EUROPEAN COMMISSION FACTS CAQ SCIENTIFIC COMMITTEE MEETING COLOGNE, 29/11/17

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Critical research questions

- Why are pilots and cabin crew more vulnerable to the effects of ‘fume events’ than the passengers, particularly for neurological sequelae? One would expect the opposite – healthy worker effect
- What is the effect of continual exposure to a low-dose complex mixture of fugitive turbine engine emissions for individual cumulative exposure times measured in thousands of hours?
- What is the effect continual exposure to an aerosol of combustion nano-particles on the kinetics of TAPS and other pyrolysis chemicals across the blood brain barrier?

Research designs worth considering

- Use of in vitro methods in an ‘Axelrad design’ low-dose long term pre-exposure model – this would give mechanistic information
- Conduct large-scale epidemiological studies to establish the true prevalence AS symptoms in pilots and air crew as compared the general population
- Conduct long term low dose animal exposure studies with gas turbine engine emissions. HOWEVER prohibitively expensive AND inadequacy of animal models for subtle cognitive deficits

Research designs not contributing to answering the research questions

- Monitoring experiments that only address high dose OELs and other regulatory limits for single chemicals. These are not designed to deal with the chronic continual exposure pattern to a complex low dose mixture
- Diluting the prime research interest, toxicity and harm to health as a consequence of engine bleed air architecture, by including other factors primarily associated with the lifestyle of passengers. ~This would come under the heading of ‘red herrings’.

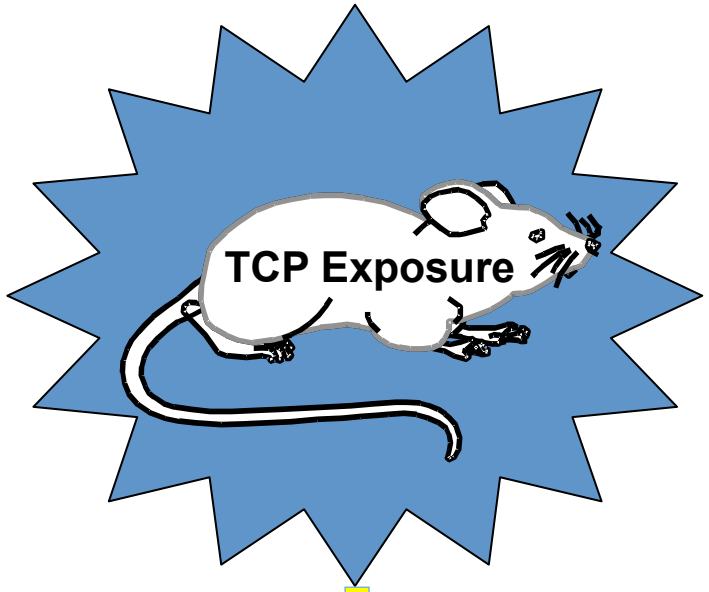
A specific suggestion for a research project

- Prof Alvin Terry's research group are internationally recognised for their work on repeated low dose exposure to OPs
- They have found effects at concentrations orders of magniture below those required for inhibition of acetylcholinesterase
- Their latest work on chlorpyrifos finds effects at 0.1 nanomolar concentration

Terry – Repeat low-dose exposure to TCP – University of Augusta

- **Determine the consequences of repeated exposures to TCP on different domains of cognitive function**
  - **Sustained attention**
  - **Spatial Learning**
  - **Recognition Memory**
  - **Working Memory**
- **Determine the consequences of repeated exposures to TCP on axonal transport in vivo**
  - **Manganese-enhanced magnetic resonance imaging (MEMRI)**
- **Elucidate molecular mechanisms responsible for TCP-induced neuronal changes to identify potential therapeutic targets**
  - **TCP effects on tubulin, kinesin, ERK, CREB and their phosphorylation states**

Terry Study Algorithm
Low dose repeat exp to TCP
University of Augusta



Cognitive Function
- 5C-SRTT
- Water Maze
- Novel Object Recognition
- Radial Arm Maze

Axonal Transport
- Mn^{2+} Enhanced MRI (in vivo)

Molecular Mechanisms
- Western Blot (ex vivo)
- Immunohistochemistry (ex vivo)

Why are UFPs in cabin air of critical importance?

1) CV Howard: nanotxicology review : University of Ulster

- UFPs can cross the BBB and chemicals adherent to their surface 'piggyback' into the brain. Pharmaceuticals are already being delivered thus. Their continual presence in cabin air will enhance the penetration of neurotoxic substances into the brain.
- A common feature of all UFPs, irrespective of their composition, is to induce inflammation, predominantly by ROS production.

- Elsaesser A, Howard CV (2012), Toxicology of nanoparticles , Adv. Drug Deliv. Rev. 64: 129–137

2) Byron Jones- Kansas State University

- Oil contamination of bleed air- Fine oil fog: 10-150 nm or below.
- particulates as a marker of oil contamination in bleed air
- Sensors to be developed for UFPs 10nm & below

Jones B, Roth J, Hosni M et al. The Nature of Particulates in Aircraft Bleed Air Resulting from Oil Contamination. LV-17-C046. In: *2017 ASHRAE Winter Conference—Papers*. Kansas State University, 2017.