May 31, 2018

ACGIH
1330 Kemper Meadow Drive
Cincinnati, OH 45240-4148, USA
Attention: TLV Committee

Sent by email: science@acgih.org

RE: Comments on NIC for Trimetacresyl phosphate (TmCP) and Triparacresyl phosphate (TpCP)

Dear ACGIH TLV Committee,

Please find below a brief discussion on my views regarding your proposed TLVs for trimetacresyl phosphate (TmCP) and triparacresyl phosphate (TpCP).

My background for your information is as a commercial pilot from 1987 to 1997, at which time I was medically retired by the Civil Aviation Safety Authority in Australia due to repeated exposure to oil fumes in the aircraft type I was operating. In 2010 I received a PhD on the topic of aircraft cabin air contamination [1], followed by an MSc in 2016 investigating how oil leaks in jet engines. [2] Both of these are publicly available via the links in the citations below. I am a visiting researcher at the University of Stirling in the UK and Head of research for the Global Cabin Air Quality Executive (GCAQE) and am regarded as one of the leading experts globally on the cabin air contamination topic.

A. ***Executive Summary*** *– Provide an executive summary with a limit of 250 words.*

Aircrew and passenger exposure to jet engine oil emissions, involving Tricresyl phosphate mixed isomers (including TmCP and TpCP) is a function of jet engine operation and the common use of pressurised air used to seal the bearing chambers as well as supplying the aircraft breathing air supply. There is evidence of acute and long-term adverse effects occurring in association with exposure to the oils including TCP as a whole, TmCP and TpCP isomers. A number of recommendations are provided outlining true caution when assigning a TLV to these isomers as the research for the TCP exposures via inhalation have not been undertaken.

B. ***List of Recommendations/Actions***

1. TmCP and TpCP should include neurotoxicity as an additional basis for the TLV.

2. Any exposure standard must be far lower than the recommended 0.05mg/m3, if applied at all.

3. There should be a single exposure limit for the mixed isomers of TCP. CAS 1330-78-5

4. Caution should be used when applying exposure limits to non-standard environments, such as an aircraft cabin.

C. ***Rationale.***

The air supply on today's jet aircraft (except the Boeing B787 Dreamliner) is provided by utilising compressed engine air. Jet engines consume oil containing TCP, used at 2-6% as an antiwear additive.

Mobil stated at the Senate References Committee of the Australian Parliament, in 1999 that *'TCP is a necessary component in jet engine oils….The TCP used in jet engine oil is a very complex mixture. The conventional TCP used in Mobil Jet II is a complex mixture prepared primarily from meta and para cresol. However other substitute phenols as well as xylenols are present in the synthesis mixture. We have identified 10- phenols and xylenols, as well as low levels of ortho cresol and phenol, in hydrolysed conventional TCP. Ortho cresol was present at about 0.16%, meta and para cresol combined at 80% and other phenols at 17%. Thus the number of triaryl phosphate combinations in TCP is very high and is not limited to the ten that can be formed from ortho meta and para cresol. It is not practical to measure all of the triaryl compounds present because standards do not exist for most of them. However, their concentrations can be computed by statistical procedures from the compounds present in hydolysates. The various phenols and xylenols have virtually the same reactivity. This procedure has been used for many years. In the TCP additive TOCP levels are calculated to be < 5ppb, mono ortho cresyl phosphate (MOCP) ~3070 ppm, and diortho cresyl phosphate ~ 6 ppm. These values are diluted by 33 fold after dilution in oil.'* [3]

"Aero bearing seals are required to operate at high speeds necessitating either a well lubricated seal or one that operates with a clearance. [2,4] *All dynamic seals are designed to leak."* [5] Therefore *"oil bearing seals are not an absolute design and will allow low-level oil leakage over the seals into the compressor and bleed air supply as a normal function of the engine cycle. Lower-level oil leakage is not exclusive to failure or mechanical abnormalities."* [2,6] This design system is supported by an increasing number of cabin air monitoring studies that are routinely identifying the synthetic jet engine lubricants in the aircraft bleed air supply and cabin. TCP (CAS 1330-78-5) including the meta and para isomers are routinely being identified during the 38 plus air monitoring studies that are publicly available, the most recent being a major study undertaken by the European Aviation safety Agency. [7]

