



18 October 2014

Letter to the editor, regarding article de Ree H, et al. "Health risk assessment of exposure to tricresyl phosphates (TCPs) in aircraft: A commentary," Neurotoxicology (2014), <http://dx.doi.org/10.1016/j.neuro.2014.08.011>

Dear Dr. Cranmer,

My name is Michel Mulder, former airline pilot and Aviation Medical Examiner, researching the effects of contaminated air in jet aircraft.

This article is in direct response to a verdict of a Dutch court case in 2013, initiated by a KLM employee, which forced the company to test the cabin air quality in the B737 fleet. Nearly 50% of measured flights were positive on TCP isomers, belonging to the group of Organophosphates (OPs). A neurotoxic compound, belonging in the category of the nerve gasses.

The report is, to my knowledge, based on incorrect measurement results and assumptions.

There are two working mechanisms: short term (A) and a long term (B).

A) Dose – Effect: tri-phenyl phosphate, tri-butyl phosphate, di-butyl di-phenyl phosphate and tri-cresyl phosphate all belong to the group of OPs present in cabin air of bleed-air equipped aircraft. All OPs inactivate both AcetylCholinesterase (AChE) and ButylCholinesterase (BChE) enzymes at first contact in the blood, followed by a process known as aging, causing irreversible loss of functionality in the central and peripheral nervous system.

In recently tested aircrew, blood samples were taken before and after a flight, with the NATO validated SECURETEC "CHE check mobile" test kit. They show a life threatening loss of up to 80% AChE. Some were, as a result, fully incapacitated during a normal flight. These patients suffered severe cholinergic symptoms. The "incapacitation-problem" is known by the company and confirmed by an internal 2011 paper, stating: "incapacitation in the cockpit to occur on a regular basis (*regelmatig mee te maken*)".

A method of analysis was developed in 2009, by TNO and myself, to detect TCP isomers in air-samples in different aircraft types. Technique used (Solbu) was a calibrated portable Spectrex PAS 500 sampler with an SKC 106 test-tube.

Aviation Medical Consultation

Michel F.A. Mulder, MD
karbouwstraat 14
1402VC Bussum
The Netherlands

T +31 35 3030100
aeromed@neomailbox.ch
IBAN: NL69 TRIO 0254 8055 74
BIC/SWIFT code TRIONL2U
Chamber of Commerce 32164454

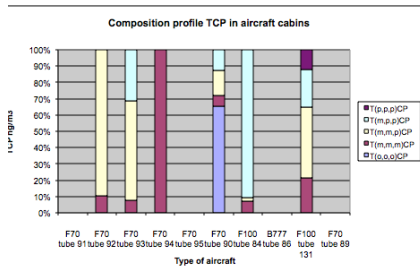


Fig 1

TNO 2009 (Houtzager-Mulder)

- A total of 33 samples were taken: 12 positive, 21 negative.
- Every TCP-GCMS fingerprint was different. (see Fig 1)
- 3 showed high levels of ToCP. One averaged 55 ng/m³ of ToCP, without any other isomers detected. The relevant B737 was grounded for a period of more than 4 weeks.
- 21 negative results, despite people having “fainted” or smelled oil fumes, suggesting contaminated sensors in the TNO GCMS analysis equipment.

Another lab was chosen for further testing (STEIN) since the TNO testing results were structurally flawed, according to Prof. Van Netten (University of British Columbia).

Aviation Medical Consultation

Michel F.A. Mulder, MD
 karbouwstraat 14
 1402VC Bussum
 The Netherlands

T +31 35 3030100
 aeromed@neomailbox.ch
 IBAN: NL69 TRIO 0254 8055 74
 BIC/SWIFT code TRIONL2U
 Chamber of Commerce 32164454

TNO 2013 (Houtzager-KLM)

- Using SKC-106 test tubes is a non-approved sampling method by the Federal Aviation Administration (FAA).
- Flow-rate of 2 L/hour is too low.
- False air leakage around the broken tube ends.
- “Background noise” during GCMS analysis too high with SKC test tubes.
- GCMS cabin air analysis:

$$\text{TNO average } 6,9 \text{ ng/m}^3 \text{ vs. STEIN average } 1027 \text{ ng/m}^3$$
 differential factor of **148**
- Swipes: Harvesting of TCP, an oily substance, with demi water wipes from cockpit glare shield is like trying to remove olive oil from a table with a wet tissue, most of it will stay on the surface. The WDR samples were taken with alcohol swabs:

$$\text{TNO } 0,079 \text{ ng/cm}^2 \text{ vs. WDR-van Netten } 77.475 \text{ ng/cm}^2$$
 differential factor of **980.696, an order of magnitude of 6.**

B) **Auto-Immune response:** Cholinergic symptoms combined with significantly raised auto-anti bodies after a flight in 27 KLM aircrew have been described in “Autoantibodies to nervous-system specific proteins are elevated in sera of flight crew members”¹

The hypothesis of neurological damage, caused by long-term exposure to contaminated cabin-air, has now been confirmed by post-mortem findings, as described in “Autoantibody markers of neural degeneration are associated with post-mortem histo-pathological alterations of a neurologically-injured pilot”²

Grossly elevated levels of serum autoantibody biomarkers for neuronal cell degeneration were found. Brain and spinal tissues exhibited axonal degeneration and demyelination. Peripheral nerves showed T-lymphocyte infiltration and demyelination. In comparison to a control group.

