

USE OF OILS COMPRISING NON-NEUROTOXIC ANTI-WEAR ADDITIVES

Technical Field

The present invention relates to the technical field of anti-wear additives used in oils such as oils for lubricating aircraft or aeroderivative turbines or hydraulic oils.

Technological background

Aircraft or aeroderivative turbine engines use synthetic lubricants generally comprising an ester base and a variety of anti-wear additives from the family of organophosphates such as triaryl phosphates. The most commercially used anti-wear additive is tricresyl phosphate (TCP), which has singular anti-wear properties that can be considered as unique to date. Its triaryl phosphate analogs are also interesting anti-wear additives.

Leakage of lubricants, especially those containing tricresyl phosphate or a triaryl phosphate analog thereof, in the aircraft cabin air may originate from worn or faulty seals, or even under normal conditions of use by the passage of the lubricants in the air for pressurizing the cabin. These repeated leaks are explained (Michaelis S. *et al. Public Health Panorama* **2017**, 3, 2, p 198-211) as being due to pressure oscillations between the bearing chamber and the air circuit exerted by the normal operating conditions (increase in engine power, take-off, ...). In some circumstances, the leak can become very significant, usually subsequent to the break of a bearing in the turbine, the latter leading to a fume event or a white mist visible in the cabin.

Aerotoxic syndrome is a pathological condition combining physical and neurological symptoms caused by short- and long-term effects of an exposure to aircraft cabin air contaminated by hydraulic oils or engine oils or any other organic pollutant found as gases and/or aerosols. The reported symptoms are typically non-specific, and the cabin air quality monitoring studies indicate contaminant levels which are lower than the limits of exposure and not harmful to human health, the challenge being to measure continuously and in operation fumes from oils, by definition non-gaseous, airborne, which deposit and concentrate episodically at various locations in the aircraft (Kasper Solbu *et al. J. Environ. Monit.* **2011**, 13, 1393).

Symptoms similar to those of the aerotoxic syndrome can also be observed in environments on the ground in the presence of aeroderivative turbines, for example on offshore platforms. Aeroderivative turbines operate in the same way as aircraft turbines and are implementing lubricants of similar composition, especially in terms of anti-wear agents.

Nevertheless, a number of studies (Michaelis, S. *et al. Public Health Panorama* 2017, 3, 2, p. 198-211) have demonstrated a relative causal relationship between acute and/or chronic exposure to substances contaminating the aircraft cabin air and neurological, neurobehavioral and respiratory symptoms.

Conventional organophosphate anti-wear additives such as tricresyl phosphate (TCP), especially the tri-orthocresyl phosphate (ToCP) isomer thereof, are known to have a strong neurotoxic effect (Craig P. *et al. Journal of Toxicology and Environmental Health Part B: Critical Reviews* **1999**, 2, 4, p. 281-300) Beyond the generic toxicity associated with the

organophosphates widely used in various fields, particularly as insecticides and pesticides, one of the specified and recognized reasons for this neurotoxic effect is the fast in vivo conversion of tricresyl phosphate isomers comprising at least one ortho substitution into a metabolite called saligenin which is a potent inhibitor of cholinesterases. ToCP poisoning leads to a pathology
 5 called organophosphate-induced delayed neuropathy (OPIDN) whose mechanism has been extensively studied. Furthermore, the TCP being also known to be reprotoxic.

Oils comprising, as an anti-wear additive, TCP which does not include ortho isomer have been developed. Nevertheless, despite the absence of ToCP in the TCP, the inhibition level of cholinesterases in the rat serum exposed to TCP is not zero and, although low, it is persistent
 10 (Mackerer C R *et al. J. Toxicol. Env Health Part A* **1999** 57(5): 293-328). Similarly, earlier works show problems of spinal cord demyelination resulting from exposure to TCP in its meta and para forms (W. N. Aldridge, *Biochemical Journal* **1954** 56, 185-189).

Very recent studies show that tricresyl phosphate and its triaryl phosphate analogs also act on other biological targets, especially at the cellular level (AV Terry, *Pharmacology and*
 15 *Therapeutics* **2012**, 134, p. 355-365; Al Salem *et al. Chemosphere* **2019**, 237, 124519).

All of these studies and this long history constitute a body of evidence and elements which made the tricresyl phosphate and its triaryl phosphate analogs additives of particular concern. In order to increase the safety level of hydraulic oils and oils used in aircraft and aeroderivative turbines, it seems to be useful to develop alternative anti-wear additives to tricresyl phosphate
 20 and its triaryl phosphate analogs.

Identification of alternative anti-wear additives to tricresyl phosphate and its triaryl phosphate analogs is an identified issue, even if there is no unanimity on the need to obviate tricresyl phosphate and its triaryl phosphate analogs.

To the Applicant's knowledge, no studies have identified alternative anti-wear additives
 25 having both satisfactory anti-wear effect and proven non-neurotoxicity. As an example, recent studies on the characterization of the potential neurotoxicity of new organophosphates developed and marketed as new generation flame retardants are for the most part of a level of hazard allegedly equivalent to that of usual materials like the TCP (Zhang *et al. Neurotoxicology and Teratology* **2019**, 73, p. 54-66, Ryan *et al. Neurotoxicology* **2016**, 53, 271-281, Sirenko *et al.*
 30 *Toxicolog. Sci.* **2019**, 167, p. 58-76). The issue of organophosphorus compound neurotoxicity remains unanswered and unresolved to date.

Furthermore, the TCP being also known to be reprotoxic, the development of alternative anti-wear additives to tricresyl phosphate and its triaryl phosphate analogs, for which lack of neurotoxicity and reprotoxicity would be established, would be advantageous and would make it
 35 possible to increase the safety level in the aviation and other aeroderivative applications.

Various solutions have been developed in the prior art.

The patent application US2016/0002565 discloses a turbine oil free of tricresyl phosphate which comprises at least one basic oil, at least one alkyl polyglycoside and a phenolic derivative

such as 3,5-di-*tert*-butyl-hydroxytoluene. Replacing tricresyl phosphate with phenolic derivative helps to prevent aerotoxic syndrome when this oil is used in aircraft turbines. Nevertheless, the implementation of such an oil in aircraft turbines seems not to be able to provide the same effectiveness as that of the oil containing tricresyl phosphate it is supposed to replace, on one hand because the described formulation does not include any agent having an anti-wear effect replacing that of the TCP, and on the other hand because the formulation comprises alkyl polyglycosides which are heat-sensitive.

So far, only phosphorus compounds showed efficient effectiveness as anti-wear agents in oils for aircraft or aeroderivative turbines. Without intending to be bound by any theory, this may be related to the fact that the phosphorus enables the formation of a protective layer, commonly referred to as tribofilm, even at the high temperatures involved by the intended applications.

The patent application WO2010/149690 discloses the reduced effect on butyrylcholinesterase, especially in relation to TCP, of specific triaryl phosphates wherein the phenyl moieties are substituted by one to three isopropyle or *tert*-butyl moieties. These inhibition results suggest a possible reduction in neurotoxicity associated with these compounds compared to that observed for the TCP. Nevertheless, the simple demonstration of a limited effect on a single cholinesterase seems not to be enough to ensure a sufficient safety level for aviation expectations.

The following documents are also known from the prior art.

The publication of Ike van der Veen *et al.* *Phosphorus flame retardants: properties, production, environmental occurrence toxicity and analysis*, Chemosphere 88 (2012) 119-1153 describes the toxicity of certain phosphorus flame retardants (PFR). These flame retardants include phosphorus compounds, such as resorcinol bis(diphenylphosphate) (RDP) or bisphenol diphenylphosphate (BADP). However, this publication is not conclusive as it does not specifically address the neurotoxicity of the flame retardants presented (neurotoxicity is never mentioned or suggested). In addition, for the two compounds mentioned above, it is precisely indicated that there are few available data related to their toxicity in humans or on their ecotoxicity. By way of example, there are no data related to the acute toxicity of these two compounds. Only reprotoxicity data are reported. Finally, this publication only mentions reduced generic data on toxicity.

However, "toxicity" is a fairly broad concept that includes, in particular:

- reprotoxicity, which corresponds to the impairment of the fertility or alteration of the unborn mammal),
- mutagenicity, which is the propensity of a substance to cause genetic mutations, -
- acute toxicity is the toxicity induced, within a short period of time (e.g. 24 hours), by the administration of a single (possibly massive) dose or several doses acquired within that period of time of a toxic product or mixture (natural or chemical),
- ecotoxicity, which is all the imbalances or nuisances caused by an industrial activity or the placement of a foreign body or product in a natural environment;

- neurotoxicity: which is the ability of a substance or compound to induce adverse effects in the nervous system of a mammal, such as human beings.

However, a compound may, for example, not be reprotoxic, show no signs of acute toxicity, or even show no CMR (carcinogenic, mutagenic, or toxic for the reproduction) characteristic on human health and may, however, be highly neurotoxic (or vice versa).

By way of example, the Applicant has however demonstrated that the tetrakis(2-chloroethyl)dichloroisopentyldiphosphate compound (V6), mentioned in the publication by Ike van der Veen *et al.* as non-neurotoxic, non-mutagenic and not causing significant skin irritation, is ultimately very neurotoxic. Specifically, the latter compound V6 has in particular a neurotoxicity in the QSAR modelling test (which will be described below) of 91% and belongs to cluster 4 in the 3D modelling test by spherical harmonics (which will be similarly described below). This reinforces the fact that the notion of "toxicity" is not precise and that a compound may very well be considered as having no CMR characteristic or acute toxicity and as being highly neurotoxic and vice versa.

Document WO2015/026566 describes a lubricant comprising: (i) a large amount (50% or more by mass relative to the total mass) of a natural or synthetic base oil and (ii) a small amount of an aryl bisphosphate ester of formula (I) as an anti-wear additive and which may correspond, for example, to resorcinol bis(diphenylphosphate).

Document EP 0 612 837 describes a lubricant based on polyphenylene ether comprising an anti-wear additive comprising a hydrocarbyl bis(dihydrocarbylphosphate) compound, such as resorcinol bis(diphenylphosphate).

Document US 5 560 849 describes a lubricating composition comprising (col. 2, lines 11-35) a base oil which may be polyol esters or phosphate esters such as tricresyl phosphate, and an aryl diphosphate ester having anti-wear properties.

Document US 2001/306530 describes a composition comprising a base oil which may be a polyol ester and a phosphorus compound. The exemplified phosphorus-based compound comprises a diphosphorus compound ("*tetraphenyl(m-phenylene) bisphosphate*") and tricresyl phosphate.

In the prior art, there is a need to develop alternative anti-wear additives to tricresyl phosphate and its triaryl phosphate analogs, even if there is no unanimity on the need to obviate tricresyl phosphate and its triaryl phosphate analogs.

In the prior art, there is a particular need to develop alternative anti-wear additives having both satisfactory anti-wear effect and allowing to increase the safety level in the aviation and other aeroderivative applications.

