# On the proportion of *ortho* isomers in the tricresyl phosphates contained in jet oil

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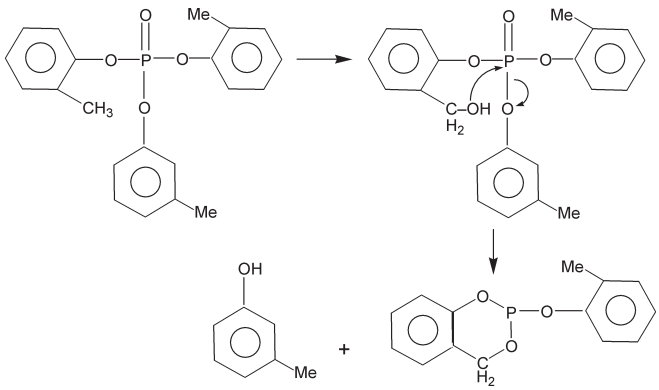
The proportion of *ortho* tricresyl phosphate isomers is supposed to be a key determinant of the toxicity of jet oils. The precursor materials currently used in oil formulation are, therefore, chosen to have very low *ortho* contents. Nevertheless, recent measurements of tricresyl phosphates in cabin air during flight indicate a significant presence of *ortho* isomers. This suggests that isomerization to increase the *ortho* content is occurring during jet engine operation.

The great technical utility of tricresyl phosphates is, unfortunately, accompanied by significant neurotoxicity. They are added to jet oils principally as antiwear agents [1], the mechanism of which appears to involve the formation of a low-friction iron phosphate film, possibly only a few molecules thick, on rubbing surfaces [2]. This film has the added advantage of passivating the iron, which otherwise catalyses the hydrolysis of the base stock of the oil [3], which is typically a medium-chain length fatty acid of pentaerythritol or dipentaerythritol [4]. The tricresyl phosphates (TCP) typically constitute around 3% of the oil, most of the remainder being the base stock [5].

Since the 1950s in many military aircraft, and since the 1960s in all commercial gas turbine-powered civilian aircraft, the air needed to pressurize cockpit and cabin has been bled off the jet engines [6]. Since a certain degree of leakage of jet oil into the air, which is of course breathed by pilots and passengers, appears to be inevitable [7, 8], considerable attention has been given to understanding and minimizing the neurotoxicity. A notable case was the ingestion by tens of thousands of people of an over-the-counter medical product contaminated with TCP during the prohibition era in the USA [9]. "TCP" comprises 10 distinguishable isomers, since each of the three cresyl groups can have the *ortho*, *meta* or *para* arrangement. If at least one *ortho* cresyl is present, the following reaction can take place (Scheme 1) to form the cyclic saligenin phosphate, 2-(o-cresyl)-4H-1,3,2-benzodioxaphosphoran-2-one (CBDP), which is a more potent neurotoxin than the TCP [10]. This reaction has been shown to take place in the liver [13], presumably catalysed by a cytochrome P450 enzyme, although precisely which one(s) still remains to be elucidated. A careful and comprehensive study of the neurotoxicities of all of the different TCP isomers revealed that the *ortho*-containing ones were the most neurotoxic in the order mono-*ortho* > di-*ortho* > tri-*ortho* [14]. Such extensive studies are necessarily carried out using experimental animals; observations on humans have been made *post hoc* following accidental exposure. Acute exposure swiftly leads to cholinergic toxicity, in which the enzyme acetylcholinesterase is inhibited at synapses, gravely disturbing neural transmission [15]; this effect is exploited in chemically similar nerve gases in warfare, and can often be fatal. Survivors of such acute exposures and those exposed chronically to low doses may develop organophosphate-induced delayed neuropathy (OPIDN) [15, 16], characterized by degeneration of the peripheral nerves and, ultimately, damage to the central nervous system including the brain, with all the behavioural sequelae that that implies. The precise molecular mechanism of the neural degeneration is still being elucidated, but it would appear to depend on the general hyperphosphorylating ability of the tricresyl phosphates and their metabolites and all that implies in terms of protein structure and function [17].




