Association Toxicologie-Chimie
The Toxicology-Chemistry Association

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DO YOU KNOW AEROTOXIC SYNDROME ?

(ATS)

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Aircraft Cabin Air Contamination
Health and Flight Safety Implications

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DO YOU KNOW WHAT AEROTOXIC SYNDROME IS?

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DO YOU KNOW AEROTOXIC SYNDROME ?

(ATS)

As you can imagine, the answer to this is 'No' far more often than 'Yes' !
There are, of course, possible exceptions among aircraft crew and it would be rare for experts in the field of toxicology to be unaware of this! The toxicologists think, quite rightly, that the syndrome consists of clinical symptoms observed in people working in the aeronautics sector, whether they are flying crew or ground staff or indeed, observed in passengers, who are a large population and are also the most uninformed about the worrying 'syndrome', which is more commonly referred to as 'Air Cabin Syndrome'[1].
However, while this describes the syndrome, it does not tell us how air can become toxic within these heavily fortified aircraft. Surely this is too far-fetched to be true?
Let us explore this rather unexpected riddle.
From a historical point of view, people have known of the possible health hazards from the air introduced in aircraft cabins, both military as well as civilian aircraft, since the 1950s. However, it was only in 1999 that these hazards were clearly described.
A group of experts comprising of Christ Winder, an Australian Professor of Toxicology, the French expert Jean-Christophe Balouet and Dr. Harry Hoffman, a surgeon in the US Navy, first named this new pathology 'Aerotoxic Syndrome'[2]. [1]

[1] What is aerotoxic syndrome ? The Telegraph (28 février 2017) - http://www.telegraph.co.uk/news/aviation/11427400/What-is-aerotoxic-syndrome.html

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AEROTOXIC SYNDROME

1. WHAT IS THE NATURE OF AEROTOXIC SYNDROME (ATS)?

Limiting ourselves to a few features, we can use the definition proposed by a toxicochemist member of the ATC. According to them, 'Aerotoxic syndrome' may be defined as a pathology associated with the exposure of aircraft crew and passengers to the pressurised air that is continuously circulated inside the cabin during flights. More precisely, the air is circulated every five minutes through the cockpit, the sections occupied by the crew and through the passenger cabin.

It may seem obvious straightaway that the air circulating within the cabin is not supposed to affect health of those who breathe it in!

But it would appear that over the long term, following prolonged exposure, some people do present with pathologies that are not very well characterised and which cause a progressive deterioration in health.

In reality, these symptoms, which lack specificity, may indeed be classified under the rather loose collection of illnesses that Anglo-Saxons term 'Multiple Chemical Syndrome' or 'MCS' [Appendix 1]. This implies hypersensitivity linked to exposure to multiple chemical products and this is what makes toxicologists so curious about this strange pathology.

Of course, whenever something lacks precision, it generates heated debates- and this is generally at the cost of the health of the patients, who are most often termed 'psychologically fragile'! This seems to be common practice these days for many disorders that are difficult to characterise or standardise.
Given this, let us try to be more specific when examining ATS.

2. HOW DOES CABIN AIR GET CONTAMINATED?

In civil aviation, the air supply in jet aircraft is taken from the compressors in the engines and is directly circulated in the cabin. This may seem bizarre, but it is exactly what happens. Boeing 787 aircraft are, today, the only aircraft that use electric air compressors that take in air directly from the outside, without the air passing through the engine compressors.

In all other planes, about half the air that is circulated in the cabin and used for pressurisation of the cabins is taken directly from the upstream part of the engines: air which, following its time in the turbines, may possibly carry contaminants.

The air taken from the engine compressors may be contaminated by an internal leak of engine oil into the compressor air. In the 1950s, air injected directly into the cabins was blamed for many problems that aircraft crew developed.

In jet engines, the fan blades, which act as a propeller, are constantly rotating around a central axis that is lubricated using a liquid seal made up of synthetic Oil. This Engine oil must withstand temperatures in the range of 500 °C. Special seals made of Carbon are used to isolate this oil and prevent leaks - however this does not always work.

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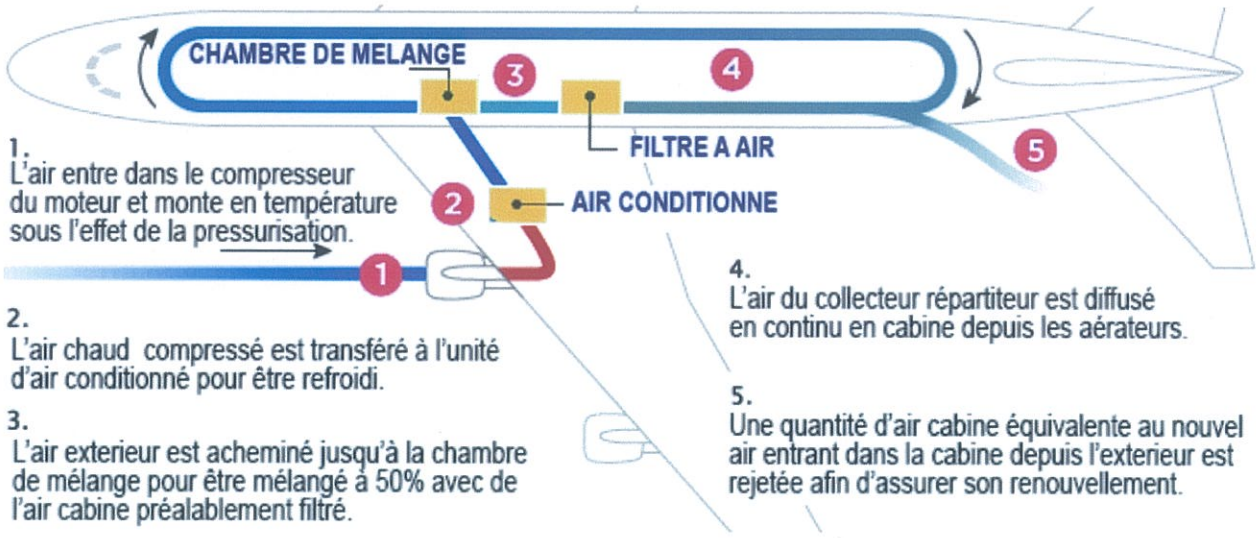
At this stage, the air meant for the cabins is taken from the low and high pressure compressors, where it heats up as a result of pressurisation. (Diagram 1, Step 1)Diagram 1.1

The remaining air then goes on towards the back of the reactor, where the compressed, warm air then enters the combustion chamber (Diagram 1, step 2). The Kerosene-type jet fuel, which contains Hydrocarbons in the range of C9 to C16, is injected into this combustion chamber. Diagram 1.1

The energy released by the combustion of the Kerosene is transferred to the turbines. The pressure and speed of the hot gases provide the force required to turn the turbines and the shaft, which in turn will drive the compressor.

The journey the outside air makes from the compressors to the cabin is summarized in Diagram 1. Diagram 1.1

There is no doubt that following uncontrollable leaks, the air has also picked up, along the way, all the impurities resulting from the components of the mineral oil and, possibly, its products of pyrolysis. In the mixing chamber, half of this air from the exterior (and through the compressor) is then mixed with 50% of the air taken from the cabin, which has, of course, been filtered in the hold through a HEPA-13 dust filter in order to trap the microorganisms resulting from the respiration of passengers and crew in the plane. However, there is no such filtration for chemical products or their degradation products. A collector-distributor ultimately circulates this compressed hot air, called "compressed air", which is now considered to be "purified", within the cabin.



January 2016 - Document from the website of the Syndicat National du Personnel Navigant Commercial (The National Union for Aircraft Crew):
Publication dated 22/11/2016 ; Aerotoxicity : http://snpnc.org/system/files/article/file/2583-air-cabin-1.pdf
Air France - Tract - À la une - International-EurECCA : http://www.snpnc.org/content/air-france/aerotoxicite [3]

Diagram 1.1 Air supply in the cabins of jet aircraft.

Quite logically, to properly ensure that the 'cabin air' is fresh, a quantity of air equivalent to that injected into the cabin, is expelled from the aircraft, as can be seen in the above flow-chart. [Step 3]. Diagram 1.1This will then be replaced by 'fresh air' from the compressor.

