Toxicology Hot Topics Part I: Smoke Odor Fumes (SOF) / Fume Smoke Events (FuSE)

Loren Hatch Memorial Lecture

AOCOPM 2024 Midyear Educational Conference
Conroe, TX, March 21-24

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In the course of my professional responsibilities as an aerospace toxicologist, I (Intertox) have provided scientific reports and expert testimony on over 800 projects related to human exposure to chemicals, including:

Manufacturers of aircraft
Airlines
Military
Aviation-related industries
Invited speaker to aerospace medicine and IATA meetings

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Topics

- What symptoms are reported
- Fundamentals of toxicology
- Cabin air quality events
- Chemical agents of interest
- Health impacts
- Conclusions
- Questions

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Fundamentals of toxicology

5

Things I consider in aerospace toxicology

I follow the accepted standard of practice in toxicology

We assess all scientific data and use the best

The unique environment of flying
- Atmosphere
- Oxygen tension
- Humidity
- Air pressure

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Risk ≈ Hazard × Exposure

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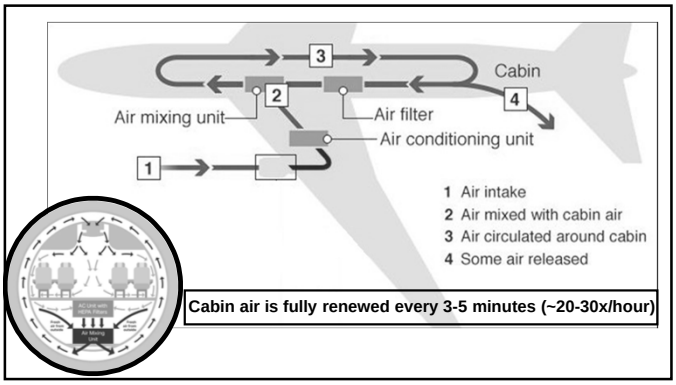

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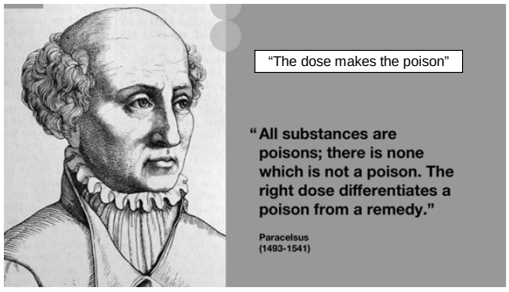

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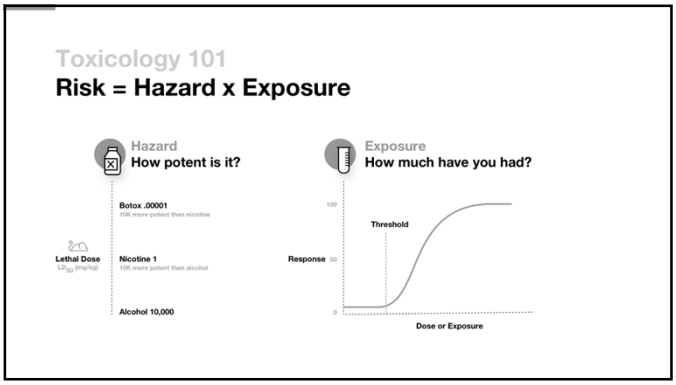

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Presence ≠ Toxicity

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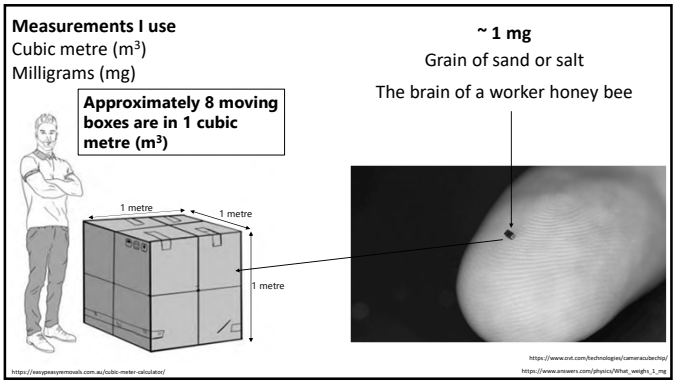

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Cabin air quality events

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What are the triggers of a cabin air quality event?

