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# Pathogenesis of Non-Specific Neurological Signs and Symptoms in Aircrew on Civil Aircraft

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**KEYWORDS**
central nervous system, organo-phosphate, aerotoxic syndrome, emissions, bleed air

**ABBREVIATIONS**

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|---|---|
| CNS | Central nervous system |
| OP | Organophosphate |

**ABSTRACT**
This paper addresses the basic neurobiology which leads to the brain being a 'target organ' for chronic low dose organo-phosphate toxicity. This includes the irreplaceability of nerve cells, the logistic problems neurons have in serving axons (that in some neurons can be over one meter long), the dependence of neurons on neurotrophins, and the vulnerability of neurons to damage through impairment of axonal transport.

## INTRODUCTION

The central nervous system (CNS) is particularly vulnerable to toxic insult for a number of reasons. The nerve cells that are a component of the adult brain have to last a lifetime. Many other organs in the body, for example the liver, can repair by cell proliferation. This does not apply to the nerve cells in the CNS (*Figure 1*). The brain has a very high metabolic rate and neurons have to maintain their microstructures over long distances. For example, the axon, which carries outgoing signals from the neuron, can be over 1 meter long. To maintain such structures in a healthy state there is a mechanism called 'axonal transport' which will deliver a number of substances and structures in both directions to and from the neuron cell body. Transmitter substances help to deliver information across synapses to the next neurons in the neuronal chain. Neurotrophins are also secreted across the synapse and are essential to maintain the target neurons in good health. Mitochondria are the 'powerhouses' in which glucose is metabolized and maintain the high metabolic rate essential for neuronal health, even in the most distant parts of the nerve cell.

The reaction of the CNS to toxic insult is variable. High dose acute toxicity will cause acute toxic damage. However, repeated low dose exposure to neurotoxic substances can cause sub-acute chronic toxicity over a long period of time.[1] This is true of organo-phosphate (OP) compounds. Nerve gas OP compounds (eg. sarin, VX) can cause acute death by attacking the enzyme anticholinesterase. However, of much more relevance to the etiology of aerotoxic syndrome, chronic low dose exposure to OPs at levels well below any cholinergic symptoms can cause neurotoxic effects. Terry has reviewed this topic and shown that axonal transport can be affected by repeated low dose OP exposure.[2] This would interfere with the delivery of transmitter substances, neurotrophins and mitochondria to target neurons and could be the basis of the development of a diffuse subacute encephalopathy.[3]

The existing literature on low dose repeated exposure to OP compounds was analyzed with respect to medical problems being reported amongst aircrew, concentrating on non-cholinesterase mechanisms at levels of exposure that produce no overt signs of acute toxicity.[4] These include covalent binding of OPs to tyrosine and lysine residues, which suggests that numerous proteins can be irreversibly modified by OPs. In addition, the mechanisms of oxidative stress and neuro-inflammation and the known OP targets of motor proteins, neuronal cytoskeleton, axonal transport, neurotrophins and mitochondria are of importance in the pathogenesis pathway.

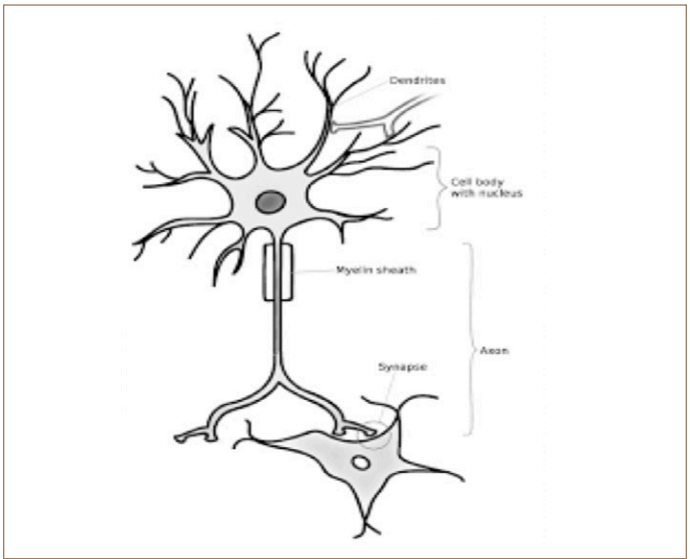


*Figure 1— Schematic diagram of a neuron showing the soma (cell body), dendritic arbor and efferent axon communicating with the subsequent neuron in the information chain. The axon has to maintain the health and normal functioning of the axon and its telodendria (terminal branching), often over long distances of up to 1 meter. This is achieved by the mechanism of axonal transport which works in both directions (anterograde and retrograde). Another important function is the maintenance of the health of target neurons through the secretion of neurotrophins.*

The nature of exposure to fugitive emissions from gas turbine engine bleed air to the concept of 'dose' when dealing with irreversible molecular processes was discussed, particularly with respect to the extended periods of exposure experienced by aircrew over a working lifetime. Additionally, the toxicology of complex mixtures was addressed and the potential effects of the continual presence of ultrafine particles in engine bleed air was considered.[5]

The overall conclusion is that a toxicological mechanism consistent with the reported symptomatology of aircrew complaining of ill health associated with cabin air quality exists. Repeated low dose exposure to a complex mixture of neurotoxic substances in engine bleed air needs to be much more seriously considered.

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