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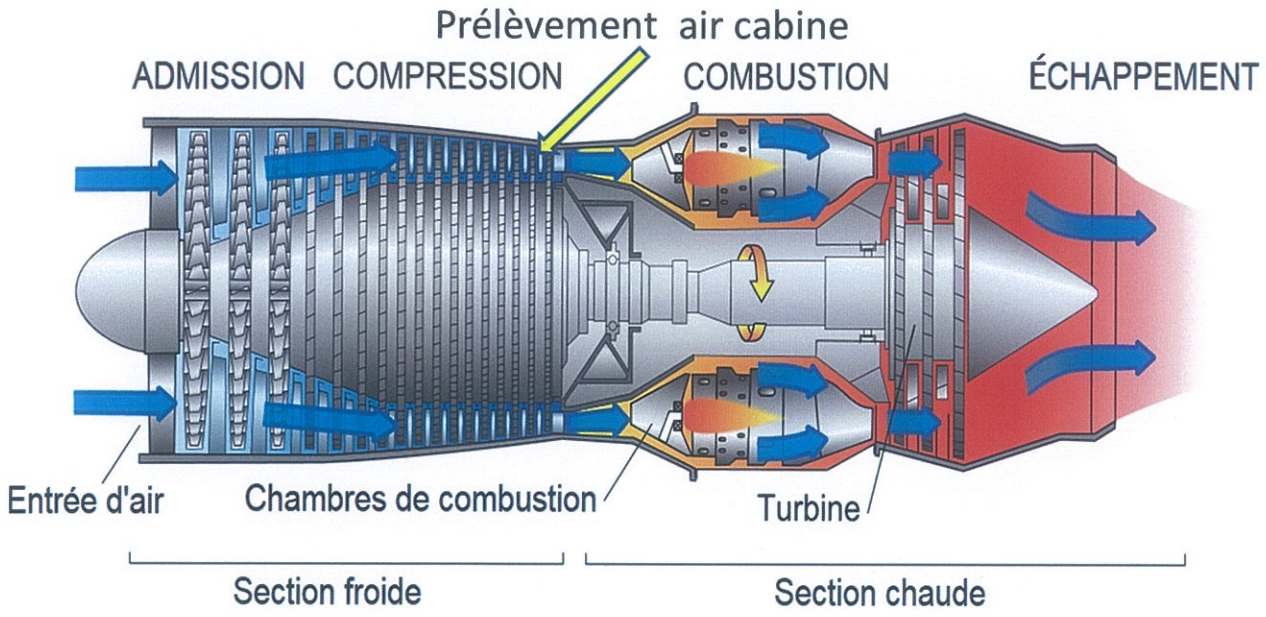
The below diagram gives an overview of the structure of an engine with its two compartments - the compression chamber and the combustion chamber (Diagram 2, cross-section of an engine) [4]. Diagram 2.2 Cross-section of an aircraft engine.
The sanitary quality of the air being inhaled by aircraft personnel currently working in these planes is certainly an open question. Today, only the Boeing 787 takes in air from outside its engine compressors. This choice was made possible due to the reduction in weight resulting from the large-scale use of composite material in aircraft construction (using 50% composites in the structure results in a 20% drop in weight compared to a conventional Aluminium structure). However, despite the air being taken in directly from outside, this still does not eliminate the possibility of chemical pollution. Indeed, all aircraft cabins, just like our apartments, are subject to contaminants both from the outside world (as the air introduced is not filtered for chemicals) as well as contaminants in the interior resulting from the discharge of chemical pollutants from the material used to construct the cabins.
As students of chemistry, it would be interesting to carry out research into which products could be implicated in 'Aerotoxic syndrome'. These products may be carried in, as they are, by the air from the outside world or may be the products of pyrolysis from the combustion chamber, whose temperature, it must be recalled, hovers around the 500°C mark.



Contaminated-Air-Overview-GCAQE-Brochure-2014.11 [INSERT ENGLISH IMAGE from http://gcaqe.org/wp-content/uploads/2015/05/GCAQE-CAQ-Brochure-17-MAY-2015.pdf]

Diagram 2.2 Cross-section of an aircraft engine.

3. *WHAT CHEMICAL PRODUCTS ARE LIKELY TO BE FOUND IN CABIN AIR?*

The air sent into cabins may be polluted by the products of pyrolysis of the Engine oil that is used to lubricate the compressor, by the products of thermal decomposition of Hydraulic fluids, as well as by atmospheric Ozone and all the Internal pollutants within the cabin. To this are added the Kerosene fumes produced during the pushback or 'taxiing'

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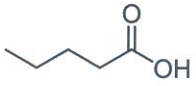
while waiting for take-off, or the spraying of the Glycol-type de-icing products, which are pyrolised and circulated in the cabin via the APU (the Auxiliary Power Unit). We must note that certain international destinations also spray insecticides inside the cabin.
What is common to both these types of oil is that they contain various additives made up of Organophosphates, which are very efficient anti-corrosion agents and flame retardants.

3.1. THE COMPOSITION OF ENGINE OILS.

3.1.1. Fatty esters

Conventionally, 95% of the components of Engine oils for aircraft are Fatty esters of polyols, chiefly Pentaerythritol (sometimes of Dipentaerythritol) and of Fatty acids with average or high molecular weight, such as Valeric acid (Pentanoic acid).

Pentaerythritol

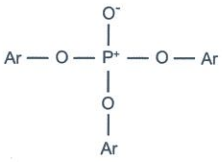


Valeric acid

Figure 1. Examples of components of aircraft engine oils.

3.1.2. Aryl phosphates.

In addition to these synthetic Fatty esters, the oils contain 2 to 6% of Aryl phosphates, including Tricresyl phosphates (TCP).



Ar = aromatic groups

Figure 2 Aryl phosphates2

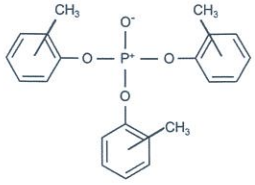


Figure 3 Tricresyl phosphates (TCP)3

The most studied of the Tricresyl phosphates (TCP) present in Engine oils is Tri-Ortho-cresyl phosphate (TOCP), which is known for its peripheral neurotoxic properties.

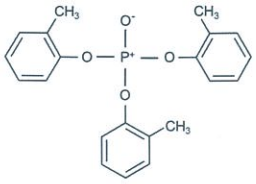


Figure 4. Tri-ortho-cresyl phosphate (TOCP)

The two other isomers, Meta- and Para-cresyl phosphates are often found in Engine oils, but their toxicity is lower than that of Tri-ortho-cresyl phosphate. The meta-isomer, especially, presents no peripheral neurotoxicity.

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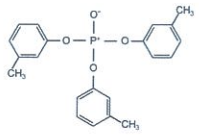

Figure 5. Tri-meta-cresyl phosphate (TMCP)

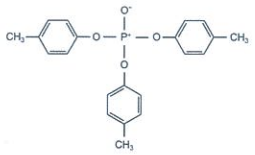

Figure 6. Tri-para-cresyl phosphate (TPCP)

Given the low amounts of Tri-ortho-cresyl phosphates, both in Engine oils as well as in cabin air, other isomers of Tricresyl phosphate (TCP) may be suspected of contributing to the neurotoxic effects observed among pilots, air hostesses and stewards. There is also the possibility of there being a synergistic effect between all these compounds?

There have also been reports that three other isomers of Tricresyl phosphate are likely to be 5 to 10 times more neurotoxic than TOCP.

These isomers are:

- Phenyl-di-ortho-cresyl phosphate (DOCPP), the most neurotoxic isomer, 10 times more neurotoxic than TOCP.
- Diphenyl-ortho-cresyl phosphate (DPOCP), which is 6 times more neurotoxic than TOCP.

Furthermore, Tri-para-cresyl phosphate (TPCP), in Figure six, is also likely to have neurotoxic activity due to its Cholinesterase-inhibitory properties. Figure 6

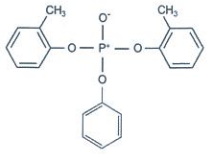

Figure 7. Phenyl-di-ortho-cresyl phosphate (DOCPP)

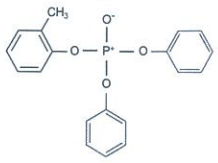

Figure 8. Diphenyl-ortho-cresyl phosphate (DPOCP)

It must be noted that very few experimental toxicology studies have been carried out on complex mixtures in conditions where there is exposure through inhalation.

3.1.3. N-Phenyl-1-naphtylamine.

Engine oils often contain about 1% of N-Phenyl-1-naphtylamine (PAN), which is an N substituted aromatic amine, used for its antioxidant properties.

This secondary Amine is allergenic, endowed with methemoglobinemia-causing properties (cyanosis, anaemia) but without any known genotoxic or reprotoxic activity.

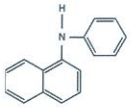

Figure 9. N-Phenyl-1-naphtylamine (PAN).

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3.2. THE COMPOSITION OF HYDRAULIC FLUIDS

Hydraulic fluids, which may also be implicated in the contamination of cabin air, also contain Organophosphates. The most abundant of these are Tributyl phosphate (TBP) and Triphenyl phosphate (TPP).

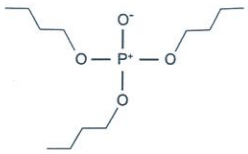

Figure 10. Tributyl Phosphate (TBP)

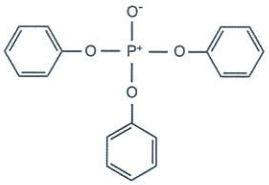

Figure 11. Triphenyl Phosphate (TPP)

3.3. INVOLVEMENT OF ANTI-ICING FLUIDS

In addition to the possible contamination of air that is introduced into jet aircraft cabins (50% of which, we have seen, is from the front part of the engines), an additional source of polluted air may be the anti-icing fluids used for de-icing aircrafts (used on specific areas of the airport for de-icing purposes).

These anti-icing fluids may play a role in the contamination of cabin air following accidental discharge during the de-icing of the engines and/or the APU (Auxiliary Power Unit), which supplies the cabin air when the aircraft is on the ground and the engines are off.

Conventionally, the components of these de-icing fluids are two Glycols (Ethylene glycol and Propylene glycol) i.e. two 1,2-Diols with two adjacent hydroxyl groups.

Figure 12. Propylene glycol

Figure 13. Ethylene glycol

The earliest versions contained Ethylene glycol. However, the use of this chemical sparked off fears due to its nephrotoxic and neurotoxic properties and it was, thus, gradually replaced by Propylene glycol which is believed to have low toxicity.

Some companies disclose the composition of the de-icing fluids that they use. For example, the Safety Data Sheet (SDS) for a de-icing fluid offered by the firm Aéro-Sense, BVBA (Roeselare, Belgium) has about 80% of Ethylene glycol and the remainder is Propylene glycol.

In general, it would be interesting to obtain and examine the SDS for various products used by airline companies. Indeed, the safety measures to be implemented when using these products will vary considerably depending on whether the product involved is toxic, such as Ethylene glycol, or poses few risks to health or the environment, such as Propylene glycol.

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3.4. WHAT IS THAT NATURE OF THE PRODUCTS OF PYROLYSIS OF ENGINE OILS AND HYDRAULIC FLUIDS?

While trace amounts of many chemical compounds present in Engine oils and Hydraulic fluids can be found in cabin air, many other chemical products that are not directly found in the composition of these oils are also found in the cabin air.

These are basically the products resulting from pyrolysis (at 500 °C in the combustion chamber) of Organic compounds and Organophosphate compounds.

Overall, upon pyrolysis, Organic compounds will form Carbon dioxide (CO_2) and a small amount of Carbon monoxide (CO), whose role in the overall toxicity of the contaminants in cabin air may be quite significant!

