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Report prepared for SAFE in response to the “The Commission compensation oil pioneers” requirement for scientific documentation on health effects from exposure to turbine engine fumes.

Title: The science behind exposure to turbine engine fumes.

Aim:
The aim of this report is to present some of the available science associated with exposure to engine oils on aircraft and aero derivative engines which include exposures to Organophosphates and a complex mixture of pyrolysed substances. This report is not intended to be a complete review of the data.

Background:
A range of substances including lubricants, hydraulic fluids, fuel, exhaust emissions and other fluids are utilised in turbine engine function. The focus of this short report will be on the engine oils /lubricants as the engine design and function ensures that exposure to oil fumes will occur. A range of adverse effects have been reported by those working on aero derivative engines on the offshore platforms, that have a very similar pattern of effects as those working on aircraft using bleed air from the turbine engines to supply the breathing air.

Design:
Turbine engines used on aircraft and offshore platforms enable oil utlised in the engines to leak into the surrounding air during normal engine operation in a variety of ways (1-3).

1. Oil passes seals into the main gas path
2. Oil exits the engine vents / exhaust
3. Oil leaks

Chemical exposure - Turbine engine fumes:
The synthetic lubricants used in the turbine engines are heated to very high temperatures, enabling exposure to the original substances in the oils as well as a complex mix of pyrolysis products (4, 5). Such exposures include:

- Synthetic ester base stock (~95%)
- Organophosphates used as antiwear additives at ~3%. These are Triaryl phosphates (TAP), most commonly Tricresyl phosphate (TCP, CAS 1330-78-5) and less commonly Phenol isopropylated phosphate 3:1 (TIPP/PIP3:1, CAS 68937-41-7). TCP is known to be neurotoxic (6).
- Antioxidants including N-phenyl-1-naphthylamine (PAN, CAS 90-30-2) or Alkylated diphenylamines (CAS 68411-46-1) at ~1%
- Anti-corrosion additives
- Complex mixture of pyrolysis products
- Proprietary substances

A number of these substances meet the EU REACH/ Classification Labelling and Packaging (CLP) hazard classification criteria on a harmonized or notified basis and therefore carry a range of hazard warnings for health and environmental adverse effects (7, 8). Some of these include:

- May cause damage to organs through prolonged or repeated exposure; causes damage to organs through single exposure; may cause an allergic skin reaction; harmful in contact with skin/ if inhaled; causes serious eye irritation; may/suspected of causing genetic defects; fatal if inhaled; may/ suspected of damaging fertility or the unborn child; may cause allergy or asthma symptoms or breathing difficulties if inhaled; may cause respiratory irritation; may/ suspected of causing cancer; causes severe skin burns and eye damage; causes serious eye damage; causes skin irritation; toxic in contact with skin/ if inhaled; may cause drowsiness, dizziness.

Exposure scenarios:
Exposure to turbine oils will occur on both a higher level acute as well as a chronic background lower-level basis. These are clearly described in Howard et al. 2017 (9).

Pattern of illness:
Adverse effects reported by aircrew and aero derivative turbine workers include a pattern of both acute and long-term adverse health effects (9-11). These include neurological (CNS, PNS), neurobehavioural, respiratory, cardiovascular, irritant, skin, sensitizing, gastrointestinal effects and other general signs and symptoms including fatigue, performance decrement, rheumatological, chemical sensitivity and immunological effects.

This pattern of effects associated with exposure to turbine engine lubricants has been identified as ‘Aerotoxic Syndrome’ and highlighted as a potential emerging occupational disease (10, 12, 13). The pattern of acute and chronic exposures to neurotoxic and a wide range of thermally degraded substances associated with turbine engine oils and fluids used in the occupational environment has been associated with a diffuse and consistent pattern of acute and chronic adverse effects (10).

Common but incorrect allegations cited why the symptoms cannot be associated with the work environment include the following:

1. Only the ortho isomer of TCP (tri-ortho-cresyl phosphate: TOCP) can be associated with Organophosphate Induced Delayed Neurotoxicity (OPIDN), the only adverse finding recognised to be associated with jet oil exposures;
2. The levels of exposure are too low to be a problem;

3. The pattern of symptoms have been suggested to be broad and non-specific making it difficult to identify a precise illness or syndrome.

