Adverse synergies between inhaled carbon monoxide and tricresyl phosphate in aircraft cabin air

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Both tricresyl phosphate (TCP) and carbon monoxide are present in aircraft cabins, albeit at low concentrations. Hitherto, attention has been focused on these toxins individually. In so far as CO directly inhibits the cytochrome P450 enzymes carrying out detoxification of tricresyl phosphate, an adverse synergy will operate between the two substances. The chemical–physiological picture is further complicated by the mild hypoxia suffered by aircrew and passengers in flight. The adverse synergy resolves the puzzle of aerotoxicity even though actual exposures of the toxins individually are below the presumed threshold for pathophysiological effects. Exposure limits should be revised to take the adverse synergy into account.

Keywords: aerotoxic syndrome, cytochrome P450, hypoxia, multiple chemical sensitivity, neurotoxicity, oxidative stress

TCP. The neurotoxicity of tricresyl phosphate (TCP) is well established by the very large number (10^4–10^5) of documented accidental poisoning cases over the last 100 years or so [1]. Nearly all these cases arose from oral or dermal ingestion. TCP is a widely used chemical—applications include polymer plasticizer, fire retardant and antiwear additive to lubricants. It is the last of these that accounts for its inclusion (a few %) in synthetic gas turbine (including aircraft jet engines) lubricants, and the practically inevitable leakage of oil into the air bled off the engines to pressurize and heat the aircraft cabin accounts for its well-documented presence in cabins [2,3]. The entry route to aircrew and passengers is, therefore, by inhalation, which has been less studied, but is generally considered to be a much more potent route to intoxication than oral or dermal [4,5].[1]

Unlike many of the oral ingestion exposures, which were acute, the inhalation of TCP in aircraft cabins mostly ranks as chronic exposure, the effects of which are more subtle and are an active field of research. "Fume events", in which the cabin is filled with visible fumes, are estimated to result in a much higher, acute, exposure [7] (no actual measurements appear to have ever been made of TCP concentrations during a fume event, despite attempts to do so [8]).

A further relevant point concerns the differential neurotoxicity of the ten different isomers of TCP (which arise because cresol has two methyl groups). Careful laboratory investigations elucidated in particular the rôle of isomers containing one or more *ortho* cresyl groups [9].[2] Work on the toxicity of the other isomers is still continuing; at the very least there is indirect neurotoxicity, since butyrylcholinesterase (BCh) in the blood scavenges all isomers apparently indiscriminately, hence the presence of non-*ortho* isomers diminishes the capacity of the blood to scavenge the *ortho* isomers [10–13], which then proceed to the liver and are metabolized into much more neurotoxic compounds [14]. Although commercial preparations of TCP (always a mixture of isomers for practical reasons—the cost of preparing isomerically pure TCP is prohibitive for large-scale applications) have been optimized to minimize the concentration of *ortho* isomers, actual measurements of TCP contamination in aircraft cabins [8] have established an *ortho*:non-*ortho* ratio of about 1:3 [15].

In the liver, the detoxification is undertaken by cytochrome P450 (CYP) enzymes; relevant isoforms have been identified [16]. Significant genetic variation in the CYP superfamily is to be noted [17–22], which could account for at least some of the observed variations in susceptibility to intoxication.

CO. Carbon monoxide has long been known as an extremely toxic gas [23–25]. One already finds comprehensive medical accounts of its effects over 150 years ago (e.g., [26]). The primary effect is due to its strong binding to haemoglobin, displacing oxygen, the supply of which throughout the body is thereby rapidly depressed, but it also binds strongly to myoglobin [27], thereby interfering with muscle function. Much less well studied is its binding to CYP, which is a haem protein and, like myoglobin and haemoglobin (human haemoglobin can be thought of as constituted from four myoglobin

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[1] Due to the high boiling point of TCP, its vapour pressure is very low and, hence, its presence will be predominantly as an aerosol [6].

