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Commentary

Health risk assessment of exposure to TriCresyl Phosphates (TCPs) in aircraft: A commentary

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ABSTRACT

Possible exposure to TriCresyl Phosphates (TCPs) has led to concerns among airline crew members. One isomer, Tri-*ortho*-Cresyl Phosphate (ToCP) is known to be neurotoxic and exposure to ToCP via contaminated cabin air has been suggested to be associated with the alleged Aerotoxic syndrome. The symptoms associated with Aerotoxic syndrome are diverse, including headaches, loss of balance, numbness and neurobehavioral abnormalities such as emotional instability, depression and cognitive dysfunction. Other *ortho*-isomers are toxic as well, but the non-*ortho* isomers are regarded as less toxic.

In a collaborative effort to increase insight into the possible association between exposure to TCPs via contaminated cabin air and Aerotoxic syndrome, we performed an exposure- and toxicological risk assessment. Measurements in KLM 737 aircraft have demonstrated the presence of non-*ortho* isomers in low concentrations, though ToCP and other *ortho*-isomers could not be detected. Based on this exposure assessment, we established a toxicological risk model that also takes into account human differences in bioactivation and detoxification to derive a hazard quotient. From this model it appears unlikely that the health effects and alleged Aerotoxic syndrome are due to exposure to ToCP. Alternative explanations for the reported symptoms are discussed, but evaluation of the current findings in light of the criteria for occupational disease leads to the conclusion that the Aerotoxic Syndrome cannot be regarded as such. Additional research is thus required to unravel the underlying causes for the reported health complaints.

1. Introduction

As a result of a major human exposure event in the 1930s, information on the delayed (peripheral) neurotoxicity of tricresyl phosphate (TCP) has been gathered over the decennia (Kidd and Langworthy, 1933). This major human exposure event was the result of consumption of (large) amounts of so-called Jamaica ginger as a consequence of the Prohibition laws. This Jamaica ginger was contaminated with tri-*ortho*-cresyl phosphate (ToCP), which was later proven to be a neurotoxic compound that causes axonal damage to the nerve cells in the (human) nervous system. Other TCPs, in particular other *ortho*-cresol-containing isomers, may have similar effects as ToCP, while the *meta*- and *para*-cresol containing isomers are generally considered less toxic (Henschler, 1958).

In more recent years, TCPs have been used as e.g. plasticizer, flame retardant and additive in lubricants, hydraulic fluids and engine oil. Due to the use of TCPs in these applications, human exposure to TCPs could occur in occupational settings, e.g. in the cockpit and cabin of aircraft as a result of leakage of engine oil into the air conditioning systems during flight. The possibility of such exposures to TCP isomers in cabin air has led to concerns among airline crew members since it has been suggested that exposure to ToCP may affect the health of pilots and cabin personnel, resulting in the so-called Aerotoxic syndrome (Winder et al., 2002; Ross, 2008; Furlong, 2011; Abou-Donia et al., 2013).

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Symptoms of Aerotoxic syndrome are diverse and include headaches, confusion, loss of balance, muscle weakness, numbness and neurobehavioral problems (Abou-Donia, 2003; Michaelis, 2003; Coxon, 2002; van Netten, 1999; Montgomery et al., 1977). As a consequence of the proposed association of exposure to ToCP with Aerotoxic syndrome symptoms, the level of ToCP in commercial TCP mixtures has been reduced over time (DeNola et al., 2008). On the other hand, the suggested association of exposure to ToCP with Aerotoxic syndrome symptoms requires confirmation as (occupational) exposure to cabin air is also known to increase exposure to pathogens, carbon dioxide, barometric pressure changes, noise/vibration, radiation and numerous other factors that may affect health (Abeyratne, 2002; Hocking, 2002; Rayman, 1997). KLM Health Services therefore invited a number of experts from the Institute for Risk Assessment Sciences (IRAS-Utrecht University), the Netherlands Center for Occupational Diseases (NCvB-University of Amsterdam), the Leiden Academic Centre for Drug Research (LACDR-Leiden University) and the European Society of Aerospace Medicine (ESAM) to perform an exposure- and toxicological risk assessment of TCPs to increase insight into the possible association between exposure to TCPs via contaminated cabin air and the alleged Aerotoxic syndrome. To that aim, KLM Royal Dutch Airlines and the Netherlands Organization for Applied Scientific Research (TNO) recently collected data on TCP exposure in the cockpit during a number of flights (Houtzager et al., 2013). In this commentary, the results and implications of these analyses will be discussed in the light of known biological and toxicological effects after exposure to ToCP, the TCP isomer for which most information is available. This commentary will not address exposure during so-called fume events, but focuses on the possible risk of chronic exposure at low concentrations for air crew members.

