Alkyl-phosphates as New Substances for Disinfection and Decontamination “Bio-Chem”

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A series of substances recommended as biological or chemical decontamination agents and new synthesized substances (e.g. Alkyl-phosphates) were tested. Among these we selected the microbiocide Alkyl-phosphate 2005, a complex mixture of aminosilts: mono- and bi- Alkyl-phosphates, which have in their molecular structures a variable percent of free acid functions were selected. It is a universal micro biocide with bactericide, fungicide, algicide effects, with multiple uses, reduced toxicity and a minimum ecological impact. The products are liquids or solids, depending on their ester groups structures (R1, R2, R3 = ALKYL or and ARIL) and amino components. The solubility of these products in water or in different common solvents is also a condition of their molecular structures. The substances are characterized by a high chemical stability to storing, solar radiation, and atmospheric oxygen etc. Also, the products are chemically stable in conditioning compositions and in direct contact to protected materials. The product is insoluble in water but is soluble in different organic solvents. After washing the objects or wetting the surfaces by spraying, the product makes a residual layer with disinfectant properties for a long period of time. The mixtures of compounds (I) and (II) are characterized by a strong microbiological activity developed, even at low levels of concentration (0.07% - 0.2 %), on a wide spectrum with bactericide, fungicide, algicide effects etc., having at the same time a repellent and insecticide action. Laboratory tests proved the effectiveness of these products for positive-gram bacteria and also for negative-gram bacteria. These substances are characterized through a low toxicity for mammals and human subjects, feature that doesn't impose specific measures in labor protection during preparation, conditioning, handling or use. Even more, when contacted with STL or toxins, these substances usually decompose into non-toxic compounds. By proper conditioning, products with multiple decontaminant effects can be obtained. The Alkyl-phosphate 2005 product can be used with very good results also as a decontaminant against bio-terrorism attacks.

Keywords: alkyl-phosphates, disinfection, decontamination, bio-chem attack

The prevention from the biological war is made by implementing the Convention of prohibition for biological weapons (BTWC, Geneva, 1972) to which over 150 countries adhered and by the international control on biological weapons and biological agents. As a matter of fact, the military use of the biological weapons is nowadays considered as being inefficient from the tactic and operational point of view, it is difficult from the tactic point of view and risky from the medical point of view, as an epidemic once started can get out of control.

The biological crisis is a major epidemiologic emergency, with infectious etiology, that, by the severity of the illnesses of men/animals/plants or by the great number of illnesses leads to the perturbation of the social and economic life of a community. The biological weapon is a system of unconventional weapons, for mass destruction, meaning that their munitions transport biological agents and contaminate the enemy with the aim of sickening him. Biological agents can be considered micro-organisms and/or microbial toxins, animal or vegetal, used as precise munitions for biological weapons, or used by terrorists in the attacks combined with biological and chemical agents, also called “bio-chem”.

Everybody talks about terrorists and terrorism, especially after September 11th 2001, when the Western civilized world got the toughest shock in the history of the terrorist attacks. Anti-terrorist coalitions were created, the surveillance measures of the populations have been intensified till the limit of ignoring the democratic normative, the funds granted by the governments to the structures that have attributions in the prevention and fighting against terrorism were have been increased. The NATO specialists appreciate that the destructive potential of the international terrorism is huge. Experts of the world are especially preoccupied and concerned by the diversity of the arsenal that the terrorist groups might own, the concerning of the whole civilized world gets dramatic accents when it comes to the access of the international terrorism to the mass destroying weapons: nuclear, biological and chemical (NBC).