Further, it is probable that when Organic compounds (a mix of Hydrocarbons in the C_6 to C_{18} range), such as the Polycyclic aromatic hydrocarbons (PAHs) present in Kerosene are pyrolysed, they may form very fine particles (among other products) which include Carbon nanoparticles.

With respect to Organophosphate compounds, on pyrolysis they release Carbon monoxide (produce from the organic part) and, in addition to this, they produce Oxides of Phosphorous, including Phosphorous pentoxide P_2O_5, which exist in the form of the dimer P_4O_{10}. The pyrolysis of organophosphate compounds may produce various Nanoparticles of an unknown nature.

Under classical conditions, Phosphorous pentoxide, a water-hungry compound, is a powerful dehydrating agent endowed with irritating properties. What do we really know about the toxicity of the mix of compounds resulting from pyrolysis? The answer is - not very much.

Based on current knowledge, it is evident that the pyrolysis of all these components will lead to the formation of nanoparticles. The toxicity of these nanoparticles is practically unknown at present. If these nanomaterials are found in the brains of persons exposed to cabin air and if these persons suffer from otherwise inexplicable disorders, can we then think abou, their true impact on the health of aircraft personnel?

4. WHAT HAPPENS WHEN ORGANIC PHOSPHATES ENTER THE BODY?

Of the organophosphate compounds that may be present in Motor oils and Hydraulic fluids, the most abundant are generally the Tricresyl phosphates (TCP), which is strongly contested by national aviation authorities.

Tri-ortho-cresyl phosphate (TOCP), also called Tri-ortho-tolyl phosphate, a minority component of the mixture of TCPs is the isomer whose metabolism and toxicity have been most studied.

As a general rule, Organic phosphates are easily absorbed by oral or dermal routes. However, in the absence of data, the possibility of absorption through inhalation must not be neglected. Tri-ortho-cresyl phosphate (TOCP) is, subsequently, quickly distributed in organs rich in fat: adipose support tissue, the liver, the kidneys and, of course, the nervous system.

In the liver, various metabolizing enzymes act on the TOCP to allow it to be eliminated in the form of water-soluble metabolites.

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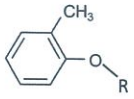
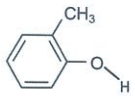
The most important pathway in TOCP toxicity is the oxidation of a Methyl group (– CH_3) in the presence of Cytochrome P-450 monooxygenases (CyP450-3A and CyP450-3A5), with the formation of the corresponding primary Alcohol (–CH_2–OH).

Next, through interaction with Serum albumin, one of the tolyl groups is removed in the form of ortho-Cresol (diagram 3).Diagram 3.3



Orthocresyl group



ortho-Cresol

The rest of the molecule forms a cyclic Cresylsaligenin phosphate (CBDP). This reactive intermediate attack the primary Alcohol group on a Serine (alcohol-functional amino acid) at position 198 of Butyrylcholinesterase and, undoubtedly, other Cholinesterases. An adduct with a mass of 170 Da is formed, which loses its Cresyl group over time and leads to the formation of an 80 Da mass, as shown in the below diagram.

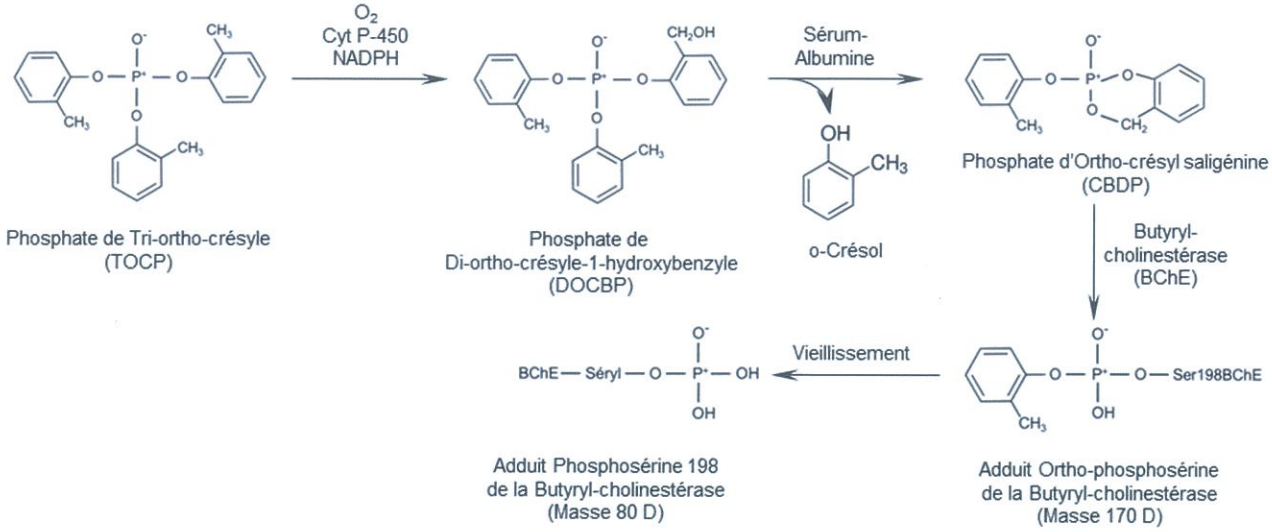


Diagram 3.3 Metabolisation of the Tri-ortho-cresyl phosphate (TOCP) in the presence of Cytochrome P-450

How is Tri-ortho-cresyl phosphate likely to be involved in the neurotoxicity of Aerotoxic Syndrome?

Today it is accepted that Aerotoxic Syndrome is likely to result from the exposure of aircraft personnel to cabin air. The chief contaminants in the cabin air are believed to be aryl phosphates (inluding Tri-ortho-cresyl phosphate), Carbon monoxide, as well as various Aldehydes, including Formaldehyde and Acetaldehyde.

Tri-ortho-cresyl phosphate (TOCP) is an Organophosphate that is used as a lubricant, anti-wear agent and heat-proof agent in Engine oils.

Let us consider the example, given in diagram 3, of the metabolism of TOCP. When metabolised, this compound ultimately produces:

2-(ortho-Cresyl)-4-H-1,2,3-benzodioxaphosphoran-2-one

commonly called ortho-Cresyl saligenin phosphate (CBDP).

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This final toxic product irreversibly inhibits two enzymes present in the human nervous system, namely: Butyrylcholinesterase (BChE, EC3.1.1.8) and acetylcholinesterase (AChE, EC3.1.1.7). These Cholinesterases, which rapidly lose their property of hydrolysing Acetylcholine, are not recycled.

As a result, during the aging process, the ortho-Phosphoserin adduct of Butyrylcholinesterase, with the mass 170 Da, loses an ortho-Cresol and form, as its final metabolite, an adduct, at Serine198 on Butyrylcholinesterase with the mass 80 Da.

in 2011, a Grenoble-based team headed by Patrick Masson used X-ray radio cristallograhy analysis to prove that this final adduct, with the mass of 80 Da, was likely to be responsible for the peripheral neurotoxicity of Tri-ortho-cresyl phosphate (TOCP). [6]

5. *What are the symptoms of Aerotoxic Syndrome?*

The first use of specific engine oils in engine dates back to the 1950s, when they were used by US Air Force (USAF) aircraft.

From the time they were used, pilots complained of various problems, which they attributed to the contaminants present in these Engine oils.

In May 1954, William J. Van Every [7], a USAF pilot, reported that his first symptoms were blurred vision, nausea and experiencing immense fatigue. He also experienced dryness in his mouth and throat. [7]

The same year, WN. Aldridge [8] proved that Tricresyl phosphates caused the demyelination of long nerves, which could result in polyneuropathy.

This was followed by many authors from different countries reporting similar troubles among pilots and aircraft crew.

Despite this, it took 60 long years before a toxicologist, the American, Abou-Donia [10], proved that Tri-ortho-cresyl phosphate (TOCP) was implicated in this pathology observed in a pilot. The case of the tragic poisoning of this pilot is presented in Appendix 2, p. 26.

In 2010, Suzan Michaelis [9] stated that around 45% of pilots reported experiencing several symptoms of Aerotoxic Syndrome either during or towards the end of their flight.

Going by the response of airline companies, the possibility of cabin air being contaminated following the leakage of Engine oil or Hydraulic fluid is taken into account in quite a variable and casual manner.

This casualness seems to be linked to very low awareness regarding the research around the cause of the problems experienced by aircraft crew.

It also seems that the oil fumes that can affect health over the short or long term (nausea, vomiting, diarrhoea, various irritations, respiratory problems, vertigo, fatigue) would relate to one case per 100,000 flying hours.

How far can we trust statement? A study by the British government reported that oil fumes affected 1% of flights, but these figures are hard to verify. According to Dr. Abou-Donia [10], repeated exposure to low doses of various Aryl phosphates (AP) type Organophosphate compounds leads to chronic neurotoxicity in a condition called 'Organophosphate Induced Delayed Neuropathy' (OPIDN) and it appears that this is likely to be stronger for low doses than for high doses!

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According to V. Hausherr [11[, functional neurotoxicity has been observed following exposure to very low concentrations of Tri-ortho-cresyl phosphates (TOCP), although this did not lead to visible lesions.

This would suggest that low doses of TOCP could cause brain damage, with cognitive deficiencies.

A 2011 study by Mariya Liyasova [13] showed that out of 12 passengers who were tested, 6 tested positively for exposure to Tri-ortho-cresyl phosphate (TOCP), but did not have any apparent symptoms.

In Great Britain, Tricresyl phosphate (TCP) contaminants from Engine oil were found in cabin air in 46% of flights. Furthermore, Tributyl phosphate (TBP), a significant contaminant from Hydraulic fluid, has been detected in cabin air in 73% of flights.

An international study carried out in 2011 by P. Masson *et al* [6] showed that aircraft crew with a mean age of 41 years had various neurological disorders as well as cancer rates that were 10 times higher than in a control population.

