involves three main categories:

1 Organophosphate Ester-induced toxicity due to Acetyl cholinesterase (AChE) inhibition. Recent human exposures occurred in Japan during a number of subway attacks these include: the 1994 Sarin attack in Matsumoto, Japan, where 600 individuals were exposed, resulting in 58 hospital admissions and seven deaths. Another Sarin attack took place in 1995 which targeted the Tokyo subway. This resulted in the hospitalization of 5,000 individuals and one death.[21] Many CNS symptoms were reported. It was interesting to observe that when the recommended, and standard test for exposure to these organophosphates, that is, red blood cell AChE inhibition returned to normal, there were still signs and symptoms of central nervous system effects including pupilary constriction present with normal AChE levels

2 Organophosphate Ester-Induced Delayed Neurotoxicity, (OPIDN) are the effects that have been directly linked to TOCP exposure.[14,16,19] Exposure to this agent will result in the slow destruction of the peripheral and central nervous system. The standard test for exposure to this agent is NeuroToxic Esterase (NTE) inhibition. One unexpected finding from the Tokyo experience was that humans more sensitive to Sarin induced OPIDN than animals.

3. A third class of organophosphate ester toxicity is currently being recognized and has been referred to as Organophosphate Ester-Induced Chronic Neurotoxicity (OPICN).[20] This condition is associated with chronic neurological problems persisting for years, which are distinctly different from AChE and OPIDN effects. This condition has often been referred to in the literature by various names such as: "Chronic neurological effects",[22] "Chronic neurobehavioural effects",[23]

> "Chronic organophosphate induced neuropsychiatric disorders (COPIND)".[24]

These effects are the result neuropathological lesions of cortex, cerebellum, hippocampal formation and other central nervous system targets. These lesions appear to be linked to destruction of certain nerve cells as well as an inability of the system to cull out abnormal nerve cells by preventing their normal and programmed cell death referred to as delayed apoptosis. Since these organophosphate esters are blocking normal function of a number of essential enzyme systems either reversibly and/or irreversibly, they are prime agents to have their toxicity increased many fold when exposure occurs in the presence of another agent that can act as a synergist. This phenomenon has been well appreciated by pesticide applicators who, for instance, add piperonyl butoxide to a mixture to enhance the toxicity of the actual pesticide. The final toxicity of this mixture is not the sum of the individual toxicities but in fact is many times higher. Adding piperonyl butoxide to a mixture produces a potentiation effect making the initial pesticide, in some instances, 110 times more toxic.

TCPs inhibit among other enzymes, carboxyesterases, an enzyme group that is essential in the metabolism for a number of pesticides allowing them to persist longer in the tissues enhancing their toxicity. Pesticides that can be encountered within an aircraft can include permethrin and phenothrin, both are currently used as disinsectants in the aircraft industry.[13]

Permethrin, for instance, is destroyed by the action of carboxyesterase to 3-phenoxy benzyl alcohol and 3-phenoxy benzoic acid. One can see that a previous and/or current exposure to TCP or any other agent that inhibits carboxyesterase activity would make such a person highly susceptible to the effects of a relatively low toxicity agent such as permethrin, which the body is now incapable of breaking down.

This concept might be the reason why certain individuals are highly affected by "acceptable " levels of a particular agent whereas another individual, present in the same environment does not experience ill effects. The effects experienced by certain soldiers that have been classified as Gulf War Syndrome might very well be due to the action and presence of certain synergist.[25] In this respect it should be appreciated that permethrins are liberally used in the armed forces for mosquito control and apparently often impregnates this compound into uniforms. TCP exposure is also likely to be present in this environment as gas turbines are used to power heavy equipment such as tanks and require the same class of lubricating oils as aircraft jet engines.

At this point in time there is good evidence that flight crew members are reporting symptoms that are consistent with having been exposed to an agent, or agents, that appear to have an important effect of the nervous system. There is also clear evidence that jet engine oils and hydraulic fluids can release neurotoxic agents into the ventilation system of the aircraft. What are

missing at this point in time are direct measurements and the quantification of actual personal exposure to these agents during these rare, and often unpredictable, upset conditions. Without direct exposure measurements it becomes more difficult to link the reported symptoms to the presence of neurotoxic agents on aircraft.

EXPOSURE ASSESSMENT

From an Industrial hygiene point of view direct personal exposure measurement is the most preferred method and most useful. Biological monitoring is also very useful but requires that the agents of interest are known along with their metabolites which should be succinctly different to eliminate other non work related exposures. Without actual measurements under upset conditions in the aircraft this information is only available from extrapolation using laboratory simulations. Direct measurements under upset conditions are difficult to obtain primarily due to the relatively low frequency and unpredictability of them occurring. In order to capture these infrequent exposure events one would require large numbers of identical equipment to be placed on board of many aircraft to be activated during an upset event when it does happen to occur. It is therefore not surprising that the aviation industry is reluctant to participate in such a study, specifically since current equipment would be too awkward and intrusive during normal day to day operation, might interfere with other equipment and would require a trained technician to be present to operate it properly.

Since direct exposure measurements are not realistic at this time, one could ask the question whether there are indicators on board of aircraft that can provide some insight into the quality and nature of the contaminants that might be present in the air.

One obvious source of this information is found in an analysis of the air filters that filter the air from the cabin before it is recirculated back, and mixed with a certain percentage of fresh air, into the cabin. Any contaminant that is present in these filters has been captured from the air to which passengers and crew members have been exposed.

Another source of information regarding the quality of bleed air is an analysis of the coalescer bags. These textile bags are present between the source of bleed air and before the air enters the cabin as fresh air. These bags are present to remove excess water from this air source. Since they also seem to filter the air to some degree an analysis of these bags will provide information as to what contaminants are present in the bleed air. They do not provide information regarding exposure as one could argue that, since they are located prior to the air entering the cabin, they are effective in cleaning the air, hence no exposure.

One additional indicator of exposure that provides useful information is an analysis of the uniforms that are used by crew members. The presence of

contaminants would be an indicator of surface and/or air contamination. The results could also be an indicator of dermal exposure.

The results from GC-MS analysis of a number of items from various locations in aircraft are summarised in Table 3 below.

Table 3: Results from GC-MS Analysis from Various Locations in the Aircraft Environment

Aircraft	Type of analysis	TCP presence	Comment
B-757	Flight deck roof filter	Positive	
B-737	Lavatory filter	Negative	Positive for cocaine and amphetamine
B-757	Prefilters from re-circ air	Positive	
B-757	HEPA filter analysis	Positive	930 micrograms TCP/filter (total area 4.5 m^2)
B-757	Forward lavatory ceiling filter	Positive	
BAe 146	Flight deck walls near side vent	Positive	
BAe 146	Analysis of a pilot's trousers	Positive	0.17 micrograms/pair of trousers

Aside from the presence of recreational drugs in one of the lavatories, other agents found on filters, among many others were Tripropyl phosphate (Fyrol), Triphenyl phosphate (fire proofing agent), Phthalate esters (plasticizers), Brominated compounds (fire retardants).

Some of these are potential synergists with the exposure effects of TCPs, although to what extent needs to be validated.

The data summarized in Table 3 above clearly illustrates that TCP isomers air present in the air that passengers and crew members breathe. These data show the presence and exposure to TCPs and other agents but do not tell us to what extent. In order to address this question one needs to measure the level of exposure during an actual incident.

As mentioned before current available instrumentation is rather bulky, consisting of a personal sampling pump, along with a Tygon™ tube that has to be connected to a cassette that houses a filter. In order to take an air sample the Tygon™ tube has to be connected to the filter cassette from which two stoppers have to be removed and replaced after exposure. Although not complicated for a technician, it is not recommended for crew members such as a flight attendants or pilots. This is specifically true during upset conditions when other things demand priority. Since the frequency of these events are relatively low and unpredictable, requiring the presence of a large number of technicians is also equally unrealistic.

In appreciation of these problems this author has designed and manufactured a very simple self contained air sampling pump which is a small plastic cylinder two inches in diameter and three inches tall which easily fits into a purse, briefcase, or a pocket. The unit contains a battery powered sampling pump and accommodates a standard preassembled 37 mm cassette filter that is totally enclosed. With a 45° twist of the cap of the cylinder, the system is

activated and the filter is exposed to outside air that is pulled through the filter at flow rates between 1-3 liters of air per minute for 20 to 30 minutes, depending on the type of filter and the batteries present. A reverse twist of the cap will isolate the filter from outside air and stops the pump. The whole assembly is small enough to be conveniently sent by mail to the laboratory for analysis and reassembly.

This device has now been patented and is referred to as the VN sampler (see Figure 1).[†]

Figure 1: The VN Sampler

In addition the cost of each unit is small enough to allow many of these air samplers to be provided to pilots and flight attendants to be activated when needed.

Although an analysis of these filters will provide some direct evidence of what contaminants might be present in the air at the time of activation it does not address the question of the acute exposures to toxic gases such as CO.

Information of CO levels during flight are essential as they can provide clues to potential oil seal failure before these result in to a serious air quality incident. Monitoring for CO by one flight attendant during a number of flights showed elevated, but "acceptable" levels of CO many days before an oil seal failure was detected in the APU. In addition since many aircraft are now outfitted with activated carbon filters the passengers and crew are deprived of an early warning system, that is, the presence of a burning smell or smoke that alerts them of a pending problem. Since CO is not captured by these filters, in flight CO monitoring is essential and, in fact, is one of the

[†] Self Contained Personal Air Sampling System, US Patent 6945127, issued, 20 September 2005, US Patent and Trademark Office.

recommendations of the 2002 NRC Committee.[3] Based on these recommendations, a number of pilots have been monitoring CO during a number of flights. Depending on the type of aircraft, different levels of CO have been reported. In many of these observations no odours or fumes are present. The highest level reported to date was by one pilot, operating a BAe 146, who measured CO levels as high as 60 ppm at the top of climb.

Since the air samplers described above are capable of capturing agents that can have a more chronic effect such as TCPs, it would be highly useful if they could also be used to assess acute hazards such as CO. For this reason a small data logging CO monitor has been developed which is incorporated into the VN sampler, and now referred to as the VN^{+CO} sampler. This CO component although incorporated into the sampler is totally independent from the sampler itself and provides a LED incremental bar readout of current levels. The LED readout was chosen based on pilot's input as they would have problems reading a LCD screen at nighttime. Seriously elevated CO levels during flight could also provide a trigger to activate the sampler. After activation of the sampling pump and return to the lab the CO memory can be downloaded to provide an accurate history of the CO levels previous to, and during, the last flight when the sampling pump was activated.

It is interesting to note that when the author of this article was member of the NRC committee, he argued strongly for a number of recommendations including CO monitoring, which did form part of the final recommendations. He also made two other suggestions:

1 That the level of pressurization in the aircraft should be changed from an 8000 feet equivalent altitude to 6000 feet in order to avoid hypoxia in individuals who have a compromised respiratory system; and

2 That a large number of the current bleed air problems could be entirely by-passed by not using a bleed air system to pressurize the cabin. In the past ram air from outside the aircraft was used.[26] For economical reasons this was abandoned in favor of the current bleed air system. Some experts on the committee strongly opposed this idea as they claimed "it could not be done".