However, such thinking fails to take into account the following factors: (10, 14, 15)

1. **TOCP & other TCP isomers:** The wide spread belief that only the ortho isomers of TOCP are dangerous is invalid (10, 16). Most of the toxicity testing has been undertaken on high dose animal ingestion studies, whereas aircrew and off shore workers are primarily exposed by inhalation and dermal routes.

   With regard to the toxicity of the turbine oils, there has been an almost total reliance on TOCP alone and failure to recognise the increased toxicity and concentrations of the other cresyl phosphate ortho isomers in TCP (17) used in the most commonly used turbine engine oils. Therefore, the toxicity of the other ortho isomers in TCP are being underestimated by a factor of around six million (16). Additionally, the 99.7% non-ortho isomers of TCP and other TAPs can cause demyelination and inhibit various enzymes, including those associated with cognition (10, 18-20). Further recognition that the meta and para and the mono and di-ortho isomers of TCP are neurotoxic include military and lubricant industry scientists (6, 21-24).

   This failure to take into account the non ortho isomers of TCP, while placing the sole focus on OPIDN underestimates the risk of exposure to TCP (16).

2. **Low dose exposure to OPs:** The OP principal mode of action is to disturb the process of acetylcholine metabolism found in the CNS, PNS. However, OPs can have more subtle effects at lower doses, particularly with repeated exposures. Terry (2012) reports that *"there is now substantial evidence that this canonical (cholinesterase-based) mechanism cannot alone account for the wide variety of adverse consequences of OP exposure that have been described, especially those associated with repeated exposures to levels that produce no overt signs of acute toxicity."* (25)

   Non cholinergic mechanisms of OP toxicity are well described by Terry and Naughton et al. (25, 26). These reviews report that covalent binding of OPs to various enzymes, suggest that numerous proteins can be modified by OPs. Additionally, OP concentrations up to three orders of magnitude below those required for cholinesterase inhibition can: 1) cause oxidative stress and neuroinflammation and 2) affect known OP targets such as motor proteins, neuronal cytoskeleton proteins, axonal transport, neurotrophins and mitochondria. *"This type of exposure has been associated with prolonged impairments in attention, memory and other domains of cognition, as well as chronic illness where these symptoms are manifested (e.g.. Gulf war illness, Alzheimers disease."* (25). This is precisely the spectrum of symptoms reported by aircrew by Michaelis et al. (2017) (10). These are also the symptoms that have been reported by offshore workers exposed to oil fumes on aero derivative turbine engines (11).

3. **Symptomatology:** The symptomology of OP exposure tends to be non-specific and not causing a clear-cut set of localizing signs and symptoms that

are instantly recognizable as a syndrome. Rather a diffuse pattern of neurological symptoms may occur, which are consistent with their mode of action, resulting in a diagnosis of diffuse toxic encephalopathy.

The non-specific symptomatology of OP exposure can be described as protean. It is of relevance that multiple sclerosis, a demyelinating disease can present as almost any combination of neurological symptoms.

The environmental exposure to OPs has been reported to accelerate the development of various brain diseases, (27, 28), which would be in keeping with a diffuse encephalopathy.

4. **Chronic exposure:** Michaelis et al. (2017) reported that the very low dose effects described by Terry (25) support the pattern of acute and chronic exposure among aircrew shown in the Michaelis study (10, 29) – chronic continual low dose exposure with occasional acute-on chronic, higher dose exposures. Supporting evidence to support this pattern was provided in in vitro study (30), in which in which pre-exposure of neuroblast cells to very low dose OPs made them much more susceptible to neurotoxic damage compared with non- pre-exposed cells upon further challenge by a higher dose of a variety of OPs (10, 30). In summary, repeat exposure to low levels of OP mixtures leads to increased susceptibility/ a reduced toxicity threshold to further environmental substances.

5. **UFPs:** Pyrolysed engine oils are recognised to generate considerable concentrations of ultra fine particles (UFPs) (14, 31, 32). Exposure to UFPs allow increased adverse effects of organic compounds including OPs. (14, 32, 33) As stated in Howard et al. (2018) *"A consideration of the toxicology of Nano-particles concludes that their continual presence over a typical working lifetime of up to 20,000 hours in aircrew will predispose them to chronic respiratory problems and will exacerbate the translocation of neurotoxic substances across the blood brain barrier"* (14). The same would be expected for those working on aeroderivative turbine engines.