- Detection of odour
- Exposure is generally short in duration
- Odour events are generally uncommon
- Haze can occur but is rare

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What are the reported symptoms of cabin air event-related exposures?

Common reported symptoms

Headache
Irritation of throat/nose
Eye irritations
Dizziness/Weakness
Nausea
Light headedness

Uncommon reported symptoms

Tremors
Cognitive problems
(e.g., concentrating, confusion)
Airway irritation

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What are the common symptoms of CAQEs?

- Combustion by-products can irritate the nose, throat, and eyes
- "Foul" odors can cause anxiety and physiological symptoms like headache, nausea, dizziness
- These symptoms are transient (go away quickly after removed from exposure); no long-term effects are expected.

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What are the chemicals in cabin quality air events?

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Organophosphates

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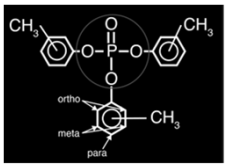
What are the chemicals of interest?

Jet Engine Oil
- Tricresyl Phosphate (TCP)
- Triorthocresyl Phosphate (TOCP)
- Other TCP Isomers

Hydraulic Fluid
- Tributyl phosphate (TBP)
- Triphenyl phosphate (TPP)
- Other chemicals



Combustion By-Products
- Carbon monoxide
- Carbon dioxide
- Oxides of phosphorus
- Aldehydes
- Other small molecules

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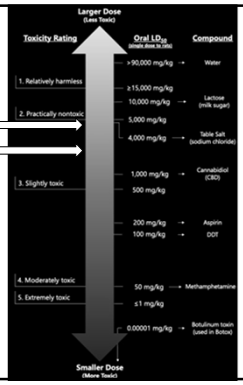
Relative potency
of chemical agents

Oral LD_{50} (single dose to rat)

TCP >5,000 mg/kg

TBP 3,000 mg/kg
TPP 3,000 mg/kg



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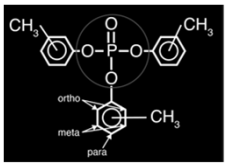

Combustion By-Products
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SAE INTERNATIONAL AEROSPACE STANDARD SAE AS5780

Core Requirement Specification for Aircraft Gas Turbine Engine Lubricants

Additives containing barium or organic compounds of titanium, and known or suspected carcinogens, are prohibited. If a tricresyl phosphate (TCP) additive is used, the TCP additive shall not contain more than 0.2% by weight of ortho cresol containing isomers of tricresyl phosphate.

Additives containing barium or organic compounds of titanium, and known or suspected carcinogens, are prohibited. If a tricresyl phosphate (TCP) additive is used, the TCP additive shall contain less than 0.20% by weight in total of mono, di and tri-ortho cresyl isomers of tricresyl phosphate.

2018

Tricresyl Phosphate (TCP) **is less than 1-3 % weight**

Tri-ortho-cresyl Phosphate (ToCP)
is less than 0.2% of weight

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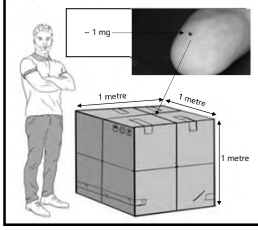
How much TCP in cabin air?

Normal operations — Mostly NON-DETECTS (<0.005 mg/m^3)

Highest concentration — Measured, including CAQE



0.03 mg/m^3 (commercial)
0.05 mg/m^3 (military)

0.015 mg/m^3 ~ 1 ppb (unit conversion)

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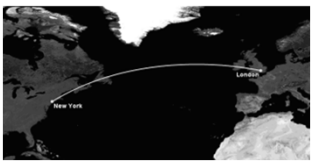
How much is 1 ppb?

- The width of 1 human hair in 68 miles
- 1 second in 32 years
- 1 sheet of toilet paper stretching from New York to London



https://www.watereducation.org/aquapedia-background/parts-notation#:~:text=Parts%20per%20billion%20is%20the,to%201%20microgram%20per%20liter.