It was therefore extremely gratifying to learn since then that the new Boeing 787, initially referred to as 7E7 is, also for economical reasons, not using bleed air to pressurize the cabin, in addition it will pressurize the cabin to an equivalent altitude of 6000 feet.[27] This was made possible with the use of composites for the construction of the fuselage, rather than the usual aluminum alloys, preventing the problems of metal fatigue that go along with the pressurization-depressurization cycles to which an aircraft is subjected.

Although the B-787 is proposed to become available in 2008, it does not solve the current problem of a large fleet of aircraft that is totally dependent on bleed air system technology in order to supply air to, and pressurize, the cabin. For this reason it is essential that close attention is paid to the potential

exposures that are the result of bleed air contamination and put into place an effective surveillance system that protects pilots, flight attendants and passengers from injury.

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ADAPTATION OF NEAR REAL TIME BIOSENSOR SYSTEMS FOR MONITORING OF CABIN AIR QUALITY

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Keywords: Surface plasmon resonance, tricresyl phosphate, biosensors, Surface Plasmon Resonance (SPR)

ABSTRACT

Recent conferences and reports have focused attention on problems of cabin air quality. One major concern of in-flight cabin air quality is the presence of toxic organophosphorus (OP) compounds when jet aircraft engine seals fail. Tri-ortho-cresyl phosphate (TOCP), a neurotoxic OP, is of particular interest. The intentional release of chemical or biological agents by terrorists is another concern. One means of addressing these concerns is to monitor cabin air in near-real time. Biosensors based on Surface Plasmon Resonance (SPR) have the capability of providing this technology. Classes of molecules that are important to detect range from small organics such as TOCP to toxic proteins such as Ricin and *botulinum* toxin and larger analytes including viruses, spores and whole microbes. We have recently developed portable SPR sensor systems capable of simultaneous detection of 6 or 24 different target analytes. To illustrate the capability of the systems for detection of small molecules like TOCP, we demonstrate detection of the small molecular weight stress hormone cortisol. We also demonstrate detection of other analyte classes that may be of interest for airborne detection of bioterrorism agents. Ricin A-chain provides an example of monitoring for toxic proteins while influenza virus and the bacterium *Francisella tularensis* provide examples of monitoring for larger analytes.

INTRODUCTION

Tricresyl phosphate (TCP), is a common lubrication component used in jet oil. Ortho-isomers of TCP have been known for many years to cause OP-induced delayed neurotoxicity (OPIDN) in humans and experimental animals.[1] Commercially available products are estimated to contain 3% TCP and 0.1-1% of the TCP is estimated to be tri-ortho-cresyl phosphate (TOCP) (0.003-0.03 % of the total). Other *ortho*-cresyl isomers in jet lubricants also have toxic potential.[2] In hydraulic fluid the ortho isomer can be as high as 1%.[3]

The consequences of TCP exposure have been known for some time. One massive incidence of TOCP poisoning occurred during the prohibition era when an ailment known as Jamaican Ginger Paralysis afflicted tens of thousands of people. The cause of this ailment was eventually attributed to consumption of a Jamaican ginger extract adulterated with TOCP, and in many cases caused irreversible neurological damage.[4] Studies of the effects of long term inhalation have been performed with experimental animals. In chickens neurotoxic signs developed after 60 days of exposure with TCP (containing 1.5% TOCP) at atmospheric concentrations as low as 23 mg/m^3.[5] Based upon data from the hen and cat, estimated human safe exposure rates for skin TOCP are estimated to be 2.5 mg/kg for a single dose, and 0.13 mg/kg/day for repetitive exposures.[1] Thus, leaks of TOCP into cabin air are of great concern, and near-real time monitoring will provide a valuable resource for detection of either equipment malfunction or intentional release of toxic chemicals or organisms in the aircraft cabin and allow procedures to be implemented to minimize exposures or treat individuals to prevent or minimize the consequences of exposure.

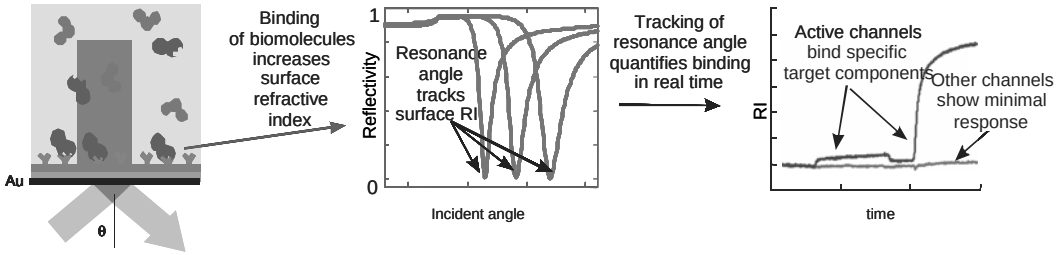
Air quality on airplanes remains an important issue.[6] In 2002 the US National Research Council published a report entitled *The Airliner Cabin Environment and the Health of Passengers and Crew* to address the problems in air cabin quality and monitoring. Along with identifying many of the potential problems, the report also outlined a number of suggestions for the monitoring and analysis of air quality incidents in aircraft. The report suggested a comprehensive approach to monitoring cabin air quality. Included in its recommendations was an integrated sampling system to monitor cabin air for particulate matter (PM) and carbon monoxide (CO) in "problem" aircraft with a history of oil leaks. The report suggested sampling airborne particles and determining the chemical composition of oil leaks.[7] To minimize or avoid exposure, analyses need to be near real time. Analyzing samples post flight does not allow for any corrective measures to be implemented for minimizing exposure or treating exposed individuals in a timely manner. Surface plasmon resonance (SPR) based sensing technology is capable of providing integrated, near real time analysis.[8]

In addition to monitoring TCP, SPR can also be used for the monitoring of many other analytes that may be found circulating in airplane cabin air. Analytes of particular concern include agents of chemical and biological

terrorism. The releases of Sarin in Japan point out the importance of developing the capabilities for rapid monitoring and identification of toxic chemicals that may be intentionally released into the environment.[9,10] Toxic proteins, viruses, spores and microbes are also agents for which near-real time monitoring capabilities need to be implemented.

SPR technology is a well-established method for detection of biological binding events.[11] The Kretschmann configuration for SPR detection is illustrated in Figure 1.

Figure 1: The Surface Plasmon Resonance Sensing Principle



Polarized light shined against the gold surface of a prism is reflected, depending on the angle of incidence. The reflection reaches a minimum at a specific incident angle, depending on the refractive index of the solution on the opposite side of the 50 nM gold coating. The system software converts the shift in minimum to refractive index as a function of time.

One surface of a prism is coated with a thin (50 nm) layer of gold. Monochromatic light (= 830 nm in the Spreeta™ sensor element) travels through the prism and strikes the backside of the gold-coated surface at a range of angles greater than the critical angle. For a certain angle of incidence, much of the illumination energy will be absorbed in a surface plasmon wave traveling along the gold surface. This resonance angle strongly depends upon the refractive index (RI) of the material immediately adjacent to the gold surface. Measurement of this angle provides a sensitive measurement of refractive index near the surface. Because biological substances (for example, proteins, RI ~1.5) have a much higher RI than water (RI 1.33), small quantities of analytes bound to specificity elements immobilized on the sensor surface can be detected and quantified in near real time. To render the sensor specific for a particular biological analyte, the surface is modified with specific receptor elements (e.g., antibodies) such that the sensor surface binds only the selected analyte and not other substances.

We previously reported the adaption of SPR sensors for use on an aircraft. An earlier version of the 6-channel SPR biosensor system was modified for airborne detection. The system was tested in a VariViggen delta-wing aircraft.[12] The nose of the aircraft was fitted with nozzles for release of mists containing either ovalbumin or horseradish peroxidase as protein simulants of toxic proteins. During one ground test and three flight tests, we were able to demonstrate airborne sample collection, analyte detection, as well as amplification and verification of the initial signals. Analyte concentrations varied from 1 to 10 nM and the altitude at which the detection was performed varied from 1,800 feet to 10,000 feet. These airborne tests illustrated the

usefulness of the portable SPR system for airborne collection and detection of analytes.

Small molecules like TCP/TOCP are difficult to detect directly using SPR because they cause only minor changes in the refractive index on the gold sensor surface compared with proteins and whole microbes, for example. Detection of small molecules can be accomplished however, using competition or displacement assays. In a displacement assay, antibodies bound to analytes immobilized on the sensor surface are displaced from the sensor surface at a rate proportional to the concentration of free analyte. In a competition assay, anti-analyte antibodies with are prevented from binding to analyte immobilized on the sensor surface by free target analyte in the sample analysis stream. Higher concentrations of analytes cause larger decreases in rates of antibody binding. As early as 1993, atrazine was detected using an early SPR-based gold-film assay with an atrazine derivative bound to the gold film, and monoclonal antibody in solution. The monoclonal antibodies were successfully competed from binding to the gold film in the presence of atrazine.[13] Other examples of detection by competition assays include the organophosphorus insecticide fenitrothion,[14] thyroxine,[15] and estradiol.[16] Pharmaceutical drug interactions with proteins,[17] lipids,[18] and DNA targets[19] have also been examined using SPR. Detection of small molecules has also been reported using conformational changes of proteins generated by small molecules.[20]

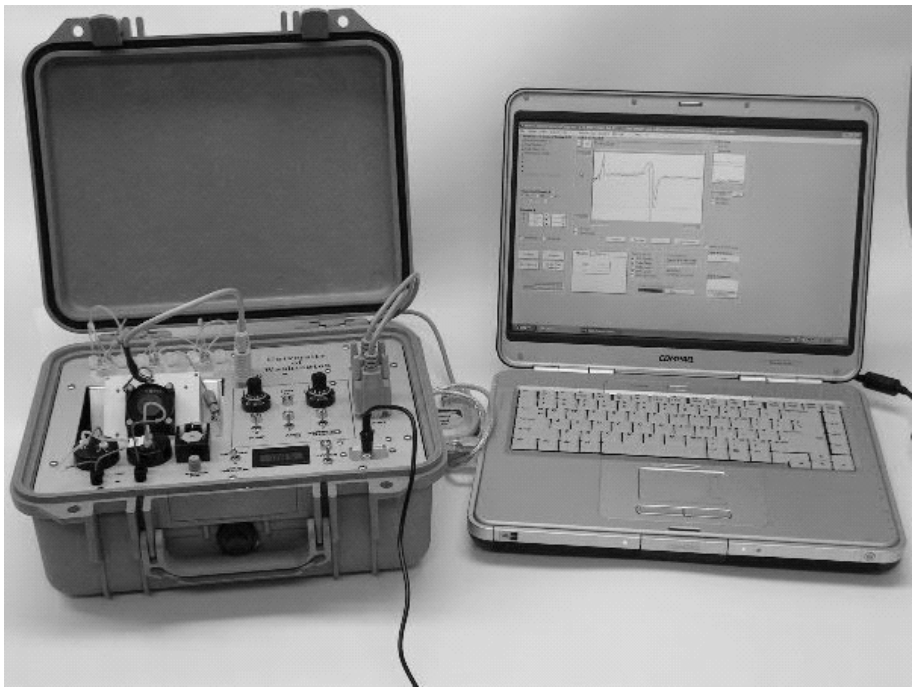
MATERIALS AND METHODS

The SPIRIT biosensor system

The 6-channel SPR sensing system dubbed SPIRIT (Surface Plasmon Instrumentation for the Rapid Identification of Toxins) (see Figure 2) was used for the experiments described here.