Disclosure of the invention

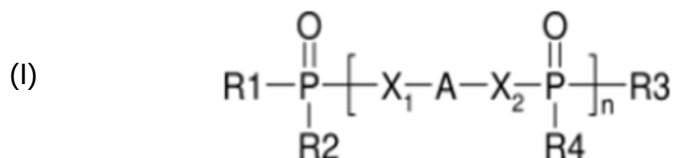
In that context, the Applicant showed that polyphosphorus compounds, especially aryl polyphosphorus compounds, which have satisfactory, or improved, anti-wear and thermal stability

properties, have a significantly reduced, or no, neurotoxicity in comparison with that of the monophosphate anti-wear derivatives such as TCP, and can therefore be advantageously used in oils, particularly for lubricating aircraft or aeroderivative turbines, for reducing and/or preventing the neurotoxicity of oils, and in particular of turbine oils. The anti-wear properties of some polyphosphorus compounds, which are aryl diphosphates, have for example been shown in the prior art, especially in the patent applications WO96/20263, US2012/0329693, WO2012/015873, EP 0612837 and WO2015/026566 or in the publication Zhao *et al.* Ind. Eng. Chem. Res. **2013**, 52, 22, 7419-7424.

They can therefore be advantageously used for the prophylaxis of aerotoxic syndrome, especially in case of fume event. While the use of polyphosphorus compounds such as aryl diphosphates as anti-wear additives has already been considered in the prior art, to the Applicant's knowledge, no study has been able to demonstrate their non-neurotoxicity and, therefore their interest to prevent aerotoxic syndrome. Furthermore, the Applicant also showed the lack of reprotoxicity of polyphosphorus compounds, which reinforces their interest as an alternative to the TCP as anti-wear agent in oils such as hydraulic oils or turbine oils.

Summary of the invention

The invention also relates to the use of at least one anti-wear additive in an oil, said at least one anti-wear additive comprising at least one polyphosphorus compound of formula (I)



wherein

each of R1, R2, R3 and R4 is independently selected from: an alkyl, O-alkyl, aryl, or O-aryl group,

A is a divalent group selected from a linear alkylene group comprising 7 to 36 carbon atoms or a branched alkylene group comprising 6 to 36 carbon atoms, a monocyclic, polycyclic or polyaromatic arylene group, or aralkylene group,

each of X₁, and X₂ is independently a single bond, an oxygen atom or a nitrogen atom, and

n is an integer ranging between 1 and 5,

to reduce and/or prevent the neurotoxicity of said oil.

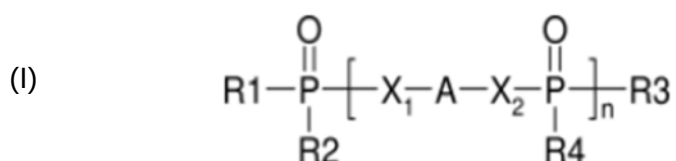
Preferably, said oil and/or said at least anti-wear additive does not include tricresyl phosphate or one of its triaryl phosphate analogs.

The polyphosphorus compounds of formula (I) can thus be used to obtain a non-neurotoxic oil or an oil having reduced neurotoxicity.

The compounds of formula (I) have interesting anti-wear properties that can be compared to those of tricresyl phosphate or its triaryl phosphate analogs. They also present a very low, or no, risk level in terms of neurotoxicity and thus reduce and/or prevent the neurotoxicity of the oil into which they are embedded.

Specifically, as shown by the experiment tests described below, the Applicant has discovered, unexpectedly, that the specific compounds of formula (I) above are non-toxic in terms of action on cholinesterases, non-neurotoxic, or even non-reprotoxic.

The invention also relates to the use of at least one anti-wear additive in an oil, said at least one anti-wear additive comprising at least one polyphosphorus compound of formula (I)



wherein

each of R1, R2, R3 and R4 is independently selected from: an alkyl, O-alkyl, aryl, or O-aryl group.

A is a divalent group selected from a alkyl group comprising 7 to 36 carbon atoms or a branched alkyl group comprising 6 to 36 carbon atoms, a monocyclic, polycyclic or polyaromatic arylene group, or aralkylene group,

each of X₁, and X₂ is independently a single bond, an oxygen atom or a nitrogen atom, and

n is an integer ranging between 1 and 5,

for the prophylaxis of aerotoxic syndrome, preferably in case of fume event.

Also preferably, for this use, said oil and/or said at least anti-wear additive does not comprise tricresyl phosphate or one of its triarylphosphate analogs. Naturally, the various characteristics, variants, and embodiments of the invention may be associated with one another in a variety of combinations providing they are not incompatible or mutually exclusive.

In the present invention, unless otherwise specified, the term "comprise" and its derivatives are to be understood as non-limiting and not excluding the presence of other components or steps.

In some particular embodiments, the term "comprise" can be understood as "essentially consist of" or "consist of".

Unless otherwise specified, intervals mentioned in the present invention are understood to be inclusive.

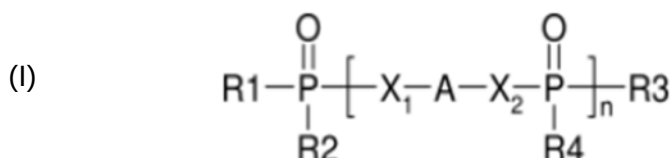
Brief description of the figures

[Fig. 1] shows molecules resulting from spherical harmonic modelling work. The compounds in the top line belong to cluster 1, the compounds in the bottom line belong to cluster 3; and

[Fig. 2 to 9] are tables grouping together the results of the tests carried out in order to study the neurotoxicity of compounds phosphorus-based according to the prior art (comparative compounds) and of compounds of formula (I) according to the invention (compounds 1 to 10).

Detailed description of the invention

A first object of the invention is the use of at least one anti-wear additive in an oil, said at least one anti-wear additive comprising at least one polyphosphorus compound of formula (I)



wherein

each of R1, R2, R3 and R4 is independently selected from: an alkyl, O-alkyl, aryl, or O-aryl group.

A is a divalent group selected from an alkylene group comprising 7 to 36 carbon atoms or a branched alkylene group comprising 6 to 36 carbon atoms, a monocyclic polycyclic or polyaromatic arylene group, or aralkylene group,

each of X₁, and X₂ is independently a single bond, an oxygen atom or a nitrogen atom, and

n is an integer ranging between 1 and 5,

to reduce and/or prevent the neurotoxicity of said oil, and preferably a turbine oil.

The expression "to reduce" the neurotoxicity of an oil means that the compound(s) of formula (I) according to the invention are capable of and/or configured to reduce the neurotoxicity of an oil in which they are embedded, namely, by their presence (generally in the majority), in particular with respect to other conventional anti-wear compounds which are generally neurotoxic, the compound(s) of formula (I) make it possible to lower/decrease the neurotoxicity of an oil and to obtain a non-neurotoxic oil or at least an oil with reduced toxicity.

The expression "to prevent" the neurotoxicity of an oil means that the compound(s) of formula (I) make it possible to prevent the oil from being regarded as neurotoxic and/or to prevent the appearance of neurotoxic symptoms in a mammal, such as a human being or an animal which would be in contact with said oil; these neurotoxic symptoms can, for example, reach the central nervous system (CNS) and have the following effects: headaches, loss of appetite, drowsiness, mood and personality disorders, cognitive impairment (learning and concentration disabilities), or reach the peripheral nervous system (PNS) and have the following effects: motor impairments such as weakness, tremor, incoordination, convulsions, etc. or sensory damages, such as reduced hearing, colour vision, tinnitus, loss of equilibrium, etc.; these effects may or may not be reversible depending on the degree of acute or chronic exposure of the mammal.

The term "neurotoxicity" means the ability of a substance or compound to induce adverse effects in the nervous system of a mammal, such as a human being. The nervous system is divided into central nervous system (CNS) and peripheral nervous system (PNS). CNS is situated in the cranial cavity and the vertebral column. It comprises the brain, the brain stem, and the spinal cord. Its role consists in receiving, recording, and interpreting signals that come from the periphery. It then organizes the response to be sent. The PNS consists of nerve ganglia, sensory nerves responsible for transmitting sensations to the brain, such as pain, and motor nerves responsible for movement by stimulating muscles. They circulate information between the CNS and the organs. Thus, according to the invention, a neurotoxic substance or compound usually acts by disturbing or paralyzing the nerve impulse, in particular by acting on the synaptic emitters or receptors or on the enzymes which act on these synaptic emitters or receptors, such as cholinesterases. In biochemistry, a cholinesterase is an enzyme that catalyzes the hydrolysis reaction of a choline ester (acetylcholine, butyrylcholine) to choline and acetic or butyric acid. In physiology, this reaction is necessary to allow the cholinergic receptors to return to their rest state after activation.

In the present application, the Applicant has demonstrated that, unexpectedly and surprisingly, certain specific polyphosphorus compounds of formula (I) above have both an excellent anti-wear property adapted in particular to the demanding field of aeronautics, while being weakly or not at all neurotoxic. This latter quality thus makes it possible to reduce and/or prevent and/or avoid the neurotoxicity of an oil in which they are embedded.

These tests also show that the compounds of formula (I) selected by the Applicant are not arbitrary and have a different technical effect (i.e., they make it possible to reduce/prevent/avoid the neurotoxicity of an oil) compared with other anti-wear compounds, in particular compared with other (poly)phosphorous anti-wear compounds.

For the present invention, the Applicant has demonstrated the non-neurotoxicity of the specific compounds of formula (I) both by *in vitro* experiment tests relating to cholinesterases and by modelling tests (3D molecular modelling by spherical harmonics and QSAR modelling for neurotoxicity and for reprotoxicity).

Preferably, the 50% inhibitory concentration of said at least one compound of formula (I) on the biological activity of an acetylcholinesterase (AChE) enzyme, called IC_{50} hAChE is greater than or equal to 15 mg/L, preferably greater than or equal to 16 mg/L and the activity on a butyrylcholinesterase enzyme, called IC_{50} eqBuChE is greater than or equal to 15 mg/L, in particular greater than or equal to 50 mg/L, preferably equal to or greater than 55 mg/L, in particular equal to or greater than 60 mg/L and typically equal to or greater than 70 mg/L.

According to the invention, a value greater than or equal to 15 mg/L for IC_{50} hAChE includes the following values and all the intervals between these values: 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 35; 36; 37; 38; 39; 40, etc.

Also, according to the invention, a value greater than or equal to 15 mg/L for IC₅₀ eqBuChE includes the following values and all the intervals between these values: 15; 16; 17; 18; 19; 20; 21; 22; 23; 24; 25; 26; 27; 28; 29; 30; 31; 32; 33; 34; 35; 36; 37; 38; 39; 40; 45; 50; 55; 60; 65; 70; 75; 80; 85; 90; 95; 100; 105; 110; 115; 120; 125; 130; 135; 140; 145; 150; 155; 160; etc.

Advantageously, the compound(s) of formula (I) belong to cluster 3 determined according to molecular modelling by spherical harmonics as described in the publication "Benchmarking of HPCC: A novel 3D molecular representation combining shape and pharmacophoric descriptors for efficient molecular similarity assessments », Karaboga *et al.* 2013 Journal of Molecular Graphics and Modelling 41; 20-30.

According to another characteristic of the invention, the compound(s) of formula (I) have a percentage value (%) by quantitative structure activity relationship (QSAR) modelling less than or equal to 0.70%, preferably less than or equal to 0.50% and typically less than or equal to 0.15% for the measurement of neurotoxicity (neurotoxic QSAR) and less than or equal to 1.5%, preferably less than or equal to 1.15% and typically less than or equal to 0.55% for the measurement of reprotoxicity (reprotoxic QSAR).