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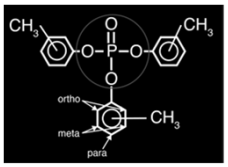

Combustion By-Products
- Carbon monoxide
- Carbon dioxide
- Oxides of phosphorus
- Aldehydes
- Other small molecules

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How much TBP & TPP is in aviation hydraulic fluid?

TBP ~58-68% by weight

TPP ~1-2% by weight

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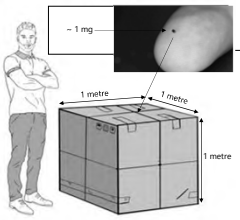
Measures of TBP & TPP in cabin air?

TBP

Normal operations — Mostly NON-DETECTS (<0.01 mg/m^3)

Highest concentration — Measured, including CAQE 0.02 mg/m^3



0.01 mg/m^3 TBP ~ 1 ppb (unit conversion)

TPP

Has not been measured in cabin air

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How much is 1 ppb?

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- 1 second in 32 years
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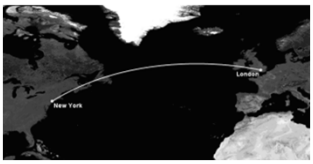

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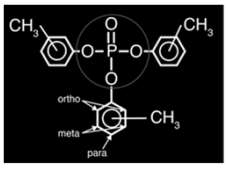

Combustion By-Products
- Carbon monoxide
- Carbon dioxide
- Oxides of phosphorus
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- Other small molecules

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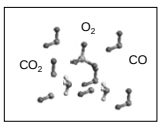
Combustion by-products

Thermodynamic degradation



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Measures of combustion by-products in cabin air?

Carbon Monoxide
ND – 4.6 mg/m^3 (~ 4%)

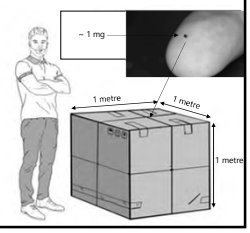
Carbon Dioxide
0.9 – 8.8 mg/m^3

Formaldehyde
ND – 0.044 mg/m^3

Acetaldehyde
0.003 – 0.09 mg/m^3

Other aldehydes
95th percentile between
0.013 – 0.07 mg/m^3

Small Particles
PM_{10} : <0.01 mg/m^3
$PM_{2.5}$: <0.01 mg/m^3



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Health impacts

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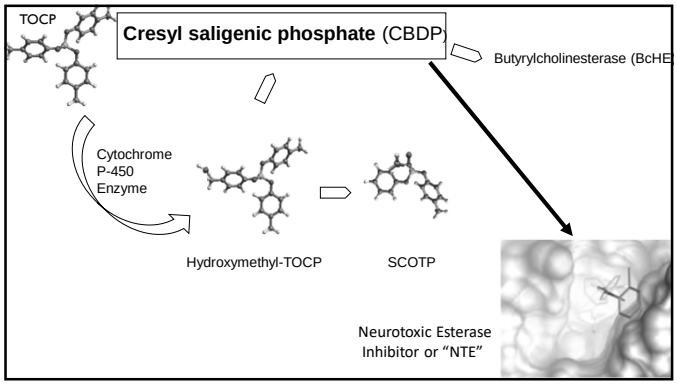

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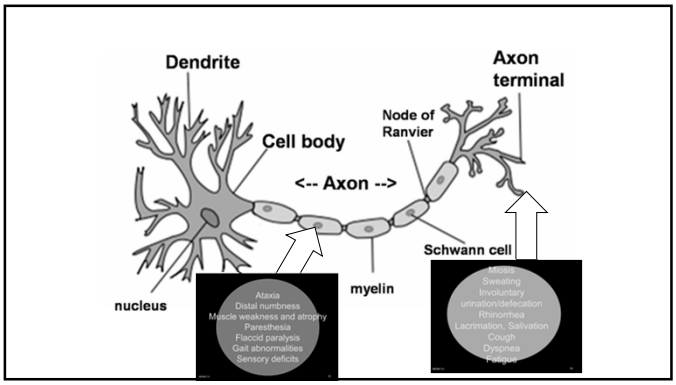

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Reported symptoms vs organophosphate-induced *syndromes*

Common Symptoms

Headache
Irritation of throat/nose
Eye irritations
Dizziness/Weakness
Nausea
Lightheadedness

Uncommon Symptoms

Tremors
Cognitive problems
(such as difficulty
concentrating confusion)
Airway irritation

VS

Acetylcholinesterase (AChE) Inhibition

Salivation
Lacrimation
Urination/defecation
Diaphoresis
Gastrointestinal upset
Emesis
S.L.U.D.G.E.