The 6-channel SPIRIT system contains two 3-channel Spreeta™ 2000 sensor elements, fluidic and electronic components, including a thermoelectric temperature control system that maintains temperature within ± 0.01°C of the set temperature. The current laboratory prototype contains integrated fluidics designed for analysis of liquid samples injected into a chromatography-like system sample port.

Figure 2: The 6-Channel SPR SPIRIT Biosensor

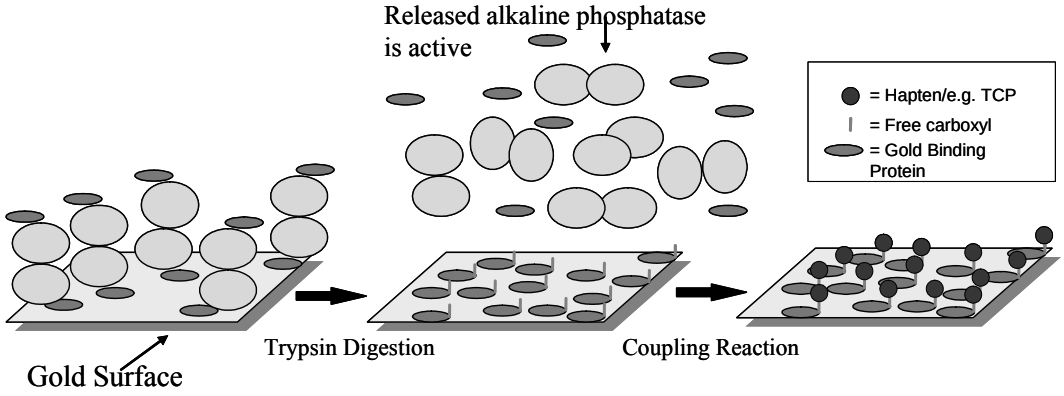


When connected to a laptop computer, this lunchbox-sized instrument contains all of the equipment necessary to perform sensitive biochemical analyses of solutions suspected to contain toxic materials. The instrument can screen solutions for up to 6 different biological or chemical toxins simultaneously, and its low power consumption allows portable operation.

Surface Plasmon Resonance Sensor Functionalization

SPR biosensors require the gold surface to be coated with highly specific antibodies or other specific recognition element such as a receptor molecule.[21] Texas Instruments Spreeta™ 2000 sensor chips were functionalized for protein or large analyte detection using the method described in Naimushin et al,[12] and as depicted in Figure 3.

Figure 3: Preparing the Sensor Surface



GBP fused to alkaline phosphatase is bound to the gold sensor surface. Following binding, a brief trypsin treatment cleaves the trypsin domain form the bound GBP domain. Anti-analyte antibodies or analyte are then attached to the gold surface.

Briefly, after washing the sensors with ethanol, a foundation layer of gold binding peptide (GBP)[22] was laid down by incubating the sensor surface for 30 minutes with bacterial shock fluid containing GBP fused to alkaline phosphatase in PKT-50 (10 mM KH_2PO_4, 50 mM KCl, 1% Triton X-100, pH 7.0) followed by removal of the alkaline phosphatase by tryptic digestion with 100 µg/ml trypsin for 45 minutes at 23°C in trypsin buffer (10 mM Tris, 10 mM $CaCl_2$, pH 8.0 buffer). Trypsin was neutralized with a ten minute incubation in 100 µg/ml trypsin inhibitor, followed by washing the sensor surfaces in trypsin buffer. The GBP-alkaline phosphatase coating, trypsinization and trypsin inhibitor incubation were repeated to ensure maximal coverage of GBP on the sensor surface.

Antibodies for target analytes were covalently attached to the GBP foundation layer by activating the carboxyl groups on the GBP using standard EDC (1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide Hydrochloride), S-NHS (N-hydroxsulfo-succinimide) chemistry.[23,24] EDC (100 mg) from Pierce (Rockford, IL) and S-NHS (27.5 mg) from Fluka (Milwaukee, WI) were dissolved in 5 ml distilled water. Next, 200 µl of the EDC/S-NHS solution was used to cover the sensor surface for 30 min. The surface was then rinsed with double distilled water. Antibodies were coupled to the carboxyl-activated GBP foundation layer by adding 20 to 50 µl of 100 µg/ml of a thoroughly dialyzed antibody solutions in 100 mM MES pH 5.5 buffer to the sensor surface, coating all three channels of individual sensor elements with the same analyte. After 30 minutes, the sensor surface was rinsed with 10 mM Tris, pH 8.0 followed by phosphate buffered saline (PBS).

For small molecule detection, the gold surface was functionalized as outlined in Figure 3, or by coating the gold surface with a small target analyte covalently linked to a protein. For cortisol detection, cortisol linked to BSA was incubated directly on the clean gold surface at a concentration of 100 µg/ml for 30 minutes followed by washing with PBS. The BSA-conjugated cortisol was adsorbed directly onto the gold surface. For a reference sensor, 100 µg/ml BSA (unconjugated) was used.

Detection of Large Analytes

Direct detection of Ricin A-chain was carried out by covalently linking goat anti-Ricin antibody to the GBP surface as described above. At a flow rate of 25 µl/min., 50 nM Ricin A-chain in PBS was flowed over the sensors for 10 minutes. The Ricin A chain and Ricin antibody were kindly provided by Dr. James Whitehead.

For *Francisella tularensis* detection, surface functionalisation was carried out as described above using goat anti-*F tularensis* (ABE159, CRP Antibody Repository) covalently attached to the sensor surface. A PBS solution containing $1x10^5$ colony forming units of *F tularensis* (cfu)/ml was flowed over the sensors at a flow rate of 40 µl/min. During detection, 0.1% Tween-20 was added to all detection buffers. The Tween-20 helped eliminate non-specific binding to the reference sensor. In order to confirm detection of

Francisella tularensis, a monoclonal antibody (ABE183, CRP Antibody Repository) was used at a concentration of 30 µg/ml for amplification and verification of detection.

For detection of influenza virus, surface functionalisation was performed as described above using a monoclonal antibody (MAb8256, Chemicon, Temecula, CA) specific for influenza A H1N1 covalently linked to the GBP foundation layer on the sensor surface. At the 5 minute time point, a buffer solution containing influenza A strain PR/8/34 and 0.1% casein was flowed over the sensor surface. To verify the observed detection, a solution containing 20 g/ml of MAb8253 (Chemicon) antibody and 0.1% casein was flowed over the gold surface at the 20 minute time point.

Detection of Small Molecular Weight Analytes

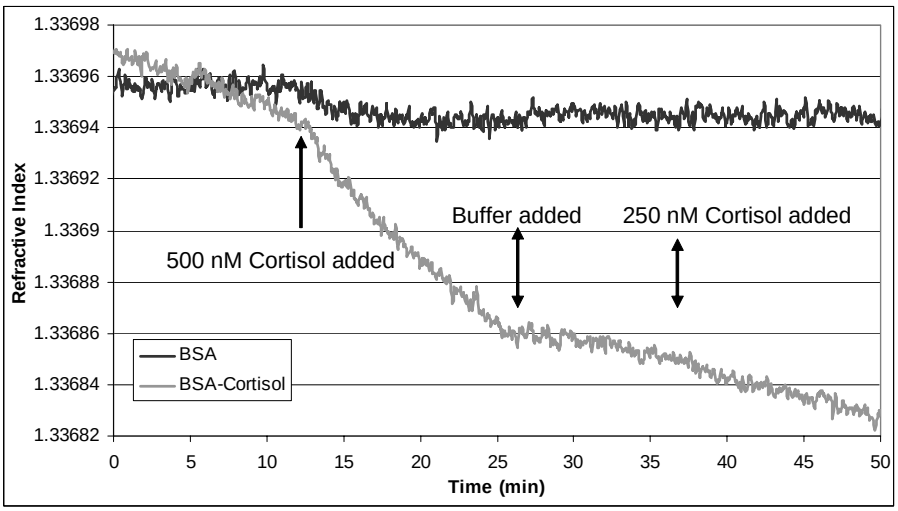
For cortisol detection, the sensor surface was derivatized with BSA-cortisol adsorbed to the gold sensor surface as described above. Buffer containing 10 µg/ml mouse anti-cortisol monoclonal antibody ab9367 (Abcam, Cambridge, UK) in PBS was flowed (25 µl/min) over the sensors for 15 minutes to preload the sensor with antibody (not shown). After washing with PBS for 15 minutes, a solution of 500 nM cortisol was flowed over the sensor elements for 10 minutes followed by 7 minutes of buffer, then 10 minutes of 250 nM cortisol in buffer.

RESULTS AND DISCUSSION

Detection of Small Molecular Weight Analytes

Cortisol was used as a model small molecule to demonstrate the displacement assay. Cortisol (molecular weight 362 Da) a steroid hormone found in serum and saliva is an indicator of stress. Because the binding of small molecules does not cause a refractive index change as large as that caused by the binding of proteins or microbes, special displacement or competition assay protocols are used to increase sensitivity. For these assays, the target itself rather than analyte specific antibodies is immobilized on the sensor surface. For the displacement assay, antibodies specific for that target are then loaded onto the sensor surface. The surface-bound antibodies are then displaced by target molecules present in the analyzed sample. Antibody displacement is detected as a negative change in refractive index. The reference channel generally has a non-cross-reacting analyte immobilized on it. The normal levels of cortisol in human serum range from 2 to 30 µg/ml and are found to be elevated much above normal levels in stressed patients.[25] Rapid measurement of cortisol levels in patients can be an easy way to evaluate stress level. Figure 4 shows the rates of displacement of anti-cortisol antibodies by 500 nM cortisol and 250 nM cortisol. We have successfully detected cortisol at levels as low as 1 nM in PBS buffer using a competition assay (Stevens et al, unpublished).

Figure 4: Detection of Cortisol using the Displacement Assay

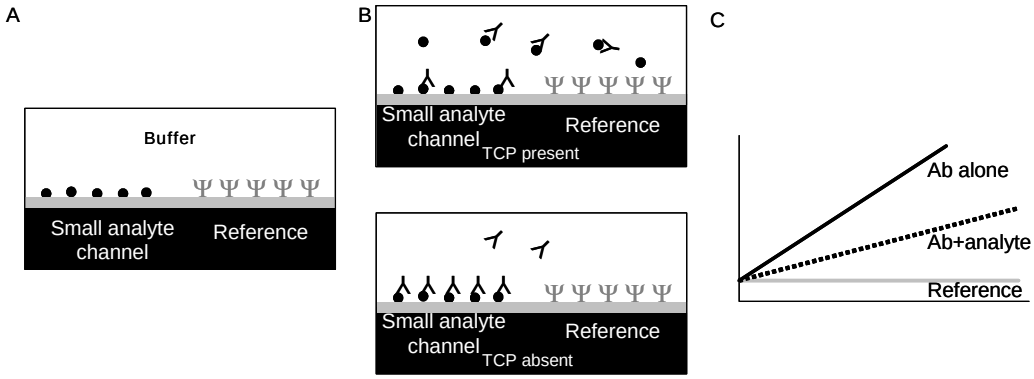


A positive detection in the cortisol displacement assay is characterized by a rate of decrease in refractive index over time that is proportional to the concentration of analyte for the BSA-cortisol sensor, but little or no change in the reference BSA sensor.