According to the invention, a value less than or equal to 0.70% for the neurotoxic QSAR modelling includes the following values and all the intervals between these values: 0.70; 0.69; 0.68; 0.67; 0.66; 0.65; 0.64; 0.63; 0.62; 0.61; 0.60; 0.59; 0.58; 0.57; 0.56; 0.55; 0.54; 0.53; 0.52; 0.51; 0.50; 0.49; 0.48; 0.47; 0.46; 0.45; 0.44; 0.42; 0.40; 0.38; 0.36; 0.34; 0.32; 0.30; 0.28; 0.26; 0.24; 0.22; 0.20; 0.18; 0.16; 0.14; 0.12; 0.10; 0.09; 0.08; 0.07; 0.06; 0.005; 0.04; 0.03; 0.01; 0.00.

Also, according to the invention, a value less than or equal to 1.50% for reprotoxic QSAR modelling includes the following values and all the intervals between these values: 1,50; 1,48; 1,46; 1,44; 1,42; 1,40; 1,38; 1,36; 1,34; 1,32; 1,30; 1,28; 1,26; 1,24; 1,22; 1,20; 1,18; 1,16; 1,14; 1,12; 1,10; 1,08; 1,06; 1,04; 1,02; 1,00; 0,80; 0,60; 0,50; 0,40; 0,30; 0,20; 0,10; 0,00.

Thus, the compounds of formula (I) according to the invention have a risk level in terms of neurotoxicity which is very low and which generally corresponds to a score of 0 or to a score of 1 (very low or non-existent risk of neurotoxicity), preferably to a score of 0.

The risk level as defined above and also illustrated in the experiment part below is very exhaustive and encompasses all the data obtained via the various tests on neurotoxicity described above and therefore encompasses both *in vitro* tests and 3D modelling tests.

In particular, the risk level takes into consideration all of the following tests:

- the *in vitro* acetylcholinesterase (AChE) inhibition test,
- the *in vitro* butyrylcholinesterase (BuChE) inhibition test,
- the type of cluster taking into account the shape and functionality of spherical harmonics (3D modelling),
- the semi-empirical prediction of neurotoxicity, and
- the semiempirical prediction of reprotoxicity.

By "oil" is meant in the present invention any organic material, especially any hydraulic or turbine oil liable to create pollution in the form of gas and/or aerosol in the cabin. In some embodiments, the oil is selected from the group consisting of oils for aircraft or aeroderivative turbines, helicopter transmission oils and weapon fluids. Preferably, in the present invention, the
 5 oil is an oil for aircraft or aeroderivative turbines.

The oil is preferably used for lubricating aircraft or aeroderivative turbines.

As mentioned above, the groups R1, R2, R3 and R4 of the polyphosphorus compounds of formula (I) according to the invention are independently selected from: an alkyl, O-alkyl, aryl, or O-aryl group.

10 By "alkyl group" according to the invention is meant a linear or branched saturated hydrocarbon group comprising (unless otherwise mentioned) 1 to 36 carbon atoms (C_1 to C_{36}), more preferably 1 to 18 carbon atoms (C_1 to C_{18}), in particular 1 to 10 carbon atoms (C_1 to C_{10}), and typically 1 to 4 carbon atoms (C_1 to C_4). Examples of alkyl groups according to the invention include methyl, ethyl, propyl, isopropyl, n-butyl and tert-butyl groups.

15 According to the invention, the alkyl group may optionally be a substituted alkyl group.

According to the present invention, the expression "substituted alkyl group" designates a linear or branched saturated hydrocarbon chain as defined above and substituted, at one or more of its atoms, by one or more radicals selected from: an OH hydroxyl radical, an NH_2 amine radical or an NHR primary amine radical with R being an alkyl or aryl group, preferably an OH hydroxyl
 20 radical. Thus, the alkyl group may not be substituted by a halogen, such as chlorine.

By "O-alkyl group" is meant an alkyl group, as defined above, linked to the rest of the molecule (here, generally phosphorus atom) via an oxygen atom.

By "aryl group" is meant a monovalent organic moiety derivate from an aromatic hydrocarbon comprising 5 to 14 carbon atoms and corresponding for example to an aromatic
 25 hydrocarbon ring (such as a phenyl) or two aromatic hydrocarbon fused rings (such as a naphthyl).

According to the invention, an aryl group may be substituted or unsubstituted.

According to the invention, by "substituted aryl group", is meant a ring or two substituted aromatic hydrocarbon fused rings at one or more of its atoms, by at least one substituent consisting of C_1 to C_{18} alkyl groups, OH hydroxyl group, NH_2 amine group or NHR primary amine
 30 group with R being a C_1 to C_{18} alkyl group or aryl group, preferably by C_1 to C_{18} alkyl groups, such as methyl group, or OH hydroxyl group.

By "O-aryl group" is meant an aryl group, as defined above, linked to the rest of the molecule via an oxygen atom.

In some embodiments, at least one of R1, R2, R3 and R4 is an alkyl or O-alkyl group. In
 35 this configuration, preferably each alkyl group is an alkyl group comprising 1 to 22 carbon atoms (C_1 to C_{22}), preferably 1 to 18 carbon atoms (C_1 to C_{18}), in particular 1 to 10 carbon atoms (C_1 to C_{10}), and typically 1 to 4 carbon atoms (C_1 to C_4).

In some preferred embodiments, at least one of R1, R2, R3 and R4 is an aryl or O-aryl group. Preferably, at least two of R1, R2, R3 and R4 are aryl or O-aryl groups. In particular, R1, R2, R3 and R4 are four aryl or O-aryl groups, such as O-phenyl or is a substituted O-aryl group, such as O-dimethylphenyl.

5 In some embodiments, at least one of R1, R2, R3 and R4 is a phenyl group. Preferably, R1, R2, R3 and R4 are phenyl groups. R1, R2, R3 and R4 are usually unsubstituted phenyl groups or phenyl groups substituted by at least one methyl group, preferably two methyl groups (such as 2,6-dimethylphenyl).

10 In some embodiments, at least one of R1, R2, R3 and R4 is a O-phenyl group. Preferably, R1, R2, R3 and R4 are O-phenyl groups. R1, R2, R3 and R4 are usually unsubstituted O-phenyl groups or O-phenyl groups substituted by at least one methyl group, preferably two methyl groups (such as 2,6-dimethylphenyl).

In general, "A" of formula (I) according to the invention may be selected from an alkylene group, an arylene group or an aralkylene group.

15 By "alkylene group" is meant a linear saturated hydrocarbon divalent group comprising (unless otherwise mentioned) 7 to 36 carbon atoms (C_7 to C_{36}), preferably 7 to 22 carbon atoms (C_7 to C_{22}), preferably 7 to 18 carbon atoms (C_7 to C_{18}), or a branched saturated hydrocarbon divalent group comprising (unless otherwise mentioned) preferably 6 to 36 carbon atoms (C_6 to C_{36}), preferably 6 to 22 carbon atoms (C_6 to C_{22}), preferably 6 to 18 carbon atoms (C_6 to C_{18}), in
20 particular 6 to 12 carbon atoms (C_6 to C_{12}).

An alkylene group may be unsubstituted or optionally substituted.

By "substituted alkylene group" is meant an alkylene group as defined above substituted at one or more of its atoms, by at least one substituent selected from the group consisting of linear or branched C_1 to C_{18} alkyl group; OH hydroxyl group; NH_2 amine or primary NHR amine group
25 with R being an alkyl group (as defined above) or an aryl group (as defined above); O-phosphate group, such as the O-diphenylphosphate group $O-P(=O)(OPh)_2$, and halogen atoms, such as fluorine. Usually, the "substituted alkylene group" is substituted by at least one substituent selected from the group consisting of linear or branched C_1 to C_{18} alkyl group; OH hydroxyl group; O-phosphate group, such as O-diphenylphosphate group $O-P(=O)(OPh)_2$. Thus, the alkylene
30 group substituted by an O-phosphate radical may correspond to a 1,3-(2-ethyl-2-[methyl-O-diphenylphosphate])propyl group.

By "arylene group" is meant a monocyclic or polycyclic aromatic carbon group derived from an aromatic hydrocarbon and including at least two anchoring points (divalent) which are linked to X1 and X2 arranged on the aromatic ring(s) (the two anchoring points may be on the
35 same ring of the polycyclic group). Each aromatic or polyaromatic ring may comprise from 5 to 14 atoms. An arylene group may correspond, for example, to an aromatic hydrocarbon ring (such as a phenylene), to two fused aromatic hydrocarbon rings (such as a naphthalene) or to two aromatic hydrocarbon rings linked by a covalent bond between two distinct atoms each belonging

to one of the rings. According to a characteristic of the invention, the aromatic rings may optionally be interrupted by one or more heteroatoms which can be selected, in particular, from the group consisting of nitrogen atom, oxygen atom and sulfur atom, preferably consisting of oxygen atom or sulfur atom. Preferably, the arylene group does not comprise nitrogen atom internal to the
 5 monocyclic or polycyclic aromatic carbon group. Thus, generally, the arylene group cannot correspond, for example, to a pyridine or to a pyrimidine.

Each ring can be unsubstituted or can be substituted to form a "substituted arylene group".

By "substituted arylene group" is meant an arylene group as described above substituted, at one or more of its atoms, by at least one substituent selected from the group consisting of C₁
 10 to C₁₈ alkyl groups; OH hydroxyl group; NH₂ primary amine group or NHR primary amine with R being an alkyl or aryl group; O-phosphate group, such as the O-diphenylphosphate group O-P(=O)(OPh)₂ which may be, for example, substituted on one of the rings of the polycyclic group and halogen atoms, such as fluorine and except chlorine. According to one characteristic of the invention, the arylene group is preferably substituted by at least one C₁ to C₁₈ alkyl group, hydroxyl
 15 group, or at least one O-diphenylphosphate group O-P(=O)(OPh)₂, and even more preferably, the arylene group is substituted by at least one C₁ to C₁₈ alkyl group, or at least one O-diphenylphosphate group O-P(=O)(OPh)₂. Thus, the substituted arylene group may correspond to an O-diphenyl phosphate radical, such as a 1,3-(5-O-[(diphenyl)phosphate])phenyl group.

When the arylene group is a polycyclic group in which at least two rings are connected by
 20 at least one covalent bond between two distinct atoms each belonging to one of the rings, the covalent bond between the at least two rings can be interrupted by at least one alkylene group, such as a C(CH₃)₂ group or a C(CH₃) group when the polycyclic group comprises three rings, a carbonyl group -CO-, a heteroatom or heteroatomic group such as an oxygen atom, a sulfur atom, an NH or NR amine group, an sulfite group OS(=O)O, a sulfone group -S(O₂)- or a linear or
 25 branched perfluorinated group comprising, for example, 3 carbon atoms such as C(CF₃)₂.

Examples of monocyclic arylene groups include in particular phenylene group (C₆H₄).

When A is or comprises a monocyclic arylene group such as a phenylene, or a thiophene derivative, X₁ and X₂ are preferably diametrically opposed, in particular at the 1,4-position when the monocyclic arylene group comprises 6 carbon atoms (such as phenylene). A is preferably a
 30 1,4-phenyl group, which is optionally substituted.

