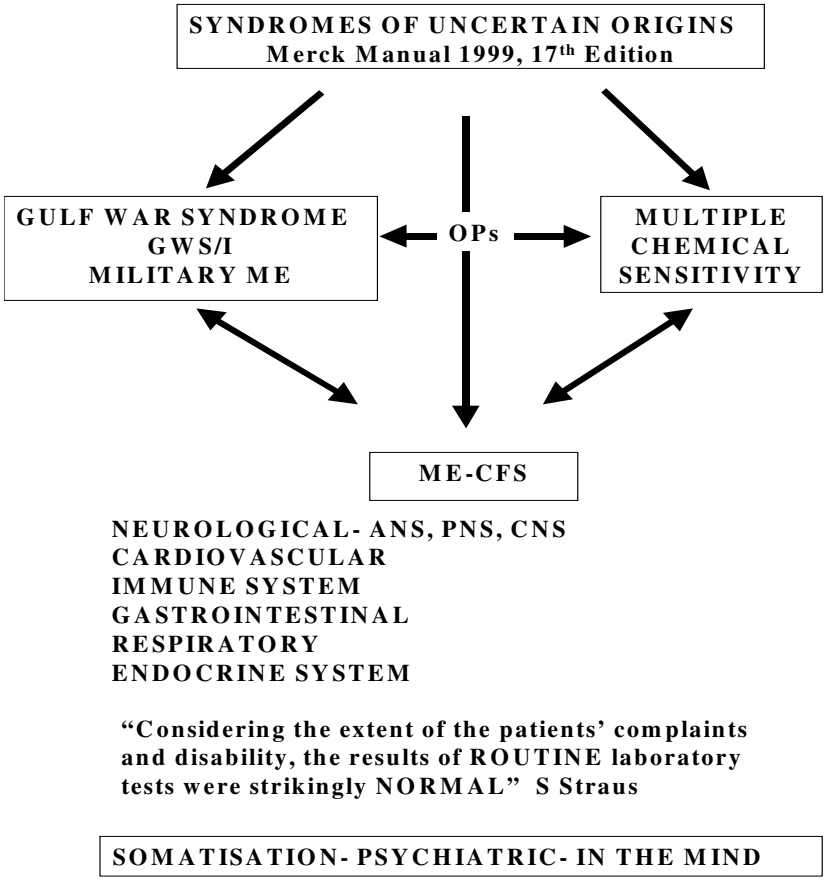
AEROTOXIC SYNDROME
Notes to support Parliamentary Presentation June 18th 2007.

Aerotoxic Syndrome, AS, is yet another "Syndrome of Uncertain Origin," Merck Manual, 1999, **Figure 1**. For a comprehensive review of all the factors associated with contaminated air see the Aviation Contaminated Air Reference Manual, Michaelis, 2007. All these syndromes involve multiple biological systems and organs with an extensive number of symptoms associated with considerable dysfunction and disability being reported, **Table 1**. Despite this, routine tests are surprisingly normal indicating that complex and inter-related biological mechanisms may be disregulated or dysfunctional. Conventional investigative procedures will therefore reveal little of significance in understanding these syndromes. There is clearly a need for careful research. An alternative view that all these modern illnesses are of psychogenic origin and may be treated by psychiatric techniques and neuropsychiatric drugs is now discredited, Research Advisory Committee, 2002, 2004; Hooper 2007; Walker, 2004. There has been much obfuscation, deception and even downright lying by responsible authorities to sustain the psychogenic theory. It is still appealed to by some uninformed clinicians an others badly advised by the Department of Health and some legal authorities. This continues to cause great distress to many suffering from these syndromes.

Figure 1. Syndromes of Uncertain Origin



Gulf War Syndrome, GWS, is the best known and most widely investigated syndrome in this category and extensive research has identified several novel mechanisms that provide an understanding of GWS and allied syndromes and at the same time reject the so-called "stress theory" that seeks to label all these syndromes as of psychogenic origin, Research Advisory Committee, 2004, -provides a comprehensive review of the research evidence. One significant aspect of GWS is that large numbers of American and UK veterans were involved that provide significant cohorts for epidemiological studies.