Detection of TCP will require the generation of anti-TCP antibodies. It should not be necessary to generate specific anti-TOCP antibodies since the main reason for monitoring is to determine when engine seals have failed and detection of TCP should be a good indicator of seal failure. The sensitivity required for detection will determine whether displacement or competition assays will need to be developed. Very high affinity monoclonal antibodies are the best reagents to use in competition assays, while antibodies with moderate affinities are most useful for displacement assays. The advantage of the displacement assay is that protocols can be developed that conserve antibodies and thus reduce the costs of analyses.

Competition assays can also be used for small analyte detection. An example of how the competition assay would work for TOCP detection is shown in Figure 5.

Figure 5: Detection of Small Analytes using Competition: Proposed System for TCP Detection



The sensor surface is coated with TCP-hapten or a reference protein (A). Next, a low concentration of antibody specific for TCP, which binds to the TCP-hapten channel, is flowed over the surface either in the presence or absence of TCP (B). When samples containing TCP

are flowed over the surface, the TCP antibody binds at a lower rate causing a reduction in the slope of the TCP channel signal when compared to binding in the absence of TCP (C).

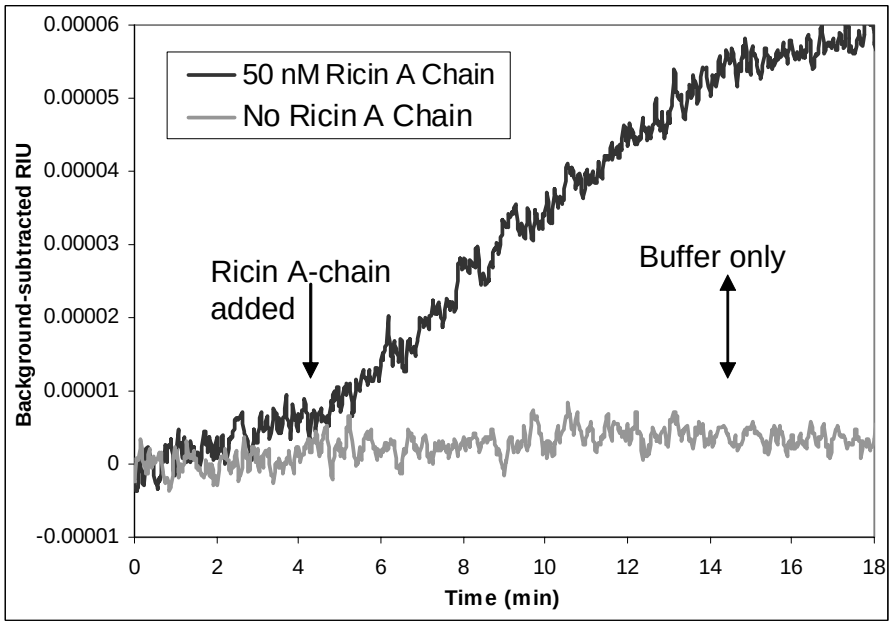
A low concentration of high affinity antibody is exposed to the sensor surface and allowed to bind to the immobilized target until the rate of binding can be calculated. Antibody is then mixed with sample and allowed to flow over the sensor. The reduction in binding rate indicates the presence of analyte in the sample. The rate of antibody binding to the surface is decreased in proportion to the concentration of free target present in the analyzed sample. Samples of known concentration can be run in the laboratory to standardize the sensor system. It is only necessary to run the analysis long enough to establish a rate of binding. Thus, several analyses can be determined from each binding isotherm before the surface is saturated with antibody. Because very dilute concentrations of antibody are needed for the competition assay, antibody reagent sufficient for many sensing cycles may be stored and used for weeks or months.

Verification of detection with secondary antibodies will most likely not be possible due to the small size of the analyte. The best approach for verification of the presence of analyte will be to have different anti-TCP antibodies attached to different channels.

Detection of Toxic Proteins

Ricin A-chain was used as an analyte to demonstrate direct detection of toxic proteins. Ricin is a toxic protein extracted from castor beans listed as a category B bioterrorism agent/disease by the Center for Disease Control. The Ricin A-chain was used as a less-toxic model for Ricin. Ricin A-chain was easily detected at levels as low as 50 nM using a goat anti-Ricin antibody covalently linked to the sensor surface (see Figure 6).

Figure 6: Direct Detection of Ricin A-Chain



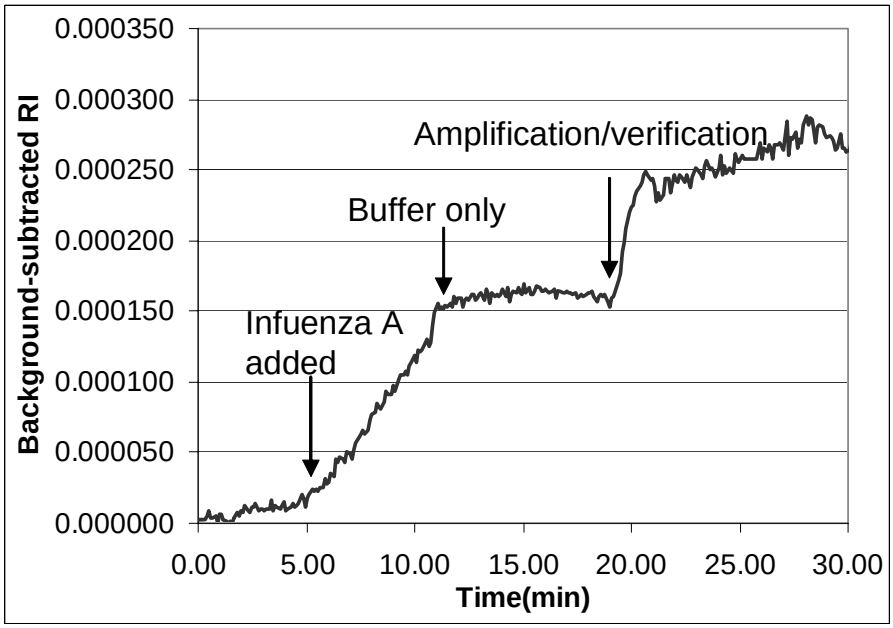
Antibodies raised against Ricin A-chain were covalently linked to the gold surface and either 50 nM Ricin A-chain or buffer was flowed over the sensor for 10 minutes.

Using three steps of amplification, we have previously reported the detection of femtomolar levels of the protein toxin *Staphylococcus* enterotoxin B.[26]

Detection of Virus

Influenza A (H1N1) virus was used as a model to demonstrate viral detection with the SPIRIT system (see Figure 7).

Figure 7: Detection of Influenza A with Amplification/Verification



Monoclonal antibodies (MAb8256) raised against the H1N1 influenza A PR8 strain were covalently linked to the gold surface with antibodies against an H3 strain linked to the

reference sensor. Influenza A strain PR8 viruses were flowed over the sensors followed by a wash step. Next, secondary antibodies (MAb8253) against the PR8 strain were flowed over the sensors to amplify and verify the detection. Reference sensor data values were subtracted from the detection sensor signal.

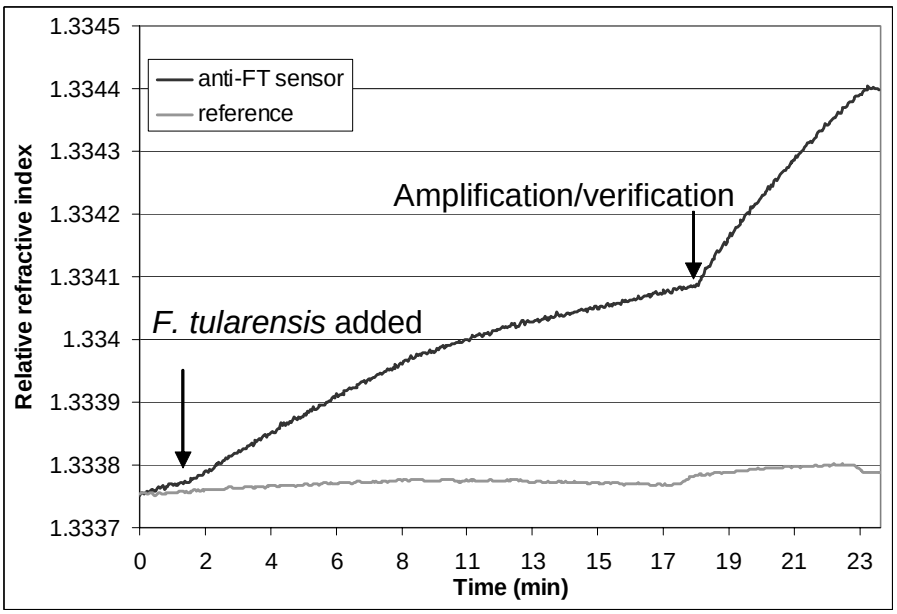
Influenza A is an enveloped virus responsible for worldwide pandemics. One monoclonal antibody (MAb8256) was immobilized to the sensor surface and used to capture the virus particles and a second monoclonal antibody (MAb8253) was used to verify detection as well as amplify the signal. Again, verification and amplification was carried out with a second antibody with specificity to the target analyte.

The use of in-line concentrators can be used to increase the levels of sensitivity of collector/detector systems. It is important to note that the secondary antibodies can also be used to speciate target analytes. For example, a generic antibody to a genus can be used as the capture antibody followed by pulses of species specific antibodies to verify and speciate the bound target(s) species.

Detection of Infections Microbes

Francisella tularensis, the causative agent of tularemia, is a gram negative, facultative intracellular coccobacillus. The bacterium is characterized as "very infectious" by the CDC since only 10-50 cells are needed to cause the disease, whose clinical manifestations include a "sudden fever, chills, headaches, diarrhea, muscle aches, joint pain, dry cough and progressive weakness" (source: http://www.bt.cdc.gov/agent/tularemia/facts.asp). Currently, tularemia and *F tularensis* are characterized as type A bioterrorism agents/diseases by the CDC. *F tularensis* was easily detected at levels of $1x10^5$ cfu/ml (see Figure 8).

Figure 8: Direct Detection of F tularensis Cells Followed by Amplification/ Verification



Goat antibodies against *F tularensis* were covalently linked to the sensor surface, with antibodies against *botulinum* A on the reference sensor surface. Bacterial cells at a concentration of $1x10^5$ cfu/ml were flowed over the sensors. To amplify and verify the detection, monoclonal antibodies (ABE183) against *F tularensis* were then flowed over the sensors.

Verification and amplification were achieved with secondary antibodies. As noted for detection of viruses, generic antibodies can be used to bind members of a given genus, followed by pulses of secondary antibodies to amplify and speciate the bound target(s).