In particular, when A is a phenylene, X₁ and X₂ are not in the ortho or meta position unless at least one and preferably all of the groups of R₁, R₂, R₃ and R₄ are O-phenyl groups substituted by two methyl groups, in particular in the 2,6-position. In this case, X₁ and X₂ may be in the meta position.

Also, when A is a phenylene group substituted by an O-diphenylphosphate group O-P(=O)(OPh)₂, then preferably X₁ and X₂ are at the 1,3-position so as to obtain the 1,3-(5-O-[(diphenyl)phosphate])phenyl group.

When A is or comprises a polycyclic group, or a polyaromatic group comprising for example two fused rings, such as the naphthalene group, X_1 and X_2 are preferably diametrically opposed in order to maximize the distance between X_1 and X_2 .

In particular, when A is a naphthalene, X_1 and X_2 are not in the ortho or meta position (in particular in the 1,3-position), but may be in the 1,4 or 2,7-position.

Preferably, the group A does not comprise electron-withdrawing groups or atoms, such as chlorine, carbonyl functions (aldehyde, carboxylic acid, $C(O)-O$), one or more nitrogen atoms internal to the carbon monocyclic or polycyclic group (pyridine or pyrimidine). Thus, the group A cannot be a pyridine or pyrimidine.

Examples of polycyclic arylene groups include 4,4'-biphenyl, 4,4'-diphenylthioether, 4,4'-diphenylether, 4,4'-diphenylphenylethylidene, 4,4'-dimethyldiphenylmethylidene, 4,4'-diphenylsulfone, 4,4'-benzophenone, 2,2'-benzophenone, 1,4-naphthalene, 1,3-naphthalene, 2,7-naphthalene, 2,6-anthracene, 9,10-anthracene and phenanthrene.

By "aralkylene group" is meant an alkyl group covalently linked to an aryl group and comprising two (divalent) anchoring points situated on the alkyl group and/or on the aryl group.

Similarly, an "aralkylene" group may be substituted or not. By "substituted aralkylene" group is meant an aralkylene group as defined above substituted, at one or more of its atoms, by at least one substituent selected from the group consisting of C_1 to C_{18} alkyl group, OH hydroxyl group; NH_2 amine group or NHR primary amine group with R being an alkyl or aryl group; O-phosphate group, such as O-diphenylphosphate group $O-P(=O)(OPh)_2$, and halogen atoms, such as fluorine (except the chlorine). Preferably, the aralkylene group is substituted by a substituent selected from the group consisting of C_1 to C_{18} alkyl group, OH hydroxyl group and O-phosphate group, such as O-diphenylphosphate group $O-P(=O)(OPh)_2$.

Examples of aralkylene groups include in particular 4,4'-[diphenyl(dimethyl)methylidene] group and 4,4'-diphenylhexafluoropropane group.

In some embodiments, A is selected from the group consisting of a 1,4-phenyl, 4,4'-biphenyl, 4,4'-diphenylthioether, 4,4'-diphenylether, 1,3-(5 O-[(diphenyl)phosphate])phenyl, 1,3-(2-ethyl-2-butyl)propyl, 1,3-(2-ethyl-2-[methyl-O-diphenyl phosphate])propyl, 4,4'-[diphenyl(dimethyl)-methylidene], 2,2'-benzophenone, 2,7-naphthalene, 1,2-ethyl, 4,4'-[diphenylphenylethylidene], 4,4'-diphenylsulfone, 4,4'-diphenyl-hexafluoropropane, 1,4-[(2-phenyl)phenyl], 1,4-[(2,5-ditertbutyl)phenyl], 1,4-[(2-chloro)phenyl], 4,4'-benzophenone, 1-hydroxy-3-thiophenyl, 1,6-hexyl, 1,4-naphthalene, 2,6-anthracene, 9,10-anthracene, 1,10-decyl, 1,12-n-dodecyl, 2,5-dimethyl-2,5-hexyl, 1,12-dodecyl and 1,3-naphthalene group.

In some preferred embodiments, A is selected from the group consisting of a 1,4-phenyl, 4,4'-biphenyl, 4,4'-diphenylthioether, 4,4'-diphenylether, 1,3-(5 O-[(diphenyl)phosphate])phenyl, 1,3-(2-ethyl-2-butyl)propyl, 1,3-(2-ethyl-2-[methyl-O-diphenylphosphate])propyl, 4,4'-[diphenyl(dimethyl)methylidene], 2,2'-benzophenone, 2,7-naphthalene and 1,2-ethyl group.

In some more preferred embodiments, A is selected from the group consisting of a 1,4-phenyl, 4,4'-biphenyl, 4,4'-diphenylthioether, 4,4'-diphenylether, 1,3-(5 O-[(diphenyl)phosphate])phenyl, 1,3-(2-ethyl-2-butyl)propyl, 1,3-(2-ethyl-2-[methyl-O-diphenylphosphate])propyl group.

5 In particular, A is selected from the group consisting of a 4,4'-diphenylthioether, 4,4'-diphenylether, 1,3-(5 O-[(diphenyl)phosphate])phenyl, 1,3-(2-ethyl-2-butyl)propyl, 1,3-(2-ethyl-2-[methyl-O-diphenylphosphate])propyl group.

In an embodiment, A is an optionally substituted alkyl group, a substituted monocyclic arylene group or a polycyclic arylene group wherein at least two rings are linked by at least a
10 covalent bond between two distinct atoms each belonging to one of the rings, the covalent bond between the two rings being interrupted by at least one heteroatom or heteroatomic group.

By "halogen atom" is meant (unless otherwise indicated) an atom selected from the group consisting of chlorine, bromine, fluorine and iodine.

Each of X_1 and X_2 is independently selected from the group consisting of a single bond,
15 an oxygen atom and a nitrogen atom, preferably a single bond or an oxygen atom. In some preferred embodiments, X_1 and X_2 are two oxygen atoms; in other embodiments, X_1 and X_2 are two nitrogen atoms; finally, in last embodiments, one of X_1 and X_2 is an oxygen atom and the other of X_1 and X_2 is a nitrogen atom.

When X_1 or X_2 is a nitrogen atom, it may be in the form of an NH or NR group, R being an
20 alkyl or aryl group.

When X_1 or X_2 is a single bond, this means that A is directly linked by only one single bond to the phosphorus atom of the $P(=O)R_1R_2$ or $P(=O)R_3R_4$ group.

n is an integer comprised between 1 and 5. n may in particular be equal to 1, 2, 3, 4 or 5. In some embodiments, "n" is 1. When the value of n is not explicitly specified, a polyphosphorus
25 compound refers to at least one of the oligomers comprising 1 to 5 $-X_1-A-X_2-P(O)R_4-$ units, or any mixture of at least two of these. For example, it can be a mixture of oligomers comprising 1 to 3 $-X_1-A-X_2-P(O)R_4-$ units. Preferably, $n=1$.

In some embodiments, the polyphosphorus compounds used according to the invention are aryl diphosphates, i.e. they are such that X_1 and X_2 are two oxygen atoms, and each of R1,
30 R2, R3 and R4 is an O-aryl group (as defined above), optionally substituted for example by two methyl groups.

Surprisingly, non-toxicity, particularly non-neurotoxicity and non-reprotoxicity of the polyphosphorus compounds of formula (I), was demonstrated by the Applicant.

Anti-wear properties of some polyphosphorus compounds, including aryl diphosphates,
35 are known in the art and have been already demonstrated previously. Thus, polyphosphorus compounds, in particular aryl polyphosphorus compounds, have an anti-wear effectiveness at least as interesting as the one obtained with conventional anti-wear additives such as TCP.

Preferably, said oil and/or said at least one anti-wear additive does not comprise tricresyl phosphate or one of its triaryl phosphate analogs.

The expression “an oil that does not include tricresyl phosphate” refers to an oil in which the amount of tricresyl phosphate, regardless of its type of substitution (ortho, meta, para) is less than the detection limit of usual analytical techniques such as for example the gas chromatography-mass spectrometry. A technique suitable for detecting tricresyl phosphate in oil is described, for example, in De Nola G. *et al.*, *J. Chromatogr. A* **2008**; 1200 (2), pp.211-216.

In some embodiments, the oil used according to the invention or the anti-wear agent used according to the invention does not substantially comprise, preferably does not comprise, any aryl monophosphate anti-wear additive. In some embodiments, the oil used according to the invention or the anti-wear agent used according to the invention does not substantially comprise, preferably does not comprise, an organophosphate anti-wear additive other than the polyphosphorus compound additive(s).

In some embodiments, the oil used according to the invention or the anti-wear agent used according to the invention does not substantially comprise, preferably does not comprise, anti-wear additive other than the polyphosphorus compound additive(s).

In general, the anti-wear agent according to the invention of general formula (I) represents, by mass, relative to the total mass of the anti-wear agents present in the oil, from 50% to 100%, preferably from 80% to 100%, and in particular from 90% to 100% and typically 100%.

According to the invention, “50% to 100%” means the following values or any interval between these values: 50; 55; 60; 65; 70; 75; 80; 85; 90; 95; 100.

In an embodiment, the polyphosphorus compound in the oil used according to the invention is selected from the group consisting of:

- hydroquinone bis(diphenylphosphate) HDP,
- 4,4'-dihydroxybiphenyl bis(diphenylphosphate) and oligomers thereof,
- 4,4'-dihydroxydiphenyl thioether bis(diphenylphosphate),
- 4,4'-dihydroxydiphenyl ether bis(diphenylphosphate),
- 1,3,5-phloroglucinol tris((diphenylphosphate)),
- 2-butyl 2-ethyl 1,3-propanediol bis(diphenylphosphate),
- trimethylol propane tris(diphenylphosphate),
- 4,4'-dihydroxydiphenyl phenylethylidene bis(diphenylphosphate),
- 4,4'-dihydroxydiphenyl sulfone bis(diphenylphosphate),
- 4,4'-dihydroxybenzophenone bis(diphenylphosphate),
- 2,2'-dihydroxybenzophenone bis(diphenylphosphate),
- 4,4'-dihydroxydiphenyl hexafluoropropane bis(diphenylphosphate),
- 1,4-dihydroxynaphthalene bis(diphenylphosphate),
- 1,3-dihydroxynaphthalene bis(diphenylphosphate),
- 2,7-dihydroxynaphthalene bis(diphenylphosphate),

- ethanolamine diphenylphosphate diphenylphosphoroamidate,
- 4,4'-diaminodiphenyl ether bis(diphenylphosphoroamidate),
- 2,6-dihydroxyanthracene bis(diphenylphosphate),
- 9,10-dihydroxyanthracene bis(diphenylphosphate),
- 5 - 1,4-dihydroxy[(2-phenyl)phenyl] bis(diphenylphosphate),
- 1,4-dihydroxy[(2,5-diterbutyl)phenyl] bis(diphenylphosphate),
- 1,4-dihydroxy[(2-chloro)phenyl] bis(diphenylphosphate),
- 1,3-dihydroxythiophene bis(diphenylphosphate),
- 1,6-hexanediol bis(bis(diphenylphosphate),
- 10 - 1,10-decanediol bis(diphenylphosphate),
- 2,5-dimethyl 2,5-hexanediol bis(diphenylphosphate),
- 1,12-n-dodecanediol bis(diphenylphosphate),
- tetrakis(2,6-dimethylphenyl)-m-phenylene bisphosphate,
- tetrakis(2,6-dimethylphenyl)-p-phenylene bisphosphate,
- 15 - phenylhydroquinone bis(diphenylphosphate) DPP,
- tert-butyl hydroquinone bis(diphenylphosphate),
- 2,5-di-tert-butyl hydroquinone bis(diphenylphosphate),
- 1,4-dihydroxynaphthalene bis(diphenylphosphate),
- 2,7-dihydroxynaphthalene bis(diphenylphosphate),
- 20 - 4,4'-dihydroxybenzophenone bis(diphenylphosphate),
- bis(4-hydroxyphenyl)sulfone bis(diphenylphosphate),
- 4,4'-(hexafluoroisopropylidene) bis(diphenylphosphate),
- 4,4'-(α -méthylbenzylidene)bisphenol bis(diphenylphosphate),
- 1,1-bis-(4-hydroxyphényl)cyclohexane) bis(diphenylphosphate),
- 25 - 9,9-bis(4-hydroxyphenyl)fluorene bis(diphenylphosphate),
- 1,1,1-Tris(4-hydroxyphényl)ethane tris(diphenylphosphate), and
- any mixtures thereof.

