Updated literature on potential health risks from organophosphate exposure in aircraft cabin air

This is a draft statement for discussion.

It does not reflect the final views of the Committee and should not be cited.

Introduction

1. In 2007, the Committee on Toxicity (COT) published a statement on aircraft cabin air, relating to organophosphate (OP) compounds, the cabin air environment, ill-health in aircraft crews and the possible relationship to smoke/fume events in aircraft (COT, 2007). Subsequently, the COT reviewed the results of DfT-funded aircraft cabin environment research commissioned in response to recommendations made by COT in 2007, after which the COT issued a position statement on cabin air (COT, 2013).

2. The COT has now been asked by DfT to investigate any new data have been published and to re-evaluate their previous view in the original statement from 2007 (COT, 2007) and position statement from 2013 (COT, 2013). Following the May 2022 COT meeting, the request of COT has been further refined to: "Is there evidence of exposure to chemical contaminants in cabin air that could have long-term health impacts, either from acute exposures or due to long-term low level exposures including mixtures, e.g. of VOCs?"

Background

3. The COT reviewed an introductory paper on this topic in May 2022 (<u>TOX/2022/30</u>), which provides a full background on the Committee's previous conclusions.

4. Specifically with respect to organophosphates, the Committee previously considered that "The patterns of illness that have been reported

following fume events do not conform with that which would be expected from exposure to triaryl phosphates such as ortho-tricresyl phosphate (o-TCP) [to note in this paper tri-ortho-cresyl phosphate (ToCP) is used for the same compound] (which differs from the pattern of illness that occurs with over-exposure to organophosphate insecticides and nerve agents). Over-exposure to tricresyl phosphates would be expected to cause delayed peripheral neuropathy. Given the short duration of reported fume incidents, in order to cause such toxicity, peak exposures would have to be much higher than those which have been indicated by monitoring to date" (COT, 2013).

Current paper

5. Literature searches were carried out using the original search terms, inclusion and exclusion criteria, focussing on literature published between 2013 and 2021. The searches were limited to the chemicals included in the original searches, which largely focussed on OP-type chemicals.

6. The current paper presents the five papers identified from these searches for which the title and abstract was considered to possibly be of relevance; two were primary research papers (Reneman et al. 2016 and Heutelbeck et al. 2016), two were review papers (de Boer et al. 2015 and Wolkoff, Crump and Harrison (2016) and de Ree et al. (2014) carried out a risk assessment.

7. Further papers are planned to cover other aspects flagged in the introductory paper (TOX/2022/30).

Papers

Reneman et al. (2016)

8. Reneman et al. (2016) investigated whether they could objectify cognitive complaints in aircrew and find a neurobiological cause of the symptoms reported.

9. Participants consisted of aircrew (pilots, flight attendants and one platform supervisor; n=12) that exhibited cognitive complaints and visited a clinic for occupational neurological disease due to experiencing cognitive complaints shortly after flying. Air crew had normal neurological examinations and were aged between 29 and 55 years of age. Flying hours were used as a proxy for exposure

to OPs and were estimated from self-reported questionnaires. Air crews with a history of neuropsychiatric disease, alcohol abuse, diabetes mellitus, liver and kidney insufficiency, endocrine disease, malignancy, contraindications for magnetic resonance imaging (MRI) or claustrophobia were excluded from the study. Controls (n=11) consisted of healthy volunteers, primarily race car drivers, who did not professionally fly, matched for gender, age and IQ. Race car drivers were selected as they have response capabilities similar to those required by aircrew, particularly pilots.

10. Depressive symptoms were assessed with the centre for epidemiological studies depression scale and subjective cognitive symptoms were assessed with the Medical Outcomes Study (MOS) scale. Fifteen widely used standardised psychometric neurophysiological tests were selected based on their sensitivity for measuring potential neurotoxic effects of engine oil fumes. Diffusion tensor imaging (DTI) was used to provide information on axonal integrity by measuring diffusional motion of water molecules using fractional anisotropy (FA).

11. As TCP and other OPs are potent inhibitors of acetylcholinesterase (AChE), brain neuro-metabolism with proton MR-spectroscopy including choline containing compounds was carried out. In addition, cerebral blood flow was assessed non-invasively using arterial spin labelling. Executive function was also tested using functional MRI.