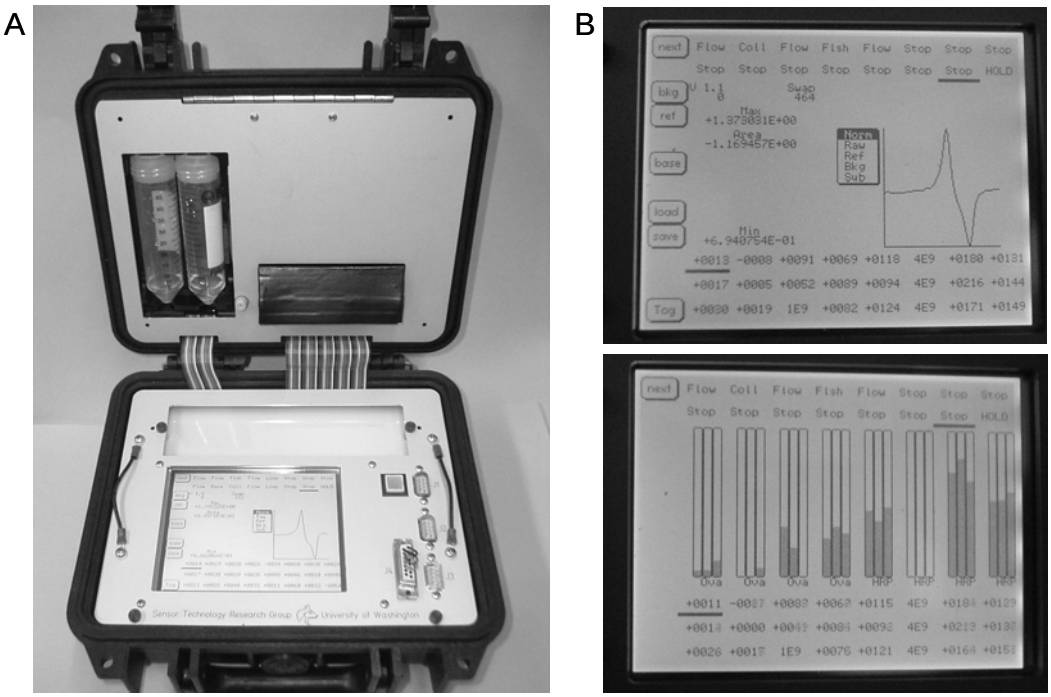
Evolution of the SPIRIT system

The first 6-channel SPIRIT system used for the experiments described here was designed for near-real time detection of chemical and biological substances (up to 6 different types simultaneously), including whole bacteria, viruses, proteins, and small molecules. In this instrument, SPR is observed using Texas Instruments' Spreeta™ 2000 sensing chips developed by TI in collaboration with our UW team.[27] The SPREETA SPR sensor element consists of a plastic prism molded onto a small printed circuit board (PCB) containing LEDs and a diode array detector. The SPIRIT biosensor system is built around the SPREETA sensor elements and measures biomolecular binding to the surface of the Spreeta™ chips at six separate immobilized antibody strips (three on each of two Spreeta™ chips). Each strip is coated with chemistry specific for a particular analyte. The current SPR systems are equipped with sample injection ports, however, with minor modifications and the addition of a commercially available or custom built sample collector, the SPIRIT can be transformed into a fully automated device. The system weighs just eight pounds and occupies less than 1.0 cu ft of space (see Figure 2). The SPR sensor may be connected to sample collectors as well as in-line concentrators for detection of analytes in water or air samples. We have used a

commercially available (SAS 2000™, Research International, Monroe, WA) air sampler to demonstrate mist collection integrated to the 6-channel SPR biosensor.[12] Cabin air monitoring will require the use of a collector to deliver airborne analytes to the SPR sensor for detection.

The most current version of the SPIRIT system is a 24-channel SPR biosensor with fully integrated signal processing software with no external laptop computer required (shown in Figure 9).

Figure 9: The Next Generation SPIRIT Biosensor



Our working version of the SPIRIT system is a 24-channel, fully-automated biosensor system with integrated data processing and touch-screen interface.

This system is capable of automated fluidics control and delivery as well as automated detection and signal analysis. The 24-channel SPIRIT has a simple touch-screen interface but will also be capable of fully automated stand-alone monitoring.

The SPR detection hardware and chemistries have several advantages over other detection techniques. SPR is unique in that for many implementations, it requires no special labeling chemistry. Detections can be performed directly, without addition of reagents, so continuous operation is possible. Any type of analyte for which an appropriate receptor is available can be detected – detection can be extended to most classes of analytes, unlike nucleic acid-based PCR which requires the presence of nucleic acid. The SPR surface is conducive to regeneration without damaging the antibodies or other surface elements allowing for many repetitions of detection and prolonged use.

CONCLUSION

In summary, we have described the detection of cortisol as an example of small molecule detection via SPR sensor technology, Ricin A-chain as an example of a toxic protein analyte, flu virus and *F tularensis* as examples of detection of infectious agents. The use of secondary antibodies for simultaneous amplification of analyte detection signal and verification of analyte presence provide important enhancements to the SPR detection technology. It is critical to avoid false positive signals. The use of different antibodies with specificity to the same analyte makes a major contribution to reducing false positive signals. The ability to amplify the detection of small quantities of analytes helps to avoid the generation of false negative analyses. The use of generic capture followed by pulsed secondary antibodies provides the capacity to detect and speciate target analytes.

The systems that we are developing are well suited for coupling to continuous collector systems for providing near-real time monitoring in the aircraft cabin environment. As shown, these systems are capable of monitoring small as well as large analytes. Our aim is to make the systems simple and inexpensive to operate.

Near real time detection of toxic chemicals and pathogenic organisms is necessary to minimize exposure and arrange for immediate treatment of exposed individuals. The data presented here and in earlier publications by our research group[12] and others[28] demonstrate the potential for this type of system for monitoring cabin air quality. Also, with the current threats of chemical and biological terrorism, increased security onboard airplanes during flight is essential. Rapid analysis of chemicals such as TCP and biological toxins such as Ricin or botulinum toxin and whole organisms will identify exposures and provide information necessary for minimizing the exposure and treating exposed individuals.

ACKNOWLEDGEMENTS

This work was supported by the following grants: NA16RG1044 from Washington State Sea Grant; a grant from UW Center for Process Analytical Chemistry; NIH Grant 1-UO1DE14971-01, NIH P50 ESO12762/NSF OCE-0434087; Army Office of Research Grant DAAD 13-03-C-0024 and FDA grant FD-U-002250.

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From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 271-273.

ACTIVATED CARBON FIBERS APPLIED TO AIR TREATMENT

Pascal Contini
Sofrance-Safran Group

BIOGRAPHICAL SKETCH

Pascal Contini started his career as a mechanical engineer in the automotive industry. He was employed in a laboratory specialised in engines and components testing. He joined Sofrance in 1990 to create the test laboratory service. At the head of this service during several years, he had the opportunity to direct successively a design office and a research department. He is, now, in charge of the air treatment expertise.

CABIN AIR FILTRATION

High Efficiency Particulate Air Filters (HEPA) provides effective protection against particulate matter and micro-organisms.

These filters offer efficiency greater than 99.97% for 0.3 µm particles. This technology is currently used in most of recent aircraft.

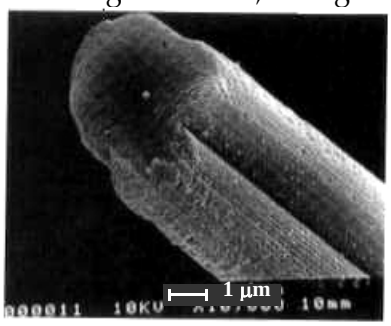
As an option, adsorption device, using activated carbon, can be associated to these particulate filters. The option allows capturing gases up to the saturation level of the carbon with efficiency depending on the activated carbon type.

Cabin air recirculation filter

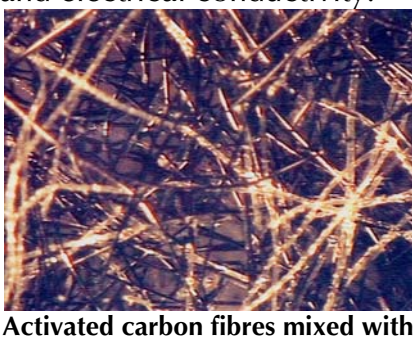
Activated carbon fibres

Activated carbon can be produced in different forms (grains, beads, fibres).

Activated carbon fibres provide high efficiency on odours and on volatile organic compounds (VOC). The main advantages of the fibres are: A large contact surface area, a microporous structure, the possibility to mix them with synthetic or glass fibres, and good thermal and electrical conductivity.



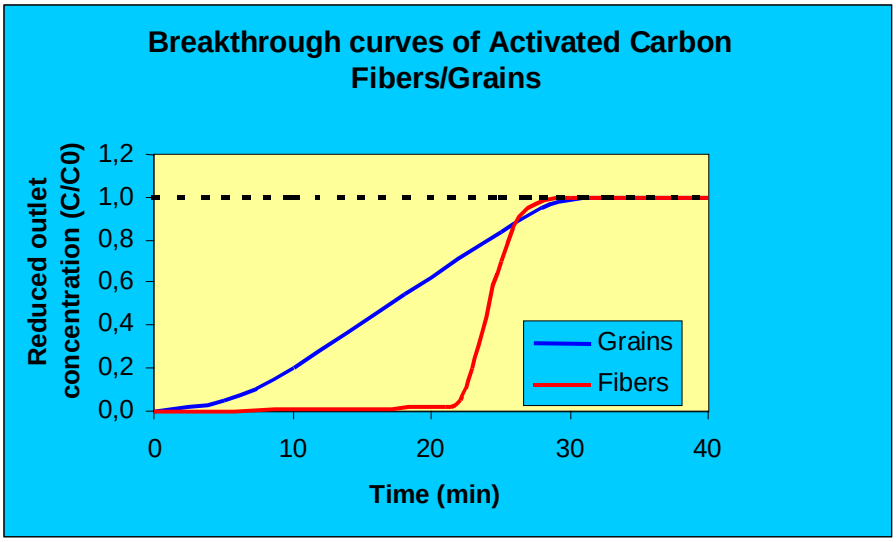
Activated carbon fibre



Activated carbon fibres mixed with synthetic fibres

The advantages of the fibres can be seen in Figure 1 below. The breakthrough curve for fibres has a flatter profile for a longer time than one from grains. It means that the efficiency will stay at a very high level during a long time.

Figure 1: Typical breakthrough curve of activated carbon (fibers or grains)



Cabin air recirculation filter with activated carbon fibres media

HEPA filtration and activated carbon fibers technologies can be combined on a unique filtration device, offering a global solution for particles, micro-organisms and gases protection.

Bleed air filtration

Everywhere when bleed air is used and where protection is required, solutions can be developed to remove particulate matter, liquid or gases from air flows.

For example, activated carbon fibres can be used in a cloth form. This configuration gives very good thermal and electrical conductivity which

enhance the safety characteristics of the filter. With no hot point and no electrical charge on the filter any potential fire or explosion hazards are avoided.

This filter has been designed to protect a fuel tank from particulate contamination and to protect passengers against jet fuel vapour.

The activated carbon fibres are used here in the form of a cloth and the electrical connection to the earth is realised via a pin.