Table 1. Common Symptoms found in Syndromes of Uncertain Origin

SYMPTOMS	OPs	GWS/I	MCS	FMS	CFIDS	MS	HIV/AIDS
JOINT PAIN	+	+	+	around joint area	+	+	+
FATIGUE	+	+	+	+	+	+	+
HEADACHE	+	+	+	+	+	+	+
MEMORY PROBLEMS	+	+	+	+	+	+	+
SLEEP DISTURBED	+	+	+	+	+	?? due to medicines	+
SKIN PROBLEMS	+	+	+	+	+	burning skin	+
CONCENTR^{N} PROBLEMS	+	+	+	+	+	+	+
DEPRESSION	+	+	+	+	+	+	+
MUSCLE PAIN	+	+	+	+	+	+	+
DIZZINESS	+	+	+	+	+	+	+
G.I. - Irr. Bow.	+	+	+	+	+	+	+
PERIPH PARESTHES/ TINGLING	+	+	+	+	+	+	+
CHEM/ENVIR SENSITIVITY	+	+	+	+	+	Reported	_
EYE PROBLEMS	+	+	+	+	+	+	+
ANXIETY	+	+	+	+	+	+	+
TACHY&/OR CHEST PAIN	+	+	+	+	+	+	+
BREATHING PROBLEMS	+	+	+	Reported	+	+	+
LIGHT SENSITIVITY	+/-	+	+	Reported	+	+	_

+ Literature Reported ie. Anecdotal Adapted from Jackie Burkhead

OP = Organophosphate Poisoning; GWS/I = Gulf War Syndrome/Illness; MCS = Multiple Chemical Sensitivity; FMS = Fibromyalgia Syndrome; CFIDS = Chronic Fatigue Immune Dysregulation Syndrome = ME/CFS; MS = Multiple Sclerosis; HIV/AIDS = Acquired Immune Deficiency Syndrome.

The comparison with the symptoms reported by cabin crews affected by fume events shows striking similarities, **Table 2**. A much more comprehensive list of symptoms and exposure effects can be found in the the recently published Aviation Contaminated Air Reference Manual, Michaelis, 2007, chapter 6.

Table 2. Commonly Reported Symptoms by Aircrew, Winder 2005

Symptom Cluster	Sign or Symptom
Loss of consciousness/inability to function	Fainting/loss of consciousness/grey out
Direct irritation to eye, airways or skin	Irritation to eyes , nose and throat- eye pain
Respiratory symptoms secondary to irritation	Sinus congestion, Nose bleed, Throat irritation, burning throat , gagging, coughing, cough. Difficulty in breathing, tight chest. Loss of voice.
Skin symptoms secondary to irritation	Rashes, blisters (on uncovered body areas).
Gastrointestinal symptoms	Nausea, vomiting, pain. Abdominal spasms/cramps/diarrhoea
Neurotoxic symptoms	Blurred vision, loss of visual acuity. Shaking/ tremors/ tingling numbness (fingers, lips, limbs)loss of sensation.
Neurological symptoms related to basal nervous system function	Trouble thinking or counting, word blindness, confusion, co-ordination problems. Memory loss, memory impairment, forgetfulness.
Cognitive/neuro-psychological symptoms related to higher nervous system function	Disorientation Dizziness/loss of balance Light-headed, feeling faint or intoxicated
Non-specific General symptoms	Chest pains Sever headache, head pressure Fatigue, Exhaustion Chemical sensitivity Immune system effects Behaviour modified , depression, irritability. General increase in feeling unwell. Change in urine Joint pain, muscle weakness, muscle cramps.

In contrast ME/CFS has been known since 1969 but the numbers available for study and the absence, until recently of well defined clinical criteria, have led to attempts to reclassify the illness from neurological to psychiatric to the great disadvantage of patients, carers and others involved with their care, Hooper, 2007, Gibson, 2006.
Organophosphate poisoned farmers and people suffering from multiple chemical sensitivity provide still fewer numbers for large studies.
The organophosphates which are isomers of tricresyl phosphate, TCP, are a significant anti wear component of all oils used in jet engines. They enter the cabin along with a

whole variety of other noxious chemicals when worn engine seals fail to prevent leakage. For more details see Michaelis, 2007.