Finally, a 2014 American study at Harvard showed that in addition to neurological problems, there was a greater incidence of cancers affecting sexual health among female aircraft crew.

In the last evaluation it carried out in 2017 [14] the European Aviation Safety Agency (EASA) displayed great confidence in the good quality of cabin air, which they said was better than interior air in other settings (inside houses, inside schools ….)!

In its evaluation, the EASA stated that the concentrations of volatile organic compounds (VOCs), Carbon dioxide (CO_2) and Carbon monoxide (CO) must be considered normal compared to the concentrations of these products in other indoor settings.

As an example: the global concentration of VOCs in cabin air, is between 0.024 and 2.1 mg/m^3, with low levels of Formaldehyde (between 0.03 and 48 µg/m^3) and Acetaldehyde (between 0.02 to 42 µg/m^3).

The EASA accepts that Organophosphate compounds (OPCs) were detected in all 516 samples analysed (on average between 0.009 to 0.020 µg/m^3) without, however, the ortho-isomer of Cresyl phosphates being detected.

The two most commonly detected organophosphate compounds were Tributyl phosphate (TBP) (between 0.037 and 2.484 µg/m^3) and, above all, Tris(2-chloroisopropyl) phosphate (between 0.023 to 9.977 µg/m^3), which is, at present, the flame retardant compound that is most often analysed and which, upon pyrolysis, cannot but increase the level of Dioxins, by contributing the Chlorine that is required for their synthesis!

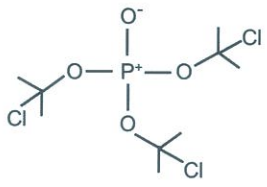

Figure 14. Tris(chloroisopropyl) phosphate.

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It is important to note that the two Organophosphate compounds found by the EASA [14] are also present in cabin air in the Boeing 787 (between 0.037 to 1.198 µg/m^3 for TBP and between 0.041 and 2.633 µg/m^3 for Tris(chloroisopropyl) phosphate). Despite all that we have seen this is still quite startling!

Overall, when considering the official data established in the European Union by the EASA, we cannot help being confused by their optimism, especially when we look at other studies that have been carried out in Great Britain, Germany and the United States.

A simple example: while the Carbon monoxide (CO) concentration established by the EASA was less than 0.5 ppm [14], an American study in 2000 by C. Van Netten [15] indicated that the average concentration of CO was in the range of 100 ppm – quite a curious difference!

Further, several recent studies have highlighted an increase in cancers and neuro-degenerative illnesses (including Amyotrophic Lateral Sclerosis [16]) among aircraft crew.

In the wake of these different studies, which are quite worrying, the concentration of Tri-ortho-cresyl phosphate (TOCP) in Engine oils was gradually reduced and today is only present in trace amounts in most oils, while certain Engine oils manufacturers have opted to change the Organophosphate compounds used.

The diversity of these alternative Phosphates is astonishing. For a long time now, the American army has used oil from the company NYCO, which uses the alternative additive Tri-isopropylphenyl phosphate (TIPP). Tri-ortho-isopropylphenyl phosphate (TOIPP) seems likely to be less toxic than TOCP especially as concerns effects on the peripheral nervous system. It may still, however, be a male endocrine disruptor, interfering with androgen receptors.

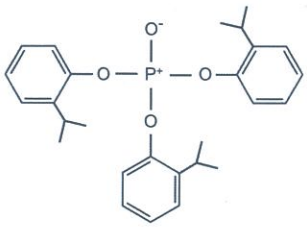

Figure 15. Tri-ortho-isopropylphenyl phosphate (TOIPP).

Despite accepting that TOIPP has lower neurotoxicity than TOCP, especially as concerns the peripheral nervous system, it would still seem reasonable to assume that the pyrolysis of all Organophosphate compounds in the Engines (up to 500 °C) would lead to the formation of derivatives that are very similar, including the Phosphorous nanometric structures, which seems quite troubling.

From our point of view, the possible formation of nanometric compounds that are capable of crossing first the alveolar barriers (where air from the respiratory process reaches the lungs) and then the blood-brain barrier (the meninges), which protects the central nervous system, would certainly pose health risks that must be taken into account on an urgent basis.

Indeed, there is nothing that prevents nanoparticles from travelling to the brain - and who can predict their real impact?

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It was in 2007 that the hypothesis about the formation of nanoparticles during the pyrolysis of Organic or Organometallic compounds (constant components of Engine oils and Hydraulic fluids) was first postulated [17].
It is undeniable that upon contact with the metallic surfaces of the turbines, whose temperature may go up to 1700 °C, these compounds may release Nanoparticles, among others, Ultrafine particles.

Jones *et al* [18] were able to prove that the components of the fumes formed in the turbo compressor included ultrafine, nanometric dusts, the majority of which measured between 50 and 70 nm in size. What remains to be done is characterising these Nanoparticles, which is not likely to pose a problem. We must then establish any possible correlation with Aerotoxic syndrome. Once this is done, will the mystery begin to clear up?

6. *PREVENTIVE MEASURES THAT SEEM VERY DISTANT STILL!*

Any real prevention of Aerotoxic Syndrome must necessarily involve improvements or 'retrofit' renovation. Secondly, existing fleets must have some or all their aircraft replaced by aircraft with 'purified air'.

It is obvious that a factor that will complicate these operations is the absence of any incentive to airline companies during the period when they will have to freeze their fleet for replacement.

For information: in 2017, the handling of aircraft that were incriminated in incidents of contaminated air was left to the discretion of airline companies, who refused to communicate on the subject. In fact, in early 2016, they denied, wholesale, any incident at all! Nevertheless, there has been an observable change in the course of action, given the scope of the matter. Thus, in France, there have been reluctant admissions of about 60 such cases. Nonetheless, given the discreet communications, the potentially explosive revelations and the lack of awareness around the issue, we may be justified in believing that these numbers remain largely under-reported, when comparing them with the numbers put out by various aviation bodies outside of France.

In addition, aircraft crew remain poorly informed on the subject and are often alone and helpless in the face of such incidents to which they are exposed several days in a row on different aircraft.
An illuminating example is that of a televised report in Germany, which discussed these problems. In the year following the broadcast of this programme, over 1000 cases were reported by crew (who were sensitised to the issue by this report).

At present, the average lifespan of an aircraft is between 25 and 30 years. It thus seems quite difficult to establish the time required to renew the entire fleet of French aircraft, replacing them by 'clean' aircraft.

As we wait for this 'promised revolution', there are improvements that can be immediately implemented and which would not be very expensive.

Among the measures that could be put in place quickly are:

- Detectors, alarms and indicators
- Filters placed along the air supply circuit, placed directly at the output from the engine and which would be capable of capturing nanoparticles.

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Of course, the cost of putting in place a prevention policy will be quite high and the crucial question is: Who will pay? The aviation industry is currently living through a scandal similar to the scandal the automobile industry witnessed with Diesel and Gasoil engines. While everyone knows about the health risks posed by this fuel, it is sadly true that as always, financial considerations are prioritised over public health. However, apart from the ethical considerations of the matter, the effects of these decisions on health result in a financial impact, in terms of public healthcare, that is at least equal to, if not greater than the cost of new policies.

In this context, it is easy to see that putting in place an effective policy for the prevention of Aerotoxic Syndrome runs up against the passive resistance of the majority of concerned actors and authorities, which is a depressing realisation.

7. Conclusion

Like a dancer at a carnival, Aerotoxic syndrome advances, but is masked and in disguise!

To conclude - the question "Do you know what Aerotoxic Syndrome is?" remains practically impossible to answer, given the number of actors working in the shadows!

On the one hand, the authorities and decision-makers in the aviation industry seem to be eternally optimistic, saying, "Don't worry, a new generation of so-called 'clear aircraft' is on the way!"

Does this mean, however, that (apart from the Boeing 787), the aircraft from older generations are 'unclean'?

And what do the Associations for the victims of Aerotoxic Syndrome think?

According to the GCAQE (Global Cabin Air Quality Executive) and AVSA (Association des Victimes du Syndrome Aérotoxique, or the Association of Victims of Aerotoxic Syndrome), this fight is too one-sided. Indeed, at present it is very hard for potential victims of Aerotoxic Syndrome to get recognition. This is, after all, a familiar step along the path of all those fighting for victims of professional illnesses - look no further than the history of the fight against Asbestos!

As with anything else, trade secrets and the intense competition between aircraft manufacturers, equipment manufacturers and airline companies will only conspire to maintain the silence!

In the scientific sphere, three researchers in Australia described Aerotoxic Syndrome in 1999. Ever since this date they have published little or nothing more!

With respect to the toxicology aspect, concerning the contaminants that may be present in cabins, it is at present extremely difficult to definitively prove the implication of one or another of the products discussed, especially as Nanometric dust particles were, until now, completely ignored!

It is certain, nonetheless, that Carbon monoxide, well as Aldehydes, such as Formaldehyde and Acetaldehyde, as well as the different Aryl phosphates (TOCP and others) contribute to the contamination of air circulated in aircraft cabins. As these components pass through the compressor, where the temperature is around 500°C, any Aryl phosphate undergoes pyrolysis and forms Phosphorous oxides, whose composition and structure remain unknown.

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What is certain is that it necessarily forms Ultra-fine dusts that is probably rich in nanoparticles. Who has been curious enough to study these Nanoparticles? What do we know at present about what happens when these nanoparticles enter the human body? If any studies exist on the subject, they have been kept secret.

Given their extremely small sizes (a Nanometre correspond to a billionth of a metre – 10^{-9}), if we refer to Carbon nanoparticles, which result, among other things, from the pyrolysis of Polycylic aromatic hydrocarbons (HAP), we can see that they can easily cross the alveolar barriers in the lungs, pass into blood and travel throughout the body, including to the brain. A direct passage into the brain is also possible through the olfactory nerve, which serves the nasal cavity, passing through the ethmoid bone. This may explain the neurological complaints observed and described in various reports by people affected by Aerotoxic Syndrome. It seems evident, moreover, that regardless of which Aryl phosphates is present in Engine oil or Hydraulic fluid, there will be very little difference between their final Phosphoric products of pyrolysis, which will undoubtedly include Nanoparticles. For this reason, it is extremely important to undertake research into replacing Aryl phosphates with non-Phosphoric products.