This configuration avoids any fire or electrical discharge problems

Breather combined filter

Adsorption on activated carbon is a reversible phenomenon. With heat or vacuum, the activated carbon can be regenerated. This characteristic can be used for continuous operation system. Such system uses two filters in parallel. While one filter is in use, the other one is regenerating.

This system can be a Pressure Swing Adsorption System (PSA) when the regeneration is achieved with pressure difference - or a Temperature Swing Adsorption System (TSA) when the regeneration is obtained with a temperature difference.

CONCLUSION

There are many potential solutions for the air treatment, including VOC removal.

Among these solutions, activated carbon fibers offer interesting characteristics which lead to compact and very efficient solutions. They can be combined with particulate filtration and/or liquid separation.

For safety concerns, electrical and thermal conductivity properties are also a big advantage of activated carbon fibres.

From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 275-281.

ITF-ENDORSED ACTIONS TO ADDRESS CONTAMINATED AIRCRAFT AIR

Ingo Marowski
International Transport Workers' Federation (ITF)

BIOGRAPHICAL SKETCH

Ingo Marowsky started his union work as a shop steward in Lufthansa German Airlines. He held key union positions in its negotiating committee and repeatedly gained mandates as member of the works council, which he was president of from 1990 to 1993. He also was elected into the highest political mandate within the German system of Co-Determination, a union seat in the airline group's Board of Supervisors, overviewing the Executive Board's decisions and activities. He successfully completed academic education at Frankfurt University (Germany) and Harvard University (USA) in the period from 1993 to 1995. Currently holding the position of Aviation Secretary at the International Transport Workers Federation (ITF), he is responsible for liaising with international organisations and regulatory bodies, executing the Section's industrial policies, especially in multinational companies and groupings, and developing the Section's educational program. Ingo is currently living in London.

ABSTRACT

In response to the history of reports of ill health due to air supply contamination from its member unions, the ITF created the International Task Group on Aircraft Air Quality. A history of the task group will be described, along with two examples of ITF-endorsed actions that airlines and manufacturers can implement to significantly reduce the frequency and impact of supply air contamination.

INTRODUCTION

By means of introduction, the ITF represents five million transportation workers who collectively belong to 600 unions, employed in 140 countries. We advocate on issues that affect jobs, employment conditions, and safety and health, and the safety and health hazard that I'm here to talk about today, of course, is contaminated aircraft air.

The fact that all of us are here is a tribute to that fact that, by now, it is difficult to dispute that crew and passengers can be exposed to airborne toxins via the air supply system. Everyone here is aware of this potential, and while there may be some debate over frequency and health impact, this issue is clearly recognized in the scientific community.

THE ITF TASK GROUP ON AIRCRAFT AIR QUALITY

I'm going to tell you about the ITF task group on aircraft air quality - why it was formed and what it does, I'm going to then describe some of the highlights on this issue over the past five years to put our task group activity in context. Finally, I'll describe two recommendations that have emerged from the experience of our task group members, recommendation that the ITF considers vital to making progress on this issue.

First though, I want to make it clear that contaminated bleed air is not simply an issue of academic interest, it is a serious public and worker health hazard that has had a tremendous impact on the lives of those affected. I invite you then, to put yourself in the position of someone who has been exposed to these airborne toxins: you develop chronic neurological problems, but have no recourse with your employer; you have no evidence of what you were exposed to, no right to access the evidence from the airline to support your case, and so in all likelihood, your claim for work-related compensation is denied; you will be very lucky if your doctor has heard of it and they may well just prescribe valium or antibiotics; if you live in the States, you can be sure that your employer will recommend that you find a lawyer, but you can't afford to pay for it; depending on the severity of your case, you may be unable to work; and if you are a pilot, you may lose your license. All this for something that the ITF has deemed both provable and preventable. This is why the ITF got involved.

In June 1999, our ITF air quality task group held its first meetings. This task group was formed in response to reports from our member unions around the world of crewmember illness. Illness that followed exposure to mist, fumes, smoke, or distinctive odors that came from the air supply systems, especially during particular phases of flight.

Most of the documented reports date from 1989 onwards, perhaps explained by the smoking ban implemented on selected flights the year prior and spread from there. That is, cigarette smoke could mask incident-related fumes and mists, so although crewmembers would not have been less likely to get sick, they would have been less likely to make the connection. Also, even in 1999, some members of our ITF task group were surprised by the interest in these events, having come to accept them as a “normal“ part of their work environment, assuming they could still work.

Over the years, we've got reports that describe odors as “toxic“, “unusual“, or “chemical.“ Others describe a strong smell of dirty socks and would try to find the offending passenger or pilot who had taken their shoes off. The dirty sock odor was later identified as carboxylic acids, originating largely from thermal decomposition of engine oil.

The symptoms that ITF members described were (and are) diverse, but remarkably similar between airlines and countries. Typical symptoms during a flight are severe headache, stomach cramping, dizziness, and impaired

judgment. In some cases, crew report chronic disorders such as muscle weakness, memory loss, numbness and tingling, tremors, and poor coordination.

Crewmember unions that got back door access to aircraft maintenance records were able to identify patterns that they shared with our task group. For example, some aircraft records indicated an unusually frequent pattern of topping up oil, later found to be necessary because a particular oil seal had failed, causing the excess oil to leak into the air supply system. A similar pattern emerged with the excessive addition of hydraulic fluid because one or more lines had ruptured.

Independent of leaky seals and ruptured lines, ITF maintenance workers have confirmed that refilling the reservoirs that hold oil or hydraulic fluid can also cause air supply contamination because some reservoirs are difficult to fill without overfilling or spilling fluids into adjacent systems.

Some aircraft types were more prevalent in these reports than others, but the events were not limited to just one or two aircraft types.

Those first meetings of our task group were more or less an exchange of information among worker representatives, a grass roots realization that the infrequent but persistent descriptions of these symptoms, that are consistent with exposure to carbon monoxide and neurotoxic agents, were being reported by crews in Canada, and they were the same as those being reported in the UK, as those in the US, as those in France, Australia, Mexico and so on. And while this realization was disconcerting, it was also empowering because crew at a given airline had been told that they were "the only ones", but it was becoming increasingly clear that they weren't the only ones. Rather, there was a common denominator that could be defined, and therefore, in the minds of the ITF, remedied.

In giving this history, I don't mean to imply that the phenomenon of bleed air contamination was or is anything new. There is evidence that the industry has been aware of this potential for more than 35 years, but certainly, in recent years, there has been a steady increase in publicly available documents and attention on the subject.

So, six years ago, the fact that these odors and fumes with their attendant health problems were being documented by crewmembers around the world, and moreover that there was specific information on how to fix these problems, was new to many of us sitting around that table at our first ITF task group meeting.

Since then, there has been a surge in available records and reports. Here are some highlights:

Starting with 1999 when we formed our task group, there was a documented and high profile incident that involved a series of BAe146 flights in Sweden. On the first two of three flights, cabin crew reported symptoms that included

fainting, “odd pressure in the head,“ and the “feeling of moonwalk.“ On the third flight, both the pilot and copilot were affected and had to don their oxygen masks. Prior to these flights, the airline had found a minor external oil leak in one of the engines, and a subsequent government investigation attributed the crew symptoms to “probably polluted air.”

In the year 2000, the Australian Senate Inquiry released its report as we heard from former Senator Woodley in his paper.

That same year, the US Congress funded a National Research Council committee to review potential problems with air quality on passenger aircraft. They too issued a series of recommendations, including an incident reporting system and a regulation for continuous air supply monitoring of carbon monoxide with emergency procedures.

That same year, here in the UK, the CAA issued a Flight Ops Department Communication noting that "there have been a number of recent incidents where, due to smoke or fumes entering the aircraft, both pilots of a multi-pilot aircraft have been affected to the extent that their ability to operate the aircraft may have been impaired…"

The CAA is right to raise awareness. In that December 2000 communication, it described the likelihood of multi-pilot incapacitation due to toxic fumes as remote but possible (after all, it had been reported). In response, the CAA suggested that airlines run pilot incapacitation drills and raise awareness among cabin crew.

Unfortunately, none of these procedures are required, just recommended. The CAA also suggests that "if it appears that both pilots are suffering from some form of incapacitation, or that one pilot appears to be in any way incapacitated for no obvious reason, then the flight crew should don oxygen masks without delay." The ITF agrees with the CAA that bleed air contamination can be an aviation safety issue, but we urge the CAA to take a stronger stand and regulate this issue to better ensure that flight safety is not compromised and to ensure that all contaminated air events are reported, because clearly this is not currently the case.

In 2001, British Aerospace issued yet another Inspection Service Bulletin for its 146 series aircraft, adding to over 200 existing service bulletins and service information leaflets related to the potential for cabin air contamination over the past 20 years. This time though, aviation regulators around the world adopted the oil contamination inspection procedures, presumably because of reported incidents involving impaired performance of flight crew. British Aerospace noted that "whilst investigations are being carried out, oil leaks and cabin flight deck smells must be regarded as a potential threat to flight safety, not just a nuisance."

In 2002, the CAA published more recommendations for pilot incapacitation procedures, citing a rise in the number of reported smoke/exposure events and four aircraft types with a "higher than normal history" of events, stating

that "CAA specialists believe that reducing occurrences of oil contamination will also reduce the risk of flight crew incapacitation."

The following year, the US Congress passed legislation to fund bleed air contamination research, and to develop an incident reporting system to systematically collect data on reported health effects.

Finally, in 2004, Exxon-Mobil was cited with a serious violation of the US Occupational Safety and Health Administration Health Hazard Communication Standard. Exxon-Mobil had inappropriately tried to remove requisite health hazard warnings from the label and Material Safety Data Bulletin of one of its jet engine oils regarding the potential for nervous system disorders following prolonged or repeated exposure.

During this time, the ITF task group had been meeting every year and exchanging, not only the type of regulatory and research highlights that I've described, but also what's going on at their own airlines, providing an international response to the question of what works and what doesn't in terms of addressing air quality incidents.

ITF RECOMMENDATIONS

Based on the exchange of information between task group members, the ITF recommends the following:

- First, that all crewmembers have the right to access aircraft maintenance records, including the technical log; and
- Second, that airlines be required (and in the meantime, pressured) to adopt proven maintenance and operating practices intended to mitigate bleed air events.

These ITF recommendations do not apply in five years when the recently funded aviation health research projects are completed, or in ten years when those research papers are published. We don't have to wait for regulators to convene a working group to revisit regulatory language. These recommendations can be implemented now. Today.

Obviously aircraft maintenance records don't define exposure, but they do define the potential for exposure because they document the source of air supply contamination. After a flight, the pilot will make an entry in the aircraft technical log. This log is aircraft specific and the entry will include the date, the flight segment, and the nature of the problem. Maintenance must review this entry and then indicate what was done to remedy the problem. In some cases nothing is done because the source of the air supply contamination is not always identified, but even that is useful information.

For example, ITF members have shared maintenance records that document the failure of two newly-installed ozone converters - within days - on a single aircraft that continued to fly despite documented an unusual loss of oil. Two cabin crewmembers on those flights got sick. One of them had respiratory

irritation followed by confirmed neurological damage and she is still unable to work more than four years later.

Generally, airlines are under no obligation to provide maintenance records to affected crewmembers, even though (or maybe because) these records are the only documents that describe the leak, spill, or failure that would cause - and explain - air supply contamination.