Effects on the Brain

The most dominant finding of GWS research, Research Advisory Committee, 2002, 2004; Morris et al., 2007, is extensive chemically-induced damage to the deep brain regions (basal ganglia, hypothalamus, thalamus, amygdala, hippocampus limbic system, and associated cortical regions- eg. insula) and the brain stem. The first group of structures are associated with memory, mood, cognition, signal processing, movement, balance, spatial awareness whilst the brain stem is especially involved in mechanisms of central autonomic control of heart rate respiration, temperature control, eye movement, and auditory function. Dysfunction and disregulation in these areas are consistent with the symptoms described by affected cabin crew members and some members of the public. The general picture seems to involve damage to numerous brain areas with widespread systemic consequences. Extensive investigations using Magnetic Resonance Spectroscopy, MRS, have identified major chemical deficits, indicative of neurone loss, in various regions of the brain in GWVs and one sick pilot.

The effects on the heart are of growing concern to those connected with the health and treatment of Gulf War Veterans, Haley, 2004: Morris, 2007.

The blood-brain barrier, BBB, provides a defensive barrier of tight cell junctions that restrict access to the brain of circulating toxins of chemical and biological origin. This barrier can be breached by several classes of chemicals including organophosphates thus allowing other toxins to enter. It is also weakened by stress thereby enhancing the toxicity of some chemicals including organophosphates, Abou-Donia, 2001.

A particularly important route into the brain that bypasses the BBB is inhalation which allows intraneuronal transport directly into the deep brain structures, Ashford and Miller, 1998; Research Advisory Committee, 2004. Inhalation is the route whereby cabin air contaminants will enter the bodies of cabin crew and the travelling public most commonly and effectively. Absorption through the lungs and skin also provide important routes of entry.

Epidemiology

Epidemiological studies are difficult in groups of patients who will appear intermittently from exposed cabin crew. Studies involving large numbers in order to obtain reliable statistical data and analysis are expensive and not easily organised. The pilots have carried out a preliminary study that points to serious adverse health effects from cabin fume events. However, the Gulf War Veterans, GWVs, provide an extensive cohort of formerly very healthy individuals whose health has been chronically damaged by chemical and other exposures. Epidemiological studies reported on GWVs found that 28-32% of all veterans became ill with GWS indicating that a significant proportion of this population are susceptible to the chemical exposures involved, Research Advisory Committee, 2002, 2004.

The short pilot study by Michaelis, unpublished data, 2007, reported to the parliamentary launch, June 18th 2007, is summarised in **Table 3.** This shows that a similar proportion of pilots, comparable to sick GWVs, are suffering medium to long term effects of their exposures with severe cases leading to retirement on health grounds. Since the BAe 146

is the worst but not the only offending aircraft larger surveys are needed to consolidate and refine this disturbing data.

Table 3. Results of a preliminary study on UK BAe 146 pilots, Michaelis, 2007.

UK BAe 146 Pilots (146) out of 250 responded	
86%	**smelt contaminated air**
57%	**Short medium of long term symptoms**
25%	**medium to long term effects**
8%	**Retired on ill health grounds**

The health problems associated with these exposures cannot be dismissed as idiosyncratic or merely anecdotal. They are serious and affect a significant proportion of people that have been exposed. Although pilots were the subject of this first study it is clear that other cabin crew and civilians have also suffered serious ill health, Sabatino, 2007, reported at the Parliamentary launch. Further studies are now urgent in order to obtain firmer statistical evidence and better insights into the short and long term clinical consequences of these exposures.

Challenges in toxicology

Conventional toxicological understandings of dose, synergism, timing of exposure, delayed responses, mechanisms of action, and genetics are all being challenged by contemporary science.

