OVERVIEW TO ACCOMPANY THE UNIVERSITY OF WASHINGTON
RESEARCH PROPOSAL & REQUEST FOR FUNDING
TO DEVELOP A BLOOD TEST FOR AVIATION ENGINE OIL ADDITIVES &
CHARACTERIZE THEIR TOXICITY

J. Anderson, MSc CIH
Industrial Hygienist
Air Safety, Health, & Security Department
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This document provides an overview of the technical issues, research-to-date, and proposed research, relevant to the toxicity of engine oil and hydraulic fluid fumes that are known to sometimes contaminate the ventilation air on commercial and military aircraft. It is intended to provide a layperson’s overview to accompany the attached summary proposal and budget for funding written by Prof. Clem Furlong at the University of Washington. In response to requests from airline crewmember health and safety specialists, Prof. Furlong and his research team have designed a multi-faceted research study intended to specifically target the remaining biochemical questions that are so essential to crewmember and passenger health and safety regarding both the evidence of exposure to, and the toxicity of, aviation engine oil fumes onboard aircraft. To execute this research, they are seeking a total of 717,100 USD in funding over three years from multiple sources.

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Since the 1950s, airline crewmembers have documented ill-health during and after exposure to neurotoxic oil fumes which contaminate the ventilation air supplied to the cabin and flight deck as a consequence of the design of using engine bleed air on all commercial jet aircraft, except for the (Boeing 787). Ill-conceived designs and inadequate maintenance of the relevant aircraft systems can produce both fumes (odors) and smoke and haze in the cabin and flight deck. It is irresponsible of the industry to rely on designs that extract breathing air off engines that leak by design highly toxic oil, and to do so without the protection of either filters or chemical sensors, but that is the reality for people who rely on air travel, with exception of those who fly the Boeing 787.

And even though the airline industry has recognized the potential for oil fumes to enter the cabin/flight deck breathing air for more than 60 years, it has declined to address the problem, and instead continues to invest time and energy into denying the problem and discrediting affected crews. As an example, in the early 1990s, management representatives at one US airline invited the onsite cabin crew union to join its “Unexplained Illness Committee” in order to get to identify the cause of the reported symptoms that “defied explanation” (Alaska Airlines, 1998). Subsequently, the airline’s document production in response to a lawsuit brought by ill cabin crewmembers showed that the airline had known the source of the problem all along. As a more recent example, a major airline recently reassured its pilot group that “[a] level of 7,000 mg/m³ [of oil fumes] for a sustained period of
time is necessary in order to cause a longer term health concern” (USAirways, 2011). To put this claim in context, the cited exposure limit for neurotoxic oil fumes is 1,400 times higher than the occupational exposure limit for mineral oil.

In 2004, a safety representative with a major UK airline pilot union first brought the problem of contaminated cabin air with associated health and flight safety impacts to Prof. Furlong’s attention. The following year, Prof. Furlong attended a conference at Boeing Field, Everett, WA, followed by an important two-day conference hosted by the UK airline pilot union in London. During these two meetings, he met pilots and cabin crewmembers who reported neurological and respiratory damage during and after exposure to oil fumes inflight, along with representatives from airlines and manufacturers who denied that the ill health effects were in any way related to flying.

The fact that crewmembers and passengers continue to risk inhalation exposure to toxic oil fumes on aircraft represents a failure at every level - the aircraft and component manufacturers, the airlines, the regulators, and even militaries around the world. And it will continue until there is a means for crews and passengers to prove exposure to aviation oil fumes, and until the science behind the toxicity of the doses received on aircraft has been properly investigated by researchers without financial ties to the oil and aviation industries. As such, funding this research is essential because health and safety regulations and practices concerning chemical exposures on aircraft need to be grounded in science, not in politics and financial interests.

Technical basics/background

To understand the research that has been completed - and is yet to be completed - it is necessary for the reader to understand some technical aspects of the toxic chemicals that crews inhale when engine oil contaminates the aircraft air supply system, as follows:

The neurotoxic tricresyl phosphates (TCPs) anti-wear additives in engine lubricants (2-6%, by weight) are considered to be a primary contributing cause to the neurological symptoms reported by exposed airline crews for decades. Scientists have known since the 1930s that TCPs are neurotoxic, and the aviation industry has recognized the potential for airline crews to be exposed to oil fumes that contain TCPs since the 1950s. In light of these two facts, one may wonder how it is that aircraft continue to be designed with “bleed air” ventilation systems known to be prone to oil contamination, without any filters, chemical sensors, proactive and preventive maintenance strategies, and crew training/education.