Scheme 1. The conversion of *ortho* cresyl phosphates to CBDP. Initially the TCP (for illustration, *oom*) is oxidized and can then undergo cyclization with the departure of one cresol [11]. The reaction is of course facilitated if the leaving group is scavenged; serum albumin is able to take on this rôle [12].

Following the realization that the *ortho* isomers are the most toxic [14],[1] efforts were made to reduce the *ortho* isomer content of the manufactured product (it

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[1] A marker of TCP exposure is the inhibition of the blood enzyme butylcholinesterase (BChE), and recent studies have shown that the *ortho* isomers inhibit BChE more than the *para* isomers [18].

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would be prohibitively expensive, for industrial applications, to selectively remove isomers by purification); the desired technical attributes of which do not depend on the isomeric constitution. At the time of what was essentially a mass poisoning in the 1930s [9, 14], the *ortho* isomers comprised about 30% of the TCP (Class 1) [14]; at the time of Henschler's work, the *ortho* content of "modern" (Class 3) TCP was down to about 3% [14], and these efforts have continued: Class 4 "conventional" TCP, commercially available from about 1992 onwards, are supposed to contain about 0.3% of the *ortho* isomers; and Class 5 "low-toxicity" TCP, commercially available from about 1997 onwards, are at least tenfold less potentially neurotoxic than Class 4 TCP [19].[2]

This should be reassuring for aircrew and frequently flying passengers who are likely to be chronically exposed to small concentrations of jet oil leaking into aircraft cabins. Increasing attention paid to the possibly adverse health consequences of such exposure (e.g., the inquiry in the year 2000 undertaken by the UK House of Lords [20]) has led to specific attempts to measure the concentration of TCP (and other contaminants) in aircraft cabins during flight. The study commissioned by the UK Department for Transport (DfT) has probably been the most comprehensive and useful to date [21, 22], despite some criticisms [23, 24]. Other published studies are those of van Netten [25], Solbu et al. [26] and Denola et al. [27] but all are less comprehensive than the DfT study and none of them were able to separately identify any *ortho* isomers of TCP (chromatographic profiles could be recorded for the four most abundant isomers *mmm*, *mmp*, *mpp* and *ppp*, with elution times *mmm* < *mmp* < *mpp* < *ppp* and peak areas *mmp* > *mmm* > *mpp* > *ppp* [26, 27]).

Table 1 summarizes the TCP data from the DfT study [21] from which it can be seen that the proportion of the tri-*ortho* isomer is very much more than 0.3%.[3]

The question then arises, why is the ratio of the tri-*ortho*-isomer to total TCP found in aircraft cabin air so much higher than expected from the supposed *ortho* content of the precursor material? One possibility is that the manufacturers' assertions of an ultralow *ortho* content represent a "best case" and that the bulk of manufactured output is still at the level of (at best) the "modern" TCP investigated by Henschler. It is interesting that Solbu et al.

Table 1. Tri-*ortho* cresyl phosphate and total TCP measured in aircraft cabins in flight [21].[a]

| | ToCP / μg m$^{-3}$ | TCP / μg m$^{-3}$ | Ratio |
|---|---|---|---|
| All flights | | | |
| Arithmetic mean[b] | 0.08 ± 0.38 | 0.23 ± 1.06 | 0.35 |
| 95th percentile | 0.29 | 0.73 | 0.40 |
| Maximum value | 2.5 | 8.0 | 0.31 |
| B 757 (cargo) | | | |
| Arithmetic mean[b] | 0.24 ± 1.01 | 0.81 ± 3.74 | 0.30 |
| Maximum value | 7.8 | 36.0 | 0.22 |
| B 757 | | | |
| Arithmetic mean[b] | 0.14 ± 1.66 | 0.24 ± 2.73 | 0.58 |
| Maximum value | 22.8 | 37.7 | 0.60 |
| BAe 146 | | | |
| Arithmetic mean[b] | 0.002 ± 0.02 | 0.02 ± 0.14 | 0.10 |
| Maximum value | 0.007 ± 0.06 | 0.05 ± 0.27 | 0.14 |
| A 319 | | | |
| Arithmetic mean[b] | 0.007 ± 0.06 | 0.05 ± 0.27 | 0.14 |
| Maximum value | 0.7 | 3.2 | 0.22 |

[a] The study comprised of total of 100 flights using five different aircraft each flown 20 times (no TCP was detected on flights with the A320/1). Unfortunately no further details concerning the aircraft are given in the report [21, 22]. In particular, specifications of the engines (including time since overhaul and the type of engine oil used) are missing.

