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Biologically Active Compounds of Silicon

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The literature data and the studies by the authors of the review on biologically active organosilicon compounds are reviewed. The role of silicon in living organisms, the toxicity and biological activity of its organic derivatives, and the therapeutic applications of its compounds are discussed.
The bibliography includes 358 references.

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1. INTRODUCTION

The unusually wide practical applications of inorganic and organic compounds of silicon resulting in daily and frequently direct contact with the human organism, the increasing use of organosilicon polymers in medicine, cosmetics, and the food industry, and also the continued contact of all living terrestial organisms with natural silicon compounds led to the widely held view that this element is biologically inert. Silicon does not belong either to macro- or oligo-biogenic elements [1] and it is usually believed that it does not play an appreciable role in the vital processes of higher animals and man. However, in reality this is not the case.

Silicon compounds play a significant role in vital processes and many of them (particularly organic derivatives) have specific effects on living organisms.

The present paper, which is based on the plenary report by one of the authors (L. G. Voronkov) at the Second International Symposium on the Chemistry of Organic Silicon Compounds in Bordeaux (July, 1968), is a brief review of studies devoted to the elucidation of the role of silicon in living organisms and in particular the biological activity of organosilicon compounds. Its aim is to draw the attention of specialists in the field of organosilicon chemistry, biochemists, biologists, pharmacologists, and physicians to a new and extremely interesting and important branch of the chemistry of silicon.

2. THE ROLE OF SILICON IN LIVING ORGANISMS

The scientific data accumulated so far leave no room for doubt that silicon is one of the principal elements and not only in non-living nature. About 10 000 million tons of silicon are involved in the life cycle of living matter on our planet [2]! This element is included (albeit in slight amounts) in the composition of all plant and animal organisms and their existence without it is impossible [2-23].

Silicon compounds play a particularly important role for many living entities at a lower stage of evolutionary development (silicate bacteria, the simplest algae, spore plants, etc.) in whose organisms it is present in very large amounts [23-54]. Silicon is also important for many higher plants, which have come to be called "siliceous" because of their high silicon content. Silicon compounds play extremely important functions also in the organisms of higher animals and man, despite the fact that in the majority of their organs the content of this element is relatively small. In the tissues of human and animal organisms silicon compounds are present in three principal forms [14,55-76].

1. Water-soluble inorganic compounds capable of passing through cell walls which can be readily eliminated from the organism. These include orthosilic acid and ortho- and oligo-silicate ions.

2. Organosilicon compounds and complexes soluble in organic solvents and containing Si–O–C groups. These include ortho- and oligo-silicate ethers derived from carbohydrates, proteins, cholesterol and other steroids, choline, lipids, and phospholipids. Compounds containing Si–N–C bonds may also be present. Organosilicon compounds containing Si–C bonds have not been detected in higher animal and human organisms but they have been found in the bacteria *Proteus Mirabilis* [29,31].

3. Insoluble silico-polymers. These include polysilicic acid, amorphous silica, and insoluble silicates and quartz. In the organism the surface of these polymers is always covered by a chemisorbed layer of organic compounds containing hydroxy- or amino-groups.

It has now been firmly established that silicon compounds are essential for epithelial and connective tissues to which they impart, in particular, strength, elasticity, and impermeability. It is also suggested that silicon compounds play an important role in all metabolic processes in living matter, in particular in the metabolism of lipids. They probably participate in the dynamics of living plasma, their role consisting in altering the surface potential of cells. It is suggested that silicon compounds also participate in oxidation processes and enter into the composition of diastases as a coenzyme.

Thus the presence of silicon compounds in organisms is not only normal but necessary. Furthermore, living tissues exhibit a definite affinity for silic acid ("silicotropism"). The metabolism of silicon compounds in the cells of the organisms is evidently determined by the activity of special enzymes.