In 2007, Prof. Furlong and his team committed to develop a TCP blood test intended to enable crews and passengers to determine (and prove) exposure to oil fumes on aircraft. To understand the history of the TCP blood test development, it is necessary for the reader to know that there are 10 types of TCPs (“isomers”), each with the same chemical formula, but slightly different configurations. Six of these forms are termed “ortho” isomers, two “meta” isomers, and two “para” isomers. The presence of different TCP isomers is highly significant because the structural variations influence toxicity. The UN based chemical classification regulations classify TCPs as hazardous in a variety of ways, including that
TCPs are neurotoxic and may sensitize the skin, irritate the eyes, damage internal organs, impair fertility, cause heritable mutations, and cause harm to the unborn.

The form of TCP that has been most closely studied is triorthocresyl phosphate (ToCP). This isomer has received the most attention because of some mass poisonings in the 1930s, when thousands of Americans (and, later, Moroccans) were poisoned by accidentally ingesting ToCP. It was not until 1954, though, that the UK biochemist, Normal Aldridge, determined that ToCP had to be “bioactivated” in the liver before it exerted its neurotoxic effects. In those early days, it was shown that liver-bioactivated ToCP significantly inhibited an enzyme called neurotoxic esterase (NTE) and that, when NTE was inhibited enough, the test animals that were force fed ToCP (usually rats and chickens) developed balance problems and, eventually, were paralyzed. Paralysis was a reasonably easy measure of toxicity to assess – researchers could measure NTE and observe their gait and ability to walk. On this basis, ToCP became recognized as neurotoxic, and the observed medical condition became known as “OPIDN” or “organophosphate-induced delayed neuropathy.” As the name suggests, the animals developed neuropathy and paralysis, but not immediately; rather, there was some delay on the order of days or even a couple of weeks.

These findings are of interest to crewmembers and passengers concerned about onboard exposure to TCPs in oil fumes, but only peripherally and here’s why: First, crews and passengers are not eating or drinking TCPs at room temperature like the test animals in these studies; rather, they are inhaling air contaminated with oil fumes that contain TCPs, combined with likely as many as hundreds of other chemical compounds, many of which are created upon heating the oil up to temperatures as high as 950°F. Inhalation toxicity is expected to be greater than ingestion toxicity, but is more challenging to measure. Second, in recognition of the toxicity of ToCP (an ortho isomer), and as a nod to the suspected toxicity of the remaining five ortho isomers, aviation regulatory bodies require that the TCPs added to aviation engine oils contain no more than 0.2% of all of the ortho isomers combined. That means that at least 99.8% of the TCPs in engine oils are meta and para isomers, such that the four meta/para TCPs are present at levels at least 500 times greater than as many as six ortho isomers combined.

Given this background, it is clear that any aviation oil company that genuinely wanted to assess the health impact of inhaling oil fumes would either expose animals to the oil fumes or the types of TCPs in the oil fumes. But instead, all but one of the oil company-funded studies assesses ingestion exposure of TCPs, and usually ToCP. The obvious question – the elephant in the room - is, what is the inhalation toxicity of meta and para TCPs; that is, the types of TCPs and the type of exposure relevant to airline crews? And the answer is that, despite decades of exposure and reported ill health, nobody quite knows. As recently as 2013, ExxonMobil, one of the manufacturers of synthetic jet engine oils, formally stated that the company is unaware that any inhalation toxicity testing has ever been conducted on its oils.

It is known that the meta and para TCPs that dominate commercial engine oil formulations do not inhibit NTE appreciably, and so they do not induce paralysis. But the industry’s insistence that this makes them “non-toxic” is nothing more than a smoke and mirrors game: NTE inhibition is not the only measure of neurotoxicity, and affected crews are reporting symptoms of central nervous system
damage (e.g., chronic headaches and impaired executive functioning such as slowed reaction time, cognitive processing, working memory, and cognitive flexibility), not paralysis.

There has been so little research into the toxicity of the meta and para TCPs, and so little research into the inhalation toxicity of any types of TCPs, that one is left to conclude that these omissions are by design. For example, in 1955, US Air Force (USAF) researchers published a paper which concluded that ingestion and dermal (skin) toxicity of aviation oils that contain TCPs was moderate, but inhalation toxicity of oil mists was greater, and inhalation toxicity of oil fumes (i.e., oils heated to high temperatures) was significantly greater, and the toxicity was greater still as temperature increased (Treon et al., 1955). The obvious next step to further investigate these findings as they apply to aircraft systems would be to conduct additional tests on the inhalation toxicity of oil fumes, but it took 40 years for the USAF to conduct a study in which rats were exposed to various heated TCP blends (and one engine oil) for four hours (Lipscomb et al., 1995). The researchers noted that the observed neurotoxic effects appeared to be a function of the TCPs/oil being heated to high temperatures, which also reflects what crewmembers and passengers inhale onboard when the air supply system is contaminated with oil.