Therefore it is expected that low levels of TCP (meta and para isomers) will leak into the cabin air supply during normal engine operations. EASA stated that *"Based on reports and technical considerations, most engines might have a certain turbine oil leak rate."* [7] This is supported by reports from several decades ago such as:

- *"Air bled from the compressors of some high compression ratio turbojet engines is contaminated because of internal oil leakage into the compressor air…… the compressor bearing seals are the main source of oil leakage."* [8]
- Evaporation loss of oil *"constitutes only a minor part of the oil consumption in Rolls-Royce gas turbines, the major part of the consumption representing loss of liquid oil arising from permissible leakage past certain seals, escape of mist or aerosol through breathers and losses incurred during filter inspections in service." These losses are made good by 'topping up' the system with fresh oil."* [9]

The pattern of effects being seen in aircrew who are routinely working in the aircraft cabin (pilots and cabin crew) are consistent with exposure to organophosphates including TCP mixed isomers including TmCP and TpCP, as well as other oil, hydraulic fluid and pyrolysis products. The supporting data is briefly highlighted below.

1. A clear pattern of acute and chronic effects as well as jet oil and other aircraft fluid exposures, along with medical findings and diagnoses have been reported [10] The effects seen include neurological, neurobehavioural, respiratory, gastrointestinal, irritant, cardio, rheumatological, fatigue, and other effects. These were examined alongside effects expected from exposure to the substances in the fluids used in aircraft and there was a clear cause and effect pattern seen. The diffuse non specific nature of the reported effects is consistent with "chronic low dose exposure to OPs." [10]
2. Research undertaken by Terry [11,12] addressing chronic low-dose exposure to OPs is consistent to what has been reported by Michaelis et al. (2017). [10]

    - *"The mechanism of the acute toxicity of OPs in both target and non-target organisms is primarily attributed to inhibitory actions on various forms of cholinesterase leading to excessive peripheral and central cholinergic activity. However, 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. This type of exposure has been associated with prolonged impairments in attention, memory, and other domains of cognition, as well as chronic illnesses where these symptoms are manifested (e.g., Gulf War Illness, Alzheimer's disease). Due to their highly reactive nature, it is not surprising that OPs might alter the function of a number of enzymes and proteins (in addition to cholinesterase). However, the wide variety of long-term neuropsychiatric symptoms that have been associated with OPs suggests that some basic or fundamental neuronal process was adversely affected during the exposure period. The purpose of this review is to discuss several non-cholinesterase targets of OPs that might affect such fundamental processes and includes cytoskeletal and motor proteins involved in axonal transport, neurotrophins and their receptors, and mitochondria (especially their morphology and movement in axons*)." [11]

    The clinical picture is further complicated by at least 3 factors. [13]

1. The complexity of the mixture to which crews are exposed and enhancement [14] of OP toxicity in mixtures.
2. Wide variability between individuals to metabolize and detoxify OP compounds. [15]
3. Low dose repeated exposure to OPs has been demonstrated in vitro to increase vulnerability of neurons to a subsequent high dose event. [16]

A further explanation identifying that some of the interactions between low dose OPs and biological matrices being delayed and irreversible is discussed in Howard et al (2018). [5]

An additional area of concern now involves the release of ultrafine particles (UFPs) identified by Jones et al. (2018) when reporting that *"measurements showed that oil contamination in the compressor will result in a fog of very fine droplets in the bleed air under most operating conditions. Typically these droplets are in the 10-150 nanometer range*." [17] The issue of OPs and other substances piggybacking on the UFPs across the blood brain barrier and increasing the OP toxicity is discussed in Howard et al. (2018) [5]

Several further major issues are outlined in brief as follows:

1. Occupational exposure limits and TLVs are not protective of aircrew exposed to jet oil and other aircraft fluid emissions in flight. By examining a range of publicly available aircraft air monitoring data it is very clear that impairment, incapacitation and acute and chronic ill health is occurring at levels far below exposure limits and TLVs. In the case of exposure to TCP (CAS 1330-78-5) mixed isomers, TmCP and TpCP, incapacitation and impairment has been repeatedly reported in a variety of ways at levels far below the OELs and TLVs. Fume events, associated with engine oils generally without smoke, or in some cases even an odour, have caused minor through to major effects to the flight crew in flight, yet measurements undertaken show levels far below the TLVs and OELs. It is quite clear that crews exposed regularly to a low-dose of oil fumes in the cabin are displaying very different effects generally to those exposed occasionally. Further information can be found in our 3 recently published papers addressing this topic. [5,10,13]

2. Crews are not exposed to individual isomers of TCP. As indicated by Mobil above [3], jet oil exposure will involve exposure to a wide range of the TCP isomers and triaryl phosphates. Therefore there ought to be at least a TLV covering the exposure to the mixed isomers of TCP 1330-78-5.

3. TLVs should not be applied to the environment of an aircraft cabin. This is very well acknowledged by your own ACGIH under the section Appendix F on minimal oxygen content and appendix E covering mixtures. In this case crew are working at cabin altitudes up to 8000 feet and are exposed by design to a complex mixture of jet oil emissions and the pyrolysis and thermally degraded products, including TCP mixed isomers, ToCP, MoCP, DoCP, TmCP and TpCP. It is widely acknowledged within the aviation industry that TLVs and OELs are not applicable to the unique aircraft cabin environment. Many of these can be seen in a report I have prepared and made publicly available. [18] These include clear references by scientists from the 1950s and ExxonMobil referencing the inappropriate use of the ToCP TLV. They are suggesting reference must be made to TCP as a whole, while the World Health organization, suggests there is no safe level of exposure to ToCP. The same rationale should apply to non ortho isomers of TCP.

However the aviation industry and Government's continue to apply the TLVs and OELs to the aircraft cabin environment inappropriately and suggest all levels identified are below such limits. Given that acute and chronic ill health are being cited, consistent with jet oil and other aircraft fluid emissions, including TCP at levels far below published limits, I urge true caution when applying any new limit.

4. Another point of interest are 2 references identifying adverse effects associate with exposure to the non ortho isomers of TCP.
    - In 1954 Aldridge reported that TmCP and TpCP showed *"traces of demyelination in the spinal cord."* [19]
    - In 2012 Baker et al. reported that TpCP and DURAD 125 (the commercial formulation of TCP used in many engine lubricants) inhibited various enzymes. [20]

5. TCP inhalation toxicity studies have not been undertaken except for a couple of early US military studies that identified toxicity. ExxonMobil has reported that it's studies have been via oral ingestion and dermal application, [21–25] while the European Chemicals Agency (ECHA), recently reported on *"the lack of data covering all aspects of possible neurotoxicity and …. lack of inhalation studies"* for TCP. [26] Therefore I urge caution when applying oral and dermal studies to an environment in which humans are exposed via inhalation.

I would be happy to discuss this further with you & to provide a more comprehensive review.

D. ***Citable Material*** *– Provide citable material to substantiate the rationale.*

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11. Terry AJ. Functional Consequences of Repeated Organophosphate Exposure: Potential Non-Cholinergic Mechanisms. *Pharmacol Ther NIH Public Access* 2012; 134: 355–365.

12. Gao J, Naughton SX, Beck WD, et al. NeuroToxicology Chlorpyrifos and chlorpyrifos oxon impair the transport of membrane bound organelles in rat cortical axons. *Neurotoxicology* 2017; 62: 111–123.

13. Howard C, Michaelis S, Watterson A. The Aetiology of ' Aerotoxic Syndrome ' - A Toxico-Pathological Viewpoint. *Open Acc J Toxicol* 2017; 1: 1–3. https://juniperpublishers.com/oajt/pdf/OAJT.MS.ID.555575.pdf

14. Axelrad JC, Howard C V., McLean WG. Interactions between pesticides and components of pesticide formulations in an in vitro neurotoxicity test. *Toxicology* 2002; 173: 259–268.

15. Cherry N, Mackness M, Mackness B et al. 'Dippers' flu' and its relationship to PON1 polymorphisms. *Occup Environ Med* 2011; 68: 211–217.

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Kind regards

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