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Letter to the Editor

Reply to letter to the editor

To the Editor,

In 2013, an airline pilot with health problems started a lawsuit against his employer KLM Royal Dutch Airlines. Based on the exposure data available at that time (Cranfield University, 2011), toxicologists from the Institute for Risk Assessment Sciences (IRAS-Utrecht University) concluded that it could not be excluded that ToCP was a possible causal agent. Also based on this statement, KLM was eventually court-ordered to prove that the occupational environment was safe to work in by performing a TCP exposure assessment in the cockpit of some of its Boeing 737s. To that aim, KLM Royal Dutch Airlines commissioned the Netherlands Organisation for Applied Scientific Research (TNO) to measure TCP levels in the cockpit during flight (Houtzager et al., 2013).

Next, KLM Health Services 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 a toxicological risk assessment of TCPs to increase insight into the possible association between exposure to TCPs through contaminated cabin air and symptoms of the alleged aerotoxic syndrome (AS).

Our commentary (de Ree et al., 2014) is the outcome of the expert meeting. Results and implications of the on-board measurements were discussed in the light of known biological and toxicological effects of exposure to ToCP, the TCP isomer for which most information is available. Due to a lack of documented and characterized exposure data, our commentary explicitly did not address exposure (to TCPs or other chemical oil constituents) during so-called fume events, but focused on the risk for aircrew members of chronic TCP exposure at low concentrations during normal operation. However, this logical focus on chronic TCP exposure relates directly to the common concern of the letter writer: Given the presence of numerous potentially toxic compounds in aircraft engine oil and thus possibly also in cabin air, a health risk assessment of only TCP appears too limited.

While this is likely true, it is important to note that the large majority of (recent) papers on AS suggest a potential relationship with TCP or the ToCP metabolite CBDP. This emphasis on TCPs appears justified given that the limited research in which non-*ortho* TCP isomers were included (e.g. Henschler, 1958, also see sections 1 and 6 of de Ree et al., 2014) indicates that non-*ortho* isomers are less toxic. However, it may also be indicative of an incomplete hazard characterization of the different TCP isomers. This is why we argued throughout our commentary for additional research to include non-*ortho* isomers as well as for investigation of additional modes of action (sections 6 and 9 of de Ree et al., 2014), basically inline with the concerns of the letter writer.

Although the symptoms of AS currently do not constitute an occupational disease in the Netherlands, it should be noted that we do not question the reported health effects. However, as outlined in this response and the risk assessment in our commentary, we do consider it highly unlikely that the reported, diverse health effects are related to current ToCP exposure levels. This is inline with the notion of Dr. Anderson that ToCP levels in cabin air will be low given the composition of aircraft engine oil (this notion is confirmed in the exposure assessment of Houtzager et al., 2013). We therefore pleaded for investigating alternative explanations and additional (chemical or physical) exposures (e.g. sections 1, 6 and 7 of de Ree et al., 2014).

All in all, our commentary as well as the letter from Dr. Anderson clearly indicates that the health risk associated with ToCP exposure is limited, highlighting the need for alternative explanations for the reported health symptoms. This is exactly why we argued for a full hazard characterization of *ortho*- and non-*ortho*-containing TCP isomers, investigation of different modes of action as well as other alternative explanations (sections 1, 6 and 7 of de Ree et al., 2014). The potential link between TCP – Ces1 and/or APH – aerotoxic syndrome-associated health effects, as suggested by Dr. Anderson, is currently hypothetical. The same holds for the potential endocrine disruptive and/or non-linear dose–response properties. Nevertheless, these could be good suggestions for further research to reveal other modes of action of TCPs, as already argued for in our commentary. While the study by Hausherr et al. (2014) does not describe any clinical effects as suggested by Dr. Anderson, it is a good example of a successful attempt to derive a more complete hazard characterization of ToCP and thus fully inline with the recommendations in our commentary.

Conflicts of interest

Hans de Ree and Brinio Veldhuijzen van Zanten are employed by KLM Health Services; Gerard J. Mulder acts as contracted advisor of KLM Health Services; and Teus Brand acts as independent advisor of KLM Health Services. The other authors do not have any competing financial interest or any other conflict of interest regarding the submitted article.

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