In an embodiment, the polyphosphorus compound in the oil used according to the invention is selected from the group consisting of:

- 30 - hydroquinone bis(diphenylphosphate) HDP,
- 4,4'-dihydroxybiphenyl bis(diphenylphosphate) and oligomers thereof,
- 4,4'-dihydroxydiphenyl thioether bis(diphenylphosphate),
- 4,4'-dihydroxydiphenyl ether bis(diphenylphosphate),
- 1,3,5-phloroglucinol tris((diphenylphosphate))
- 35 - 2-butyl 2-ethyl 1,3-propanediol bis(diphenylphosphate),
- trimethylol propane tris(diphenylphosphate),
- 2,2'-dihydroxybenzophenone bis(diphenylphosphate),
- 2,7-dihydroxynaphthalene bis(diphenylphosphate),

- 4,4'-dihydroxybenzophenone bis(diphenylphosphate),
- bis(4-hydroxyphenyl)sulfone bis(diphenylphosphate),
- 4,4'-(hexafluoroisopropylidene) bis(diphenylphosphate),
- 4,4'-(α -méthylbenzylidene)bisphenol bis(diphenylphosphate),
- 5 - 1,1-bis-(4-hydroxyphényl)cyclohexane) bis(diphenylphosphate),
- 9,9-bis(4-hydroxyphenyl)fluorene bis(diphenylphosphate),
- 1,1,1-Tris(4-hydroxyphényl)ethane tris(diphenylphosphate) - any mixtures thereof.

In an embodiment, the polyphosphorus compound in the oil used according to the invention is selected from the group consisting of:

- 10 - hydroquinone bis(diphenylphosphate) HDP,
- 4,4'-dihydroxybiphenyl bis(diphenylphosphate) and oligomers thereof,
- 4,4'-dihydroxydiphenyl thioether bis(diphenylphosphate),
- 4,4'-dihydroxydiphenyl ether bis(diphenylphosphate),
- 1,3,5-phloroglucinol tris(bis(diphenylphosphate)),
- 15 - 2-butyl 2-ethyl 1,3-propanediol bis(diphenylphosphate),
- trimethylol propane tris(diphenylphosphate),
- 1,12-n-dodecanediol bis(diphenylphosphate),
- tetrakis(2,6-dimethylphenyl)-m-phenylene bisphosphate,
- tetrakis(2,6-dimethylphenyl)-p-phenylene bisphosphate, and
- 20 any mixtures thereof.

In an embodiment, the polyphosphorus compound in the oil used according to the invention is selected from the group consisting of:

- 4,4'-dihydroxydiphenyl thioether bis(diphenylphosphate),
- 4,4'-dihydroxydiphenyl ether bis(diphenylphosphate),
- 25 - 1,3,5-phloroglucinol tris(bis(diphenylphosphate)),
- 2-butyl 2-ethyl 1,3-propanediol bis(diphenylphosphate),
- trimethylol propane tris(diphenylphosphate),
- 1,12-n-dodecanediol bis(diphenylphosphate),
- tetrakis(2,6-dimethylphenyl)-m-phenylene bisphosphate,
- 30 - tetrakis(2,6-dimethylphenyl)-p-phenylene bisphosphate, and
- any mixtures thereof.

Polyphosphorus compounds are present in the oil used in the present invention in such an amount as those conventionally used in the art. For example, they can be used in an amount of from 0.1 to 10 wt. %, preferably 0.5 to 5 wt. % based on the total weight of the oil.

35 An oil suitable for the present use will be described below.

The oil used according to the invention may comprise all the conventional constituents and additives known in the art for this type of oil.

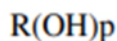
The oil used according to the invention preferably comprises an ester base, at least one amine antioxidant, and at least one polyphosphorus anti-wear additive of formula (I).

In some embodiments, the oil used according to the invention also comprises at least one further additive. The at least one further additive can especially be selected from the group consisting of lubricant agents, other anti-wear additives, antioxidants, metal corrosion inhibitors, passivators, viscosity index improvers, detergents or dispersing agents, defoamers, surfactants, blowing agents, tackifiers, stabilizers, bulking agents, hydrolysis stabilizers, additives suitable for extreme pressures, pigments and odor-masking agents. Such additives and agents are well known to those skilled in the art and are commercially available.

The ester base is a conventional ester base well known in the art. It is typically synthetic oil that can be selected from monohydric alcohol or polyhydric alcohol esters, preferably polyhydric alcohol esters, with a mono or dicarboxylic acid reagent.

Particularly suitable polyhydric alcohols are neopolyols such as neopentyl glycol, 2-ethyl-2-methylpropane-1,3-diol, trimethylol ethane, trimethylol propane, trimethylol butane and mono-, di- or tri-pentaerythritol.

Other suitable polyhydric alcohols include any polyhydric alcohol of formula



wherein R is an optionally substituted linear, branched or cyclic aliphatic hydrocarbon moiety, and p is an integer equal to or greater than 2. The polyhydric alcohol can be selected from the group consisting of 2-ethyl-1,3-hexanediol, 2-propyl-3,3-heptanediol, 2-butyl-1,3-butanediol, 2,4-dimethyl-1,3-butanediol, ethylene glycol, propylene glycol and polyalkylene glycols.

Particularly suitable monohydric alcohols are neoalcohols such as 2,2,4-trimethylpentanol and 2,2-dimethylpropanol. Alternatively, the monohydric alcohol can be selected from the group consisting of the methyl, butyl, isooctyl and octadecyl alcohols.

The carboxylic acid reagent used to form the ester with the monohydric or polyhydric alcohol can be selected from optionally substituted aliphatic carboxylic acids comprising one or two carboxylic acid functions or any mixtures thereof. The person skilled in the art will know how to select the carboxylic acids to be used depending on the desired properties for the ester and on the monohydric or polyhydric alcohol used.

Ester bases that may be contained in an oil used according to the invention include the octyl acetate, decyl acetate, octadecyl acetate, methyl myristate, butyl stearate, methyl oleate monoesters, as well as the dibutyl phthalate, dioctyl adipate, di-2-ethylhexyl azelate and ethylhexyl sebacate polyesters. Polyol ester-type base oil can be an oil prepared from technical pentaerythritol or trimethylol propane and a carboxylic acid mixture having from 4 to 12 carbon atoms. The technical pentaerythritol is a mixture that comprises from about 85% to 92% by weight of monopentaerythritol and from 8% to 15% by weight of dipentaerythritol.

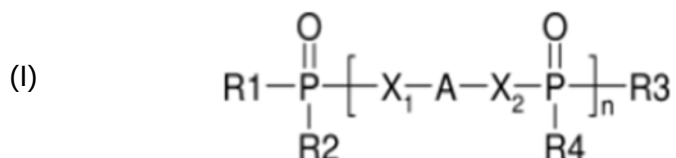
A commercially available conventional technical pentaerythritol contains about 88% by weight of monopentaerythritol and about 12% by weight of dipentaerythritol, based on the total weight of said ester-type base oil. The technical pentaerythritol may also contain an amount of tri- and tetra-pentaerythritols usually formed as by-products during the technical pentaerythritol
5 production.

Aromatic amine antioxidants are well known in the art and can be monomeric or polymeric aromatic amine antioxidants belonging to the family of aromatic amines and/or phenolic compounds.

Monomeric aromatic amine antioxidants may comprise especially at least one
10 diphenylamine unsubstituted or substituted by at least one hydrocarbon group, at least one naphthylphenylamine unsubstituted or substituted by at least one hydrocarbon group, at least one phenothiazine unsubstituted or substituted by at least one hydrocarbon group, or any mixture thereof. The hydrocarbon groups substituting the amines are (C₁ to C₃₀)alkyl groups, or styrene.

Polymeric aromatic amine antioxidants are the polymerization products of aromatic amine
15 antioxidants as defined above, either with each other or in the presence of a different comonomer. Examples of oligomeric or polymeric aromatic amine antioxidants that can be used in turbine oils according to the invention include those described in the patent applications FR 2 924 122 and WO 2009/071857.

The present invention may thus relate to a method for manufacturing an oil which is non-
20 neurotoxic or has a significantly reduced neurotoxicity (in comparison with tricresyl phosphate based oils and its analogs or oils containing other neurotoxic phosphorus compounds) used in particular for lubricating devices/machines, such as aircraft or aeroderivative turbines, comprising the following step: incorporating into a base oil, such as an ester oil, at least one anti-wear agent, characterized in that said at least one anti-wear agent is selected from at least one
25 polyphosphorus compound of formula (I)



30 wherein

each of R1, R2, R3 and R4 is independently selected from: an alkyl, O-alkyl, aryl, or O-aryl group,

A is a divalent group selected from a linear alkylene group comprising 7 to 36 carbon atoms or a branched alkylene group comprising 6 to 36 carbon atoms, a monocyclic, polycyclic
35 or polyaromatic arylene group, or aralkylene group,

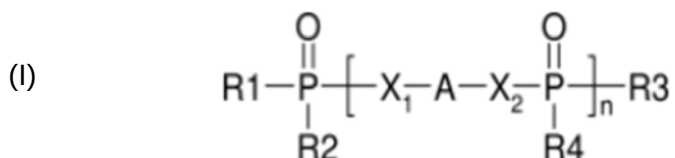
each of X₁, and X₂ is independently a single bond, an oxygen atom or a nitrogen atom, and

n is an integer ranging between 1 and 5,

and having in particular a risk level in terms of neurotoxicity of 0.

Naturally, the various embodiments described above for the use of polyphosphorus compounds to prevent and/or reduce the neurotoxicity of an oil also apply to this method of manufacturing an oil and will not be repeated below.

The invention also relates to the use of at least one anti-wear additive in an oil, said at least anti-wear additive comprising at least one polyphosphorus compound of formula (I)



wherein

each of R1, R2, R3 and R4 is independently selected from: an alkyl, O-alkyl, aryl, or O-aryl group.

A is a divalent group selected from an alkylene group comprising 7 to 36 carbon atoms or a branched alkylene group comprising 6 to 36 carbon atoms, a monocyclic polycyclic or polyaromatic arylene group, or aralkylene group,

each of X₁, and X₂ is independently a single bond, an oxygen atom or a nitrogen atom, and

n is an integer ranging between 1 and 5,

for the prophylaxis of aerotoxic syndrome, preferably in case of fume event.