During the nearly 60 years since that first inhalation toxicity study of engine oils was published, there have been many research studies on ToCP toxicity (which, again, is of limited application to the aircraft issue, given that ToCP content in the oils will range somewhere between 0 and 0.006%). And there have been a handful of ingestion studies of the meta/para isomers, reminding us that when test animals drink those types of TCPs, they don’t develop paralysis. There is one published inhalation toxicity study which concluded that the neurotoxicity observed in the exposed animals could not be accounted for by the minor amount of ortho TCPs in the oil fumes (Freudenthal et al., 1993). This was significant, but there has been no follow up since then, or at least nothing published in the public domain.

The following example serves to illustrate the misleading and flawed nature of the oil industry-funded “research.” In 1999, ExxonMobil published a “human risk assessment” which appropriately assumed that the ortho TCPs are toxic. But it incorrectly assumed that the remaining constituents (99.8% or more) of an oil are non-toxic, and further that inhaling chemicals is toxicologically-equivalent to drinking them. This enabled the company to conclude – in a published, peer-reviewed journal that is frequently cited - that an “average man” could safely inhale 1.3 kg of oil a day, making it “virtually impossible” to inhale enough oil on an aircraft to cause neurotoxicity (Mackerer et al., 1999). Along these lines, the UK Civil Aviation Authority accepted ExxonMobil’s assessment of the toxicity of its own product, and concluded that an “average man” could ingest seven metric tons of pyrolyzed oil per day for 74 days “without effect” (CAA, 2004).

Research-to-date

Returning now to the first meeting with Prof. Furlong in 2004, the goal of the initial research project was to develop a biomarker (blood test) for the TCPs. Because crew unions did not know about the requirement that the ortho TCP content in the oils be so limited (i.e., < 0.2% of the total TCPs), a biomarker that confirmed evidence of exposure to bioactivated ToCP was an obvious choice, because...
ToCP is recognized as a potent neurotoxin, and the chemical structure of the liver metabolite of ToCP is well-established (unlike the liver metabolites of the other types of TCPs). During those early years, Prof. Furlong and his team worked to identify predictable and measurable changes in specific blood proteins after exposure to ToCP. He also invited affected crews and passengers to ship blood samples to his lab, but after receiving more than 200 such samples (that he continues to store), it was necessary to stop accepting blood samples from affected crews because of storage limitations, as well as the considerable effort required to process samples which is better spent on developing the blood test.

Over time, it became clear that ToCP was not the best candidate because crew unions learned the otherwise well-hidden truth that there is little, if any, ToCP in oil fumes. This was an unanticipated setback, but despite almost no funding, Prof. Furlong and his research team continued in their quest for answers to questions that plague crew health and safety advocates. First, he shifted his team’s focus to the toxicity of the meta and para isomers of TCPs, and especially, to one of two commercially available TCP blends added to engine oils called Durad 125.

In 2012, members of Prof. Furlong’s team published a paper that, arguably, is one of the most influential papers on the oil fumes issue today. They demonstrated a physiological effect in mice that had ingested either Durad 125 or the tri-para isomer of TCP (i.e., one of four sorely understudied isomers that dominate both commercial TCP blends added to aviation oils). Specifically, the activity of liver acyl peptide hydrolase (APH) and carboxylesterase1 (CES1) was inhibited (Baker et al., 2012). Assuming these findings apply to human inhalation exposure to these same TCPs, they are highly significant because: (1) The APH enzyme is implicated in cognition (Pancetti et al., 2007; Richards et al., 2000). Thus, the finding that TCPs (after being bioactivated in the liver, as well as other tissues, including the brain) suppress APH activity may help to explain the prevalence of individuals who report cognitive effects after inhaling these types of TCPs during airline flights; and (2) The CES1 enzyme plays a role in the body’s detoxification processes (including the lungs and central nervous system), and the inhibition of CES1 has been shown to suppress the activity of an important type of white blood cell which can affect overall immune function and the control of tumor cells/inflammatory processes (Markey, 2011). Thus, the finding that TCPs (after being bioactivated in the liver) suppress CES1 activity may help to explain reports of immune system deficiencies, as well as reduced tolerance to subsequent exposures of toxic compounds, among affected airline crews. CES1 activity is known to vary widely between people, influenced by genes, gene expression, and environmental factors (NCBI, 2014; Ross et al., 2012). So, it is possible that low CES1 activity (whether naturally low or artificially depressed by a fume event) may increase a person’s susceptibility to ill effects following exposure to oil fumes. Likewise, high CES1 activity may offer some protective effect.