To conclude, there seems be an urgent need, for more knowledge on Aerotoxic Syndrome, to develop, scientific research both in chemistry as well as biology in order to better understand how Aryl phosphates, before and after pyrolysis, attack (among other structures) both the central and the peripheral nervous system.

In all more or less clearly defined pathologies affecting individuals exposed to so-called 'clean' cabin air, it is imperative that we obtain precise responses about the origin of the problems they suffer from and, above all, help them in their brave fight to gain recognition for their illness, classified at present under 'origins unknown'!

We can only hope that the whistle-blowers will soon be heard, not only by authorities in the field of aviation but doctors in charge of Personnel Health.

It is essential that everyone at all levels understands that prevention cannot remain a distant utopia!

Paris, June 18, 2018.
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Appendix 1

Comparison between the symptoms related to ATS and those related to specific poisoning

APPENDIX 1A
COMPARISON OF THE SYMPTOMS ASSOCIATED WITH ORTHO-TOLYL PHOSPHATE POISONING AND THOSE ASSOCIATED WITH AEROTOXIC SYNDROME

TOXICITY TYPE	SYMPTOMES ASSOCIATED WITH ORTHO-TOLYL PHOSPHATE POISONING			SYMPTOMS ASSOCIATED WITH AEROTOXIC SYNDROME
ACUTE TOXICITY	1 to 8 days	Gastrointestinal problems	Nausea Vomiting Intestinal pain Diarrhoea	→Nausea →Vomiting →Intestinal pain →Diarrhoea
	8 to 35 days	Absence of problems		
		Irritations	Rhinitis Conjunctivitis Pharyngitis Cough	→Rhinitis →Conjunctivitis →Cough
		Peripheral neuropathies of the limbs	Numbness Muscle weakness Paraesthesia Flaccid paralysis of anterior limbs and them posterior limbs.	→Paraesthesia
	2 to 3 months	Recovery or aggravation	Flaccid paralysis of limbs Muscle atrophy	
LONG-TERM TOXICITY	Mild digestive disorders Minor peripheral neurological problems, often reversible.			

More specific syndromes

Central neurotoxic symptoms:
- Depression
- Memory problems
- Sleep disorders
- Confusion

Continuous, chronic fatigue

Cardiac problems
Palpitations
Tachycardia

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APPENDIX 1B
COMPARISON BETWEEN SYMPTOMS ASSOCIATED WITH OXYCARBON POSIONING (OC) AND THOSE ASSOCIATED WITH AEROTOXIC SYNDROME AND WITH MULTIPLE CHEMICAL HYPERSENSITIVITY

TOXICITY TYPE	CARBON MONOXIDE	AEROTOXIC SYNDROME	MULTIPLE CHEMICAL SENSITIVITY (MCS)
ACUTE TOXICITY	Non-irritant Central nervous system problems (in relation to the percentage of carboxyhemoglobin in blood) - 10 % Hb CO o Reduced mental acuity o Exertional dyspnoea - 20 % Hb CO o Headaches o Exertional dyspnoea - 50 % Hb CO o Headaches o Irritability o Visual disturbances o Mental confusion - 60 to 70 % Hb CO o Coma o Convulsions o Death	Irritant effects - Rhinitis - Conjunctivitis - Cough Gastrointestinal problems - Nausea - Vomiting - Diarrhoea Peripheral neuropathy - Polyneuropathy Paresthesia→ Central nervous system problems - Headaches - Sleep disorders - Mental confusion - Anxiety - Depression Cardiovascular problems - Cardiac rhythm disorders o Arythmia o Palpitations	ACUTE EFFECTS IN THE MEDIUM OR LONG TERM Gastrointestinal problems - Nausea - Vomiting - Diarrhoea Peripheral neuropathy - Tingling in the hands - Muscle pains, cramps Central nervous system problems - Headaches - Sleep disorders - Anxiety - Depression Cardiovascular problems - Cardiac rhythm disorders o Arythmia o Palpitations
LONG-TERM TOXICITY	- Neurological damage o Headaches o Insomnia o Memory problems o Parkinson's syndrome - Cardiac impairment o Rhythm disordes o Atherosclerosis o Angina pectoris o Infarction - Reprotoxic effects o Embryotoxic o Fetotoxic o Teratogenic effects	- Neurological damage o Headaches o Insomnia o Memory problems o Mental confusion - Cardiac impairment o Rhythm disorders Palpitations Tachycardia - Continuous, chronic fatigue o Muscle weakness	

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APPENDIX 2

THE TRAGIC END OF A BRITISH PILOT POISONED BY AN ORGANOPHOSPHATE COMPOUND.

In 2014, the American toxicologist Abou-Donia and two Dutch doctors, F. van de Goot et M. Mulder, examined the case of a 43 year old pilot with a British airline, who had been treated for a long-term, incapacitating illness and who had died in the Netherlands [19].

Before he died, the pilot attributed his illness to repeated exposure, during his time as a commercial aircraft pilot, to engine oil fumes (released from the compressor present in the engine, whose seal may have contained flaws).

Aircraft engine lubricants often contain Cresyl phosphates (2 to 6% by weight) as flame-retardant agents. These compounds are supposed to contain less than 0.1% of the ortho-isomer (TOCP), which is believed to be the most neurotoxic of the chemicals in these mixtures.

Using the excellent report published by Abou Donia and his two colleagues, it is possible to trace the slow agony the late pilot underwent.

For over 10 years, several pilots and aircraft crew have complained of neurological problems following exposure to air inside the cockpit that was suspected to be polluted. The hypothesis that was proposed is that these neurological symptoms could be due to exposure to contaminants such as, among others, Organophosphorus esters and their products of pyrolysis.

Before the pilot died, his blood had been collected and analysed. It showed a high increase in the serum level of Autoantibodies, which were specifically directed against seven nerve cell Proteins. These Proteins include two Proteins that are very important for the cytoskeleton: Tubulin and Tau protein, which are the major targets in several neurodegenerative processes.

The death of the pilot was officially attributed to an overdose of Pentobarbital, a medicine he used to take to combat a chronic lack of sleep.

During the autopsy carried out at the Netherlands Forensic Institute (NFI), it was seen that there was demyelination along the long nerves (Myelin is a protective fat around neurons) and tissues had been infiltrated by T lymphocytes, which are involved, among other things, in inflammatory processes.

Similarly, brain and spinal tissue showed axonal degeneration and demyelination.

This post-mortem analysis seems to indicate neurotoxicity induced by Organophosphorous esters.

The pilot's career had spanned 15 years, during which he flown 8000 hours.

The initial neurological problems appeared after three years of flying: flickering in the eyes, headaches, and mental confusion, all accompanied by a great fatigue.

After about ten years, the characteristic signs of polyneuropathy emerged (numbness in the hands and legs, tingling ….).

According to the experts, the demyelination observed along the long nerves was characteristic of a delayed neurotoxicity induced by Organophosphorous esters and called OPIDN.

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As the neurological and muscular problems worsened, the pilot was forced to stop flying (September 2, 2011). The ataxia led to constant and intense pain as well as a lack of sleep.

Six months after his final flight, a biopsy of adipose tissue revealed the presence of metabolites of Organophosphorous compounds. Subsequently, the neurological problems, both those of the central as well as the peripheral nervous system, worsened and caused him to lose sleep, a problem he fought with Phenobarbital.

He was finally found dead in his hotel room following an overdose of Barbiturates. It is possible that brain lesions associated with prolonged exposure to Organophosphorous esters could have heightened the acute toxicity of Phenobarbital.

Ultimately, the symptoms observed while the pilot was alive seem to be very similar to those that are seen in long-term Organophosphorous ester poisoning. It cannot be denied that the timeline of the disorders of the central and the peripheral nervous system seems to indicate long-term poisoning by Organophosphorous esters used as flame-retardant agents, which form Nanoparticles upon pyrolysis.

The two Dutch toxicologists and their collaborators who had carried out the autopsy of the British pilot analysed the engine oil of a Boeing 737 from the Dutch airline company KLM. This analysis revealed, among other things, Organophosphorous esters of the Tricresyl phosphate type, without the ortho-isomer.

According to our hypothesis, the pyrolysis of this type of oil, which contains Organophosphorous esters, necessarily forms Phosphorous nanoparticles. At present, we are completely ignorant about the exact nature of these particles and their real impact on health.

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APPENDIX 3

TOXICO-ECOTOXICO-CHEMISTRY DATA SHEET OF TRI-ORTHO-CRESYL PHOSPHATE (TOCP)

FTEC N° 7

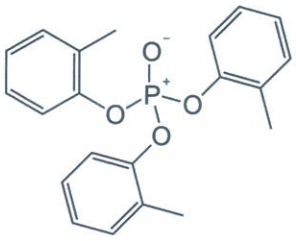
Family : Organophosphates.

Authors: André Picot[2], Jean Ducret[3].

TRI-ORTHO-CRESYL PHOSPHATE (TOCP)

Synonyms:

- Tri-Ortho-Tolyl Phosphate, Orthotolyl Phosphate, Orthocresyl Phosphate,
-
- Tri-o-cresyl Phosphate
- o-Cresylphosphate,
- o-Tolylphosphate
- Phosphoric acid, tris(methylphenyl)ester etc.



IDENTIFICATION OF HAZARDS

Labelling (CLP Regulation):

DANGER

H370 Proven risk of serious organ damage
H411 Toxic for aquatic animals.

GENERAL INFORMATION:

CAS:78-30-8
EC Number: 201-103-5
Molecular formula: $C_{21}H_{21}O_4P$
Molecular mass: 368.37 g·mol^{-1}
Origins:
Preparation by synthesis. These aryl phosphates are prepared by reacting trichloride with a phenol, here an orthocresol.