Dose

It can no longer be assumed lower doses will elicit smaller responses. Toxic responses have now been identified at doses orders of magnitude below the extrapolated zero risk from classical studies. Such responses have been found with radiation, Busby, 1995, oestrogen-like compounds, Palanza et al, 2002, and drugs used to treat autism spectrum disorders, Busse, 1988, nerve agents and related compounds. In animal models the total dose from small cumulative doses of an organophosphate pesticide caused chronic adverse effects equivalent to a single oral dose up to 250 times larger, Abou-Donia, 2005. In cabin crews the exposure to repeated low doses have often lead to assurances that they too small to cause any adverse effects. This is grossly misleading and it is now clear that repeated low level exposures can cause extensive adverse effects which is some cases are known to evoke serious and delayed long term damage. The delayed long term of these exposures is particularly disturbing since the major symptoms can appear several years after the initial exposures, Research Advisory Committee, 2004; Morris et al., 2007.

Synergism

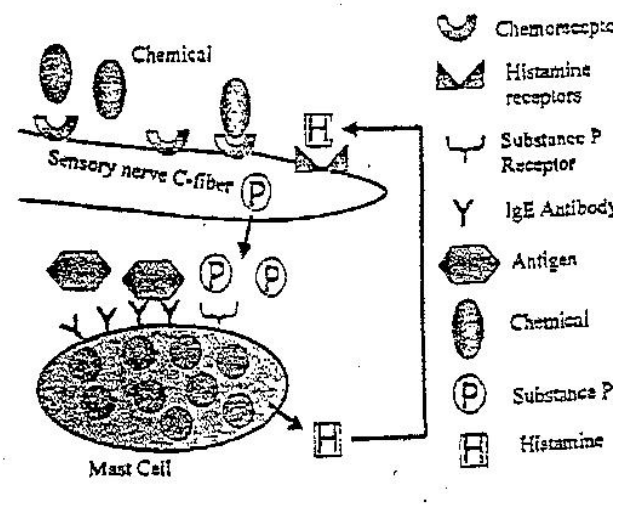
Toxic effects of some chemicals can be multiplied by orders of magnitude in the presence of structurally different compounds, for example, pyrethroids, organophosphates and DEET (an insect repellent), Abou-Donia et al., 1996: Abou-Donia, 2001. It has been established that malathion and permethrin act synergistically making their use as a

combined treatment for head lice in children particularly unwise, Furlong, 2005. Many pesticide formulations contain more than one active ingredient. Furthermore, compounds used as solvents, dispersants and wetting agents in pesticide formulations that are generally regarded as inert may also be toxic in their own right, eg. epichlorohydrin. Some compounds can trigger MCS, and/or act synergistically, for example phenols in organophosphate pesticides, COT, 1999, and POEA in some herbicide formulations, Matrinez and Brown, 1991; Koyama et al., 1997. It is unusual for pesticides to be applied alone therefore mixtures of active compounds and 'inerts' must be fully tested. In addition to pyrethroids being widely used in aircraft cabins when both crew and passengers are exposed there are also complex and variable bioaccumulative chemicals in the environment. These include PCBs, polybromoaromatics used as flame retardant, polyfluoro compounds used as non-stick and stain repellents, WWF, 2004(a), and carbon monoxide. The bleed air drawn in through the engines brings into the cabin a variety of volatile organic compounds, VOCs, and complex mixtures of pyrrolysed engine oil components some of which are known to evoke biological pathways rendered dysfunctional by organophosphates and related compounds, Vodjani and Lapp, 1999; Winder, 2005. Michaellis, 2007, provides extensive information on the chemistry of engine oils and the components of bleed air.
Much more needs to be known about the complex chemistry and biology of these individual chemicals, their mixtures, and possible synergy.