As examples of the practical and worker-oriented nature of Prof. Furlong’s research team, there are two more key research findings-to-date that are notable:

First, they demonstrated, experimentally, that a component of grapefruit juice (naringenin) may have a protective effect after exposure to engine oil fumes. Specifically, Baker et al., 2012 describes how the inhibition of the BChe enzyme was significantly lessened when physiologically-relevant concentrations of naringenin were included in the in vitro bioactivation assay. This finding suggests that a physiologically relevant “dose” of grapefruit may provide a
protective effect for crews exposed to oil fumes. The likely explanation for this is that one or more of the mouse liver enzymes that would otherwise convert TCPs into biologically active compounds were “distracted” by the naringenin. Thus, the “parent” TCPs (that were not bioactivated) did not have the same negative impact on the BChe enzyme.

Second, after exhaustive search and experimental testing, Prof. Furlong’s team has assisted a French oil company and successfully identified a less toxic engine oil additive intended to offer a workable alternative to TCPs in engine oils that are not so easily converted to highly toxic metabolites that inhibit enzymes crucial to normal physiology. Baker et al., 2012 describes the characterization of a number of potential additives, and on in particular that they demonstrate is less toxic but still has chemical characteristics that reduce engine wear and provide thermal stability. Clearly, the best option is for airline manufacturers to design either non-bleed systems or oil-free bleed systems, but an interim measure for current aircraft designs is for engine oils to contain less toxic additives. So this research development is relevant and important.

For decades, airline industry officials have referred to crewmembers sickened by breathing oil-contaminated ventilation air inflight as suffering from a “mystery illnesses.” And while the industry still denies any potential for long-term illness caused by oil fumes, there has been significant progress. By now, the industry has no choice but to formally recognize that crews can be exposed to oil fumes inflight, and that exposure can cause acute symptoms which can compromise flight safety (AAIB, 2012; AAIB, 2007; SAAIB, 2006; AAIB, 2004; FAA, 2004; CAA, 2002; ATSB, 1999; Rayman, 1983; Montgomery, 1977).

On Sept. 3, 2010, eighteen years after her exposure to oil fumes onboard a domestic flight, former Australian flight attendant Joanne Turner won her long fight for justice when the High Court of Australia upheld a ruling that: “The plaintiff was exposed to pyrolysed effects of Mobil Jet Oil II on 4 March 1992,” and “that pyrolysed effects of Mobil Jet Oil II are harmful to the lungs.” In 2014, an autopsy of a British Airways pilot who had a long history of exposure to oil fumes and accompanying neurological symptoms, confirmed extensive damage to the brain, consistent with exposure to the types of organophosphates in oil fumes (Abou-Donia et al., 2014).

Despite the important legal ruling and pathology report, crews are without a means to prove exposure. And with insufficient research into the toxicity of the meta and para TCPs that dominate engine oil fumes, the industry still claims that oil fume concentrations in the cabin air are too low to cause chronic neurological effects. The industry has even offered alternative explanations for reported symptoms, ranging from hyperventilation (Bagshaw, 2013) to “a nocebo effect” (i.e., a psychologically-mediated response to a perceived risk) (COT, 2014; Coggon, 2005).

**Proposed research**

Prof. Furlong and his team have proposed to answer the following questions:

1. What is the impact of exposure to trimetacresyl phosphate, triparacresyl phosphate, Durad 125, and Syn-o-ad 8484 on the activity of four useful biomarker enzymes (e.g., liver CES1, liver
APH, plasma BChe, and red blood cell AChe), once those TCPs have been “bioactivated” in the liver?

This component would clarify some of the biochemical impacts of specific TCP isomers/blends, which would address the oft-asked question of what is the toxicity mechanism of some of the key constituents of engine oil fumes?

2. Which of the liver metabolites associated with the dominant types of TCPs and commercially-available TCP blends inhibit the above-listed enzymes; that is, which are the most potent inhibitors of the important enzymes listed above?

This component would define the more potent toxins in oil fumes, and again speaks to toxicity mechanisms.