---

[2] André PICOT, Toxicochimiste, Directeur de recherche honoraire du CNRS, Expert français honoraire auprès de l'Union européenne pour les Produits chimiques en Milieu de travail (SCOL, Luxembourg).
[3] Jean DUCRET, Physicochimiste, Ingénieur de recherche honoraire du CNRS, ancien Chargé de mission aux risques chimiques de la délégation Alsace du CNRS.

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ortho-Crésol | Trichlorure de phosphoryle | Phosphate de Tri-ortho-tolyle | Acide chlorhydrique

Uses:

- Plasticizer for plastic materials (polystyrene, PVC etc.)
- Flame-retardant agents (incorporated in polymers),
- Pigment solvents
- Hydraulic fluids,
- Additives for non-flammable hydraulic fluids
- Additive in petrol, gasoil, kerosene

CHEMICAL AND PHYSICAL PROPERTIES:

Chemical and physical state: Viscous liquid, colourless to pale yellow.
Odour: Mildly aromatic
Melting point: 11 °C
Boiling point: 410 °C (101.3 kPa) - Decomposition.
Flash point: 225 °C
Self-ignition temperature: 385 °C
Density(d_4^{20}) : 1.196
Vapour density: 12.7
Soluble in:

- Ether
- Carbon Tetrachloride
- Toluene

Slightly soluble in Ethanol,
Practically insoluble in water (10 mg·L^{-1} at 25 °C)
Octanol-Water partition coefficient: log P_{OW} = 5.93

CHEMICAL PROPERTIES

Fire stability:
Non-flammable, non-explosive.
Stability:
Relatively stable compound under normal use and storage conditions.
Thermal stability
At high temperatures, Tri-ortho-cresyl phosphate slowly decomposes, releasing phosphoric oxides (P_2O_5 ...) and volatile aromatic compounds.
Hydrolysis:
In an alkaline medium, at ambient temperature, this phosphoric ester is hydrolyzed to finally produce alkaline phosphate and ortho-cresol.
The hydrolysis is very slow in a neutral or acidic medium (e.g. H_2SO_4).
Oxidation:
It is often reported in literature (e.g. INRS) that Tri-ortho-cresyl Phosophate reacts violently with strong oxidants. This seems surprising as the phosphorous is at its maximum degree of oxidation and the oxidation can only occur on the aromatic nuclei.

ROUTES OF ENTRY:

Easy entry through:

- Oral route.

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- Dermal and mucosal routes.

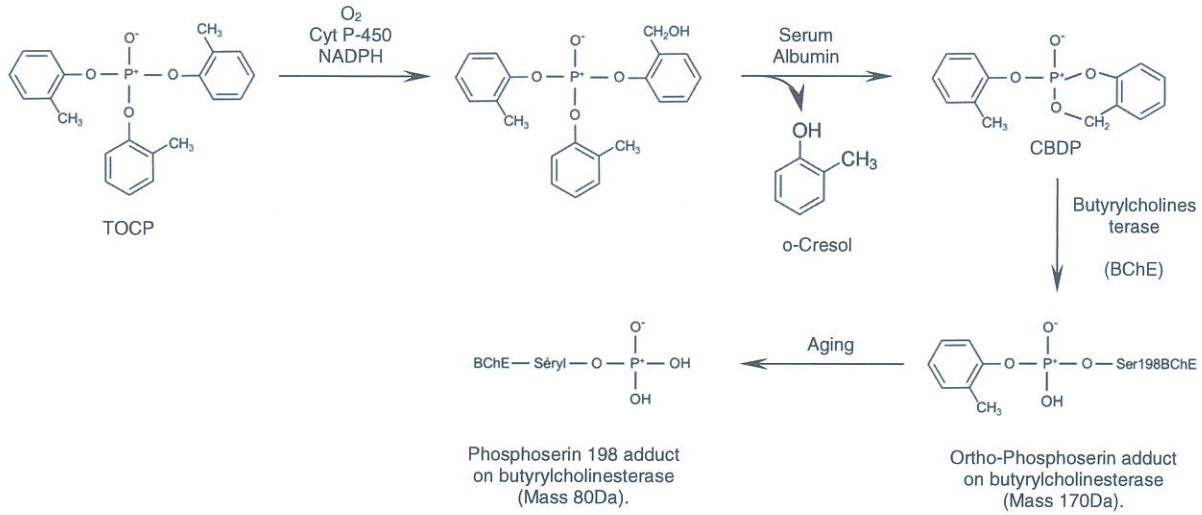
In the absence of any data, absorption through the respiratory tract must not be neglected.

DISTRIBUTION:

Distribution in tissues, concentrated in lipid-rich tissue (supporting tissues, liver, kidney, the nervous system etc.)

METABOLISATION

The very first step is the oxidation of TOCP at the site of one of its methyl groups, in the presence of a monooxygenase, to form Cytochrome P-450.
The primary alcohol that is formed may undergo subsequent oxidations and finally results in the corresponding carboxylic acid.
Through interaction with serum-albumin, one of the tolyl groups is eliminated with the formation of a cyclic phosphate, ortho-Cresylsaligenin phosphate. This reactive intermediary attacks the primary alcohol group of a serin at the site 198 of Butyrylcholinesterase (BChE), forming an adduct with the mass 170 Da. Over time, this adduct loses its Cresol group and forms an adduct whose mass is 80Da, as indicated in the below diagram.



Metabolization, in the presence of Cytochrome P-450, of the Tri-ortho-cresyl phosphate (TOCP).
to form ortho-Cresylsaligenin phosphate (CBDP),
a reactive intermediary which reacts on the serin 198 site of the Butyrylcholinesterase.

ELIMINATION

When a single dose of TOCP was administered to rats, 76 to 90% was eliminated in 24 hours through urine and faeces.

MECHANISM OF ACTION

The ortho-Cresylsaligenin Phosphate (CBDP) that is formed, is considered to be the chief cause of the neurotoxicity of Tri-ortho-cresyl Phosphate (TOCP), through the inhibition of esterases, including Cholinesterases.

TOXICITY

Toxicity in animals

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Acute Toxicity:

- DL50 (Rat, oral route): 1160 $mg.kg^{-1}$.
- DL50 (Rat, Peritoneal route): 2500 $mg.kg^{-1}$

Acute exposition to TOCP causes demyelination of the spinal cord, the cerebellum, and the brain (among others), linked to an irreversible inhibition of serum esterase.
Damage to the Peripheral Nervous System (PNS) may cause polyneuropathy, with a possible paralysis of the paws.
Long-term toxicity:
After exposure through gavage to 150 or 300 $mg.kg^{-1}.j^{-1}$ of TOCP, a neurotoxic inhibition of esterase and of acetylcholinesterases was observed. This led to the degeneration of nerve fibres in the spinal cord and of peripheral nerves, with progressive paralysis of the extremities.

There was also damage to the spermatozoa seen in male rats and mice.
Absence of mutagenicity and genotoxicity.

Toxicity in humans

Acute Toxicity:
Acute poisoning is observed following ingestion or skin contact. However, the inhalation of aerosols is also a possibility.
When ingested through the oral route, TOCP is lethal at a dose of approximately 1 g/kg, while a dose of 6 to 7 mg/kg could lead to severe paralyses. However, important individual differences in sensitivity to TOCP are described.
Gastrointestinal problems (nausea, vomiting, diarrhoea) appear in the first few days, followed by a period of calm (8 to 35 days) after which ENT irritations commence and, progressively, neuropathies of the PNS, which could lead to paralysis of the limbs.
The evolution of the poisoning is variable and there could either be recovery after some months, or muscular atrophy could persist.
In the 1930s, following the consumption of food contaminated by TOCP, 15000 were affected and 10 of them died.
Other cases of serious poisoning through contaminated food have been described in the United States (through an alcoholic drink called Jamaica Ginger), in Morocco (10,000 cases in 1959 due to contaminated olive oil) etc. leading to many cases of severe paralysis.
Long-term toxicity:
Some rare cases of long-term poisoning at the workplace have been described, with a decrease in cholinesterases in blood. Digestive and neurological disorders may be observed (flaccid paralysis, peripheral neuropathy etc.)

FIRST AID MEASURES

IN THE CASE OF POISONING OR CONTACT WITH THE SUBSTANCE:
Call the nearest 'Poison Control and Toxicovigilance Centre'.

Inhalation:
In the case of massive inhalation of aerosols, remove the subject from the polluted zone and move them to open air.
Transfer them to a hospital.
Contact with skin:
In case of skin contact, immediately rinse with water, warm water if possible, for 15 minutes. Consult a doctor.
Contact with eyes:
In case the product comes into contact with eyes, immediately wash the eyes with water, warm water if possible, for 15 minutes.
In case of redness of the eye, consult with an ophthalmologist.
Ingestion :

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In the case of accidental ingestion, do not provide anything to drink and do not induce vomiting.
Place the subject in a lateral recovery position while waiting for help and rapidly shift them to a hospital.

PREVENTION

Prevention technique:

- In case of a fire.

In case of excess heat, toxic fumes rich in Carbon monoxide (CO) and phosphoric oxides (P_2O_5 etc.) will be produced.
In the case of a fire, use water, foam or powder extinguishers or carbon dioxide based fire extinguishers.

- In the case of accidental release:
  - Ventilate the location,
  - Prevent any spill into the environment,
  - Use Vermiculite, fine sand or a commercial absorbent to absorb the liquid.
  - Collect the resulting mixture in an appropriate container, which is properly labelled.
  - Dispose of the special waste through an accredited, specialised company.

Medical prevention:
Biological monitoring
The level of Erythrocyte Acetylcholinesterase (AChe) in red blood cells is the best indicator of the effects of TOCP, epecially on the nervous system.
The ACGIH considers the reduction of cholinesterase activity to 70% of the refrence value as the Biological Exposure Index.