Organophosphate induced delayed neuropathy (OPIDN)

Ataxia
Distal numbness
Muscle weakness and atrophy
Paresthesia
Flaccid paralysis
Gait abnormalities
Sensory deficits

(1-4 weeks post exposure)

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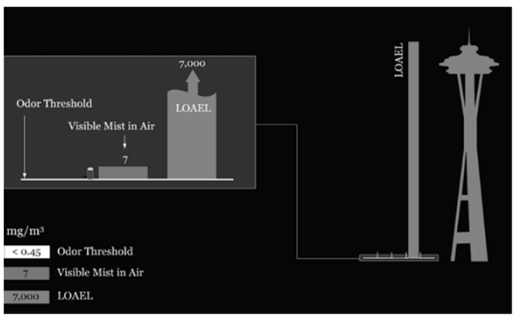
How much jet engine oil to cause OPIDN?



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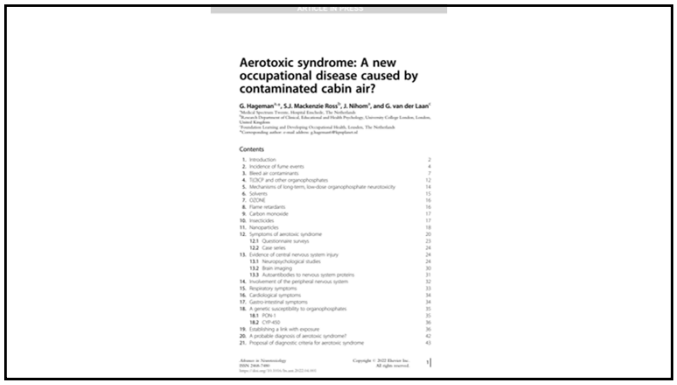

Aerotoxic syndrome: A new occupational disease caused by contaminated cabin air?

G. Hageman[1*], S.J. Mackenzie Ross[2], J. Nihom[3], and G. van der Laan[1]

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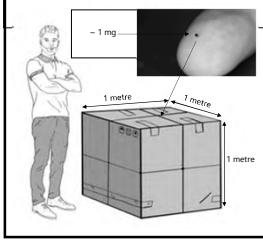
What is an acceptable exposure limit for TBP and TPP?

Protective Action Criteria (PACs)

Exposure guidelines used to protect from health effects of short-term exposures to hazardous chemicals in the air



TBP
PAC-1 15 mg/m³ or 1,400 ppb
> 690x than max. detected in cabin air

TPP
PAC-1 9 mg/m³ or 674 ppb
Not been measured in aircraft

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What is an acceptable exposure limit for some combustion by-products?

Carbon Monoxide
PAC-1 75 mg/m³
(over 16x greater than max. detected in cabin air)

Carbon Dioxide
PEL-TWA CAL/OSHA 9,000 mg/m³
(over 1,000x greater than max. detected in cabin air)

Formaldehyde
PAC-1 1.1 mg/m³
(over 25x greater than max. detected in cabin air)

Acetaldehyde
PAC-1 81.1 mg/m³
(over 900x greater than max. detected in cabin air)

24-hr NAAQS PM_{10}
0.15 mg/m³
(15x greater than detection limit)

24-hr NAAQS $PM_{2.5}$
0.035 mg/m³
(35x greater than detection limit)

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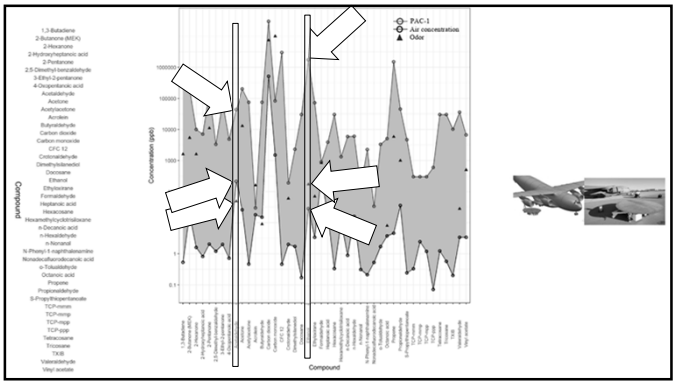