Naturally, the various embodiments described above for the use of polyphosphorus compounds to prevent and/or reduce the neurotoxicity of an oil also apply to that use and will not be repeated below.

In the case of aeroderivative turbines, the pathology referred to as “aerotoxic syndrome” is a pathology with at least some of the same neurological and reproductive symptoms as those observed in aircrafts for aerotoxic syndrome, but which is contracted by exposure to organophosphates, such as tricresyl phosphate, in installations with industrial ground turbines such as offshore platforms.

The term “aerotoxic syndrome prophylaxis” refers to the decrease in the occurrence and/or the intensity, or the virtual or total disappearance, of at least one symptom identified as being related to acute or chronic exposure of individuals to the air of aircraft cabin contaminated by oils such as turbine oils or hydraulic oils in the form of gases and/or aerosols. In some embodiments, aerotoxic syndrome prophylaxis means the decrease in the occurrence, or the virtual or total disappearance, of several symptoms, preferably, of all symptoms, identified as being related to acute or chronic exposure of individuals to the air of aircraft cabin contaminated by oils such as turbine oils or hydraulic oils in the form of gases, products dispersed in the air, of the aerosol type.

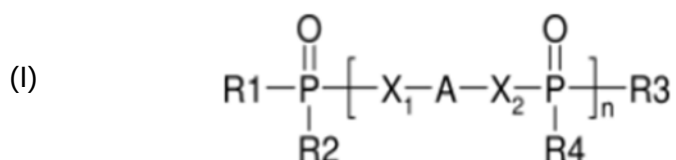
In particular, the symptom can be a neurological, neurobehavioral, neuromotor symptom and/or a symptom related to reproduction. Symptoms whose occurrence and/or intensity may be

diminished by the use according to the invention include for example psychological or psychosomatic disorders, chronic fatigue syndrome, severe migraine headaches, multiple chemical sensitivity, mystery viral infections, sleep disorders, depression, stress and anxiety.

The term "fume event" refers to acute or chronic exposure, preferably acute, of at least one individual to the air of aircraft cabin contaminated by oils such as turbine oils or hydraulic oils in the form of gases and/or aerosols. A fume event, if it is significant, can in particular be detected by the perception of an unpleasant characteristic odor, typical of "dirty socks" or "wet dogs". In the most severe cases, for example, following the breakage of a bearing in the turbine, a smoke or thick white mist could be visible.

The present invention may thus relate to a method for lubricating a machine/device, such as aircraft or aeroderivative turbines, comprising the following steps:

- providing an oil non-neurotoxic or with a significantly reduced toxicity (risk level at a score of 0), preferably free of tricresyl phosphate and/or its analogs, said oil comprising at least one anti-wear agent selected from a polyphosphorus compound of formula (I)



wherein

each of R1, R2, R3 and R4 is independently selected from: an alkyl, O-alkyl, aryl, or O-aryl group,

A is a divalent group selected from a linear alkylene group comprising 7 to 36 carbon atoms or a branched alkylene group comprising 6 to 36 carbon atoms, a monocyclic, polycyclic or polyaromatic arylene group, or aralkylene group,

each of X₁, and X₂ is independently a single bond, an oxygen atom or a nitrogen atom, and

n is an integer ranging between 1 and 5,

- applying an effective amount of said oil to said machine/device.

Naturally, the various embodiments described above for the use of polyphosphorus compounds to prevent and/or reduce the neurotoxicity of an oil also apply to this method for lubricating and will not be repeated below.

Examples

Example 1: Toxicity study and in particular neurotoxicity study

The polyphosphorus compounds according to the invention were studied and compared to other phosphorus compounds, including to TCP, in terms of cholinesterase inhibition, 3D molecular modelling by spherical harmonics, and in terms of QSAR modelling for the neurotoxicity and the reprotoxicity. The correlation between the results obtained made it possible to determine

a “safety level” for the use of these compounds as anti-wear agent in oils for aircraft or aeroderivative turbines.

Protocol of the Different Tests Performed:

Inhibitory Concentration Measurement on Two Cholinesterases:

5 In the extent that the toxic activity of TCP especially involves its action on cholinesterases, the effect of the compounds used according to the invention, as well as comparative compounds, on two cholinesterases was studied. The concentration values of each compound required to inhibit 50% of the activity of two cholinesterases were measured. The higher the 50% inhibitory concentration (IC₅₀), the less the compound is neurotoxic since it has a weaker action on the
10 cholinesterase.

The inhibitory capacity of the compounds on the acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) biological activity was assessed using the spectrometric method of Ellman (Ellman *et al.*, *Biochem. Pharm.* **1961**, 7, 88-95).

The acetylthiocholine and butyrylthiocholine iodide, and 5,5-dithiobis (2-nitrobenzoic) acid
15 (DTNB) were purchased from Sigma Aldrich (Steinheim, Germany).

The BuChE freeze-dried from equine serum (**eqBuChE**, Sigma Aldrich) was dissolved in 0.1M phosphate buffer (pH 7.4) to obtain enzyme stock solutions with an enzymatic activity of 2.5 units/mL. The human erythrocyte AChE (**hAChE**, aqueous buffer solution, ≥500 units/mg of protein (BCA), Sigma Aldrich) was diluted in 20 mM HEPES buffer, pH 8, with 0.1% Triton X-100
20 to obtain enzymatic solution with an enzymatic activity of 0.25 unit/mL.

In the procedure, 100 µL of 0.3 mM DTNB dissolved in phosphate buffer, pH 7.4, were added in 96-well plates, followed by 50 µL solution of the test compound and 50 µL enzyme (final 0.05 U). After 5 minutes of pre-incubation at 25°C., the reaction was initiated by injecting 50 µL of 0.1 mM acetyl or butyryl thiocholine iodide solution. The acetyl or butyryl thiocholine hydrolysis
25 was followed by the formation of yellow 5-thio 2-nitrobenzoate anion as the product of the reaction of DTNB with the thiocholine released by the enzymatic hydrolysis of the acetyl or butyryl thiocholine, at a wavelength of 412 nm, using a microplate reader (Synergy 2, Biotek, Colmar, France). The compounds to be tested were dissolved to 5×10⁻³M in analytical grade DMSO. Donepezil or tacrine were used as reference standards. The absorption increase rate at 412 nm
30 was determined 4 minutes after the addition of the acetyl or butyryl thiocholine iodide solution. The tests were carried out with a blank containing all the compounds except the acetyl or butyryl thiocholine in order to take into account non-enzymatic reactions.

The percentage of inhibition due to the presence of the test compounds was calculated using the following expression:

35
$$((v_0 - v_i) / v_0) \times 100$$

wherein v_i is the rate calculated in the presence of the inhibitor, and v_0 is the enzymatic activity.

IC₅₀ values were graphically determined by plotting the percentage of inhibition as a function of the logarithm of six inhibitor concentrations in the test solution using the GraphPadPrism software (version 6.01, GraphPad Software, La Jolla, Calif., USA). All the experiments were carried out in n=3.

5 Molecular modelling by spherical harmonics

The 3D modelling method used in the invention is described in the publication: "Benchmarking of HPCC: A novel 3D molecular representation combining shape and pharmacophoric descriptors for efficient molecular similarity assessments », Karaboga *et al.* **2013** Journal of Molecular Graphics and Modelling 41; 20-30.

10 Two clusters (clusters 1 and 2) were defined by similarity from especially the monophosphate compounds known to be neurotoxic and reprotoxic such as tri(*ortho*-cresyl)phosphate ToCP, tri(*meta*-cresyl)phosphate, tri(*para*-cresyl)phosphate, trixylyl phosphate and saligenin cresyl phosphate.

A third cluster of possibly toxic compounds was identified (cluster 5) including in particular
15 a reprotoxic mutagenic carcinogenic RMC compound such as tri-(n-butylphosphate).

The study of the polyphosphorus compounds used according to the invention showed that they belong to a different cluster (cluster 3) related to non-toxic molecules according to the toxicological studies described to date.

Modelling by QSAR

20 The neurotoxicity and reprotoxicity degrees of various compounds used according to the invention and other monophosphate compounds were assessed by QSAR (Quantitative Structure-Activity Relationship) modelling.

Selection of the training and validation sets

The training set was defined with chemical structures compiled from several publicly
25 available sources: HSBD (Hazardous Substances Data Bank), EPA (U.S. Environmental Protection Agency), ECHA (European Chemicals Agency) and NTP (National Toxicology Program). 247 compounds were classified as neurotoxic compounds, 2214 compounds were classified as reprotoxic compounds and 1697 compounds were classified as neither neurotoxic nor reprotoxic and forming the non-toxic training set.

30 The validation set was built using compounds derived from data sets different from those used for the training set. The molecules already found in the training set have been removed. The validation set was comprised of 70 compounds classified as neurotoxic compounds, 506 compounds classified as reprotoxic and 256 compounds classified as neither neurotoxic nor reprotoxic and forming the non-toxic validation set.

35 *Performance of the QSAR model*

A Generalized Linear Model (GLM) method has been chosen to perform a Quantitative Structure/Activity Relationship (QSAR) approach. The GLM models were separately trained to discriminate the chemical structures (i) between neurotoxic and non-neurotoxic compounds and

(ii) between reprotoxic and non-reprotoxic compounds. This approach resulted in a GLM model with 210 significant descriptors within the training sets. During the training, the performance of the QSAR models was measured by ROC (Receiver Operator Characteristic) curves and gave rise to Area Under Curve (AUC) values of 0.90 and more for the prediction of the neurotoxicity and the reprotoxicity, respectively.

To validate the robustness of the QSAR models, they were then used to predict (i) the neurotoxicity categories of the compounds of the validation set (i.e., neurotoxic/non-neurotoxic categorization), (ii) the reprotoxicity categories of the compounds of the validation set (i.e., reprotoxic/non-reprotoxic categorization). During the validation, the performance of the QSAR models was measured by area under the curve (AUC) values and provided significant values of 0.70 and more for the prediction of the neurotoxicity and the reprotoxicity, respectively.

The GLM-based QSAR models were then used to study the polyphosphorus compounds according to the invention.

Synthesis of the polyphosphorus compounds according to the invention

In a four-necked flask fitted with a stir bar, a coolant, a separating funnel, a thermowell and a nitrogen bubbler, are introduced 1 molar equivalent of the reagent A (dialcohol, diamine or aminoalcohol) and 3.35 molar equivalents of triethylamine. The reaction medium is diluted with toluene, about 10 volumes relative to the reagent A. Depending on the nature of the reagent A, the reaction medium is heated between 25-110° C. and then, by using the separating funnel, 2.2 molar equivalents of phosphate chloride are introduced dropwise. At the end of the reaction, the triethylamine salt formed is removed by filtration and then washed with 5 volumes of ethyl acetate. Then the filtrate is washed two times with 0.1N HCl solution, two times with 0.1N KOH solution and then with water to neutral pH. The organic layer is then dried with MgSO₄, filtered, and then concentrated under reduced pressure. The resulting reaction crude is purified either by silica gel chromatography or by liquid-liquid extraction, or by precipitation. The thus obtained products are characterized by GC (Gas Chromatography) or GPC (Gel Permeation Chromatography) chromatographies, by ¹H and/or ³¹P-NMR analyses. The yields obtained range from 15 to 75%.