12. The aircrew and controls did not significantly differ on age, gender or IQ. Aircrew had an average of 8,130 flying hours compared to 233 in the controls.

13. The aircrew showed significantly more self-reported cognitive complaints on the MOS scale compared to controls as well as more depressive symptoms.

14. The average number of abnormal neuropsychological performance tests were significantly different between aircrew and controls. On average 1.7 tests were abnormal in aircrew compared 0.5 in the controls. However, the groups did not significantly differ in their mean scores on individual neurocognitive outcome measures except for working memory, where aircrew performed better, and two reaction time measures, where aircrew performed significantly poorer than controls.

15. Neuroimaging showed small but significantly lower FA values in aircrew in specific white matter regions, indicative of brain white matter microstructure being affected. In line with this, no brain region was found in which FA was higher

than the controls. A significantly higher cerebral blood flow was also seen in the left occipital cortex in aircrew. Significant differences were seen in blood-oxygenlevel-dependent (BOLD) activation in the precuneus and right prefrontal cortex where aircrew showed significantly less brain activation than controls.

16. The extent of cognitive complaints was positively correlated with the extent of abnormal tests such that the more cognitive complaints a subject reported, the higher the number of abnormal neuropsychological tests that were obtained. A similar relationship was seen for depressive symptoms where the extent of cognitive complaints predicted the extent of depressive complaints. Moreover, the number of neuropsychological tests that were impaired in aircrew was negatively correlated with FA in two white matter regions implicated in cognition, with two significant clusters being identified in the right middle cerebellar peduncle and the right posterior corona radiata. The extent of cognitive impairment was also associated with the estimated number of flight hours controlled for age at testing. However, the estimated number of flight hours was not associated with reductions in FA, which showed an inverse trend of reverse association.

17. Overall, the authors concluded that the extent of cognitive impairment correlated with the extent of cognitive complaints and depressive symptoms and was strongly associated with white matter integrity, but the extent of estimated number of flight hours or reductions in white matter microstructure were not associated with cognitive impairment. However, defects in brain white matter microstructure and cerebral perfusion were potential neurobiological substrates for cognitive impairments and mood deficits reported in aircrew.

Heutelbeck et al. (2016)

18. Heutelbeck et al. (2016) investigated individual AChE and neuropathy target esterase (NTE) activities in flight crew members experiencing fume events.

19. Eleven flight crew (nine female and two males, ages 23-58 years) requested medical examination at the Environmental Outpatient Department within five days of a fume event. A face-to-face medical examination was conducted for patients as well as neurocognitive tests. Data were compared against age-matched and, if applicable, education-matched population reference values. The neurocognitive testing was comparable to that carried out by Reneman et al., 2016.

20. Individual AChE activities in erythrocytes were determined using a ChE check mobile kit. NTE activities were determined from isolated lymphocytes using a human biomonitoring standard procedure (Lewalter et al., 2012 cited in Heutelbeck et al., 2016).

21. All patients showed signs of intoxication attributed to (neuro)toxic agents, including irritation of skin and mucosa, effects on respiratory system and gastrointestinal tract and peripheral/central nervous system. The most common symptoms were cognitive disorders (11 of 11 cases), fatigue (9/11), headache/muscle pain (8/11), motor disorders/paraesthesia/hemiplegic symptoms (7/11), gastrointestinal symptoms (7/11) and respiratory distress/pain while breathing/chest pain (6/11). Other symptoms included vertigo/loss of balance (4/11), disturbances of consciousness (4/11), ravenous appetite/thirst (3/11), increased salivation/seating (3/11), vision/hearing problems (2/11), mood changes, muscle twitching and impaired sensual perception (1/11), the intensities of which varied considerably.

22. The AChE values of aircrew were all within the reference range of the assay (26.5-50.9 U/g haemoglobin) ranging from 37.0 to 50.0 U/g haemoglobin, hence authors stated that no marked inhibition of AChE was detectable. Authors suggested that the AChE activities indicated a subordinate contribution of OPs to the symptoms reported.