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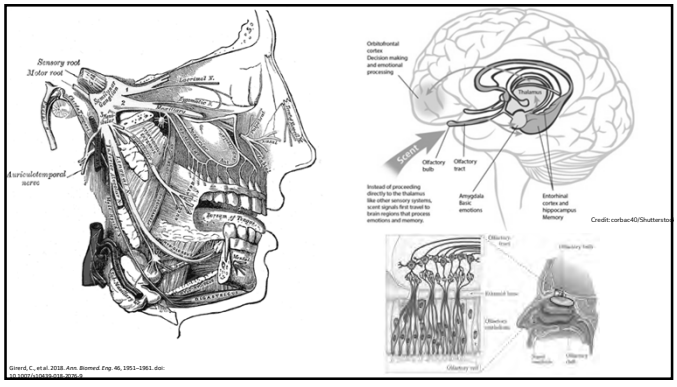

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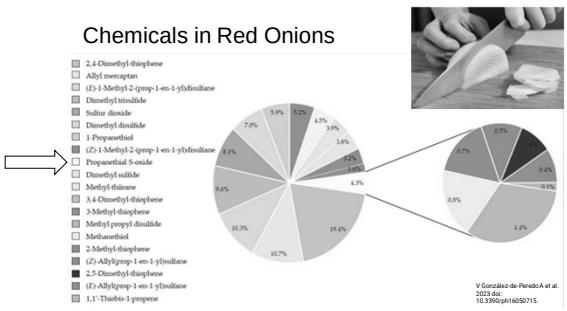
Common sources of odors that induce physiological reactions



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Biomarkers

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Blood or urine biomarkers

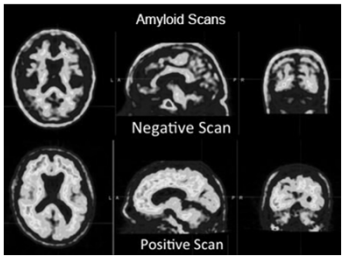
- Neuronal autoantibodies
- Metabolites of TCP

Brain analysis

- PET/SPECT/MRI
- EEG
- Other (Sway)

Hair testing

Genetic testing



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Genetic testing

The CYP2C19*17 allele is associated with an increased enzyme activity. The wildtype allele is named CYP2C9*1. Carriers of the homozygous variant or the compound heterozygous genotype generally display a "poor metabolizer" (PM) phenotype, i.e. have a reduced capacity to metabolize CYP2C19 substrates. Carriers of a heterozygous genotype for one of the two analyzed polymorphisms generally display an "intermediate metabolizer" (IM) phenotype. Carriers of the CYP2C19*17 allele generally display an "ultra-rapid metabolizer" (UM) phenotype. Genotyping of CYP2C19 allows to identify individuals who have a predisposition for an increased relative risk of thrombosis and associated cardiovascular events (stroke, heart attack) with fatal outcome in some cases, as well as of adverse side effects of treatments with anticonvulsants and antidepressants.

PON1_M55L vt/vt
PON1 Q192R wt/vt

The presence of the LL and QR genotypes for the polymorphisms PON1 [M55L and [Q192R] respectively is associated with an only slightly reduced predictive enzyme activity of PON1. Presence of a slight genetic predisposition for oxidative stress, which plays an important role in atherosclerosis, myocardial infarction and ischemic cardiomyopathies.

The variant allele CYP2B6*4 results from a exchange of adenine to guanine at the DNA level which, at the protein level, results in the replacement of lysine by arginine in position 262 of the active enzyme. This variant seems to be related to an increased enzymatic activity.

The frequence of the CYP2B6*4 allele is very different from an ethnic group to another. The prevalence in the Caucasian population is of about 40 %.