[2] See ref. [6] for a more detailed account.

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subunits) has an iron centre that can be complexed by CO [28], leading to its inhibition [29].

CO is an almost inevitable result of the combustion of carbon-containing fuel. In aircraft, although air for the cabin is bled off upstream of the combustion zone, CO has been measured in aircraft cabins [8]. It may originate from the partial decomposition of the synthetic hydrocarbon lubricating oils, which are exposed to high temperatures (cf. refs 2 and 3 concerning leakage of oil into cabin air).

Hypoxia. According to US federal regulations (which are widely adopted in many other jurisdictions), "Pressurized cabins and compartments to be occupied must be equipped to provide a cabin pressure altitude of not more than 8000 feet at the maximum operating altitude of the airplane under normal operating conditions".[3] At this altitude, air pressure is about 0.75 bar; hence, especially in view of the rapid ascent, affording little opportunity for acclimatization, occupants suffer from mild hypoxia during flight.

Sequelae. The consequences of TCP exposure are well documented elsewhere [6] (see also refs 30 and 31)—cholinergic toxicity, organophosphate-induced delayed neurotoxicity (OPIDN) and organophosphate-induced chronic neurotoxicity (OPICN). It has, however, been pertinently pointed out that the symptoms of those presumed to be suffering from aerotoxic syndrome are not entirely commensurate with those associated with OPIDN and OPICN [32] (cholinergic toxicity is an acute effect akin to that evoked by nerve gases on the battlefield, and may be relevant to the sudden incapacitation of pilots in the course of a fume event, but is not considered to be relevant to chronic effects). Of particular importance to those in demanding occupations are the cognitive deficits that seem to be engendered [33].

The extreme toxicity of carbon monoxide has been known for a long time, but the initial thought that the pathophysiology of CO poisoning was exclusively due to cellular hypoxia imposed by carbon monoxide replacing oxygen in haemoglobin has now been replaced by the realization that clinical presentations are diverse and to some extent nonspecific [34], to the extent that diagnosis may be difficult [35,35a], and that the pathophysiology is much more complex [36]. The rôle of oxidative stress is worth noting [37,38] which might be particularly relevant for the neuropsychiatric sequelae that are now recognized. Also worth noting is the cytoprotective rôle and consequential therapeutic potential of CO [39].

Although acute CO exposure has generally been at the forefront of interest [40], and for which, logically enough it would seem, hyperbaric oxygen is considered to be an effective therapy [41], there has also been some interest in the effects of low concentrations [42,43].[4] Gilinskiy et al. recommended a maximum permissible concentration of carbon monoxide in pressurized passenger aeroplane cabins of 10 mg m^{-3} (8.7 ppm); Townsend and Maynard opined that "long-term exposure to low concentrations may cause neurological damage" (see also refs 43a and 43b). Federal regulations for aviation state that carbon monoxide concentrations in excess of 50 ppm are considered hazardous.[5,6]

Summarizing the interrelationships between TCP, CO and hypoxia, CO depresses TCP detoxification, and would appear to exacerbate hypoxia [44] (and conversely hypoxia exacerbates CO toxicity [45]), although Pugh's findings in seals suggest the opposite [46].

Actual exposures. Table 1 reports results from measurements in flight on aircraft. Both sets of measurements used pumped tube sampling for the tricresyl phosphates (albeit with considerable differences in details—reference should be made to the original reports). Carbon monoxide was measured continuously with an electrochemical sensor [8], hence cannot be compared directly with the short-interval pumped-tube sampling [8]. Ref. 47 also pumped air during the entire flight, the duration of which possibly exceeded the breakthrough time, which would account for the far lower values measured. In ref. 8, measurements were taken on each of 10 flight phases (climb etc.) of 100 flights, hence the TCP data comprises about 1000 measurements and the CO data 100. In ref. 47, measurements were taken during 38 flights.[7]

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[3] Code of Federal Regulations (CFR), Title 14—Aeronautics and Space, Chapter I—Federal Aviation Administration (FAA), Department of Transportation (DoT), Subchapter C—Aircraft, Part 5—Airworthiness Standards: Transport Category Airplanes, Subpart D—Design and Construction, Pressurization, §25.841 Pressurized cabins, (a).