   The exposure to the OPs that adhere to the particles in the aerosols would be of considerable importance, as discussed in Howard et al. (14, 16).

6. **Individual susceptibility:** Individual susceptibility to damage by OP exposure appears to be highly variable. Some people have constitutionally low levels of liver enzymes, such as paraoxonases, that detoxify OPs in the liver. It was demonstrated that farmers with lower paraoxonase levels are more likely to suffer from dippers flu as a result of exposure to OP sheep dips (34).

7. **Respiratory effects:** Respiratory abnormalities are commonly reported by aircrew and those chronically exposed to low levels of OPs (10, 14, 35, 36). The signs and symptoms are consistent with lung injury secondary to hydrocarbon and particulate inhalation, with cases often irreversible (14). More recently an in vitro lung cell study identified that *"exposure to engine oil and hydraulic fluid fumes can induce considerable lung toxicity, clearly reflecting the potential health risks of contaminated aircraft cabin air"* (37). Again, this finding should be relevant to offshore platform workers exposed to turbine engine oils.

8. **Complex mixture:** The classical *'one chemical at a time approach'* ignores the toxicity of complex mixtures. Some work has been done on the enhancement of OP toxicity in mixtures (38) supporting that the individual chemical approach will not suffice (15). Toxicological consequences of individual chemicals for which threshold limits have been set, will fail to identify the consequences of exposure to a highly complex mixture associated with pyrolysed oils and other fluids (14). In excess of 127 substances and hundreds of other VOC peaks were identified in a turbine engine oil pyrolysis study (39). Inappropriate reliance on exposure standards are highlighted in Watterson et al. (2017) (40). A European Commission-funded study identified the need for: *"precautionary actions on the assessment of chemical mixtures even in cases where individual toxicants are present at seemingly harmless concentrations"* (41).

9. **Inhalation:** The reliance on oral ingestion studies, as has been the case, fails to take into account that exposure via inhalation is more toxic than dose for dose, than by ingestion as discussed in Howard et al. (2018) (14, 16). This is clearly recognised by the US EPA (42). The continuing reliance on oral routes of exposure to engine oils and TCP in toxicology studies (identified in table 3 of Howard (2020)) while failing to address inhalation routes, represents a major weakness in toxicology risk assessments (16).

10. **No air monitoring/filtration:** Air supplied via or surrounding turbine engines is not monitored for contaminants and there is no filtration of this air as it exits the engine. As such the only measurements undertaken have been of a few dozen ad-hoc studies in aircraft cabins over the last 3 decades during mostly normal operations. The levels identified have been below exposure limit thresholds, however as stated above, this does not provide any assurances about the suitability of the working environment for those exposed to this air.

Summary:
The continuing reliance on oral studies of acute exposure to high levels of engine oils and specifically the toxicology of TOCP, fails to take into account the pattern of exposure that workers breathing air from turbine engines are experiencing. Chronic low-level exposure to OPs on top of acute exposures to oil fumes presents a very differing pattern of effects as indicated in the available science.

Sincerely,

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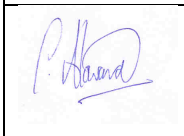	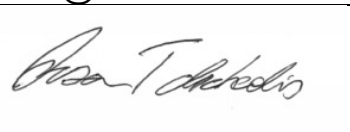

Biographical notes:

Susan Michaelis is an Honorary Senior Research Fellow at the University of Stirling within Occupational and Environmental Health Research Group. She is a former commercial airline pilot holds a PhD [ref 29] in Safety Science: the flight safety and health implications of exposure to aircraft contaminated air. She holds an MSc [ref 2,3] in Air Safety and Accident Investigation specifically addressing oil seal leakage into aircraft bleed air supplies. Her expertise also covers hazardous substances in the workplace and air accident/incident investigation.

Professor Howard is a medically qualified toxico-pathologist specialising in the problems associated with the action of toxic substances on health. He is currently Em. Professor of Bioimaging at the University of Ulster and has authored/co-authored over 130 peer reviewed scientific papers, predominantly in the field of quantitative toxicology. He has investigated the neurotoxicological properties of organophosphorous compounds both individually and in mixtures. He has also been involved in the investigation of pre-exposure to extremely low-levels of organophosphorous agents on subsequent susceptibility to toxic change in a biological substrate.

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