[b] The measurements were carried out by pumping cabin air through sorbent tubes packed with quartz wool and Tenax TA at about 500 mL/min for, typically, 5 min. Typically 10 samples were taken per flight, one per distinguishable flight sector (e.g., "take off", "start of descent"). After landing, the tubes were heated and the thermally desorbed substances were separated by gas chromatography and identified by mass spectrometry. All readings below the limit of detection were given a value of zero. The uncertainty is given as ± one standard deviation.

found triphenyl phosphate (TPP) "in 47% of the samples from model A airplanes, though no oils with TPP are supposed to be in use in these airplanes" [26].[4] Such a finding hints at the possibility of extensive divergences between specifications and what happens in practice.

Another possibility is that isomerization of the TCP takes place within the engine during operation. Investigations on the isomerization of cresol at 380 °C using a solid phase catalyst resulted in an equilibrium composition of 36% *ortho*, 48% *meta* and 16% *para* (the corresponding percentages calculated from thermodynamic data are 37, 58 and 5 respectively) [28].[5]

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[2] The evaluation of potential neurotoxicity is complicated by the fact that commercial TCP contain phenols and xylenols as well as cresols [19]; thus, Class 4 TCP are not necessarily less neurotoxic than those of Class 3 despite the tenfold lower *ortho* content [19].

[3] The proportion is likely to be an underestimate, since only the tri-*ortho* isomer was individually identified; the two di- and three mono-*ortho* isomers would, therefore, be included in "total TCP".

[4] Unfortunately "model A" airplanes are not further identified in the study.

[5] Similar results on the production of the *ortho* isomers in the presence of aluminium silicate zeolites are described in [29, 30]. The temperatures in a modern jet engine considerably exceed 380 °C [8].

The second explanation seems more likely, because, given the ratios of *ortho* to total TCP reported (Table 1), the first one would imply that, in some cases, the oil formulators are still using Class 1 TCP, which seems highly unlikely. Recent measurements on fresh jet oils found low levels of (mono-) *ortho* TCP, in the range 0.013–0.15 g/L [31], implying Class 4 or Class 5.

Consideration should also be given to the possible influence of deficiencies in the experimental approach adopted for the DfT study [21, 22]. Tenax TA (a porous polymer resin made from poly(2,6-diphenyl-*p*-phenylene oxide) [32]) does not appear to have been previously used for collecting the rather polar TCP (it seems to be best for collecting apolar organic compounds), for which it may not be appropriate. Furthermore, limiting sampling to five-minute intervals necessarily limits the achievable sensitivity. Both these deficiencies would, however, diminish the apparent concentrations of TCP in the cabin air; they are not expected to differentially affect some isomers more than others, at least not to any significant extent. Therefore, the T*o*CP[6]/TCP concentration ratios should be more reliable than the absolute concentrations themselves.

The variability of the T*o*CP/TCP concentration ratios among the different flights (Table 1) presumably reflects the use of different jet oils in different engines and the different reaction conditions in the different engines. If the in-use isomerization proposition is correct, the extent to which it occurs may sensitively depend on oil temperature and the chemical nature of the surfaces to which the oil is exposed. Furthermore, if it is assumed that the fresh oil has a very low T*o*CP content, the content measured in the cabin air must depend on the filling history of the aircraft engines.

Measurements of cognitive dysfunction in the pilots of commercial jet aircraft [33] indicate that the chronic neurotoxicity of aircraft cabin air is a real contemporary problem urgently requiring a solution not least because of the risks to flight safety, apart from the adverse health effects. If the present findings indicate that the *ortho* content of industrial TCP cannot be further reduced with any practical effect, then attention needs to be given to continuously monitoring the presence of TCP in aircraft cabin air and purifying it.[7] The cumulative nature of some aspects of the hazards associated with inhaling TCP implies that there may be no truly safe exposure limit.

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[6] Tri-*ortho*-cresyl phosphate.

[7] See [34] for a possible approach to removing contaminants like TCP before they enter the cabin.

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