23. Ten air crew showed NTE activities in the range of 3.14-6.3 nmol phenyl valerate/(min x mg protein) and one showed low NTE activity of 1.4 3 nmol phenyl valerate/(min x mg protein). Overall, NTE activities from air crew members were lower than those of the reference collective. The authors suggested that the NTE inhibition may be regarded as the first indicator for the onset of organophosphorus-induced delayed neuropathy (OPIDN) and correlated with the symptoms reported with medium and high frequency, which have the potential to be indicative for developing OPIDN.

24. Overall, authors concluded that the laboratory parameters were in agreement with the described symptoms but can only account for a minor portion of the signs of intoxication and other yet identified chemicals may play a role in the toxicity observed. Moreover, it was not possible to infer a direct correlation between manifestations and AChE-inhibiting compounds.

de Ree et al. (2014)

25. de Ree et al. (2014) discussed the results and implications of data obtained from an exposure- and toxicological risk assessment of TCPs during which data on TCP exposure were collected in the cockpit during a number of KLM Royal Dutch Airline flights. Such analyses were discussed in the light of known biological and toxicological effects after exposure to orthoTCP in particular. Exposure during fume events were not reported as the focus was on the possible risk of chronic exposure at low concentrations for air crew members.

26. Concentrations of five TCP isomers were measured inside the cockpit during 20 flights of nine different Boeing 737-700, -800 and -900's aircraft (Houtzager et al., 2013 as cited in de Ree et al., 2014). During each flight, four air samples were taken: one during climb, one during descent, one during cruise and one from the whole flight, covering all three phases thus representing a timeweighted average. In addition, wipe samples were taken from the glare shield before and after each flight.

27. The five TCP isomers were quantified using gas chromatography-mass spectrometry (GC-MS) were tri-ortho-cresyl phosphate (T(o,o,o)CP; ToCP), and the four isomers with only the p- and m-cresols: tri-meta-cresyl phosphate (T(m,m,m)CP), T(m,m,p)CP, T(m,p,p)CP and tri-para-cresyl phosphate (T(p,p,p)CP).

28. Authors reported that ToCP levels in the cockpit air samples were below the LOD, although this varied slightly, ranging between 0.3–0.75 ng/m3 depending on the length of the flight. The other TCP isomers could be detected in the ng/m3 concentration range in ten out of 20 flights, ranging between 0.27 ng/m3 (whole flight) to 155 ng/m3 (when climbing). In the other ten flights all TCPs were below the LOD (0.5 ng/m3).

29. During the climbing phase of the flight, TCP was detected in eight flights, with total TCP concentrations ranging from 1.8 to 155 ng/m³, with a mean and median of 25 and 5.9 ng/m³, respectively. No TCPs were detected in the other 12 flights during the climbing phase. During cruising, TCP was detected in nine flights with values ranging from 0.5 to 17 ng/m³, with a mean and median of 4.7 and 2.9 ng/m³, respectively, and during descent, values were between 1.6 and 66 ng/m³, with a mean and median of 15 and 6 ng/m³, in ten flights in which TCP was detected. Overall, during the whole flight, values were between 0.27 and 32 ng/m³ (mean and median of 6.9 and 2.9 ng/m³, based on nine flights). Although not discussed by the authors, the lower value of 0.27 ng/m³ is below the reported limit of detection of 0.3 – 0.75 ng/m³.

30. Across the flights in which TCPs were detected, the authors noted that the median concentration of TCPs was much lower than the mean concentration reflecting comparatively high maximum concentrations detected, compared to the rest of the samples. Authors stated that such high incidental maximum values may suggest that small TCP-containing particles may be released into the cockpit air rather than gaseous TCP dissolved in air, explaining why the minimum value for the whole flight is lower than the minimum value for all three separate flight phases (CAA, 2004 as cited in de Ree et al., 2014), although authors suggested that further work is needed to substantiate this.

31. As well as ToCP not being detected in cabin air, it was not detected on the glare shield nor in engine oil. Analysis also failed to measure other ortho-TCPs in the engine oil.