¹ <http://www.tandfonline.com/doi/abs/10.1080/15287394.2013.765369?journalCode=uteh20>

² <http://www.colbas.org/ibpc/poap.htm>



Many of the physical symptoms observed during incapacitation are directly related to: (A) Short term effects by acute inactivation of cholinesterase and (B) Long term effects of a related auto-immune reaction resulting in an acute loss of functionality of the central, peripheral nervous system and different organs.

Summary:

- I. No mention has been made regarding this particular employee, or what has become of him. According to the trial documentation this person reported severe exposure related health problems. Most of them were cholinergic in nature.
- II. TNO values appear structurally too low and as such do not constitute a credible scientific basis for a subsequent risk analysis.
- III. TNO, as they claim Innovation for Life, refrained from putting a general health warning to the travelling public at the end of this report. This contrary to a similar 2009 Fresenius study³ in Germany on request of CONDOR. *(Aufnahme über die Atemwege eine gesundheitliche Gefährdung durch eine mögliche Hautresorption nicht auszuschließen ist).*
- IV. Sum total effects of all organophosphates present have not been included. Several recently documented cases within this airline show a dramatic loss of cholinesterase after a normal flight, resulting in full incapacitation of crewmembers during flight.

KLM diagnosis: fainting. Oxygen administered during flight, no appropriate medical testing or assistance on arrival, person will go home on his or her own accord, symptoms remain.

NATO diagnosis: Soldiers becoming unwell in a war theatre undergo a CHE check. Values below minima of ACHE or BCHE are proof of acute intoxication with OP nerve gasses; person will be brought to an Emergency Room and treated with Atropine or Obidoxime.
- V. Authors have taken the attention away from the real problem by putting the sole focus on the presumable absence of ToCP. A so called mouse among the elephants.

This ToCP isomer, a <0,2% contamination in DURAD 125 additive to the base stock of turbine oils, is by definition too low in concentration in cabin air to be detected with the SKC106/GCMS technique in use (van Netten).

Aviation Medical Consultation

Michel F.A. Mulder, MD
karbouwstraat 14
1402VC Bussum
The Netherlands

T +31 35 3030100
aeromed@neomailbox.ch
IBAN: NL69 TRIO 0254 8055 74
BIC/SWIFT code TRIONL2U
Chamber of Commerce 32164454

³ **Untersuchung von Wischproben auf TCP-Belastungen (Trikesylphosphat) in den Flugzeugen (Airbus/Boing) der Condor Flugdienst GmbH**, Bearbeiter: Auftrags-Nr. 1322897 , Auftraggeber: Condor Berlin GmbH Flughafen Berlin-Schönefeld Berlin erstellt durch: SGS INSTITUT FRESENIUS GMBH, Im Maisell4 65232 Taunusstein , Dipl.-Ing. Josef Spark



ToCP however was previously detected, in a similar situation within this airline, with another technique developed by Carletti et Al.⁴ in blood:

"It was estimated that 1.4% of his butyrylcholinesterase was modified by tri-ortho-cresyl phosphate".

VI. The much stronger auto-immune response, caused by minute levels of OPs, via a T-memory Lymphocyte mediated IgG immune response in sensitized individuals, is not included.

VII. Conclusions drawn by the authors are not supported by:

- a) Other comparable laboratory results (Stein, van Netten).
- b) Observed findings in above mentioned articles.
- c) Content of a 2011 company paper.

Aviation Medical Consultation

Michel F.A. Mulder, MD
karbouwstraat 14
1402VC Bussum
The Netherlands

T +31 35 3030100
aeromed@neomailbox.ch
IBAN: NL69 TRIO 0254 8055 74
BIC/SWIFT code TRIONL2U
Chamber of Commerce 32164454

It seems that information provided in this article is partial, scientifically incorrect and biased. I would like to ask the editor to withdraw this publication.

Yours sincerely,

Michel Mulder, MD

⁴ **Reaction of Cresyl Saligenin Phosphate, the Organophosphorus Agent Implicated in Aerotoxic Syndrome, with Human Cholinesterases:** Mechanistic Studies Employing Kinetics, Mass Spectrometry, and X-ray Structure Analysis Eugenie Carletti, Lawrence M. Schopfer, Jacques-Philippe Colletier, Marie-Therese Froment, Florian Nachon, Martin Weik, Oksana Lockridge, and Patrick Masson*