[4] A translation of the paper by Gilinskiy et al., which is of especial interest, is reproduced in full in the Appendix because of the inaccessibility of the original source.

[5] Code of Federal Regulations (CFR), Title 14—Aeronautics and Space, Chapter I—Federal Aviation Administration (FAA), Department of Transportation (DoT), Subchapter C—Aircraft, Part 5—Airworthiness Standards: Transport Category Airplanes, Subpart D—Design and Construction, Pressurization, §25.831 Ventilation, (b)(1).

[6] Paragraph (b)[5] starts with the general stipulation that "Crew and passenger compartment air must be free from harmful or hazardous concentrations of gases or vapors". Only carbon monoxide, in the following paragraph (1), and carbon dioxide in the following paragraph (2), are explicitly mentioned.

[7] Both the two studies cited (refs 8 and 47) have some shortcomings regarding sampling methodology for what is, admittedly, a difficult experimental challenge, but the main criticism is that the equipment (i.e., the engines and aircraft) being tested are not exactly specified. In particular, apart from the missing specification of the engine, there is no mention of time since overhaul,

Table 1. In-flight measurements of TCP and CO.

TCP (measured concentrations)	Min. /μg m^{-3}		Mean/μg m^{-3}		Max./μg m^{-3}		Ref.
	0.0 [a]		0.22		38		[8], Table 4
	0.011		0.059		0.217		[47], Table 4
CO (numbers of flights)	< 1 ppm	1 ppm	2 ppm	3–5 ppm	> 5 ppm		
	6	45	23	6	1		[8], Table 11

[a] A value of 0 was used for all readings below the detection limit, which may be 0.1 μg m^{-3}, since no values lower than this are reported.

A TCP concentration of 0.22 μg m^{-3} corresponds to 0.625 nmol m^{-3}. The median CO concentration of 1 ppm corresponds to 1.146 mg m^{-3} or 41 μmol m^{-3}. Hence there is a great excess of CO over TCP.

Timescales. We have hitherto tacitly assumed that exposures are simultaneous, but they do not need to be for augmented hazard to emerge. Someone boarding an airplane with a prior elevated CO concentration will be at greater risk from chronic TCP exposure than an otherwise similar person with lower prior CO concentration, and similarly with prior exposure to TCP and possibly other organophosphates capable of causing similar neurotoxic effects—such prior exposure increases the hazard of CO exposure on board the aircraft.

Conclusions. The simultaneous presence of TCP and CO in aircraft cabins (a hypoxic environment) has raised concern that they may be hazardous to health, albeit that the concentrations of these substances individually, and the resulting human exposures, seem to be too low to constitute a hazard [48], a conclusion also reached by others with specific reference to TCP [47,49]. This puzzle is resolved by the synergy of the major toxins TCP and CO, exacerbated by the relative lack of oxygen. We have thus an example of a kind of multiple chemical sensitivity [50].[8] Chemical sensitivity is acknowledged to be "an elusive phenomenon" [51]; central mechanisms have been sought [52,53], but have been hard to pin down. The central message of the present paper is simply that through the CO-engendered inhibition of TCP-detoxifying CYP enzymes, individually low concentrations of the key toxins CO and TCP act together to create a pathophysiological hazard. This adverse synergy has previously been hinted at [54, 31], without providing any definite evidence for a molecular mechanism.[9]

Do any practical recommendations follow from the above? The 50 ppm limit for carbon monoxide[6] seems to be too high, especially considering that intercontinental flights can last 8 or more hours.[10] There is no mandated limit for TCP; one notes that the terrestrial long-term (8 h) workplace exposure limit for tri-*ortho*-cresyl phosphate is 0.1 mg m^{-3} [56]. Aviation limits should be set with due regard not only to the low oxygen pressure but also to the simultaneous presence of adverse interacting substances.[11] Further progress in safety will come with the prescribing of minimum intervals following prior exposure to substances having hazardous synergies with those present in aircraft cabin air, and minimum intervals following air travel before exposure to such substances. To avoid complete paralysis of action through compliance with a complex web of restrictions, it will be advisable to specify a threshold level of risk, below which it can be disregarded.