32. Based on the exposure assessment of Houtzager et al., 2013, de Ree et al. (2014) developed a toxicological model to derive a Hazard Quotient (HQ) for ToCP. As no ToCP was detected above the LOD, the average detection limit of 0.5 ng/m³ was used as the maximum exposure for cockpit crew. A daily exposure of six flight hours was assumed, based on three 2-hour flights per day. An average air consumption of 3 m³ was also assumed. Therefore, the maximum intake was 0.02 ng/kg bw/day for a 70 kg adult, based on a detection limit of 0.5 ng/m³ and 100 % bioavailability (step 1 of the toxicological model).

33. This intake was initially compared to the no observed adverse effect level (NOAEL) of 1.25 mg/kg bw/day, determined from a 90-day study in chickens carried out by Craig and Barth (1999; as cited in de Ree et al., 2014). However, for the HQ model, a NOAEL of 1 mg/kg bw/day was used and an uncertainty factor (UF) of 5 was applied to the NOAEL (step 2). Authors stated that 'the combined toxicity studies with two non-rodent animal species – chicken and cat – indicate a close similarity in NOAELs and the lowest observed adverse health effect (LOAEL) for ToCP. From a neurotoxicity point of view these two species are also considered to represent the human sensitivity rather well. It is therefore not necessary to add an additional (UF) for comparison with the human situation (UF = 1)'.

34. To account for differences in cytochrome P450 and paraoxonase-1 enzymes (enzymes involved in the metabolism of ToCP), UFs of 100 and 40 were used, respectively. As a result, a combined UF of 4000 for these enzyme differences x 5 as above was used to account for metabolism and clinical/neuropathological symptoms and neurobehavioral effects and was applied to the NOAEL of 1 mg/kg bw/day. This gives a tolerable daily intake (TDI) of 50 ng/kg bw/day for the most sensitive population of cabin crew (step 3).

35. Comparing the estimated exposure of 0.02 ng/kg bw/day with the TDI of 50 ng/kg bw/day gives a HQ of 0.0004 (0.02/50), which the authors noted was four orders of magnitude lower than a HQ >1 which would indicate a health concern.

36. Authors noted a number of limitations to their model. Firstly, the HQ is derived based on a worst-case scenario regarding differences in individual enzyme activities, focusing on a highly sensitive subpopulation. Secondly, it only applies to the Boeing 737s from KLM studied for the exposure assessment using the specific engine oil. Authors noted that the exposure assessment may have been different in the past, for other aircraft models or flight schedules and with other engine oils. The existence of different exposure scenarios is supported by an earlier study by Cranfield University, which found ToCP levels in the range of 1–20 mg/m³ (Cranfield University, 2011), corresponding to a HQ of 1–20. This represents a potential health risk for sensitive individuals that have both a high cytochrome P450 and low paraoxonase-1 activity. Lastly, the model does not take into account the occurrence of fume events during which exposure to ToCP has the potential to be higher than normal flight scenarios used in the model.

37. Overall, authors concluded that an exposure assessment of ToCP in 20 flights of nine Boeing 737s from KLM, have shown no ToCP concentrations above the detection limit of 0.5 ng/m³. Using a risk assessment model with detection limits of ToCP as intake values, it is unlikely that health effects and aerotoxic syndrome are due to exposure to ToCP in isolation.

De Boer et al. (2015)

38. de Boer et al. (2015) investigated the current gaps in knowledge regarding 'aerotoxic syndrome' of flight crews and described the analysis, toxicity and comparison of TCP levels with threshold values, as well as other opinions regarding the cause of aerotoxic syndrome.

39. Cold air from outside the aircraft is heated by the engines and supplied to the cabin and flight deck. When passing through the engine, small amounts of engine or jet oil, which contain traces of additives, can accumulate in the air. TCP is one of the most commonly used additives which is known to be neurotoxic.

40. During a fume event, seals within the engine leak and smoke enters the flight deck, necessitating the use of oxygen masks by aircrew. Chronic exposure

to engine vapours that continuously leak from seals in small amounts may also occur. This has resulted in reports of 'aerotoxic syndrome', manifesting as tunnel vision, memory loss, headaches and other neurotoxicity symptoms.