The pathogen biological agents are very dangerous. They are quite easy to get and have great effectiveness, being able to produce the contamination of thousands of individuals in a short time, many of the cases being lethal; as for the biological weapons, there are great risks also for the ones that manipulate and use them. In a recent report of the Pentagon it was noted that most of the terrorist groups do not have the technical and financial resources necessary for the acquisition of nuclear armament, but they

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can get the substances to permit the fabrication of biological and chemical agents for war, of radio-active means etc. The conclusion is that there is an obligation of all the civilized countries to prepare themselves to restrain a terrorist attack with NBC weapons and at the same time to be able to annihilate the consequences of this kind of actions. Making the “bio-chem” decontaminants of high effectiveness, the necessary machines for their fabrication and used, the training of the specialized personnel etc., are considered by the experts as measures that are to be urgent.

Taking into account the necessity of having polyvalent decontaminants NBC, as well as the existence of the phenomenon of microbial resistance induced towards the anti-microbial medication in use, it is necessary to study new groups of potential anti-microbial substances: project, synthesis, pharmacological testing and authorization.

Material and method

Laboratory experimental research regarding the obtaining of decontaminants “bio-chem” out of the ammonium salts of the equimolecular mixtures of o-mono and o,o bi-alkyl [aryl] ester acid phosphates.

There are various ways to obtain the o-mono and o,o bi-alkyl [aryl] ester acid phosphates. After having studied them from the technical and economic point of view, the conclusion is that this category of organic phosphoric compounds can be obtained in technical and economic conditions that have a certain advantage because of the reaction between the phosphoric pentaoxide and alcohols, according to the following main chemical reaction (fig. 1).

During the next phase we shall obtain the salts of the alkaline or ammonium metals of the acid ester phosphates. The neutralizing is made in a percentage of 65 – 75%. The contained impurities are also corresponding to the amine derivates, are usually effective micro biocides.

The amine salts from the equimolecular composition of o-mono and o,o bi-alkyl [aryl] ester acid phosphates synthesized have an advanced purity of more than 95%. The contained impurities are also corresponding ammonium derivates of the phosphoric acid, present as an impurity in the mixture of alkyl [aryl] ester acid phosphates introduced in the reaction (fig. 3).

In order to manage the experimental researches we made an installation in thermo resistant glass, specific for the organic synthesis, having a glass balloon with round base, with four necks on which we assembled: an ascendant refrigerant with bubbles, a hole for solid substances, a thermometer and a mechanic blender with blades. After making a series of exploratory experiments, the work technique was established. The equimolecular mixture of o-mono and o,o bi-alkyl [aryl] ester acid phosphates remains in the still. The product from the still will be deposited in a glass or polyethylene container of corresponding capacity. The mixture of o-mono and o,o bi-alkyl [aryl] ester acid phosphates obtained from the reaction contains, in equimolecular quantities, the two derivates (mono- and bi-).

Through physical and chemical analysis it was established that from the reaction result the two acid ester phosphates (more than 95%) with superior capacity. The reaction product is unpurified with little quantities of phosphoric acid formed from the contact of P₂O₅ with the humidity in the atmosphere (2.5 – 3.5%). The quantity of phosphoric acid contained is determined in the conditions of realizing the weighing of P₂O₅, and its adding in the reaction mixture of the pentaoxide suspended in anhydride benzene. The presence of the phosphoric acid in the equimolecular mixture of mono- and bi- ester acid phosphates does not represent, in fact, an impurity that cannot be used, as the reaction to be done will transform the acid in to the correspondent ammonium salts. The said salts, depending on the structure of the used amine derivates, are usually effective micro biocides.

Ammonium bi- or tri- phosphates are formed, considering the quantity of amine introduced in the reaction. Considering the structure of the amine derivate, the amine salts of the phosphoric acid present as an impurity in the mixture are substances with micro-biocide effect.

\[
\begin{align*}
\text{R} &= \text{a) CH}_2\text{CH}_3;\quad \text{b) CH}_3\text{CH}_2\text{CH}_3;\quad \text{c) CH(CH}_3)_2;\quad \text{d) CH}_2\text{CH}_2\text{CH}_3;}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{C}(\text{CH}_3)_2\text{CH}^-\text{CH}_2^- \\
\text{CH}_2\text{CH}_3
\end{align*}
\]

Fig. 3. The resulted impurities are as well ammonium derivates of the phosphoric acid.