Canada is the only country with a health and safety regulation for crewmembers that provides access to aircraft maintenance records, although even there, there have been disputes over whether the word "access" gives a crewmember the right to a printed copy or simply the right to view the record on a computer screen.

On the subject of maintenance practices, crewmembers on the ITF air quality task group employed in Canada and Europe shared detailed information on the success of maintenance practices that have been implemented by their airlines. Some of these practices may be aircraft type specific, but some of them will apply system-wide. Bleed air events on their aircraft have not been eliminated, but they are now *considerably* less frequent.

Examples of upgraded maintenance practices include:

- Shorten the period between ECS and APU inspections to start, and over time, prolong the period between inspections as appropriate;
- Monitor oil consumption more carefully;
- Inspect oil seals and fluid lines that are prone to failure twice as frequently as the manufacturers recommend;
    - As an aside, the ITF recognizes that there is some motivation for manufacturers to claim that their product can last longer than it in fact can to tempt airlines by the cost-savings.
- Upgrade oil seals to the state of the art, and replace them more frequently than manufacturers recommend;
- Purge the overflow hydraulic fluid reservoir bottle more frequently so that it can not overflow and contaminate the ECS; and
- Improve the procedures for filling oil reservoirs to reduce the chances of spilling or overfilling

One of these airlines also put air quality reporting forms on all their aircraft, educated crews on the subject of toxic air, instructed affected crews to report to a company doctor, and trained pilots to respond rapidly.

These examples demonstrate that airlines can and should address bleed air contamination, and the ITF applauds the airlines that did make these changes.

Unfortunately, other ITF task group members have not had success at convincing their airlines to make these changes, but will continue to try.

CONCLUSIONS

To conclude, the ITF takes the issue of contaminated aircraft air supply seriously. Our task group meets annually to enable all members to stay current on this issue and to facilitate an exchange of information intended, not only to inform, but first, to press for information that demonstrates the relationship between exposure and ill health and second, to advocate for specific, practical changes so that bleed air contamination can be a thing of the past.

From: *Contaminated Air Protection Conference*: Proceedings of a Conference, held at Imperial College, London, 20-21 April 2005, Winder, C., editor, University of New South Wales, Sydney, 2005, pp 283-288.

OHRCA RESEARCH PROJECT

Laurel Kincl, Judith Murawski, Steven Hecker
University of Oregon, Oregon

BIOGRAPHICAL SKETCH

Dr Laurel Kincl (corresponding author) is a researcher at the University of Oregon, Labor and Education Research Center. She has a PhD in ergonomics and a MS in industrial hygiene. Dr Kincl has extensive occupational health field research experience, including exposure monitoring and worker training. She is Project Manager for the Occupational Health Research Consortium in Aviation (OHRCA). Judith Murawski is at the Association of Flight Attendants CWA AFL-CIO. Steven Hecker is at the University of Oregon.

INTRODUCTION

In October 29, 2003, Congress delegated the Federal Aviation Administration (FAA) to initiate research to address five major air quality issues within commercial aircraft (Vision 100 – Century of Aviation Reauthorization Act, Public Law 108-176).[1] These areas of research were specified largely in response to the findings of an expert committee convened by the National Research Council (NRC) in Washington DC. The findings and recommendations of this committee have since been published.[2] What follows is a description of a proposal submitted by the "Occupational Health Research Consortium in Aviation" (OHRCA) in collaboration with some members of the "Air Transportation Center of Excellence for Airliner Cabin Environment Research" (ACER) to respond to two of these five research directives: to collect air quality samples and health effects information.

OHRCA is a consortium of three universities, University of Oregon, University of California - San Francisco and University of British Columbia. OHRCA has partnered with two labor organizations – the Association of Flight Attendants-CWA, AFL-CIO (AFA) and the British Airline Pilots' Association (BALPA). This partnership is to ensure that the proposal was not a distant academic effort that missed the mark, but a real and meaningful assessment of the aircraft work environment, with results that could be put to practical use. ACER is a consortium of researchers from eight universities in the United States. The Harvard School of Public Health and University of California – Berkeley are involved in this project.

BACKGROUND

Recent assessments have unequivocally recommended comprehensive and independent studies of aircraft air quality to improve our understanding of the relationship between potential cabin exposures and reports of adverse health effects among crew and passengers.[2,3,4,5] Beyond the obvious benefit of developing and implementing an air quality reporting system for

crewmembers and passengers, the importance of this research is two-fold: first, there is evidence that exposure can pose a serious health risk to passengers and crew;[6,7,8,9,10,11] second, there is evidence of some significant flight safety concerns, as indicated by recent incidents in which the pilots became incapacitated.[10,12] The NRC committee described a number of case studies and anecdotal reports are available from other reporting systems.[2]

Specifically, the 2002 NRC report concluded that phosphate esters and aldehydes found in engine oils and hydraulic fluids, and their pyrolysis products, "may cause respiratory and neurological effects, particularly at high concentrations", but noted that "more data are needed to establish an association between the presence and concentrations of cabin contaminants and potential health effects in passengers and crew." Furthermore the 2002 NRC committee stated there is a need "to document systematically health effects or complaints of passengers and crew related to routine conditions of flights or air-quality incidents." The committee went on to recommend that a program be conducted "for the systematic collection, analysis, and reporting of health data with cabin crew as the primary study group."[2] It is anticipated that the proposed research will ultimately enable the assessment of the health effects associated with cabin air exposures during incidents.

RESEARCH PLAN

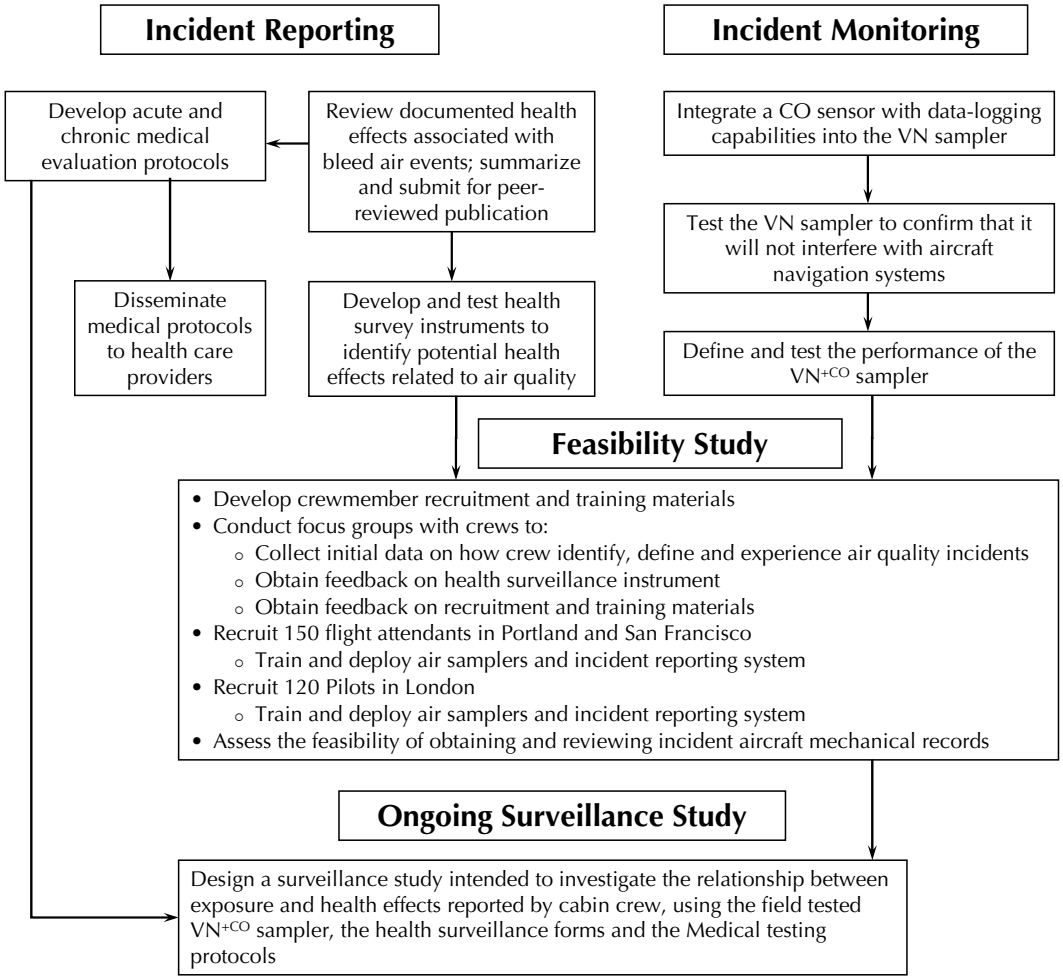
This research is divided into four components: incident reporting, incident monitoring, feasibility study and design for full-scale surveillance study. Each of these components is described briefly below and shown in Figure 1.

Incident Reporting

The development and implementation of an incident reporting system includes several tasks. We will collect, review and critique documented case studies of health effects associated with bleed air events. We will summarize and submit these findings to a peer-reviewed journal. Physicians on our team will then develop standardized medical protocols for the diagnosis and treatment of acute and chronic health effects experienced by airline crewmembers during and after exposure in an air quality incident. Finally, these components will lead to the development of an incident reporting system for the collection of health data in relation to air quality incidents. We will test the feasibility of distributing the data instruments and of crews using them.

The health effects review and medical protocols will provide important medical information to the occupational medicine community and to crewmembers who seek medical care after air quality incidents at work. These will also provide the basis for the systematic collection of health data in a future surveillance study design.

Figure 1: Diagram of Proposed Research



Incident Monitoring

To control costs but maximize sample size, it is necessary to limit the number of chemical agents to as few as will be representative of the incident, allowing a larger number of samples to be collected and analyzed. Tricresylphosphates (TCPs) and carbon monoxide (CO) are among the principal toxic constituents of smoke following the introduction of heated jet oil into the cabin air via the engines or APU, and are suspected as the cause of long-term neurological damage alleged by airline workers,[9] even at low-level concentrations.[13,14] The 2002 NRC committee recommended air monitoring equipment that is easy for a layperson to operate, inexpensive, and reliable. The VN sampler offers a preassembled filter arrangement in a small (two-inch diameter and three inches tall) PVC cylinder. The cylinder houses the appropriate filter of interest along with a small vacuum pump and a set of batteries to provide power to the electric motor. The system is activated with a simple 45-degree twist of the cap of the cylinder that aligns a set of pre-existing inlet and exhaust ports and activates the pump, causing outside air to flow through the filter. After an appropriate sampling period, the outer cap is twisted in the reverse direction misaligning the inlet and exhaust ports, so that the standard filter cassette is protected from the outside

air when not in use. The VN sampler is small enough that it can be conveniently mailed to a testing laboratory for analysis. The simplicity of operation along with its relatively low cost allows many units to be deployed and operated by crewmembers after a very brief training.

Although the VN sampler is capable of identifying complex mixtures of semi-volatile organic compounds through laboratory analysis, the basic version with a simple filter does not provide immediate feedback to the operator at the time of activation. In order to address this need, we intend to incorporate a small, direct-reading data-logging CO monitor into the VN sampler that can be independently switched on at the beginning of a flight. The information provided by the CO readout can also be used as a signal to the operator that an air quality event may be in progress, reminding him/her to activate the air sampler.