CYP2C19*2 wt/wt
CYP2C19*3 wt/wt

The wildtype for the two CYP2C19*2/*3 polymorphisms is associated with a genetic predisposition for a normal CYP2C19 enzyme activity. There is no increased relative risk of adverse drug reactions during a treatment with drugs, which are substrates of CYP2C19, in relation to the CYP2C19*2/*3 polymorphisms. A

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Blood Biomarkers

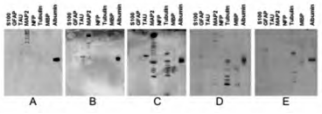
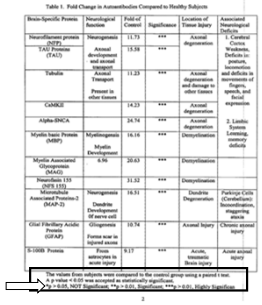


FIGURE 4. Western immunoblots of autoantibodies against tested nervous system proteins in sera of control and case-study pilot before and after exposure to cockpit air emissions: (A) control, (B) the pilot serum before flying, time "0," (C) the pilot after "12 days" of flying, (D) the subject "16 months" after the first sample, and (E) the subject "21 months" after the first sample.

In: Abou Donia et al., 2013



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Testing Hair

You collected a hair sample and sent it to [redacted] to search for Tri-Cresyl-Phosphate compounds.

The analysis results inform you about your exposure to Tri-Cresyl-Phosphate compounds over a period of 1 to 3 months depending on the hair length analyzed (1 to 3 cm). Presence of one or more TCP isomers in your hair attest your exposure to that chemical(s) with a strong probability. Exposure can reflect elevated dose and time limited exposure (acute exposure) or low dose and regular/extended exposure (chronic exposure) or a combination of both.

We draw your attention to the fact that to date there is no reference scale or relationship between TCP hair concentration and a defined health risk level and/or the exposed dose. However, a great amount of TCP in hair strongly suggests a high level of exposure[1].

In the table below, you will find the results of the analysis performed on your hair sample for 5 main TCP isomers. The indication **PRESENCE** in the table confirms that the molecule was quantified (concentration above the quantification limit LQ of the analytical method) or detected (concentration below the quantification limit LQ of the method but higher than the detection limit LD of the instrument).

Name of the molecule	Results	Concentration (pg/mg of hair) Measured	Limit of Quantification	Limit of Detection
ToooCP (CAS No. 78-30-8) Tri-ooo-Cresyl-Phosphate	< LD	< 0,7	2,0	0,7
TmmmCP (CAS No. 563-04-2) Tri-mmm-Cresyl-Phosphate	< LD	< 0,7	2,0	0,7
TmmpCP* Tri-mmp-Cresyl-Phosphate	PRESENCE	< 2,0	2,0	0,7
TmppCP* Tri-mpp-Cresyl-Phosphate	< LD	< 0,7	2,0	0,7
TpppCP (CAS No. 78-32-0) Tri-p-Cresyl-Phosphate	< LD	< 0,7	2,0	0,7

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Authoritative organizations' conclusions regarding cabin air quality events

anses

de l'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail – 2023
[translated] Recent research focuses on the health effects of certain compounds in cabin air, particularly organophosphates. Current data do not show significant health effects of these compounds at low concentrations in the air.

UK Civil Aviation Authority

UK Civil Aviation Authority – 2022
"Long-term ill health due to any toxic effect from cabin air is understood to be unlikely, although such a link cannot be ruled out."
"...symptoms usually resolve, however, once the fumes or smell have disappeared."

COT

Committee on Toxicity (COT) – 2022
"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"

Aerospace Medical Association (AsMA) – 2011
"There is no evidence to support a causative association between cabin air fume exposure and short or long-term nerve damage."

Australian Civil Aviation Safety Authority (CASA) – 2009
"The evidence for the existence of an 'Aerotoxic Syndrome' related to smoke/fume events is, however, still based almost entirely on case-series reviews, remains self-reported and should be categorized epidemiologically as Inadequate or Insufficient Evidence to Determine Whether an Association Exists."

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Clinical considerations

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A good history is needed
A good understanding of the exposure
Objective tests
AChE?
COHb?
Toxicology assessment

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Conclusions

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Exposure × Hazard ≈ Risk

Generally short in duration and uncommon in occurrence	×	Chemicals non-detect or detected below levels designed to protect health	≈	None to very low

There is no reliable toxicological evidence that CAQEs cause long-term neurologic toxicity

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