Ammonium bi- or tri-phosphates are formed, considering the quantity of amine introduced in the reaction. Considering the structure of the amine derivate, the amine salts of the phosphoric acid present as an impurity in the reaction mixture are substances with micro-biocide effect.

R = mono and o,o bi-alkyl [aryl] ester acid phosphates synthesized during the experimental researches

During the experimental researches we synthesized a series of mixtures made of equimolecular conglomerations of o-mono and o,o bi-alkyl [aryl] ester phosphates where the group alkyl contained C₂₄ (fig. 4).

Fig. 4. From the reaction of synthesis the results are equimolecular mixtures of o-mono and o,o bi-alkyl aril ester phosphate acid.
We also synthesized a series of acid ester phosphates using as an alcoholic component the polyethylenglycols, meaning the polyethylenglycol-200 (PEG 200). From the reaction a complex mixture of acid ester phosphates resulted (fig. 5).

The molecular structures resulted from the reaction of P_2O_5 with polyethylenglycol-200 (PEG 200) were established by researching the chemical reactions mechanisms of the phosphor pentaoxide with alcohols and were confirmed by chemical and physical analysis.

The ammonium salts of the o-mono- and o,o-bi alkyl [aryl] ester acid phosphates synthesized during the experimental researches

During the experimental researches we synthesized and studied a series ammonium salts of the equimolecular conglomerations of o-mono and o,o bi-alkyl [aryl] ester phosphates. Out of these we chose seven, transmitted then to test the “bio-chem” capacities of decontamination (fig. 6-10).

![Chemical structures](image)

Fig. 6. The ammonium salts of the equimolecular mixture formed by the o-ethyl and o,o-bi-ethyl ester - acid phosphates with mono-ethanol-amine; the product has the code number “DECON-01”

![Chemical structures](image)

Fig. 7. The ammonium salts of the equimolecular mixture formed by the o-ethyl and o,o-bi-ethyl ester - acid phosphates with third-ethanol-amine; the product has the code number: “DECON-02”

![Chemical structures](image)

Fig. 8. The ammonium salts of the equimolecular mixture formed by the o-ethyl and o,o-bi-ethyl ester - acid phosphates with carbamide (uree); the product has the code number: “DECON-03”

![Chemical structures](image)

Fig. 9. The ammonium salts of the mixture formed by the mono-and bi-acids of the ester phosphates obtained from the reaction of the polyeethylene-glycol -200 (PEG-200) with P_2O_5, with mono-ethanol-amine; the product has the code number: “DECON-04”

The ammonium compounds where we used triethanolamine as an amine component were realized with the aim that these products should be tested to be used as “bio-chem” decontaminants for the personnel.

The screening microbiological and toxicological testing of the realized compositions

Selecting the biological agents for testing

Pathogen germs representative for the main groups of micro-organisms have been selected: aerobe and anaerobe bacteria: coccus, bacilli and vibrios, gram-positive and gram-negative; viruses, fungus as well as spores, and toxins [21].

Description of the apparatus

- the checking of the biological agents for testing with an apparatus Microflex LT 20 MALDI TOF made by Bruker Daltonics from Germany, able to identify the biological agents, after the laboratory of microbiology made the cultivation and isolation of some typical colonies of bacteria selected as representative for testing the antimicrobial effect was made. The system is an equipment to detect and identify the biological agents, based on a mass spectrometer MALDI-TOF (Matrix Assisted Laser Desorption Ionization Time of Flight) equipped with data base to identify the biological agents.
The techniques of testing

- the technique of the binary dilutions in liquid medium and the diffusometric antibiogram technique with buckets for positioning the substances, according to the techniques of the laboratory of microbiology were used in parallel.