Numerous pathological processes, including cancer, atherosclerosis, tuberculosis, and diabetes, goitre, certain types of dermatitis, stone formation in the urethra, etc., are associated with the breakdown of the metabolism of silicon compounds. The latter play an important protective role in the organism, improving its self-protective functions and the capacity for detoxication. Partly this is due to the fact that silicon compounds facilitate the removal with urine of metabolites and extraneous and toxic substances, serve as a barrier preventing the propagation of degenerative processes [13], and intensify the biosynthesis of collagen [77].

3. THERAPEUTIC APPLICATIONS OF SILICON COMPOUNDS

Bearing in mind the important role of silicon in the normal activity of the organism, one may hope that the regulation of its metabolism by the introduction into or the removal from the organism of definite compounds of this element will lead to considerable advances in the treatment of many diseases and in the fight against old age. The first attempts on these lines were made long ago although they were not always entirely successful. Their inadequate effectiveness can be explained by the extremely narrow range and lack of variety of the silicon compounds used in the attempt at therapy (silic acid, silicates of sodium, potassium, cobalt, magnesium, iron, and copper, kaolin, and talc) [78-109]. All these inorganic compounds are insoluble or give rise to the insoluble silic acid on contact with gastric juices and therefore they are assimilated by the organism with difficulty.

At the same time mineral waters rich in soluble compounds (containing 20–80 mg litre^{-1} of silica) are distinguished by high physiological activity and have been used for a long time in treatment at spas [110]. They exhibit sympathomimetic activity, have a favourable effect on cardiac muscle, sharply intensify cardiac activity and heart rhythm, inhibit the motor function of the small intestine, intensify the capacity for work of skeletal muscle, greatly intensify the activity of the ciliary epithelium of the alimentary canal, etc. Mineral waters rich in silicon content not only improve the positive silicon balance in the organism but also significantly alter the functional state of the liver, the stomach, and the kidneys. They intensify the activity of the oxidative enzymes in the liver, increase the content of adrenaline in the adrenal glands and the content of noradrenaline and the oxidation products of aminocatechols in cardiac muscle, and have a favourable effect on the autonomic nervous system. Silicate mineral waters are widely used in the therapy of uric acid diathesis, inflammatory diseases of the urinogenital system, etc.

In the first half of the present century tuberculosis and certain other diseases began to be treated by various orthosilicate esters. These include, in particular, the preparation "Silistren" produced by the Bayer company, which consists of the tetraglycol ester of orthosilic acid [111-117]. Orthosilicate esters of hydroxycarboxylic acids and their esters and salts have also been used [118-123]. Other organic derivatives of orthosilicic [84,124-129] and even fluorosilic acid [130,131] have been proposed for use in therapy. Inorganic silicon compounds were not forgotten either. Quite recently the resistance of guinea pigs to tubercular infection was found to increase after peroral introduction of sodium silicate [132-134].

Using these and similar preparations, specialists in therapy assumed that the therapeutic effect of silicon compounds in tuberculosis consists in the stabilisation of lung tissue and in the formation of a protective coating in the affected region [78,85,89].

One of the rational approaches to the problem of "silicon therapy" consists in the use for therapeutic purposes of "plant silicon" present in plants, for example in the horse-tail [13,94,135-141]. In these plants silicon is present to a large extent as organic compounds [142] already incorporated in cellular protoplasm. Silicon compounds of precisely this type are in fact assimilated by man together with food, but, according to Monceaux [13], the human organism cannot assimilate inorganic silicon compounds in the way that autotrophic plants can.

Complexes of potassium methylsilicate [Me Si(OH)(OK)$_2$ (Ed. of Translation)] with salicylic, citric, ascorbic, heparinic, penicillic, or deoxyribonucleic acids have been proposed for the treatment of acute and chronic diseases of the joints, supercutaneous staphylococcal diseases, hypertension, sclerosis, various types of arteritis of the lower limbs, diseases of the capillaries, atrophic phenomena, the breakdown of cellular mitosis, and a number of other affections [143]. The use of silicon compounds in the treatment of atherosclerosis proved to be particularly successful. In this disease the silicon content in the tissues of the arteries is known to decrease sharply [144-150]. The introduction of sodium silicate [148], phenylpolysiloxane [151], and the complexes of potassium or sodium methylsiliconate with salicylic [150] or citric acids [143,152] not only prevents the occurrence of experimental atherosclerosis but also has a therapeutic effect.