Results

The results of the tests performed are shown in Figs. 2 to 9. The penultimate column corresponds to a risk level score for the safety of these molecules for use in oils such as turbine oils and their alleged cabin toxicity. A score of 5 corresponds to a very high risk in terms of neurotoxicity and/or reprotoxicity, whereas scores of 0 or 1 correspond to a very low or no risk level. The risk level is determined by the sum of the factors corresponding to each of the independently evaluated risks based on the *in vitro* experimental results of inhibition (hAChE IC₅₀ and eqBuChE IC₅₀), semi-empirical prediction (neurotoxicity QSAR model and reprotoxicity QSAR model) and molecular modelling via spherical harmonics (clustering) and it can range from 0 to 5. A 0 value indicates a lack of risk, and a 5 value indicates a very high multiple risk. For each

risk, a factor 0 or 1 is assigned based on whether the value is above or below a threshold. The following thresholds are applied: 15 mg/L for the IC₅₀ for hAChE, 15 mg/L for the IC₅₀ for eqBuChE, 0.2% for the neurotoxicity, 3% for the reprotoxicity.

The compounds are numbered as follows:

5 **Comparative examples:**

Compound A: 2-ethylhexyl diphenylphosphate(CAS 1241-94-7)
(<https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.013.625>)

Compound B: Tri(*ortho*-cresyl)phosphate ToCP

Compound C: Tri(*meta*-cresyl)phosphate

10 **Compound D:** Tri(*para*-cresyl)phosphate

Compound P: Tricresyl phosphate (CAS 1330-78-5) corresponds to the commercial product Durad 125 (<https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.239.100>)

Compound E: Trixylyl phosphate (CAS 25155-23-1) (<https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/2204/7/11/1>)

15 **Compound F:** Tri(2,6-difluorophenyl)phosphate

Compound G: Tri(4-isopropylbenzoate)phosphate

Compound H: di(p-tertbutylphenyl)phenylphosphate

Compound I1: tri phenyl phosphate(CAS 204-112-2) (<https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.013.625>)

20 **Compound I2:** Tri(p-tert-butylphenyl)phosphate

Compound I3: Tert-butylphenyl diphenyl phosphate (CAS 700-990-0) corresponds to the commercial product Durad 150B, (<https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.235.046>)

Compound J: Saligenin cresyl phosphate

25 **Compound K:** Diphenyl phosphoroamidate

Compound L: Tris(2-ethylhexyl)phosphate (CAS 78-42-2) (<https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.001.015>)

Compound M: tri(n-butylphosphate) (CAS 126-73-8) <https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/13548>

30 **Compound N:** tris(chloroethyl)phosphate (CAS 115-96-8) <https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.003.744>

Compound Q: Tri(isobutyl)phosphate (CAS 126-71-6) (<https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.004.363>)

Compound R: Dibutyl [[bis[(2-ethylhexyl)oxy]phosphinothioyl]thio]succinate (CAS 68413-48-9)

35 (<https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.063.817>)

Compound S: 2,6-pyridinediol bis(diphenylphosphate)

Compound T: neopentyl glycol bis(diphenylphosphate)

Compound U: 1,6'-n-hexanediol bis(diphenylphosphate)

Compound V: 1,4'-n-butanediol bis(diphenylphosphate)

Compound W: tetrakis(2-chlorethyl)dichloroisopentyldiphosphate (CAS 38051-10-4)

<https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.048.856> (Compound V6 from the publication of Ike van der Veen)

5 **Compounds of the invention:**

Compound 1: hydroquinone bis(diphenylphosphate) HDP

Compound 2: 4,4'-dihydroxybiphenyl bis(diphenylphosphate) BDP and its oligomers

<https://echa.europa.eu/fr/substance-information/-/substanceinfo/100.225.031>

Compound 3: 4,4'-dihydroxydiphenyl thioether bis(diphenylphosphate)

10 **Compound 4:** 4,4'-dihydroxydiphenylether bis(diphenylphosphate)

Compound 5: 1,3,5-phloroglucinol tris(bis(diphenylphosphate))

Compound 6: 2-butyl-2-ethyl-1,3-propanediol bis(diphenylphosphate)

Compound 7: trimethylolpropane tris(diphenylphosphate)

Compound 8: tetrakis(2,6-dimethylphenyl)-m-phenylene bisphosphate

15 <https://echa.europa.eu/en/substance-information/-/substanceinfo/100.103.102>

Compound 9: tetrakis(2,6-dimethylphenyl)-p-phenylene bisphosphate

Compound 10: 1,12-n-dodecanediol bis(diphenylphosphate)

20 The compounds of the triaryl phosphate type (TCP family) belong entirely to cluster 1 having a risk level varying from 2 to 5 with an average of 3.6 with respect to the 8 molecules having complete characteristics.

Compounds 1 to 10 having the formula (I) according to the invention exhibit high IC₅₀ values for hAChE and eqBuChE, belong to a cluster of non-toxic molecules (cluster 3), have low neurotoxicity and low reprotoxicity, and thus a level of risk equal to 0.

25 Without intending to be bound by any theory, it seems that the structure of the compounds of formula (I) allow them to achieve a particular tridimensional structure different from that of the toxic compounds such as TCP, which gives them a non-toxic characteristic.

30 The compounds of the cluster 1 are, according to the spherical harmonic 3D-modelling approach, in the form of "three-blade propeller" based on two planes perpendicular at the molecule center or core while the compounds of the cluster 3 exhibit a rather expanded and planarized shape, similar to a butterfly form. The molecules derived from the modelling work by spherical harmonics are shown in Figure 1. These compounds are therefore non-neurotoxic and non-reprotoxic alternatives to the tricresyl phosphate and its triaryl phosphate analogs.

35 Comparatively, the compound I2 described in the patent application WO2010/149690 has a reduced inhibition on butyrylcholinesterase but is found to be active towards acetylcholinesterase. Modelling classifies the latter as part of the cluster 1, which confirms the experimental result on acetylcholinesterase.

Thus, these *in vitro* and modelling tests (3D of spherical harmonics or QSAR) show that the Applicant has selected, non-arbitrarily, from all the existing phosphorus-based compounds

generally exhibiting an anti-wear action in an oil, a restricted subset of compounds of general formula (I). This subset also has a different technical effect from other phosphorus-based compounds. In fact, this subset of polyphosphorus compounds of formula (I) is at least non-neurotoxic and is capable of and/or is configured to reduce and/or prevent the neurotoxicity of an oil, in particular of a turbine oil intended for aviation. Moreover, this subset is capable of and/or is configured for the aerotoxic syndrom prophylaxis, in particular in case of fume event. This subset, by virtue of its characteristics, makes it possible to form a turbine oil, for example for aviation, which is suitable for and/or configured in order to make it possible to increase the safety level in aviation and in other aeroderivative applications.

In addition, no indication in the prior art could allow a person skilled in the art to specifically select this subset of compounds of general formula (I) in order to reduce/prevent the neurotoxicity of a turbine oil or for the aerotoxic syndrome prophylaxis.

In fact, on the one hand, the other polyphosphorus compounds and in particular the other polyphosphorus compounds used as anti-wear agent in an oil and known in the prior art do not have this novel technical effect (i.e.: reducing and/or preventing the neurotoxicity of an oil or for the aerotoxic syndrome prophylaxis). On the contrary, the other anti-wear compounds and other organophosphorus compounds known and used in the field of aeronautical lubricants and oils are neurotoxic (such as compounds E, P, I1-3, L, R and M, the latter being used in aviation hydraulic fluids).

On the other hand, prior to the tests carried out by the Applicant, most of the other commercial and registered phosphorus compounds, in particular known as anti-wear agents, such as, for example, compounds A, P, I1, I3, Q and R, are recognized in particular by the official website of the European Chemical Agency (ECHA) as not presenting a serious hazard of acute or serious toxicity (CMR characteristic). ECHA is a competent authority to decide on the toxicity of registered chemicals for the European market. It publishes public and recognized scientific data. Compound I3 is used in particular in the field of lubricants to replace TCP or its analogs. However, the Applicant's tests via the IC_{50} in vitro tests and the 3D or QSAR modelling tests show, on the contrary, that these compounds are highly neurotoxic. For example, according to the ECHA website, compound I3 is not known to be toxic to human health. Now, the table of Fig. 5 shows that this compound I3 is a mixture of neurotoxic compounds belonging to cluster 1 including triphenyl phosphate and tri(p-tert-butylphenyl)phosphate. The same applies to compound A, which, according to the ECHA website, does not show signs of neurotoxicity, yet has a risk level of 4. A person skilled in the art would therefore not have been induced or encouraged to select the subset formed by the compounds of general formula (I) (in particular from known and public generic toxicity data) in order to reduce and/or prevent the neurotoxicity of an oil or for the aerotoxic syndrome prophylaxis.

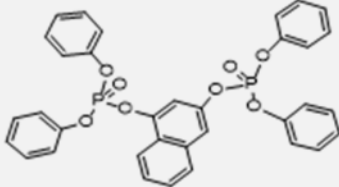
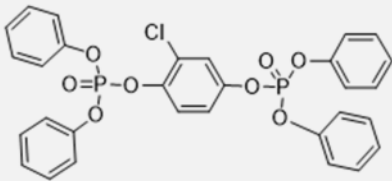
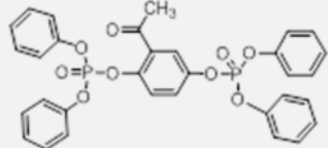
The IC_{50} inhibition values on the cholinesterases hAChE and eqBuChE were also tested for other comparative compounds and compounds according to the invention. This

complementary study confirms the very high safety level of the compounds of formula (I). Table 1 below shows the experimental results obtained.

[Table 1]

Name	Compounds	IC ₅₀ hACh E (mg/L)	IC ₅₀ eqBuCh E (mg/L)	Chemical structures
Examples according to the invention.				
11	phenylhydroquinone bis(diphenylphosphate)	23.1	16.8	
12	tert-butyl hydroquinone bis(diphenylphosphate)	15	65.5	
13	2,5-di-tert-butyl hydroquinone bis(diphenylphosphate)	18.6	76.3	
14	1,4-dihydroxynaphthalene bis(diphenylphosphate)	17.1	79.3	
15	2,7-dihydroxynaphthalene bis(diphenylphosphate)	18	56.3	
16	4,4'- dihydroxybenzophenone bis(diphenylphosphate)	27	111	

Name	Compounds	IC ₅₀ hAChE (mg/L)	IC ₅₀ eqBuChE (mg/L)	Chemical structures
17	bis(4-dihydroxyphenyl)sulfone bis(diphenylphosphate)	21.6	68.9	
18	4,4'-(hexafluoroisopropylidene) bis(diphenylphosphate)	27.2	113	
19	4,4'-(α-methylbenzylidène)bisphenol bis(diphenylphosphate)	34.7	110.9	
20	1,1-bis-(4-hydroxyphényl)cyclohexane bis(diphenylphosphate)	26	292.5	
21	9,9-bis(4-hydroxyphenyl)fluorene bis(diphenylphosphate)	24.1	86.2	
22	dimer diol (C34-36) bis(diphenylphosphate)	15.6	88.3	
23	1,1,1-Tris(4-hydroxyphényl)ethane tris(diphenylphosphate)	19.9	71.1	
Comparative examples				

Name	Compounds	IC ₅₀ hAChE (mg/L)	IC ₅₀ eqBuChE (mg/L)	Chemical structures
X	1,3-dihydroxynaphthalene bis(diphenylphosphate)	16.5	4.5	
Y	2-chlorohydroquinone bis(diphenylphosphate)	25	0.61	
Z	(2,5-dihydroxy)1-acetophenone bis(diphenylphosphate)	18.4	0.07	

From a new series of 16 compounds having at least 2 phosphate functions, a large majority (13/16, i.e., more than 80%) have low inhibition levels IC₅₀ >15 mg/L with respect to the two cholinesterases. Unexplainedly/surprisingly, compounds having groups or atoms qualified as

5 electron-withdrawing by inductive or mesomeric effect, such as chlorine, carbonyl or nitrogen atoms internal to the aromatic rings, exhibit less relevant safety levels. It would also seem that the spacing of the phosphate functions is important for the inhibition results, the functions positioned in the meta (or 1,3-) position on the aromatic ring seem to lead to a more unfavourable geometry than those positioned in the para (or 1,4) or more distant position (in the case of the

10 2,7-naphthalene derivative).

