MEMO

To: Global Cabin Air Quality Executive (GCAQE) Executive

From: Prof C V Howard

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Commentary on the EASA and EU Commission cabin air quality studies [1,2,3,4]

When designing a study to investigate possible toxicological consequences of chemical(s) exposure, it is important to look in detail at the mode of exposure and try to emulate it in any experiments set up to investigate the problem. This must include the toxicant concentration, route of exposure, period and pattern of exposure, complexity of mixtures present etc. Failure to carry this out will inevitably lead to a poor/irrelevant risk assessment. Additionally, it is useful to conduct 'thought experiments', when one assumes that the data from the proposed experiments is to hand and then try to imagine how it will help answer the scientific question that is being asked. If it doesn't help then there is little point in conducting the study. It seems that with the EASA studies, both completed and proposed, no thought experiment with respect to chronic low dose exposure of flight crew has been attempted, as I will outline below.

With exposure to engine oil contaminants in cabin air two modes of exposure are recognised. In normal operation aircraft with bleed air systems have been demonstrated to have a background low level mixture of contaminants present. These are generally at levels difficult or impossible to routinely detect but their presence is incontestable, as shown in many studies. The principal route of exposure is through inhalation. The pattern of exposure among air-crew is intermittent-continual with cumulative exposure times often summing to many thousands of hours.

The EASA and EU Commission study designs model short term exposures at concentrations higher than the likely background continual mixture exposures that flight crew will have experienced. Thus the results would, at best, be of relevance to the sequelae of high exposure 'fume events'.

There is a question about the effects of chronic repeated low dose effects of organo-phosphates (OPs) on neural tissue. There is ample scientific evidence (Terry et al [5], Axelrad et al [6]) from animal in vivo and in vitro studies that this exposure pattern results in

neurotoxic damage. When we had a preliminary meeting at RIVM/TNO in 2014 to discuss the toxicology of tricresyl phosphate, I brought up the subject of low dose OP pre-exposure. One of the Axelrad studies compared neurite outgrowth inhibition, a recognised measurement reporting neurodevelopmental damage, in neuroblastoma cells that had been exposed to 25 µM diazinon for either 6 weeks or 24 hours. The 6 week pre-exposure group proved to be much more sensitive to subsequent OP exposure at higher concentrations. I sent the papers to Dick Sijm, the leader of the research group at that time. He agreed that this was important. I urged him to consider incorporating low dose pre-exposure into his experimental design. However Dick left the project before it was finalised and long term pre-exposure was not incorporated. Exposure time for the in vitro experiments was 24 hours, which Axelrad et al found was not long enough to induce increased vulnerability to neurotoxic damage.

In conclusion the EASA in vitro experiments already reported do not provide any information or insight into the reasons why flight crew form a vulnerable subgroup to neurological and respiratory disease (Michaelis et al [7], Howard et al [8]). Similar reservations can be made over the proposed monitoring and in vivo studies. The initial oil fume simulation studies propose to heat turbine oil up to 400C. While this is above the flashpoint for turbine oils (245-270 deg C), it does not mirror the actual temperatures of up to 1,500C in the engine circulation and up to 30,000C temperature transients modelled for engine bearings. These latter extreme temperatures will favour the formation of UFPs that have been observed [9] in gas turbine engines. Furthermore the large total surface of the UFPs in the aerosol will act as a catalytic surface for the formation of OP and other organic compounds. The particular significance of the continual presence of an aerosol of UFPs in cabin air is that, apart from inducing inflammation, they will be taken up into the bloodstream from the alveoli of the lung and then spread to the brain. UFPs have been shown to be able to cross the blood brain barrier, using the same endocytotic mechanisms employed by viruses (Elsaesser et al [10]). Additionally, any organic compounds, including OPs, will be able to 'piggyback' across the blood brain barrier on the surface of the UFPs. Thus there will be a continual presence of a mechanism for enhancing the delivery of toxic substances directly to the brain. This would definitely not occur with delivery of these chemicals by ingestion, only by inhalation. Therefore, this aspect of the proposed research has to be questioned. However, it was also reported at the recent CEN TC meeting in Bordeaux that chronic long term low dose in vivo animal exposure experiments with turbine oil fumes would not be undertaken because of cost. In vivo experimentation is extremely expensive.

The overall conclusion therefore must be that none of this completed or proposed research will help with addressing the single most important set of questions concerning the health of flight crew. It might assist with some aspects of understanding the sequelae of higher dose fume events in un pre-exposed receptors – i.e. occasional flyers among the passengers.

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