In view of the particular ease of penetration of the complexes of potassium methylsilicate with organic acids into the organism via the skin [153], their anti-inflammatory and antisclerotic activity, and also the stimulating effect of silicon on the synthesis of connective and elastic tissues [149], an effective method has been developed for the treatment of coronary affections based on the use of controlled ionophoresis [154,155]. Ionotherapy using complexes of potassium methylsilicate with citric or heparinic acids is used at present in the treatment of chronic heart disease (including treatment after 1–2 myocardial infarctions), arterial hypertension, and obliterative arteriopathy of the lower limbs. A seven year clinical experiment with 500 patients resulted in 80% of complete cures [154,155].

Complexes of potassium methylsilicate with organic acids have also been used in the treatment of cancer: cancer of the bone (osteosarcoma), the lungs, and the prostate gland. According to Janet [156], in many cases, in particular in the treatment of rapidly evolving tumours, satisfactory results have been achieved.

The complex of potassium methylsilicate with penicillin G proved to be effective in the treatment of myxomatosis, a virus disease which is not affected either by potassium methylsilicate or penicillin G used separately [157]. Thus the use of the complex with potassium methylsiliconate extended the spectrum of activity of penicillin. This could also prove true of other antibiotics.

A special application of organosilicon compounds in medicine [158-168] consists in the increasing use of polyorganosiloxane liquids, resins, and rubbers in the therapy of the diseases of the stomach, eyes, and the respiratory tract, in surgery, haemotology, dermatology, dentistry, and vetinary practice. However, in this case their application is based mainly on the specific physical properties of the organosilicon polymers (hydrophobic, antiadhesive, and antifoaming effects, etc.), their high chemical stability, and high physiological inertness.

4. TOXICITY OF ORGANOSILICON COMPOUNDS

The vigorous development of the organic chemistry of silicon after the Second World War led to the creation of a wide range of organosilicon polymers and materials based on them. At present the number of known individual organic silicon compounds exceeds 15 000. The outstanding practical importance acquired by organosilicon polymeric compounds made it necessary, of course, to investigate their physiological activity and in the first place toxicity. However, the range of compounds investigated in this respect remained very narrow until recently, being largely restricted to products of industrial synthesis (alkoxysilanes [189-224], chlorosilanes, [12,23,192,195-199,202,204,206,207,212,216,221,222,225-253] and polyorganosiloxanes [174-177,200,205,254-286]). The toxicity of other classes of organosilicon compounds, in particular nitrogen-containing compounds, has been investigated very little [191,194,198,203,209,213-215,217,223,224,287-304].

No organosilicon compound with a particularly distinct or specific physiological activity closely related to the presence of a silicon atom in the molecule had been found until the beginning of systematic studies by the present authors (1962), although fairly toxic (lethal dose LD_{50} = 1–50 mg kg^{-1}) compounds with $Si-OCH_2CH_2$, [305] Si–F, [306-310] and Si–NC [254] bonds have been synthesised. However, the effect of such compounds with silicon-containing functional groups on the organism is largely due to the toxicity of their hydrolysis products ($HOCH_2CH_2F$, HF, HCN).

Table 1. Toxicity of $(CH_3)_{4-n}SiX_n$.

X	References	Test animals	Method of administration	Characteristics of toxicity	h = 1	2	3	4
Cl	222	white mice	by inhalation	LC^*_{100}	0.1	0.4	0.4	15
OC_2H_5	199	rats	oral	LD_{100}	2	10	10	5
$OCH_2CH_2NH_2$	295	white mice	intraperitoneal	LD_{50}	0.32	0.57	0.40	—
$OCH_2CH_2N(C_2H_5)_2$	295	white mice	intraperitoneal	LD_{50}	0.50	0.72	0.60	0.23

*LC = absolute lethal concentration (mg litre^{-1}); LD = lethal dose (g kg^{-1}).