41. TCP consists of ten isomers, which differ in the way the methyl groups are situated in the phenyl rings. The tri-otho isomer (0,0,0-TCP) is reportedly the most toxic, although some reports have indicated that isomers with only one ortho group exhibit up to 10-fold greater toxicity (Winder and Balouet, 2002, Hanhela et al., 2005 cited in de Boer et al., 2015).

42. The concentration of total-TCP measured in the flight deck air has been reported to be approximately 50-100 ng/m³ in various studies, although many results were below the limit of detection (LOD; value not reported) (De Nola, 2011; Solbu et al., 2011 cited in de Boer et al., 2015).

43. Solbu et al. (2011 cited in de Boer et al., 2015) reported only 4 % of 47 samples had measurable levels of TCP , with the highest concentration being 290 ng/m³.De Nola (2011 cited in de Boer et al., 2015) analysed 78 air samples from 46 different aircraft, of which 48 samples were found to be below the LOD (not reported). Nine incidents of smoke/odour were observed during monitoring but 0,0,0-TCP concentrations were still below the LOD in all samples whereas mono-ortho TCP was measured at a concentration of 0.2 ng/m³, although authors do not specify how many samples it was detected in. Schindler et al. (2012 cited in de Boer et al., 2015) analysed three TCP metabolites (0,0-, m,m- and p,p-dicresyl phosphate) in 332 urine samples. Only one sample had measurable amounts of m,m and p,p-metabolites which were close to the LOD. The authors stated that 'aerotoxic syndrome could hardly be attributed to an ortho-TCP exposure'.

44. De Boer et al. 2015 also compared measured concentrations of TCP with a threshold value for OPIDN of 1400 mg/day for a 70 kg adult, based on experiments in chickens (Mackerer et al. 1999 and Freudenthal et al. 1993 cited in de Boer et al., 2015). To account for an underestimation of toxicity due to the mono-ortho TCP and a variability in response, a safety factor of 100 was assumed, giving a threshold of 14 mg/day total TCP.

45. Craig and Barth (1999 cited in de Boer et al., 2015) determined a no effect level of 0.13 mg/kg bw/day, which corresponds to 9 mg/day for a 70 kg adult. Authors assumed 100 % uptake, and an inhalation volume of approximately 5 m³/hour. Therefore, the maximum concentration of 100 ng/m³ TCP would result in a maximum uptake of approximately 500 ng/hour or 5 μ g/10 hour flying

time/day, which is 1,800-fold lower than the no effect level of 0.13 mg/kg bw/day.

46. Authors noted that TCP concentrations during fume events may be higher but are largely unknown. However, the study by De Nola (2011 cited in de Boer et al., 2015) reported no o,o,o-TCP after one fume event that occurred during testing in a grounded aircraft but reported a 10-fold elevated total TCP level. However, no correlations of TCP levels with six other fume events were found.

47. As TCP concentrations did not directly explain the symptoms associated with 'aerotoxic syndrome', de Boer et al (2015) explored other possible toxicants that could be considered and noted that other phosphorus compounds such as dicresylphosphates and trixylenylphosphates (TCP with an extra CH3 group) may play a role (Winder and Balouet (2002 cited in de Boer et al., 2015). Centers (1992 cited in de Boer et al., 2015) and Wyman et al. (1993 cited in de Boer et al., 2015) reported the formation of trimethylolpropane phosphate (TMPP) from TCP and trimethylolpropane ester during elevated temperatures in ship turbines. As TMPP causes neurotoxic effects, Winder and Balouet (2002 cited in de Boer et al., 2015) hypothesised that it could be related to the observed health effects of pilots, although noted that although TMPP is associated with headaches and memory loss, it is also associated with epileptic attacks, which are not reported by the pilots. Carbon monoxide and ozone were also suggested to play a role.

48. Overall, authors concluded that 'TCP concentrations reported in the literature are much too low to explain the health effects reported by pilots. Unless TCP in the vapor phase is much more toxic than TCP when dosed orally, it is unlikely that chronic exposure to TCP levels only, 'normally' occurring in flight deck air of airplanes, cause neurotoxic effects such as OPIDN'. It was also noted that jet oils currently produced do not contain 0,0,0-TCP and other compounds from engine oil are present that could pose an additional effect in terms of human health effects, whether or not in combination with TCP.