3. How do the biologically active liver metabolites modify the biomarker proteins in vitro? And are those protein modifications detectable in the archived blood samples of exposed crewmembers?

This component would further the identification/development of relevant oil fumes biomarkers; that is, predictable and measurable changes to blood proteins that are specific to and caused by (in this case) specific types of TCPs.

4. Which p450 liver enzymes are converting TCPs into the toxic metabolites, and which genetic markers may be involved in the activity of those p450s? (Some progress has already been made on this front.)

This component would define measurable endpoints that denote individual susceptibility to the toxic effects of exposure to aviation engine oils.

5. What compounds may block the conversion of specific TCPs/blends into toxic metabolites?

This component would investigate means to prevent or mitigate neurological damage caused by exposure to particular neurotoxic chemicals.

6. How is animal behavior and APH and CES1 activity affected by inhalation exposure to aviation engine oil fumes?

This component would actually expose animals to heated fumes and measure the impact on the activity of the specific enzymes of interest, listed above. Exposing test animals to oil fumes under strictly controlled and defined conditions is much more technically challenging than having the animals ingest either TCPs or oils. However, after investigating the toxicity of the TCP element of the oil fumes in more detail (as described above), measuring the impact of inhalation exposure to oil fumes would illuminate potential differences in: (1) inhalation versus ingestion toxicity, and (2) exposure to TCPs versus exposure to TCPs and the other chemical constituents of oil
fumes. Access to test animals is made possible by Prof. Furlong’s affiliate appointment in the University of Washington Center on Human Development and Disability, which provides access to a first-class animal behavioral lab.

In support of the crewmembers who report ill effects of exposure to oil fumes on aircraft is an emerging body of literature that recognizes that certain types of chemicals (most notably endocrine disruptors such as TCPs) can cause ill effects at high doses and also at very low doses (Vandenberg, 2014). Further, the bodies of literature on low-dose effects and genetic markers of susceptibility to toxins are both growing (Androutsopoulos et al., 2013; Fagin, 2012; Myers et al., 2009; Mutch & Williams, 2006). Recently, German researchers demonstrated that ToCP has a negative effect on the activity of a neurotransmitter in the brain cells of mice at much lower concentrations than those which cause paralysis (Hausherr et al., 2014). It is not yet known if the meta and para TCPs also impact neurotransmitters in this way. Additional consequences of low-dose exposure to chemically-related compounds (organophosphate pesticides) include reduced testosterone levels, abnormal thyroid function, abnormal glucose and lipid metabolism, mitochondrial dysfunction, and negative effects on fetal/child brain development (Androutsopoulos, 2013). Health research to assess these types of health outcomes - in relation to inhaling the mixtures of organophosphates in aviation engine oil fumes - is needed.

It may be tempting to assume that this type of academic research and these complex biochemical questions are the responsibility of regulators; that the FAA and its equivalents around the world are conscientiously investigating the toxicity of oil fumes and err on the side of flight safety and crew and passenger health. However, despite the well-documented potential for compromised flight safety, aviation regulators have made it clear that they have no intention of investigating these issues on behalf of crewmembers. As examples, the UK Committee on Toxicity recently concluded that, while there is evidence that crews are getting sick from exposure to oil fumes on aircraft, a “nocebo effect cannot be ruled out” (COT, 2014). Likewise, in response to 2012 legislation passed by the US Congress that calls on the FAA to design and oversee research to define what concentrations of oil fumes on aircraft are toxic, the FAA has failed to act.

Instead, independent funding sources must be called on because the alternative is to accept the industry status quo that allows defective designs and substandard maintenance practices, at a cost to crewmember and passenger safety and health. Every month, crewmember unions collect more and more incident reports, including some classified as accidents (because of crewmember hospitalizations) and others in which the pilots and cabin crew were impaired. We must turn this tide.

Prof. Furlong and his research team have shown an unwavering commitment to defining the toxicity and characteristics of these oil-based toxins which is outlined in detail in their publications and presentations. They are uniquely qualified to answer these important toxicity questions that have stymied crew union efforts to convince the industry to put controls in place to stop exposing crews and passengers to oil fumes. Thus, crewmember associations around the world urge potential funders to recognize the essential nature of this valuable research and to fund it fully. Science – and not politics and financial interests – must dominate the debate on necessary protections for airline
crewmembers and passengers, to ensure an uncontaminated supply of ventilation air on commercial and military aircraft.

Additional questions should be directed to Prof. Clem Furlong at the University of Washington in Seattle, WA, USA (clem@uw.edu or 206-543-1193).

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