Nevertheless it can be asserted that the specific effect of the silicon atoms in the molecule of more or less readily hydrolysable compounds with silicon-containing functional groups in the series $R_{4-n}SiX_n$ does affect their toxicity. Firstly, the toxicity of such substances often proves to be appreciably higher or lower than that of their hydrolysis products used separately. This is clearly seen, in particular, for tetramethoxysilane [193-194], which is more poisonous and dangerous than methyl alcohol and colloidal silicic acid. Secondly it would appear that the toxicity of compounds of this type should increase with the number n of functional groups at the silicon atom, since this involves an increase in the amount of toxic agent formed in the organism on hydrolysis:

$$R_{4-n}SiX_n + n\,H_2O \rightarrow R_{4-n}Si(OH)_n + n\,HX \quad (n = 1-4).$$

However, silicon compounds with $n = 1$, i.e. the least hydrolysable compounds forming on hydrolysis a minimal amount of HX, proved unexpectedly to be the most toxic (Table 1).

In this connection it should be noted that in the series of organotin compounds $R_{4-n}SnX_n$ the monofunctional compounds ($n = 1$) are also the most toxic [311].

5. BIOLOGICAL ACTIVITY OF ORGANOSILICON COMPOUNDS

The aim of the first attempts to prepare physiologically active organic compounds of silicon was the synthesis of silicon analogues or organosilicon derivatives of organic substances known to have a pronounced and definite effect on the organism. In the course of studies of this kind the biological activity of a fairly large range of organosilicon compounds, described in Table 2, was investigated.

Table 2. Compilation of studies on biologically active organosilicon compounds.

Type of Effect	Compounds investigated
1	2
Effect on respiratory activity	*N*-trimethylsilylpyrrolidone [312], triethyliso-cyanatosilane [313], silatranes [22, 287-293], 2-aminoethoxysilanes [293, 295], 3-amino-propylsilanes [293,294,298], organosilicon arylalkylamines [301, 314], barbiturates [302, 315], carbamates [23, 300, 303, 304], aromatic acid amides [316]
Anabolic, androgenic, and oestrogenic activity	Organosilicon derivatives of steroids [317-319]
Allergic reactions	Dis(hydroxyphenyl)dialkylsilanes [320]
Inhibition of dihydronicotinamide adenine dinucleotide ($NADH_2$)-oxidase	Organosilicon carbamates [23]
Cholinergic and anticholinergic activity	2-(trimethylsilyl)ethyl acetate [321], 2-(dialkyl-amino)ethyl esters of trialkylsilylphenyl-β-hydroxypropionic acids [322], organosilicon carbamates [323], organosilicon derivates of choline [299]
Insecticidal activity	Organoisothiocyanatosilanes [324], polyorgano-silthianes [325], organosilicon derivatives and analogues of pyrrolidone [312], sulphonamides [326], carbamates [327], salts of dithiocarbamic acids [328], unsaturated diols [329], and DDT [330], trialkyl-silylalkyl phosphonic acid esters [331], organo-silicon derivatives acetylene [332], trialkyl(tri-alkylsiloxy)stannanes [333]
Insect repellent activity	Methyl (*NN*-dialkylaminomethyl)dialkoxy-silanes [334, 335], *N*-(trialkylsilylmethyl)-ethylamides of carboxylic acids [336]
Fungistatic activity	Organosilicon amines [293, 314, 337], organo-isothiocyanatosilanes [324], polyorganosil-thianes [325], organosilicon derivatives of mercury [338, 339], copper salts of dithiocarbamic acids [328], sulphonamides [326], and isothio-cynates [340]
Bacteriostatic activity	3-Aminopropylsilanes and other organosilicon amines [293, 314, 337, 341], bis(hydroxyphenyl)-dialkylsilanes [342], trimethylsilylmethanol [343], mercury-containing polyorganosiloxanes [338], organosilicon derivatives of penicillin [344, 345], alkyl esters of aziridinecarboxylic acids [346]; and 2-(dialkylamino)ethyl esters of aromatic acids [347], organoethynylsilanes [348]
Regulation of plant growth	Chloroalkylsilanes [349, 350], ethynylsilanes [351]

Of the pharmocologically investigated [299] organosilicon derivatives of physiologically active organic compounds synthesised in our laboratory [352], mention should be made of the previously unknown *C*- and *O*-trialkylsilyl derivatives

of choline—$[R_3SiCH_2NR'R''CH_2CH_2X]Y$ and correspondingly $[(CH_3)_3NCH_2CH_2OSiR_3]Y$ (Table 3).