Example 2: Anti-wear performance of the polyphosphorus compounds used according to the invention

The anti-wear performance of the turbine oils used according to the invention was measured by using the 4-ball wear test in accordance with ASTM D4172 standard test method.

15 The results obtained are shown in Table 2 below.

TABLE 2

Anti-wear compound formulated as an aviation turbine oil	4-ball wear (in mm)
Without anti-wear additive	0.83
TCP	0.46

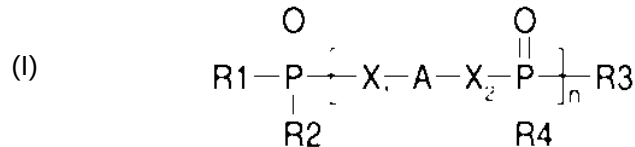
Anti-wear compound formulated as an aviation turbine oil	4-ball wear (in mm)
Compound 1	0.45
Compound 2	0.45 (n=1)
	0.42 (n=1 to 4, n average = 1,5)
Compound 3	0.57
Compound 4	0.50
Compound 5	0.47
Compound 6	0.45
Compound 7	0.48

The results confirm that the polyphosphorus compounds used according to the invention in oils have interesting anti-wear properties and potentially similar to those of the TCP, therefore that they are compatible with effective use in oils, especially oils for aircraft or aeroderivative
5 turbines.

Of course, a variety of other modifications may be made to the invention in the context of the appended claims.

CLAIMS

1. Use of at least one anti-wear additive in an oil, said at least one anti-wear additive
5 comprising at least one polyphosphorus compound of formula (I)



10 wherein

each of R1, R2, R3 and R4 is independently selected from: an alkyl, O-alkyl, aryl, or O-aryl group.

A is a divalent group selected from an alkylene group comprising 7 to 36 carbon atoms or a branched alkylene group comprising 6 to 36 carbon atoms, a monocyclic polycyclic or
15 polyaromatic arylene group, or aralkylene group,

each of X₁, and X₂ is independently a single bond, an oxygen atom or a nitrogen atom, and

n is an integer ranging between 1 and 5,

to reduce and/or prevent the neurotoxicity of said oil, and preferably a turbine oil.

- 20 2. Use according to claim 1, wherein said oil and/or said at least anti-wear additive does not comprise tricresyl phosphate or does not comprise any additive(s) other than the polyphosphorus compound(s) of formula (I).

3. Use according to any one of the preceding claims, wherein

when A is a monocyclic arylene group, X₁ and X₂ are diametrically opposed, in particular
25 at the 1,4-position when the monocyclic arylene group comprises 6 carbon atoms;

preferably when A is a phenylene, X₁ and X₂ are not in the ortho or meta position unless at least one and preferably all of the groups of R1, R2, R3 and R4 are O-phenyl groups substituted by two methyl groups, in particular in the 2,6-position or unless the phenylene is substituted by an O-diphenylphosphate.

- 30 4. Use according to any one of the preceding claims, wherein when A is a polycyclic arylene group or a polyaromatic arylene group, X₁ and X₂ are diametrically opposed, preferably when A is a naphthalene, X₁ and X₂ are diametrically opposed, typically when A is a naphthalene, X₁ and X₂ are not in the ortho or meta position.

5. Use according to any one of the preceding claims, wherein the oil is selected from the
35 group consisting of oils for aircraft or aeroderivative turbines, helicopter transmission oils and weapon fluids.

6. Use according to any one of the preceding claims, wherein R1, R2, R3 and R4 are O-phenyl group or O-dimethylphenyl groups, such as O-2,6-dimethylphenyl.

7. Use according to any one of the preceding claims 1 to 6, wherein A is selected from the group consisting of a 1,4-phenyl, 4,4'-biphenyl, 4,4'-diphenylthioether, 4,4'-diphenylether, 1,3-(5 O-[(diphenyl)phosphate])phenyl, 1,3-(2-ethyl-2-butyl)propyl, 1,3-(2-ethyl-2-[methyl-O-diphenyl phosphate])propyl, 4,4'-[diphenyl(dimethyl)-methylidene], 2,2'-benzophenone, 2,7-naphthalene, 1,2-ethyl, 4,4'-[diphenylphenylethylidene], 4,4'-diphenylsulfone, 4,4'-diphenyl-hexafluoropropane, 1,4-[(2-phenyl)phenyl], 1,4-[(2,5-ditertbutyl)phenyl], 1,4-[(2-chloro)phenyl], 4,4'-benzophenone, 1-hydroxy-3-thiophenyl, 1,6-hexyl, 1,4-naphthalene, 2,6-anthracene, 9,10-anthracene, 1,10-decyl, 1,12-n-dodecyl, 2,5-dimethyl-2,5-hexyl, 1,12-dodecyl and 1,3-naphthalene group.

8. Use according to any one of the preceding claims 1 to 6, wherein A is an optionally substituted alkylene group, a substituted monocyclic arylene group or a polycyclic arylene group wherein at least two rings are linked by at least a covalent bond between two distinct atoms each belonging to one of the rings, the covalent bond between the two rings being interrupted by at least one heteroatom or heteroatomic group.

9. Use according to any one of the preceding claims 1 to 7 and 8 (partially), wherein the polyphosphorus compound is selected from the group consisting of:

- hydroquinone bis(diphenylphosphate) HDP,
- 4,4'-dihydroxybiphenyl bis(diphenylphosphate) and oligomers thereof,
- 4,4'-dihydroxydiphenyl thioether bis(diphenylphosphate),
- 4,4'-dihydroxydiphenyl ether bis(diphenylphosphate),
- 1,3,5-phloroglucinol tris((diphenylphosphate)),
- 2-butyl 2-ethyl 1,3-propanediol bis(diphenylphosphate),
- trimethylol propane tris(diphenylphosphate),
- 4,4'-dihydroxydiphenyl phenylethylidene bis(diphenylphosphate),
- 4,4'-dihydroxydiphenyl sulfone bis(diphenylphosphate),
- 4,4'-dihydroxybenzophenone bis(diphenylphosphate),
- 2,2'-dihydroxybenzophenone bis(diphenylphosphate),
- 4,4'-dihydroxydiphenyl hexafluoropropane bis(diphenylphosphate),
- 1,4-dihydroxynaphthalene bis(diphenylphosphate),
- 1,3-dihydroxynaphthalene bis(diphenylphosphate),
- 2,7-dihydroxynaphthalene bis(diphenylphosphate),
- ethanolamine diphenylphosphate diphenylphosphoroamidate,
- 4,4'-diaminodiphenyl ether bis(diphenylphosphoroamidate),
- 2,6-dihydroxyanthracene bis(diphenylphosphate),
- 9,10-dihydroxyanthracene bis(diphenylphosphate),
- 1,4-dihydroxy[(2-phenyl)phenyl] bis(diphenylphosphate),
- 1,4-dihydroxy[(2,5-ditertbutyl)phenyl] bis(diphenylphosphate),
- 1,4-dihydroxy[(2-chloro)phenyl] bis(diphenylphosphate),
- 1,3-dihydroxythiophene bis(diphenylphosphate),

- 1,6-hexanediol bis(bis(diphenylphosphate),
- 1,10-decanediol bis(diphenylphosphate),
- 2,5-dimethyl 2,5-hexanediol bis(diphenylphosphate),
- 1,12-n-dodecanediol bis(diphenylphosphate),
- 5 - tetrakis(2,6-dimethylphenyl)-m-phenylene bisphosphate,
- tetrakis(2,6-dimethylphenyl)-p-phenylene bisphosphate,
- phenylhydroquinone bis(diphenylphosphate) DPP,
- tert-butyl hydroquinone bis(diphenylphosphate),
- 2,5-di-tert-butyl hydroquinone bis(diphenylphosphate),
- 10 - 1,4-dihydroxynaphthalene bis(diphenylphosphate),
- 2,7-dihydroxynaphthalene bis(diphenylphosphate),
- 4,4'-dihydroxybenzophenone bis(diphenylphosphate),
- bis(4-hydroxyphenyl)sulfone bis(diphenylphosphate),
- 4,4'-(hexafluoroisopropylidene) bis(diphenylphosphate),
- 15 - 4,4'-(α -méthylbenzylidene)bisphenol bis(diphenylphosphate),
- 1,1-bis-(4-hydroxyphényl)cyclohexane) bis(diphenylphosphate),
- 9,9-bis(4-hydroxyphenyl)fluorene bis(diphenylphosphate),
- 1,1,1-Tris(4-hydroxyphényl)ethane tris(diphenylphosphate), and
- any mixtures thereof.
- 20 10. Use according to any one of the preceding claims 1 to 9, wherein the oil further comprises an ester base and at least one amine antioxidant.
- 11. Use according to any one of the preceding claims 1 to 10, wherein the at least polyphosphorus compound is present in the oil in an amount of from 0.1 to 10 wt. % by weight preferably 0.5 to 5 wt. % by weight, based on the total weight of the oil.
- 25 12. Use according to any one of the preceding claims, wherein the 50% inhibitory concentration of said at least one compound of formula (I) on the biological activity of an acetylcholinesterase (AChE) enzyme, called IC_{50} hAChE is greater than or equal to 15 mg/L, and on the activity on a butyrylcholinesterase enzyme, called IC_{50} eqBuChE is greater than or equal to 50 mg/L, preferably equal to or greater than 55 mg/L, in particular equal to or greater than
- 30 60 mg/L and typically equal to or greater than 70 mg/L.
- 13. Use according to any one of the preceding claims, wherein the compound(s) of formula (I) have a percentage value (%) by quantitative structure activity relationship (QSAR) modelling
 - lower than or equal to 0.70%, preferably lower than or equal to 0.50% and typically lower than or equal to 0.15% for the measurement of neurotoxicity, named neurotoxic QSAR, and
 - 35 - lower than or equal to 1.5%, preferably lower than or equal to 1.15% and typically lower than or equal to 0.55% for the measurement of reprotoxicity, named reprotoxic QSAR.