2. Exposure assessment of TCP isomers in the cockpit

Boeing's 737 is the most widely used aircraft with first production in 1967 and over 8000 aircraft produced till mid-2014. The Dutch independent research organization TNO has measured concentrations of TCP isomers inside the cockpit during 20 flights of nine different Boeing 737-700, -800 and -900's aircraft (Houtzager et al., 2013). During each of the 20 flights, four air samples were taken inside the cockpit: one during climb, one during descent, one during cruise and finally one sample from the whole flight, covering all three phases thus representing a time-weighted average. In addition, wipe samples were taken from the glare shield before and after each flight.

For five TCP isomers pure analytical standards were available and used for quantification after chemical analysis using gas chromatography–mass spectrometry (GC–MS). These standards included T(*o*,*o*,*o*)CP (which is ToCP), and the four isomers with only the *p*- and *m*-cresols: T(*m*,*m*,*m*)CP, T(*m*,*m*,*p*)CP, T(*m*,*p*,*p*)CP and T(*p*,*p*,*p*)CP. Pure analytical standards of the other T(*o*)CPs are not available; however, the GC–MS method employed would have allowed their detection based on molecular mass without elucidating the isomeric structure. Detection and quantification of the TCPs by GC–MS was done as described previously (DeNola et al., 2008; Solbu et al., 2007).

Results from this exposure assessment demonstrated that ToCP levels in the cockpit air samples were below the limit of detection, which varied slightly depending on the length of the flight (0.3–0.75 ng/m^3). The other TCP isomers could be detected in the ng/m^3 concentration range in 10 out of 20 flights (see Table 1). In the remaining flights all TCPs were below the limit of detection.

During climb, 12 of the 20 flights were negative. However, this phase also showed the single highest level of total TCPs observed in this study, 155 ng/m^3. In the whole flight sample a maximum concentration of total TCPs 32 ng/m^3 was observed. It should be noted that the median values for flights with positive detection of TCPs were (much) lower than their mean values. This observation reflects the comparatively very high values of the apparent incidental outliers. These incidental high maximum values may suggest that rather than gaseous TCP dissolved in air, small TCP-containing particles may be (infrequently) released in the air provided to the cockpit (CAA, 2004). This would also explain why the minimum value for the 'whole flight' measurement can be lower than the minimum values for all three separate flight phases (Table 1). Further investigations are required to substantiate this suggestion.

Table 1
Exposure assessment of total TCPs in 20 flights with nine Boeing 737s. Samples were collected at different phases of the flight and TCP values are expressed in ng/m^3. Mean and median values are calculated from the 'positive flights' only, with the number of positive flights indicated between brackets.

Total TCPs	Flight phase			
	Climb	Cruise	Descent	Whole flight
Minimum	1.8	0.53	1.3	0.27
Maximum	155	17	66	32
Mean	25 (8)	4.7 (9)	15 (10)	6.9 (9)
Median	5.9 (8)	2.9 (9)	6.0 (10)	2.9 (9)

Collectively, the results from the chemical analyses show that during many of the investigated flights none of the TCPs could be measured above the detection limit of approximately 1 ng/m^3. In those flights where TCPs were detected, the levels were in the ng/m^3, but could vary up to two orders of magnitude (see Table 1). From a toxicological point of view it is interesting to note that ToCP was not detectable in any of the 20 flights that were studied.

Results from the wipe samples of the glare shield demonstrated the presence of small amounts of TCP isomers, at levels below 0.1 ng/cm^2. Again, ToCP was not detected on the glare shield of these Boeing 737's, which is in line with its absence in the cockpit air samples. Subsequent analysis of the engine oil from BP used in these Boeing 737s also showed that ToCP was not detectable, giving further support to the absence of ToCP in the cockpit air and on the glare shield. In fact, none of the *ortho*-containing TCPs could be detected in engine oil by GC–MS. Notably, according to the manufacturer, the oil used contains less than 0.2% *ortho*-isomers (typically *ortho*-isomers range 0.03–0.06%), which would be below the current level of detection. Roughly equal shares of *meta*- and *para*-containing TCP isomers were present in the engine oil. Although the pure reference compounds were not available, the used detection method would have allowed for the detection of any peaks of *ortho*-containing TCPs. Interestingly, the chemical analysis revealed a strong correlation of the non-*ortho* TCP isomeric profile in the engine oil and the cockpit air and wipe samples. This observation supports the suggestion that the non-*ortho* TCPs found in the cockpit indeed originate from (leakage of) the engine oil.

3. Biomonitoring of TCP exposure

3.1. Adducts of ToCP with butyrylcholinesterase

Liyasova et al. (2011) developed a test to determine (long-term) exposure to ToCP, in particular to its proposed toxic metabolite, 2-(2-cresyl)-4H-1,3,2-benzodioxaphosphorin-2-oxide (CBDP). The basic assumption is that cytochrome P450 (CYP) mediates the conversion of ToCP to its reactive metabolite CBDP (Fig. 1), which has been proposed to be the (major) causal agent for ToCP-induced delayed neurotoxicity (Aldridge, 1954; Eto et al., 1962). At present, it still remains to be determined which human P450 enzyme(s) is (are) involved in this bioactivation.