All compounds of this type exhibit *N*-cholinolytic activity. In this respect the most active compounds exhibit also ganglion-blocking activity on the parasympathetic ganglia of the heart. The hypotensive effect of organosilicon derivatives of choline is particularly pronounced for *C*-silyl substituted derivatives with R = R′ = R″ = CH_3 and Y = I in which the substituent X is the $OCOCH_3$ group (70–90 mmHg at a dose of 1 mg kg^{-1}) or an iodine atom (50–60 mmHg). Apart from the depressor response, these compounds cause intensified respiration in cats.

Table 3. Biological activity of organosilicon derivatives of choline.

Compound	Cholinolytic activity (straight muscle of frog stomach) EC_{50}*	Ganglion-blocking activity (in cats) ED_{30} mg kg^{-1}	Hypotensive activity (in cats) ED_{30} mg kg^{-1}	Median lethal dose (for white mice with intraperitoneal administration) LD_{50}, mg kg^{-1}
$[(CH_3)_3SiCH_2N(CH_3)_2CH_2CH_2OH]I$	$8.0\cdot10^{-4}$	0.56	2.5	266
$[(C_2H_5)_3SiCH_2N(CH_3)_2CH_2CH_2OH]I$	$4.9\cdot10^{-6}$	0.85	3.6	53
$[(CH_3)_3SiCH_2N(CH_3)_2CH_2CH_2Cl]I$	$9.1\cdot10^{-5}$	0.50	0.86	124
$[CH_3(C_2H_5)_2SiCH_2N(CH_3)_2CH_2CH_2Cl]I$	$3.2\cdot10^{-6}$	0.35	1.69	71
$[(CH_3)_3SiCH_2N(CH_3)_2CH_2CH_2I]I$	$2.5\cdot10^{-5}$	0.69	0.25	40
$[(CH_3)_3SiCH_2N(CH_3)_2CH_2CH_2OCOCH_3]I$	$2.4\cdot10^{-4}$	0.62	0.7	328
$[(CH_3)_3SiCH_2N(CH_3)_2CH_2CH_2OCOC_6H_5]I$	$2.3\cdot10^{-5}$	1.26	3.1	465
$[(CH_3)_3SiOCH_2CH_2N(CH_3)_2]I$	$4.5\cdot10^{-4}$	—	—	238
$[(CH_3)_3SiCH_2NH(CH_3)CH_2CH_2Cl]Cl$	$1.3\cdot10^{-5}$	—	—	137

*Concentration expressed in fractional units.

The trimethylsilyl ester of choline has virtually no ganglion-blocking activity. When administered to cats in doses of 2–10 mg kg^{-1} the depressor phase is replaced by a pronounced increase in the level of blood pressure. The persistence of the pressor effect in experiments on spinal cats after the vagus nerves have been severed, the exclusion of the adrenal glands from blood circulation, and the prevention of this effect by hexamethonium salts indicate a stimulating effect of the trimethylsilyl ester of choline on the autonomic vegetative ganglia, particularly the sympathetic ganglia.

The physiological activity of organosilicon derivatives or analogues of known organic medicinal preparations and other substances with a distinct biological activity is not by itself in any way surprising. Although among all the compounds of this type investigated none has found wide practical application, investigations in this field are nevertheless very interesting and promising. This claim is based on studies of the "bioisosteric" organosilicon compounds carried out in recent years in the USA by Fessenden [23,300–304,353]. The idea underlying them may be regarded as the pharmacochemical development of the once very popular "analogue hypothesis" of Wöhler, Ladenburg, and Friedel, according to which the replacement in any organic compound of one or several carbon atoms by silicon (i.e. the formation of a "sila-derivative") does not alter appreciably the physical and chemical properties. Although this hypothesis has now been disproved, it nevertheless remains to a certain degree valid when applied to organosilicon compounds which do not contain functional groups attached to the silicon atom, at any rate functional groups which are readily hydrolysed.