The VN sampler must be tested to ensure that its motor does not interfere with aircraft navigation systems per 14 CFR 91.21(b)(5). Also, given the heightened state of aviation security, the VN sampler must also get formal security clearance. We will conduct a round of basic validation and calibration tests to define the performance characteristics of the VN sampler, including comparing it to standard industrial hygiene sampling trains and measuring the flow rate and deciding on filter type. Finally, we will conduct inter-laboratory comparisons of sampler performance and assess the stability of the agents of interest once captured on the filter.

Feasibility Study

The overall purpose of deployment of the VN^{+CO} samplers is to characterize airborne contaminants introduced to the cabin and cockpit during air quality incidents, and ultimately to use this information to better understand the relationship between exposure and health effects reported by crewmembers. To assess the feasibility of deploying the VN^{+CO} samplers, the incident reporting form, and literature that describes standardized medical testing protocols to crewmembers, we will conduct a feasibility study that includes two small-scale sampling surveys. These surveys will also enable our team to collect limited descriptive data on selected air contaminants on different aircraft types during different flight phases.

We first plan to use focus groups to collect feedback on the following: (1) how crewmembers identify, define and experience air quality incidents, (2) whether our recruitment methods and training materials are suitable and user-friendly; and (3) the format and questions in our proposed incident reporting instrument. The output from these focus groups will assist in the next step: the actual recruitment and training of cabin crew and pilots to carry and activate the VN^{+CO} sampler and to use the incident reporting system.

We plan to recruit 150 flight attendants and 120 pilots. A sub-set of those flight attendants and all of the pilots will be assigned to carry a VN^{+CO} sampler and to activate it according to instructions. All of the crew trained will be

instructed to complete incident reporting forms during air quality incidents and at specified times for study purposes. The pilots would be instructed to activate the filter component of the VN^{+CO} sampler if they have reason to believe that there is an incident due to visible smoke or other sensory indicators, or if the CO sensor indicates levels much above background. We will collect control data on matched non-incident flights as a source of comparison data. For the flight attendants [given the small sample and the limited funds available to distribute the VN^{+CO} sampler more widely] our goal is more modest; we expect to collect some sampling data on different aircraft types and at different phases of flight during non-incident conditions. This exercise will allow us to test the distribution, activation, and return of the VN^{+CO} samplers and the reporting forms from cabin crew in a way that maintains sample integrity and chain of custody. All the sampling data and any incident reports will be analyzed and reported back to the participants.

Design for Full-Scale Surveillance Study

The feasibility studies that form the core of this proposed research are intended to lead to a full-scale deployment of samplers and incident reporting forms. We will develop a design for such a study for full-scale deployment of the VN^{+CO} samplers. The timing of the full-scale deployment phase will depend on 1) findings from the feasibility studies, 2) duration of the feasibility stage, and 3) further funding from FAA and/or other sources. The full-scale study is necessary to determine association between bleed air exposure and health effects. It will produce the scientific rigor necessary to sort out possible relationships between exposures and subsequent symptom reports and confounding circumstances. This project is funded by the FAA Office of Aerospace Medicine and is projected to be complete by (the northern) Spring 2007. In addition, the ongoing surveillance study may elucidate the parameters of any possible health effects such as onset, duration and intensity.

CONCLUSION

The deliverables from the proposed research activities would include:

(1) A validated and aircraft-ready VN sampler;

(2) A review paper that describes reported health effects associated with bleed air exposure;

(3) Medical protocols for assessment and treatment of acute and chronic effects;

(4) An incident reporting system;

(5) Some air monitoring data for routine and incident flights; and

(6) A design for larger-scale exposure and health surveillance study.

Crewmember unions have been calling for thorough, independent bleed air research for decades, as have two NRC committees. Now the US Congress

has also voiced its support. This research will address an important air quality question for cabin crew and passenger health.

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CONFERENCE CLOSING SPEECH

Jim McAuslan
Secretary, BALPA

BIOGRAPHICAL SKETCH

Jim McAuslan became General Secretary of the British Air Line Pilots' Association (BALPA) in January 2003. Working with the Association Chairman, Jim is responsible for developing and delivering a strategic plan for the Association that improves member's terms/conditions and lifestyles, increases the Association's influence and provides better value for money. Before joining BALPA, Jim was Deputy General Secretary of PCS, Britain's largest civil service union, where he oversaw the development of the union, developed sections for professionals and managers, and ran seminars with the Cabinet Secretary and senior officials. Prior to its merger with PCS, Jim was Deputy General Secretary of the Inland Revenue Staff Federation. During his time with the IRSF he established the first partnership agreement in the civil service. Before starting his career in the trade union movement, Jim worked for the Inland Revenue first as a Collector of Taxes and then as an Inspector of Taxes. Jim is also Chair of Unions 21, a think tank on future union organisation; and is an active Christian and trustee of various charities including a centre for the homeless.

SOME PERSONAL REFLECTIONS

It has been a most momentous couple of days. Before I get to some personal reflections about some of the ground breaking findings of this conference, I would like to thank a number of people.

Firstly, I would like to thank our sponsors, AOPIS, Pall and Sofrance for their support.

Secondly, I would like to thank all the presenters, especially those who came from across the world at substantial personal cost, to share their knowledge and experience.

Thirdly, I would like to thank Neil Stewart and Associates for organising the conference and making the arrangements for these past two days.

Fourthly, I would like to thank Julian Soddy for chairing the conference so ably.

Fifthly, I would like to thank all the various BALPA officers who gave so freely of their time and effort to get this conference going, and ensure its now obviously apparent success.

Lastly, and perhaps most importantly, I would like to thank the many, many un-named sufferers who have stepped forward to give us the evidence.

WHAT HAVE WE LEARNED?

I would like to share some final reflections with you in this last session of the conference.

This conference has been about something that has been under the radar in this industry for a number of years. The problem of oil leaks in aircraft.

Some sectors of the industry have suggested that they are occasional leaks but they are of low incidence, and any exposure that arises is largely inconsequential. Other sectors of the industry have suggested otherwise. They suggest that oil leaks cannot be dismissed, and the results of such leaks on crew and passengers is serious and not something that should be swept under the carpet.

So the questions to be asked after two days of presentations and discussion are:

Is there a problem?

The answer is quite clear – Yes.

Story after story, study after study, testimony after testimony from across the world and from other industries with similar exposures, show that chemicals exposures of the type experienced by workers in the aviation industry cause health problems.

There is a workplace problem resulting in chronic and acute illness amongst flight crew (both pilots and cabin crew).

Further, we are concerned the passengers may also be suffering from similar symptoms to those exhibited by flight crew.

Further, pregnant passengers are probably most at risk.

Is it happening in the workplace, that is, on aircraft?

Again, the answer is quite clear – Yes.

The environment where this is happening is the aircraft cabin.

This, we conclude, is resulting in significant flight safety issues, in addition to unacceptable flight crew personnel health implications.

Can we measure what is happening?

Again, the answer is quite clear – Yes.

Even though fume events are clearly being under reported, the number that have actually been reported is sufficiently serious that we reinforce the view that they should not be dismissed.

Can we measure what effect it is having?

Again, the answer is quite clear – Yes.

Can it be put right?

Again, the answer is quite clear – Yes.

THE WAY FORWARD

Action on this issue needs action on a number of fronts:

1 We need better designed aircraft, engines and APUs that don't leak

2 We need aircraft environmental systems that do not rely on bleed air

3 We need better, more safer, chemical products to be used in this industry

4 We need standard, open, non-retributive systems for the reporting of leaks

5 Organisations in this industry need to acknowledge their occupational health and safety responsibilities mandated by legislation and develop and implement appropriate systems that allow those responsibilities to be met (because their existing systems don't).

6 We need such reporting to be recorded and such records openly available

7 We need risk assessments of exposures that are inclusive of workers and passengers, not exclusive

8 We need better health systems that treat affected employees with sympathy and respect and not contempt

9 We need better models for monitoring, diagnosis, treatment, rehabilitation and compensation of affected workers. We need this for the legacy we have of pilots and flight attendants who have been affected, forced out of he industry and have been in the wilderness ever since

10 And of course, research. We need research into better engineering systems, less toxic chemicals, better diagnosis, better treatment, better risk assessments and epidemiological surveys of employees in the industry. This research must be independently funded and objectively reported. At best, it must be free of bias from vested interests that are so skilful at obscuring the issue.

11 Lastly, where operational systems are inadequate, the regulators need to properly enforce the Civil Air legislation they are charged to enforce.

12 As an example of this, the industry needs to better comply with airworthiness standards for air quality, and stop this mealy-mouthed interpretation of what they say.

WHERE DO WE GO TO NEXT?

I have a message from BALPA to all of you working in aviation:

- You are not alone
- Flight safety can be compromised
- Make sure you report it
- … and flying is still safe.

I have a message from BALPA to those responsible for public health.

- You have a real issue
- For today's passengers as well as those as yet unborn
- Get us all in the room together

How we should do it?

- BALPA's aim in hosting this conference was to get everyone together to get effective information exchange
- We need to keep loose coalitions going
- I call on all presenters to sign a communique that allows us to table a consensus position to governments and with industry that allows us to better engage with them about this issue, and get them involved
- To work towards the common goal of reseraching and collecting together the scientific and medical data relating to contaminated air and to work with the industry to identify solutions for this problem.

All of us need to be involved, and if I can paraphrase Moira Somers, all of us needs to ask:

- Am I going to make myself available?
- Am I willing to do difficult and complex work?
- Am I prepared to work outside my comfort area?

- Am I prepared to stay independent?

What emerges from the conference is:

- There is a workplace problem resulting in short term and long term illness among flight crew (both pilots and cabin crew);

- The workplace where these illnesses are being induced is the aircraft cabin environment. This is resulting in significant flight safety issues, in addition to unacceptable flight crew health problems;

- Consideration should be given to passengers, who may also be suffering from similar symptoms to those exhibited by flight crew.

We urgently call upon Government, industry and Regulators to work in partnership with cabin environment medical and analyst specialists and representatives from flight crew unions to analyse, quantify and remedy the cabin air quality problems that we have identified exist.

We also need to be making sure that there is a better future for this industry, and its staff, and its customers.

The Conference closing statement is attached.

CONFERENCE CLOSING STATEMENT

BALPA

London 21st April 2005

The undersigned were present at the International Aero Industry Conference on Contaminated Air Protection Air Safety & Cabin Air Quality, held in London 20-21st April 2005.

We wish to bring to the urgent attention of Government, Aviation Regulators and the Airline and Aerospace industry the following conclusions, distilled from the conference.

There is a workplace problem resulting in chronic and acute illness amongst flight crew (both pilots and cabin crew).

The workplace in which these illnesses are being induced is the aircraft cabin environment.

This, we conclude, is resulting in significant flight safety issues, in addition to unacceptable flight crew personnel health implications.

Further, we are concerned the passengers may also be suffering from similar symptoms to those exhibited by flight crew.

We urgently call upon Government, Industry and Regulators to work in partnership with cabin environment medical and analyst specialists and representatives from flight crew unions to analyse, quantify and remedy the cabin air quality problems that we have identified exist.

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