Timing
It is becoming clear that the timing of any exposures can be critical in their potential for damage. The foetus is especially vulnerable and can suffer extensive injury with permanent loss, for example, of the eyes, Pesticide News, 1996. Children and babies can receive a toxic load of persistent bioaccumulative and other xenobiotics through the food chain and breast milk, WWF, 2004(b), Ten Tusscher, 2002, Gee, 1999, Eskenazi et al., 1999, Tamburlini et al., 2002. Concern about mental disability in children has been linked to the widespread use of large numbers of xenobiotics in contemporary society, American Association on Mental Retardation, 2003. The impact on fertility in young people, particularly men, is also a matter for concern, Cadbury, 1997. The increased prevalence of chronic degenerative diseases in the elderly has also been linked with the rapidly escalating use of untested novel chemicals Pritchard et al., 2004. Some clinicians are drawing attention to 21st century environmental illnesses affecting growing numbers of people Baillie-Hamilton, 2005.

Mechanisms
Novel mechanisms that offer meaningful explanations of MCS and related disorders are emerging including intraneuronal transport, triggering and kindling, involving the limbic system Ashford and Miller, 1998, opening of the blood-brain barrier Vogel et al., 2002, neurogenic inflammation, Meggs, 1999a,b, intracellular messenger disruption Palanza et al., 2002.
Neurogenic inflammation involving C-fibres that form a network of nerves that respond to noxious chemicals, **Figure 2.**

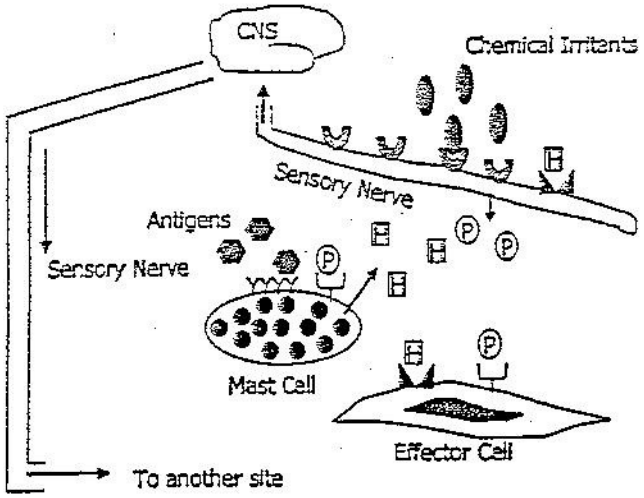
Figure 2. Detection of noxious chemical stimuli by receptors on C-fibres, Meggs, 1999.



Delayed effects

These effects originating locally are then transmitted to the brain by spino-thalamic pathways and exert further toxic effects on other brain pathways, **Figure 3,** see also Almeida et al., 2006.

Figure 3. Local reflex pathways transmit response to the brain, Meggs, 1999.



A very worrying aspect of some toxic exposures is the delayed appearance of symptoms many years after an initial low dose exposure with no identifiable immediate effects. Survivors of sarin exposure in Toyko and Matsumoto were found to have a chronic delayed neuropathy more than three years after an initial exposure that provoked no overt symptoms. In animals this effect has been widely studied, Abou-Donia, 2005, Research Advisory Committee, 2004. Similar effects have been identified with organophosphates

and would be expected with other acetyl cholinesterase inhibitors. Novel compounds must be tested for their capacity to exert such delayed effects.

Other Adverse Health Effects

Some well-defined clinical conditions have also been identified in excess among chemically injured Gulf War veterans and among sheep dippers. These include osteoporosis, Compston etal., 1999, 2002, and motor neurone disease, Haley, 2003, Horner et al., 2003, and there is anecdotal evidence of increased incidence of Parkinson's disease, and multiple sclerosis, MS, Ackerman, 2006; Coghlan, 2005.

Paraoxonase 1, PON1, plays an important protective role against atherosclerosis which can lead to serious cardiovascular disease. Levels of this enzyme are greatly reduced in sick GWVs, Mackness et al., 2000; Hotopf, Mackness et al., 2003, and sheep farmers, Cherry et al., 2002.

Organophosphates are known to dysregulate the immune system and to be associated with immune and autoimmune disorders, Repetto and Baglia, 1996.

It is imperative that sick aircrew are monitored for all these conditions and longitudinal studies carried out on cohorts of cabin crew.