As an example of the validity of the analogue hypothesis for carbon and silicon compounds in its pharmocological aspect, several pairs of isostructural substances are quoted below:

$(4\text{-}HOC_6H_4)_2M(CH_3)_2$ (I) $\quad C_6H_5(CH_3)_2MCH(CH_3)NH_2\cdot HCl$ (II)

$R(CH_3)_2M(CH_2)_nOCONH_2$ (III) $\quad R(CH_3)M[(CH_2)_nOCONH_2]CH_2OCONH_2$, (IV)

where M = C (a) or Si (b).

Thus compounds (Ia) and (Ib) exhibit the same allergic activity [320]. The organosilicon analogue (IIb) of the familiar adrenergic medicinal preparation (IIa) resembles it in both its overall biological activity and in its toxicity [301]. The toxicity of organic carbamates (IIIa, IVa) and the organosilicon carbamates having an analogous structure (IIIb, IVb) is of the same order of magnitude [303].

The similarity of the biological activities of isostructural organic and organosilicon compounds is of undoubted interest for the creation of new medicinal preparations, pesticides, and other types of biologically active substances if only because the corresponding silicon compounds are in many cases easier to synthesise and are cheaper. Nevertheless sometimes the sila-analogues of the physiologically active organic substances may differ from the latter to a greater or smaller extent in their effect on the organism. In turn this difference may be successfully used in the synthesis of new medicinal preparations and pesticides.

For example the familiar tranquiliser meprobamate (Va) and its sila-derivative (Vb), [303]

$CH_3CH_2CH_2(CH_3)M(CH_2OCONH_2)_2$ (V)

where M = C (a) or Si (b), has similar effects on the motor activity of animals and inhibits NAD-H_2 oxidase. However, their physiological activity is otherwise not the same. The effect of compound (Va) is four times more prolonged than that of (Vb). When administered orally, compound (Vb), in contrast to compound (Va), is inactive despite the fact that it is absorbed and then eliminated from the organism in urine. This suggests that the metabolic fate of both analogues (V) in the organism is different. Indeed, while compound (Va) is oxidised in the organism and eliminated as the hydroxy-derivative (VIa), compound (Vb), apart from being oxidised by an analogous process to compound (VIb), is converted into the disiloxane (VII) with elimination of an n-propyl group [23,353]:

$CH_3CH(OH)CH_2(CH_3)M(CH_2OCONH_2)_2$ [VI; M = C (a); Si (б)] $\quad [CH_3(H_2NCOOCH_2)_2Si]_2O$ (VII)

The only metabolic product of $CH_3CH_2CH_2(CH_3)_2SiCH_2OCONH_2$ is the corresponding dealkylation product $[H_2NCOOCH_2(CH_3)_2Si]_2O$†. [353] Thus the different metabolic fate of the sila-analogues of physiologically active substances may have a significant effect on the nature and duration of their action.

The carbon and silicon structural analogues of type (VIII) show particularly marked differences in their biological activity, which can probably be attributed to the β-effect of the silicon atom:

$(CH_3)_3MCH_2CH_2OCONH_2$ (VIII)

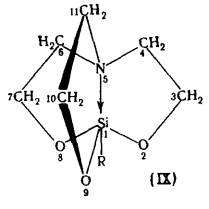
where M = C (a) or Si (b).

†Until Fesenden's investigation [353], the metabolism of organosilicon compounds in the organism was hardly studied. It was only known that $(CH_3)_3Si(CH_2)_{15}CH_3$ and $(CH_3)_3Si(CH_2)_{11}COOCH_3$ are absorbed via the gastrointestinal tract [354] and that [^{14}C] polydimethylsiloxane is not eliminated from the organism in the form of $^{14}CO_2$. [355]

Compound (VIIIa) is ten times more toxic than its sila-analogue (VIIIb). The latter is a rapid-acting muscle relaxant which does not give rise to side effects. On the other hand, compound (VIIIa) does not exhibit this type of activity, causing convulsions instead [303]. At the same time both compounds (VIII) give rise to a prolonged cholinergic response when introduced into the lateral hypothalamic region of the brain [356].