MONITORING EXPOSURE

Recommended values in France

TWA: 0.1 $mg.m^{-3}$
Recommended values in the United States (OSHA, NIOSH, ACGIH):

- TLV-TWA : 0.1 $mg.m^{-3}$
- TWA (skin): 0.1 $mg.m^{-3}$

EFFECTS ON THE ENVIRONMENT

Ecotoxicity:
Highly toxic for aquatic life.

- EC (Daphnia): *Daphnia magna*: 0.146 $mg.L^{-1}$ (48 h).
- CL (Fish): *Onchorhyncus mychis* (Rainbow trout): 0.6 $mg.L^{-1}$ (96 h).
- IC 50 (Algae): *Desmodesmus suubspicatus* (Green algae): 0,404 $mg.L^{-1}$ (72 h).

Biodegradability:
Degradation takes place quite rapidly in water (5 days in a river).
Slow degradation in an aerobic environment in soil. Very slow degradation in anaerobic environment.
Bioaccumulation
Very bioaccumulable substance.
Bioconcentration factor (BCF): 65.
Slow degradation in air, in the presence of hydroxyl radicals. •

WASTE MANAGEMENT.

Use Vermiculite or fine sand to absorb liquid.
Dispose of waste as 'special wastes' through an accredited chemical waste disposal company.
Do not dispose of material in the sink or in the environment.

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EMERGENCY HELPLINE: 01 45 42 59 59

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APPENDIX 4
TOXICO-ECOTOXICO-CHEMISTRY DATA SHEET FOR ETHYLENE-GLYCOL - FTEC N° 4

(CURRENTLY BEING UPDATED)

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Akhila PHADNIS

ETHYLENE-GLYCOL

CAS no.: 107-21-1

EC/List no.: 203-473-3

INDEX no.: 603-027-00-1

EINECS no.: 207-473-3

1.1. LABELLING

1.2. DIRECTIVES 67-548-CEE:

Xn Harmful

Régulation CLP:

HO—CH_2—CH_2—O

7.1.1.1.1.

7.1.1.1.2.

7.1.1.1.3. December 2007

7.1.1.1.4.

7.1.1.1.5. Revision:

7.1.1.1.6. March 2019

1 IDENTIFICATION

■ 1-1 Chemical name	IUPAC name	Ethane - 1,2 - Diol	
	Common name	Ethylene glycol	
	Synonyms	1,2-Dihydroxyethane	2-Hydroxyethanol
	Family	1,2-Diol (Glycol)	
	Molecular formula	$C_2H_6O_2$	
	Molecular mass	62.07	

2 PHYSICAL AND CHEMICAL PROPERTIES

■ **2-1 Physical state**	Colourless liquid, viscous, sweet taste
■ **2-2 Characteristic temperatures**	Melting point: -13°C Boiling point: 197.5°C
■ **2-3 Vapour pressure**	0.05 mm Hg at 20°C (7 Pa at 20°C)
■ **2-4 Vapour density relative to air (air = 1)** **Vapour density relative to water (water = 1)**	2.14 1.113 at 25°C
■ **2-5 Refraction index (n20D)**	1.4318
■ **2-6 Explosive limits (% of volume in air)**	Lower limit: 3.2 Upper limit: 15.3

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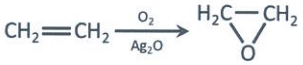
■ **2-7 Flash point**		111°C in a closed cup. 119°C in an open cup.
■ **2-8 Auto-ignition temperature**		398°C
■ **2-9 Solubility**	**2-9-1 Water**	Soluble
	2-9-2 Organic solvents	- Soluble: Alcohols: (Methanol, Ethanol, Glycerol), Ketones (Acetone…), Acetic acid, Pyridine - Slightly soluble: Diethylether - Insoluble: Alkanes, Benzene, Chloride solvents
	2-9-3 Octanol/water partition coefficient (K_{ow})	Log Kow = -1.36
3 Reactivity		
■ **3.1. Stability**		Stable (decomposition at 500 – 600°C)
■ **3.2. Reactivity with water**		Solubilisation
■ **3.3. Flammability**		Low flammability
■ **3.4. Incompatibility**		Powerful oxidants (CrO_3, $KMnO_4$…) Explosive decomposition with concentrated $HClO_4$ Violent reaction with concentrated H_2SO_4
4 PRODUCTION, USE AND SOURCES OF EXPOSURE		
■ **4.1. Production**		Oxidation of ethylene ($H_2C = CH_2$) to ethylene oxide,  and this is hydrolysed to ethylene glycol by heating with an excess of water.
■ **4.2. Uses**		Antifreeze liquid and refrigerant liquid (40%) (de-icing of aircraft windshields and engines). Synthesis of polyester plastic materials (Polyethylene Terephthalate: PET). Dehydration agents (natural gas). Organic synthesis (Ethers of glycol, blocking carbonyl groups). Excipient for medicines (Chinese medicines, and so on).
■ **4.3 Sources of exposure**		Accidental ingestion (sweet taste), deliberate addiction (sweet drinks) or used with suicidal intent. Moderate dermal absorption (anti-freeze). Low absorption through inhalation (except at high temperatures).
5 TOXICOLOGY		
■ **5.1 Acute toxicity**	**5.1.1 Experimental toxicity**	Toxicity through oral exposure is greater than toxicity through the dermal route or through inhalation. DL50 Rat (oral): 4.7 g/kg DL50 Mouse (oral): 7.5 g/kg (dermal): 20 g/kg
	5.1.2 Toxicity in	Acute toxicity, 4 to 5 times greater than among rodents.

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	humans	Lethal dose for an adult: 1.4 ml/kg (~ 100 ml) Latency period: 6 to 12 hours 4 successive stages: 1. Digestive problems (nausea, vomiting, abdominal pains…) 2. Neurological problems: (inebriation, somnolence, then convulsions…) 3. Cardio-pulmonary problems: (12 to 14 hours) Tachycardia, polypnea, pulmonary oedema, myocardial attack… 4. Kidney injury (24 to 72 hours) tubulopathy, oliguria, proteinuria etc. - Non-irritant to skin. - Weak irritant to eyes.
■ **5.2 Toxicity over the medium and long term**	**5.2.1 Experimental toxicity**	Rat: Oral exposure (greater sensitivity in males than females) Including 1 to 2% of ethylene glycol in food: - kidney damage – tubular necrosis with the precipitation of calcium oxalate into the tubular lumen - centrilobular necrosis Maximum dose tolerated without adverse effects in Rats: 100 mg/kg/day over 2 years
	5.2.2 Toxicity in humans	Contact with warm ethylene glycol vapours: - nerve damage: loss of consciousness, uncoordinated movement of the eyes etc. - irritation of the eyes and airways
	5.2.3 Mutagenicity and Clastogenicity	Short-term mutagenicity tests – the Ames Salmonella test (Salmonella typhimurium): negative.
	5.2.4 Carcinogenicity	Negative results for genotoxicity tests in animals. Absence of epidemiological studies.
	5.2.5 Reprotoxicity	Study on gestating female rodents: - Low birth weight of neonates. - Skeletal abnormalities (teratogenic effects).
6 TOXICOKINETICS, METABOLISATION, MECHANISM OF ACTION		
■ **6.1 Toxicokinetics**		Ethylene-glycol is quickly (in 2 hours) and completely (100%) absorbed by the digestive system. Dermal absorption is in smaller quantities. Rapid distribution within extra-cellular liquids.
■ **6.2 Metabolisation**		Rapid hepatic metabolization: - the first step is oxidation, in the presence of alcohol-dehydrogenase (NADH) leading to the formation of glycolaldehyde, - the second step is the oxidation of glycolaldehyde to glycolic acid in the presence of aldehyde-dehydrogenase, - the third step is the oxidation of glycolic acid to first glyoxilic acid, calatysed by glyoxilic-oxidase acid and then to oxalic acid, which is the final metabolite. - Furthermore, in the presence of glyoxilic-oxidase acid, the glyoxilic acid may be split into formic acid and CO_2. In humans, ethylene glycol is eliminated in exhaled air in the form of carbon dioxide (CO_2). It is excreted in urine in unchanged form (~ 10%), and as glycolic acid and oxalic acid (2 to 3%).