Genetics

Studies of changes in gene regulation in carefully selected ME-CFS patients showed significant up-regulation of genes associated with the immune response, mitochondrial function, and nerve function (including NTE gene which is associated with pesticide poisoning), Kausik et al., 2005. Organophosphates that reduce PON1 activity also modify the expression of multiple genes, Furlong et al., 2005, Haley, 2005, Abou-Donia, 2005. Genetic aspects of xenobiotic metabolism have been correlated with susceptibility to various toxins, McKeown-Eyssen et al., 2004, Sram, 1998.

Politics

It is a dismal comment on the official attitudes to all these overlapping syndromes of uncertain origin that the responses to patients, carers, and clinicians who take them seriously have involved obfuscation, deception and downright lying at time. Medical responses have often insisted that they all have a psychogenic origin and that treatment, compensation, insurance payments and essential benefits should be resisted or reduced accordingly. Treatment has most frequently involved the prescription of antidepressant drugs but sometimes other more potent neuro-psychiatric antipsychotic and anticonvulsant drugs combined with psychological techniques such as cognitive behavioural therapy and graded exercise. The ignorance and confusion in the Health Service is exemplified by the debate on myalgic encephalomyelitis in the House of Lords initiated by the Countess of Mar, Mar 2004, from which it emerged that wrong information had been supplied to the Minister and through him to clinicians responsible for primary care, see Hooper et al., 2003. Underhand activities by the proponents of the psychiatric approach were exposed and the influence of much vested interest from clinicians, companies, and the insurance industry, Gibson, 2006. Funding of independent science and medicine research programmes must be provided to increase our understanding of , and treatment for, these complex and debilitating illnesses.

Treatment

Dr William Rea, http://www.ehcd.com/ , has pioneered treatments in environmental and ecological medicine, Rea, 1992-1998.

In the UK treatment is available on the National Health Service from Dr Jean Monro at the Breakspear Hospital, http://www.breakspearmedical.com/, which offers a comprehensive protocol for effective therapy. The British Society for Ecological Medicine, http://www.ecomed.org.uk/ , lists medical practitioners who offer treatment based on Rea's pioneering studies. Other countries have committed physicians who treat patients by similar means.

Caring physicians must no longer be pilloried by the ideologues within medicine.

Conclusions

It is becoming clear that many chemical exposures can give rise to the serious adverse health effects including those described by sick cabin crew members and worryingly by some members of the public who have suffered fume events. These effects can be understood from research studies already published on related conditions particularly GWS and other overlapping syndromes of uncertain origin.

Whilst further studies are needed to consolidate the small scale pilot studies carried out on the initiative of the cabin crews and pilots it is imperative that these should not delay positive action to minimise fume events and provide effective treatment and where necessary compensation and support for sick personnel and their families. This should apply equally to passengers who suffered similar adverse health effects from these events.

Simple and effective actions include

- Prevent access of fumes into the cabin by placing filters in all lines carrying air into the cabin.
- The use of alternative oils that do not contain known neurotoxins such as TCP.
- Monitoring of every flight for adventitious known biologically active compounds.
- Developing biomarkers for the full clinical investigation of all crew (and passengers) who report sick with unexplained illnesses/symptoms.
- Identifying and making available effective treatment for sick cabin crew members (and passengers).
- Full admission of responsibility for fume events with appropriate compensation particularly if flying is no longer possible for those becoming sick in this way.
- Alerting the public to the possible dangers of such exposures.
- Providing reference to suitably trained medical practitioners to monitor their health and provide treatment.
- Providing appropriate compensation for passengers affected by fume events.
- Making environmental medicine/toxicology part of the medical curriculum so that new doctors are familiar with these syndromes.
- Design new aircraft to ensure air is no longer taken in through the engines.

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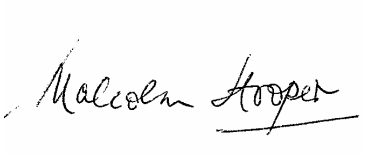

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