The last few examples clearly demonstrate that in physiological activity too the "analogue hypothesis" is not always justified even when compounds with silicon-containing functional groups are excluded from consideration. This is not in fact surprising because the much lower electronegativity, the higher covalent radius of the atom (by a factor of 1.5), and the presence of vacant 3*d* orbitals constitute appreciable differences between silicon and carbon. This difference does actually lead to the expectation in a number of cases that the sila-analogues of physiologically active organic compounds will have a quite specific effect on living organisms. This makes further investigations in this field undoubtedly promising.

We believe that even more interesting and promising is the study of the physiological activity of organosilicon compounds which have no organic analogues at all or which exhibit an activity which is closely related to the presence in their molecule of a silicon atom (or atoms). Compounds of this type, investigated up to the present time, are also listed in Table 2. These include in the first place silatranes (IX), the wide employment of which in our laboratory began in 1962. We have shown that certain silatranes, namely 1-arylsilatranes exhibit high and specific physiological activity [22,287-293,357].



(IX)

For example, 1-phenylsilatrane (IX, R = C_6H_5) and even more so 1-*p*-tolylsilatrane (R = *p*-$CH_3C_6H_4$) are unusually toxic for warm-blooded animals. Their lethal dose (LD_{50}) for white mice is only 0.33 and 0.20 mg kg^{-1}. Both compounds are several times more toxic than the widely known poisons such as hydrocyanic acid or strychnine. At the same time 1-arylsilatranes are almost harmless for cold-blooded animals (frogs, etc.), plants, and microorganisms. Below the lethal dose (0.2–0.25 mg kg^{-1}), 1-phenylsilatrane is a powerful analeptic, i.e. it gives rise to motor excitation and intensifies the respiration of animals. It is interesting that for animals under narcosis 1-phenylsilatrane proves to be much less toxic. A dose ten times greater than the lethal dose causes only an excitation of respiration and convulsive movements of skeletal muscles. In animals with damaged central nervous systems 1-phenylsilatrane does not cause muscular convulsions even in doses of 1.5 mg kg^{-1} (introduced intravenously).

A wide variety of numerous experiments showed that 1-arylsilatranes do not affect the peripheral neuromuscular apparatus. The physiological activity of 1-arylsilatranes is due to their effect on a hitherto unknown enzyme system which is important for the function of the central nervous apparatus in warm blooded animals and which is absent or is less important for the activity of the central nervous system of cold blooded animals. For this reason, 1-arylsilatranes have no toxic effect on all living organisms at a lower level of evolutionary development.

The difference between 1-arylsilatranes and many of the familiar poisons is also indicated by the fact that enzymes such as cholinesterase and acetylcholinesterase are not inhibited by them.

The physiological activity and in particular the toxicity of silatranes vary within extremely wide limits, being determined mainly by the nature of the substituent R attached to the silicon atom itself (Table 4). The wide range of variation of this activity is indicated, for example, by the complete harmlessness of alkyl- and alkoxysilatranes (R = $CH_3C_2H_5O$ etc.).

Table 4. Toxicity of silatranes $RSi(OCH_2CH_2)_3N$ for white mice with intraperitoneal administration*.

R	LD_{50}, mg kg^{-1}	R	LD_{50}, mg kg^{-1}
p-$CH_3C_6H_4$	0.20	*p*-$CH_3C_6H_4O$	1270
C_6H_5	0.33	$C_6H_5CH_2$	1115
m-ClC_6H_4	4.4	CH_3O	2100
H	100	C_2H_5O	>5000
$CH_2(CH_2)_4CH$	150	CH_3	>5000
C_6H_5O	200	C_2H_5	>5000
p-$O_2NC_6H_4O$	700	$(CH_3)_2CH$	>5000
p-ClC_6H_4O	1050	$CH_2{=}CH$	>5000

*For 3,5-dimethyl-1-phenylsilatrane and 1-phenyl-2-carboxysilatrane, LD_{50} = 14.7 and 8.1 mg kg^{-1} respectively.