49. Authors also reported that the new Boeing 787 ('Dreamliner') no longer makes use of the bleed air system, which reduces exposure to TCP.

Wolkoff et al. (2016)

50. Wolkoff, Crump and Harrison (2016) carried out a review of sensory effects in the eyes and airways and neurological symptoms such as headache reported in aircraft crew and office workers and their possible association with VOC and ToCP exposure. Authors also carried out a risk assessment of ToCP

exposure.

51. One study of 100 flights reported substantial maximum concentrations of ToCP but only in 5% of the samples, i.e. 95 % were below the limit of quantification (LOQ) of 120 ng/m3 (Crump et al., 2011 cited in Wolkoff et al., 2016). The maximum reported concentration of 22,800 ng/m3 ToCP represented a single reading out of approximately 1000 samples. Data from three other studies were below the LOQ of 75 ng/m3 (Solbu et al., 2011 cited in Wolkoff et al., 2016), below the LOD of 0.75–3 ng/m3 (Houtzager et al., 2013 cited in Wolkoff, Crump and Harrison, 2016), or were estimated as 1000 ng/m3 of ToCP and isomers (Denola et al., 2011 cited in Wolkoff, Crump and Harrison, 2016).

52. Authors noted a TDI of 50 ng/kg bw/day for ToCP was determined by de Ree et al. (2014) by applying an UF of 4,000 * 5 to a NOAEL of 1 mg/kg bw/day. Other researchers (de Boer et al., 2015 and Ali et al., 2012) calculated TDIs of 130,000 (footnote 1) or 13,000 ng/kg bw/day by applying UF of 100 or 1,000, respectively. The ECHA-derived inhalation no effect level (DNEL) of 80,000 ng/m³ for the general population and 50,000 ng/kg bw/day for oral intake was also mentioned.

53. A HQ was derived from the maximum daily intake by inhalation following an 8-hour exposure to the maximum reported air concentration of ToCP (22,800 ng/m³), assuming an inhaled volume of 7 m³ (20 m³ x 8/24 hour), 100 % absorption, and body weight of 70 kg.

54. Based on the maximum concentration of 22,800 ng/m³ recorded during measurements on 100 flights in the UK study by Crump et al. (2011), authors estimated a HQ of 46 (footnote 2) using the TDI of 50 ng/kg bw/day as determined by de Ree et al. (2014). A HQ of 0.58 was determined if the 95th percentile value (290 ng/m³) of the average concentration was used. Moreover, they stated that use of the higher TDI value of 130,000 ng/kg bw/day¹ determined by de Boer et al., 2015 would result in HQs of 0.018 and 0.0002, respectively.

55. Wolkoff et al. (2016) reported data from the study by de Ree et al. (2014), noting that in five studies ToCP was not detected, leading to a HQ of 0.001, assuming a LOD of 0.5 ng/m³ and a TDI of 50 ng/kg bw/day. In view of this, the conservative health risk assessment approach and the short infrequent exposure durations that are not necessarily associated with ToCP exposure, authors considered ToCP to be of low risk. This is in agreement with Denola et al. (2011), Schindler et al. (2013), de Ree et al. (2014), and de Boer et al. (2015).

56. Overall, authors concluded that 'regarding the hypothesis that exposure to ToCP is the cause of the reported CNS effects in aircrew, one study reported a single exceptionally high (short-term) maximum concentration of ToCP, while levels were below the LOD in five other studies, leading to HQ 0.005. In view of the conservative approach adopted here and the infrequent short-term exposure that may be related to smoke/smell-incidents (though not necessarily to ToCP exposure), and the available evidence indicate that ToCP does not pose a health risk'.

Summary

57. Five papers were identified from the literature search that presented either primary data or an overview of data relating to OPs and adverse health effects in air crew and an associated risk assessment of ToCP. Exposure during routine flights as well as during fume events were considered.