Results and discussions

Toxicological testing

Before starting the biological testing, we tested the acute toxicity of the used substances and of the conditioned compositions of decontamination, on two species of mammals (mice and rabbits). So, by intra-peritoneal injection of 0.5 mL work solution at mice of 18-22 g we noticed that the formulae do not have a lethal effect. The conjunctive irritation test, by ocular instillation of one drop of work solution at a rabbit shows a moderate sudden irritation followed by a reversible loss of sight. The skin irritation test, with applying a tampon with work solution on the skin of the rabbit, previously shaved, shows that the formulae do not have a lethal effect. The tolerance test, with applying a tampon with work solution at a rabbit shows a moderate sudden irritation followed by a reversible loss of sight. The symptoms were noticed that as the microbes are killed, they can be washed in disinfectant solution, and after that, as the microbes are killed, they can be washed in water, without the risk of the secondary contamination.

The microbiologic testing in vitro

The antibacterial effect

The effect on aerobe bacteria. It was tested on gram-positive coccus (Staphylococcus aureus producer of ESB), on gram-positive bacilli (Bacillus anthracis and its spores), on gram-negative bacteria (Escherichia coli pathogen). The cultivations have been made on specific liquid and solid mediums, incubated at 37°C for 24-48h. The bacteriostatic effect (CMI), as well as the bactericide effect (CMB) maintain until high dilutions, of 4 up to 16 times (compared to 32 as it was tested), considering the species and the prepared product. Generally, the most efficient is the code product P 059, followed by DECON 03. The work solutions kill the anthrax spores in about 15 min (compared to 30 min as it was followed the effect). The older solutions (up to 24 h) continue to have an effect close to that of the fresh ones. Examples are the data in table 1.

The effect on anaerobe bacteria

It was tested on spore (Clostridium botulinum and Clostridium perfringens), with results equally good for all the 8 prepared products. The cultivation was made in specific liquid medium (tomato sauce VF with meat, under paraffin oil) anaerobe incubated 48 and 72 h.

The antiviral effect

It was tested on tree viruses (the virus of fever West Nile and the virus of tick encephalitis) and on the virus of viral hepatitis B (HBV) which is considered to be the most resistant pathogen virus. The testing has been made both by underlining the presence of the virus with the ELISA technique and by infected cell cultures, anaerobe cultivated. Equally good results were obtained for all the 8 prepared products.

The antifungal effect

It was tested on a pathogen and mycotoxigen fungus (Aspergillus parasiticus, in vegetative and spore form). The spore effect goes up to dilutions of 1/10. Generally, the most efficient is P 059, followed by Decon 03.

The anti-toxin effect

It was tested by chromatography in slim layer (TLC) with computerized densitometry on apha-toxins, and toxicologically on the staphylococcus enter-toxin on the botulinic toxin. All the solutions had a decontaminant effect, but at high concentrations of apha-toxin the effect was only partial.

Generally, the obtained results were according to the expectations: the prepared products tested have antibacterial, antiviral, antifungal and spore effect. The prepared products can be considered as technical disinfectants from the group of the organ-phosphoric; the prepared products also present antitoxic effect in vitro.

The conditioning mode with acid pH makes the prepared products corrosive, so they must be handled accordingly in order to avoid accidents and corrosion. If possible, we advise neutralizing up to the inferior limit. The formula P 059, which is more complex, has the most powerful anti-microbial and anti-toxin effect; that is why we consider it as the optimal formula of polyvalent decontaminant (Alkyl-phosphate 2005). Conclusively, the prepared product P 059 realizes the biological decontamination (bacteria, viruses, micelles and their toxins), including the biological agents, in max. 15 min. At the biological decontamination we notice as well the spore effect (spores of Bacillus anthracis) in percentage of 100%, so “cold sterilization” effect. For common using it must be severely forbidden the pre-washing step, because it will spread the vivid pathogen germs so it will become a secondary source of contamination; in case of biological contamination the activity must be started directly with the washing in disinfectant solution, and after that, as the microbes are killed, they can be washed in water, without the risk of the secondary contamination.
The testing must be continued for the profound study of the aspects connected to the utilization of the product in practice, on various surfaces and in specialized polygon.