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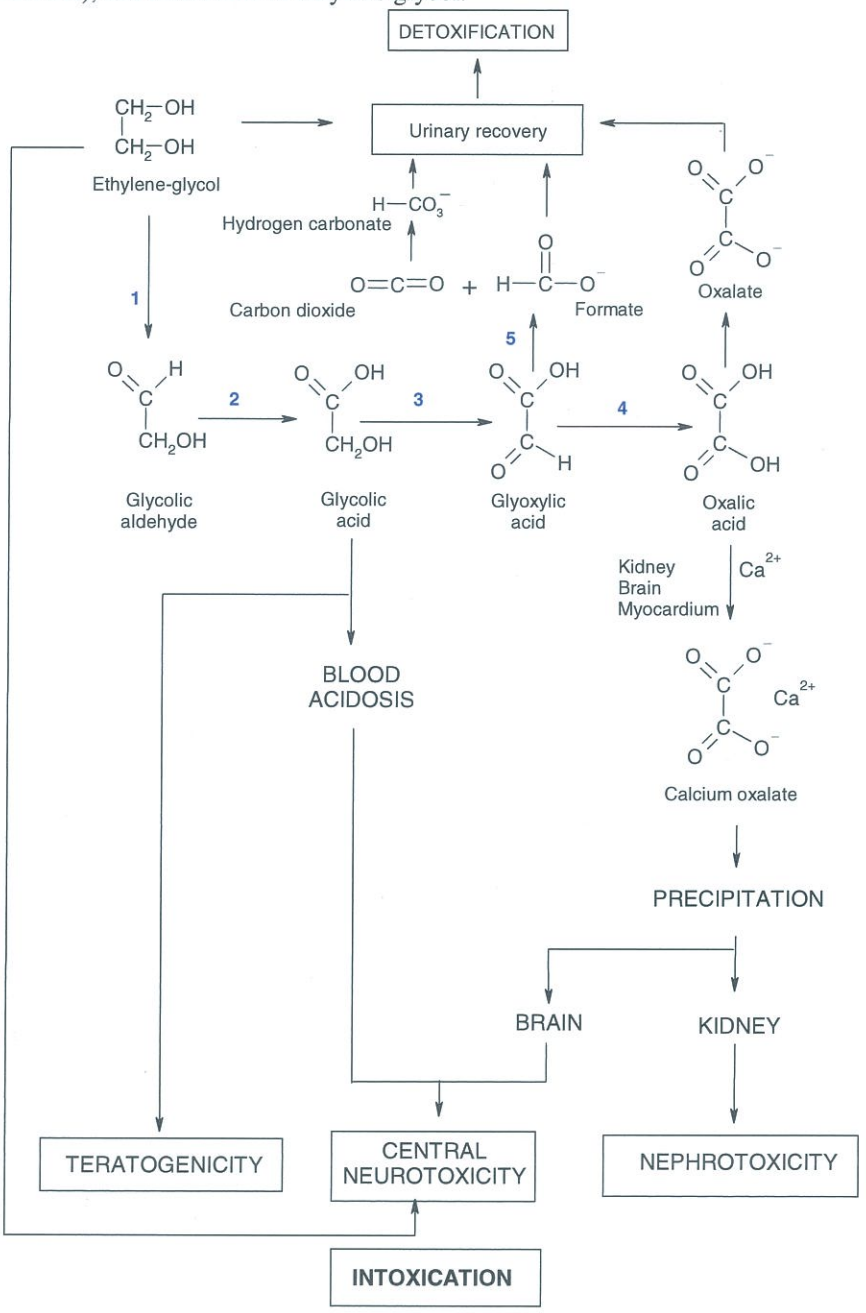
	The plasma half-life of ethylene glycol is about 3 hours.
■ 6.3 Mechanisms of action	The mechanisms of action of ethylene glycol are not perfectly understood. The toxic effects are due to the ethylene glycol itself. In humans, metabolic acidosis is especially linked to glycolic acid ($HOCH_2$-COOH) and oxalic acid (HOOC–COOH), the final product of hepatic metabolisation of ethylene glycol, which may precipitate in the presence of calcium cation (Ca^{2+}) to form insoluble calcium oxalate crystals, which can initiate inflammatory processes. At the level of the kidneys, there is renal insufficiency, related to tubulopathy, while in the brain the calcium oxalate crystals are responsible for convulsive coma.
■ 6.3 Mechanisms of action	The teratogenic effects observed in offspring (skeletal abnormalities etc.) after oral absorption of 1000 mg/kg in gestating female rats seem to be due to glycolic acid ($HOCH_2$–COOH), and metabolite of ethylene glycol.



Enyme systems

1 : Alcohol dehydrogenase to NAD,
2 : Aldehyde dehydrogenase,
3, **4** and **5** : Glyoxilic–oxidase acid.

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7 IMPACT ON THE ENVIRONMENT		
■ 7.1 General behaviour	Although ethylene glycol is a minority component of the world of living things (plants, animals, humans etc.) its presence in significant quantities in different ecosystems is solely the result of human activity. The frequent use of ethylene glycol as antifreeze, especially in the field of aeronautics (the de-icing of planes releases more than 60% of the ethylene glycol used) currently constitutes the major source of environmental contamination by this substance. The concentration of ethylene glycol vapours around airports is, on average, 22 mg/m^3. Given its physical and chemical properties, especially its complete miscibility with water, ethylene glycol is easily and quickly distributed in all ecosystems (water, air and soil) in which it then decomposes very quickly.	
■ 7.2 Stability	**7.2.1 Stability in soil**	In plants, ethylene (a phytohormone) is metabolised, leading to ethylene glycol, which will then be found in the soil. Given its high solubility in water, ethylene glycol rapidly spreads through the aqueous phase of soil. Ethylene glycol biodegrades rapidly in the soil and does not bio-accumulate.
	7.2.2 Stability in an aquatic medium	In the aquatic medium, ethylene glycol is rapidly broken down in aerated water (in a few days, in aerobic media) and broken down more slowly in anaerobic media (over a few weeks).
	7.2.3 Stability in the air	In air, as vapours or aerosols, ethylene glycol is broken down by photochemical oxidation (through the action of a hydroxyl radical (HO°)). Its half-life is 1.4 days.
8 EXPOSURE		
■ 8.1 Exposure of the population	In the general population, ethylene glycol enters the human body chiefly through the oral route, generally by the absorption of contaminated food (cakes, for instance) and drink. Ethylene glycol comes, most often, from the cellulose or plastic wrapping in which the food or drink travels. Thus, concentrations of between 27 to 34 mg of ethylene glycol were detected in fruit cakes which were stored for 84-336 days in cellulose packaging. In alcoholic drinks (wine, beer etc.) there are naturally occurring polyols, including ethylene glycol, which are present at a concentration of some ppm. In the general population in the United States, the oral ingestion of ethylene glycol, either accidentally (leaking refrigerant fluid) or intentionally (suicide attempts) lead to thousands of cases of poisoning every year, many of which are fatal (2005).	
■ 8.2 Exposure in a professional setting	In the workplace and at ambient temperature, there is most often dermal contact with ethylene glycol and sometimes contact with the eyes. Workes who use antifreeze mixtures (consisting, on average, of 50% of ethylene glycol), especially in the aviation industry, are more exposed to vapours and aerosols and may be poisoned through the respiratory or dermal route. In the presence of warm ethylene glycol vapours, inhalation is the major route of entry and individuals must be very careful in these conditions.	
■ 8.3 Exposure of children	Children (from birth to 18 years of age) must not be considered as 'young adults' since their biological parameters may differ significantly from those used for adults. According to data from literature, children do not seem to be more sensitive than adults to the toxic effects of ethylene glycol. Nonetheless, due to its sweet taste, children (and household pets) may ingest large quantities of this product, which is sometimes present in the domestic setting (antifreeze). In babies, ingesting 10 to 15 ml of ethylene glycol may be fatal.	

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9. DETERMINING LIMITING VALUES

9.1 Exposure through inhalation

Determination of the No-Observed-Adverse-Effect Level: NOAEL
Human exposure: 23 mg/m^3, 20-22 hours over 14 days.

NOAEL = 23 mg/m^3

Absence of irritant-effect on the respiratory tract.
Uncertainty factor among humans: inter-individual variations → 10
Minimum risk level:

MRL =2 mg/m^3

9.2 Oral exposure

- Acute short-term exposure

Based on skeletal abnormalities in foetal development in mice:

BMD L_{10} = 76 mg/kg/day

Uncertainty factor: 100
- Animal – Human transfer → 10
- Inter-individual variations → 10

} 100

Minimum risk level for humans:

MRL = 0.8 mg/kg/day

- Exposure over the medium term (between 13 to 364 days)

Based on kidney lesions in the male Wistar rat,
Minimum risk level = for humans:

MRL = 0,8 mg/kg/j

10 REGULATION

10.1 Workplace

European Union, France
- VME (During 8 heures): 20 ppm or 52 mg/m^3
- VLCT (During 15 minutes): 40 ppm

Classification and labelling: WARNING
Hazard Statement: H302 – Harmful if swallowed ~~when ingested~~
Precautionary Statement: P270; P301+P312+P330; P501.
France
Occupational diseases: Table no. 84

NOAEL = 23 mg/m^3

USA - NIOSH (2005)
Ceiling value (TLV – STEL): 50 ppm
ACGIH (2006) Ceiling value: 100 ppm
Germany
DFG MAK: 10 ppm or 26 mg/m^3

10.2 Environment

Drinking water
USA: EPA - Health Advisory (HA):
One-Day HA: 20 mg/L (child of 10 kg).
Ten-Day HA: 6 mg/L (child of 10 kg).

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11 PREVENTIVE MEASURES		
■ **11.1 Technical prevention**	**11.1.1 Handling**	- Avoid inhaling warm vapours. - Avoid any dermal or ocular contact. - Avoid oral absorption, especially for children (babies). - Do not eat or drink while working. - Avoid atmospheric emissions or water discharge that is polluted by ethylene glycol. - Avoid contact with powerful oxidants or strong acids.
	11.1.2 Individual protection	- Wear appropriate clothing. - Wear appropriate protective gloves (rubber gloves: latex, butyle, nitrile, PVC…)
■ **11.2 Prevention in the case of contamination**	**11.2.1 Dermal contact**	- Wash thoroughly and for a prolonged period with water. - In the case of injured skin, consult a doctor.
	11.2.2 Contact with eyes	- Wash immediately and thoroughly (15 minutes) with lukewarm water.
	11.2.3 Contact through inhalation	- In case of inhalation of warm vapours, place the victim in the open air. - Consult a doctor.
	11.2.4 In case of ingestion	- Rinse out the mouth. - Provoke vomiting (Ipecac syrup). - If it is an adult, make them imbibe 80 to 100ml of strong drinking alcohol (40-45°), in order to prevent kidney failure. - Consult a doctor. - Take them quickly to a Poison-Control Center.
■ **11.3 Prevention in case of fires**	Ethylene glycol has low flammability. Its vapours may form explosive mixtures with air. Avoid the smoke, it is very irritating. Extinguishing agents: CO_2, chemical powders, foam, water spray.	
■ **11.4 Storage**	Store in cool sites with good ventilation. Store in retention containers, away from powerful oxidants and strong acids. Dry storage, way from flammable material. Do not put ethylene glycol in bottles used for edible material.	
■ **11.5 Destruction**	For small quantities of the product, dilute it with a large excess of water and empty into a sink. Large stocks must be disposed of with incinerable waste.	
■ **11.6 Preventive healthcare**	Immediately alert a medical service in case of any accidental ingestion, regardless of the amount ingested. In case of dermal or ocular contamination, wash thoroughly with water. In case of inhalation of warm vapours of ethylene glycol, consult a doctor and take the victim to a Poison Control Center.	

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