58. Reneman et al. (2016) and Heutelbeck et al. (2016) both presented data on neurological effects in air crew and attempted to find a causal association between such effects and exposure to OPs. Reneman et al. (2016) investigated a cohort of air crew that presented at a clinic for occupational neurological disease due to experiencing cognitive complaints shortly after flying, whereas Heutelbeck et al. (2016) focussed on flight crew who requested medical examination at the Environmental Outpatient Department within five days of a fume event.

59. Neither paper presented data on OP exposure. Reneman et al. (2016) used flying hours as a proxy for exposure to OPs whereas Heutelbeck et al. (2016) made no reference to OP exposure, but only included crew that had experienced fume events and presumably exposure to OPs in their study.

60. Both authors concluded that the cognitive impairment observed was not associated with exposure to OPs.

61. de Ree et al. (2014), de Boer et al. (2015) and Wolkoff, Crump and Harrison (2016) all carried out a review of literature and risk assessments of TCP or ToCP in cabin air. Overall, it was concluded that it is unlikely that health effects and aerotoxic syndrome are related to exposure to ToCP, due to the low levels measured.

62. These conclusions are in agreement with the conclusion from the COT 2007/06 statement that stated that 'it was not possible.....to conclude that there is a causal association between cabin air exposures (either general or following

incidents) and ill-health in commercial aircraft crews' (<u>COT, 2007</u>) and the position paper from 2013, that concluded 'the Committee considers that a toxic mechanism for the illness that has been reported in temporal relation to fume incidents is unlikely' (<u>COT, 2013</u>).

Questions on which the views of the Committee are sought

63. Members are invited to consider this paper and in particular the following questions:

i. Do members want additional information on any of the papers presented?

ii. In light of the new data found, do Members want to re-state or amend previous conclusions on this point from the 2007 statement or 2013 position paper?

IEH Consulting under contract supporting the PHE COT Secretariat

June 2022

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List of Abbreviations and Technical terms

BOLD Blood-oxygen-level-dependent

- COT Committee on Toxicity
- DfT Department for Transport
- DH Department of Health
- DNEL Derived no effect level
- DTI Diffusion tensor imaging
- FA Fractional anisotropy
- CG-MS Gas chromatography-mass spectrometry

- HQ Hazard quotient
- LOAEL Lowest observed adverse health effect
- LOD Limit of detection
- LOQ Limit of quantification
- MOS Medical outcomes study
- MRI Magnetic resonance imaging
- NOAEL No observed adverse effect leve
- OP Organophosphate
- OPIDN Organophosphorus-induced delayed neuropathy
- o-TCP Ortho-tricresyl phosphate
- TCP Tricresyl phosphate
- TDI Tolerable daily intake
- ToCP Tri-ortho-cresyl phosphate
- TMPP Trimethylolpropane phosphate
 - 1. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).

- 2. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 3. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 4. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day
 HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 5. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 6. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day
 - HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 7. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 8. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day

- 9. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 10. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 11. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 12. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day

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HQ = 2,280 \text{ ng/kg bw/day} / 50 \text{ ng/kg bw/day} = 46.
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- 13. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 14. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 15. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 16. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day
 HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 17. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 18. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day
 HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 19. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 20. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day

- 21. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 22. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 23. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).

24. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day

HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.

- 25. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 26. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day

HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.

- 27. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 28. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day

HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.

- 29. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 30. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 31. [1] This was stated as a no effect level, as determined by determined by

Craig and Barth (1999 cited in de Boer et al., 2015).

- 32. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 33. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 34. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day

- 35. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 36. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day
 HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 37. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 38. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day
 HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 39. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 40. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 41. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 42. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day

- 43. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 44. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 45. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).

46. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day

HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.

- 47. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 48. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day

HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.

- 49. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 50. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day

- 51. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 52. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 53. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 54. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day HQ = 2,280 ng/kg bw/day / 50 ng/kg bw/day = 46.
- 55. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 56. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day

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HQ = 2,280 \text{ ng/kg bw/day} / 50 \text{ ng/kg bw/day} = 46.
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- 57. [1] This was stated as a no effect level, as determined by determined by Craig and Barth (1999 cited in de Boer et al., 2015).
- 58. [2] Exposure = 22800 ng/m3 * 7 m3 /70 kg/ = 2,280 ng/kg bw/day