The organ-phosphor compounds with complex molecular structures, potentially decontaminated “bio-chem” with large spectrums of action, reduced toxicity and minimal ecologic impact can be considered as a new group of antimicrobial substances, and we managed to establish technologies in order to produce them in the country, methods for testing the effect and techniques of utilization as decontaminants.

The organ-phosphor compounds with certain molecular structures proved to be micro-biocide, with an activity developed on a large spectrum and at reduced concentrations. During the last years, in the world, the scientific researchers conceived, researched and realized molecular structures with microbiocide, insecticide and insect-repellent activity, that can be used in various field and for various aims. Some of these compounds proved also to have properties of chemical decontaminants. The said products are alkyl [aryl] esters of the phosphonic (A/ and thiol-tone-phosphonic A-I), phosphoric (B) and thion [thiol] phosphoric (B-I) and bi-thiophosphoric (B-2) where: R1 = R 2.............R8 or R 1= R2 ≠ R 3 . .........R6 = alkyl [aryl] groups with normal structures or substituted with halogens, alcoxy (-OR) groups, thio (-SR), amine (-NR2) etc.

We meet microbiocide properties with large spectrums also at certain salts of phosphonium: where: R1 = R 3 or R1= R 3 ≠ R 4 etc, are alkyl groups that contain various substitutes; R = H, -OH, alkyl groups as C1-C4, containing halogens or other chemical functions etc.; X= ions of inorganic carboxylic acids.

Alkyl [aryl] phosphates, potential decontaminant “bio-chem” agents

From the research of the data in the special literature it results that the alkyl [aryl] phosphates with certain molecular structures can be considered as effective potential “bio-chem” decontaminants. The Japanese researchers synthesized 26 alkyl [aryl] thyo-phosphates having molecular structure, where: R = R1 or R ≠ R 2 ; R 2 = groups of alkyl, cycle-alkyl, aryl, etc. that proved to be pesticides with polyanivalent action, at very low concentrations (100 ppm). McIntosh HR researched and synthesized a series of salts of the mono- and bi-alkyl [aryl] esters of the phosphonic acid that proved to be microbiocides with a large spectrum of action, where: R 2 = R 3 or R 2 ≠ R 3 = alkyl groups, areas, alkyl [aryl] etc.; X= Na+, K+, NH+ R4 R5, or R 2 = R 3 where R 2 ≠ R 3 ≠ R 4 example R 2 = R 3 = -CH2-CH2-OH; R 4 =C12H 25 etc. The researches made by Mc Intosh are based on a large documentation; more than 70 patents SUA, 5 German, 4 British etc. were consulted.

The most powerful biocidal activity of the alkyl [aryl] ester acid - phosphates with the molecular structures presented before was noticed in case of their salts with aliphatic amines, hetero-cycles with basic character azotes, of the alkaline metals etc.

The maximal biocidal activity was registered in case of the equimolecular mixtures of o-alkyl [aryl] and o, o-bi-alkyl [aryl] ester acid phosphates, where there are neutralized only 65-75% of the acid functions (-OH).

The equimolecular compositions of the o-mono- and o, o-bi-alkyl [aryl] ester acid phosphates can be obtained at the industrial level by partial esterification of the phosphor oxy-tri-chloride, in the presence of substances that consume HCl (resulted from the reaction). Third amines are usually used. The obtained ester phosphate-chlorides are put under a hydrolyze process. So we get the corresponding ester acids. Continuously we partially neutralize the acid functions [-OH] with amines, sodium hydroxides, potassium etc. where: R 11 R 2 R 3 = alkyl, aryl, alkyl-aryl groups etc. The neutralization of the acid functions must be made in a percentage of 65-67%: it is compulsory to let free, neutralized acid functions.

The equimolecular mixtures of o-mono- and o, o-bi-alkyl [aryl] can be synthesized with the reaction P 2O 5 with the corresponding alcohols; continuously, the mixture of alkyl ester acid phosphates is partially neutralized with alkaline hydroxides, aliphatic amines hetero-cycles with azote atoms with basic character.