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type of engine oil, and mean times between failure (and the distribution of times) of components critical for preventing oil leakage into the cabin.

[8] That is, sensitivity to multiple chemicals present simultaneously but not to their presence alone.

[9] In a certain sense the adverse synergy mechanism proposed bears some relation to the phenomenon of particles, which have been found to be present at rather high concentrations in aircraft cabin air [8], acting as physical carriers for TCP [55].

[10] The long-term (8-hour) workplace exposure limit is 20 ppm [56].

[11] This could sensibly be done for workplace exposure limits as well, but the complexity of the undertaking is daunting.

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Appendix

Translation of ref. 42.[12]

THE EFFECT OF LOW CONCENTRATIONS OF CARBON MONOXIDE ON MAN IN PRESSURIZED CABINS OF PASSENGER PLANES

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N. M. Kulikova and A. Ya. Loshak

The human organism in general and during flight in particular requires careful observance of certain environmental conditons, i.e., the so-called comfort conditons that make it possible for a flier to live and remain fit with minimal fatigue during flight.

[12] NASA technical translation: *Aviation and Space Medicine* (NASA TT F-228). Washington DC: NASA (1964).

Many authors (A. A. Letavet, E. E. Grigor'yev, L. S. Gorsheleva, I. I. Datsenko, and others) have concluded that prolonged exposure to low concentrations of carbon monoxide may adversely affect health by causing chronic carbon monoxide poisoning.

We found no references in the available Soviet or foreign literature to carbon monoxide effect on human beings in pressurized cabins exposed for 3 hours to maximum permissible concentrations and to low concentrations under ground conditions (pressure-chamber experiment) and at altitudes of 8000-10,000 meters.

There is as yet no consensus either in international practice or in the Soviet Union on the maximum permissible concentration of carbon monoxide in pressurized airplane cabins. The specialized literature contains no data that confirm the soundness of applying the maximum permissible CO concentration (0.02 mg/liter) established for ground conditions to the conditions of low partial pressure of oxygen in inhaled air.

We performed pressure-chamber experiments on 82 persons to study the effect of low concentrations of carbon monoxide. We also made 30 flights on IL-18, AN-10, and TU-104 planes during which we examined 185 members of the crew and passengers and studied 347 air samples obtained in the cabins.

The results of the investigations showed that 3 hours' exposure to carbon monoxide (starting with 0.01 mg/liter or more), both under experimental conditions (ground and pressure-chamber at 2400 m) and during actual flight had adverse effects on the functioning of several organs and systems, namely:

(a) Higher nervous activity (manifested in a breakdown of differentiations; deterioration of memory, capacity and concentration of attention; increase in amount of time required for a proof-reading test, etc.).

(b) Functions of the visual and vestibular analyzers (increase in latent period and decrease in duration of the after-image, shortening of the time of illusion of counter-rotation, etc.).

(c) Metabolic processes (change in bodily temperature).

(d) Cardiovascular system (change in arterial pressure, oscillatory index, change in myocardial function, etc.).

(e) Muscular strength (decrease in indices of manual dynamometry).

(f) Tissue respiration (formation of carboxyhemoglobin in the blood).

(g) Leukopoiesis (change in composition and formed elements of the blood).

On the basis of the physiological-sanitary data obtained and the results of laboratory tests, it is suggested that the maximum permissible concentration of carbon monoxide in pressurized passenger airplane cabins be 0.01 mg/liter.