In the selection of the molecular structures of the ester-alkyl [aryl] phosphates as a base for conceiving and realizing compounds with potential decontaminant “bio-chem” properties we must also take into account another important characteristic of this class of organ-phosphoric, meaning the anionic surfactant property. We also see as having an important surfactant activity the esters of the phosphoric acid, with molecular structures mono-, bi-or third-.

The alkyl phosphates find applications as emulsifiers, anti-corrosive agents, reason for which they are added at the fluids that come into contact with metals etc.

The surfactant properties in case of the “bio-chem” decontaminants will facilitate a better contact with the chemical agent that must be destroyed and allow the penetration of the disinfector in the microbiological structures. At the same time, the surfactant properties will permit the penetration of the decontaminant in the aspersities of the treated objects, an optimal contact with the areas to be decontaminated.

We consider that through the anti-corrosive properties of the alkyl phosphates will accomplish one of the important conditions imposed to the chemical decontaminants. So, the decontamination DS-2 was abandoned by the field specialists of US Army, precisely because it had an anti-corrosive action on metals and their alloys, which showed a great disadvantage in case it was used for the decontamination of the weapons and of the fighting technique.

Taking into account the considerations regarding the biological, physical and chemical properties of certain molecular structures of the alkyl-phosphates, namely of the o-mono- (2) o, o-bi-alkyl ester acid phosphates, respectively of their salts with alkaline or amine metals, it is appreciated that by conceiving of certain molecular structures from this chemical class we can realize “bio-chem” decontaminants that can fulfill at maximal parameters the demands imposed for a superior decontaminant polyanivalent NBC capacity, reduced toxicity towards the human subjects, minimal ecologic impact, the possibility of fabrication in acceptable technical and economical conditions etc.

We consider that in the present geo-political and military context there must be a development of the “bio-chem” decontamination means, in order to answer immediately at an eventual NBC aggression, and the phenomenon of microbial resistance (natural, induces by pressure selection or genetically manipulated) towards the antimicrobial substances requests to find new classes of potentially biocide substances, in order to ensure a reserve portfolio of decontaminants. Based of our testing and the previous experience we can certify that the organ-phosphoric with reduced toxicity and large anti-microbial spectrum confirm our expectations. The technology of synthesis, at the laboratory level, was arranged, for various series of organ-
phosphoric potentially biocide substances, and methods and techniques of toxicological testing for these substances were adapted. The moderate toxicity of the tested substances permits their testing and utilization without risks and with special measures of protection for the operators and for the environment. Methods and techniques of microbiological testing of these substances were adapted, the anti-microbial effect (bactericide, virucide, fungicide and partially sporicide) permits that the tested substances should be proposed as technical disinfectants or biologically decontaminants, the noticed anti-toxemic effect noticed allows to consider an eventual chemically decontaminant effect. Methods and techniques of conditioning and using these substances as disinfectants, at the laboratory level, were adapted, and the new products, synthesized and tested by us, are to be patented and proposed for certification as disinfestants, according to the valid legislation. After ending the physical, chemical, microbiological and toxicological tests, the product will be registered for certification at the Ministry of Health, in order to be made and commercialized as a technical disinfectant.

Conclusions
The chemical synthesis of the new substances from the group of the alkyl phosphates, potentially usable as disinfectants or decontaminants, can be managed to a purity of more than 95%.

The antimicrobial effect presents a large spectrum, the substances are active on aerobe and anaerobe bacteria, viruses, fungi and partially on spores, so we may consider that it might be a biological decontaminant;

The substances present anti-toxin effect, so we may consider that it might be a chemical decontaminant.

The acute toxicity of the tested substances is within the limits of the "toxically moderated substances".

The aromatic phosphates tested and synthesized and tested by us can be considered as substances potentially usable for disinfection and/or decontamination "bio-chem".

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