The introduction of methyl radicals into the silatrane system of 1-phenylsilatrane or the replacement of one of the oxygen atoms by a CH_2 group (1-phenyl-2-carbasilatrane) greatly reduces the toxicity of the compound. When the aromatic ring in 1-arylsilatranes is separated from the silatrane system by a methylene group (1-benzylsilatrane), the compound virtually loses its toxicity and the introduction of an oxygen atom into the Si–C_6H_5 bond (1-aryloxysilatranes) lowers the toxicity by several powers of ten. It is interesting that the hydrogenated analogue of 1-phenylsilatrane, i.e. 1-cyclohexylsilatrane, and also silatrane itself (1-hydrosilatrane) exhibit some, albeit low, toxicity.

In order to establish whether the structure of 1-arylsilatranes is specific for high physiological activity, we investigated the toxicity of open-chain silatrane analogues —a wide variety of 2-aminoethoxysilanes containing the Si–O–C–C–N group (derivatives of tri-, di-, and monoethanolamine) and also the initial amino-alcohols (Table 5). [295] It was found that all the organosilicon ethers of monoethanolamine in the series $R_{4-n}Si(OCH_2CH_2NH_2)_n$ with n = 1–3 are 2–9 times more toxic than $HOCH_2CH_2NH_2$ itself. At the same time the analogous derivatives of *NN*-dialkylaminoethanols usually prove less toxic than the corresponding amino-alcohol $HOCH_2CH_2NR_2$ (particularly for R = CH_3 or C_4H_9), or their toxicity is of the same order of magnitude (for R = C_2H_5).

Trialkylsilyl derivatives of triethanolamine are less toxic than triethanomaline itself, while the analogous diethanolamine derivatives are somewhat more toxic than diethanolamine itself. The toxicity of compounds in the

series $H_{3-n}N(CH_2CH_2OSiR_3)_n$, where R = CH_3 or C_2H_5 and n = 1–3, decreases appreciably as n increases. A change in the nature of the hydrocarbon substituent of the silicon atom in all types of the compounds investigated has little effect on the toxicity. On the whole, the toxicity,of organosilicon ethers of amino-alcohols is low and varies in the range from 120 mg kg^{-1} for $(C_2H_5)_2Si(OCH_2CH_2NH_2)_2$ to 4000 mg kg^{-1} for $N[CH_2CH_2OSi(C_2H_5)_3]_3$.

Table 5. Acute toxicity (LD_{50}) of 2-aminoethoxysilanes and 2-aminoethanols and dose which impairs the co-ordination of movement (ED_{50}) on intraperitoneal administration to white mice.

Compound	LD_{50}, mg kg^{-1}	ED_{50}, mg kg^{-1}
$HOCH_2CH_2NH_2$	1050	350
$(CH_3)_3SiOCH_2CH_2NH_2$	320	175
$(C_2H_5)_3SiOCH_2CH_2NH_2$	165	60
$(CH_3)_2Si(OCH_2CH_2NH_2)_2$	570	280
$(C_2H_5)_2Si(OCH_2CH_2NH_2)_2$	125	63
$CH_3Si(OCH_2CH_2NH_2)_3$	400	500
$C_2H_5Si(OCH_2CH_2NH_2)_3$	500	410
$C_6H_5Si(OCH_2CH_2NH_2)_3$	500	210
$HOCH_2CH_2N(CH_3)_2$	210	530
$(CH_3)_3SiOCH_2CH_2N(CH_3)_2$	620	265
$(C_2H_5)_3SiOCH_2CH_2N(CH_3)_2$	670	390
$HOCH_2CH_2N(C_2H_5)_2$	500	250
$(CH_3)_3SiOCH_2CH_2N(C_2H_5)_2$	630	50
$(C_2H_5)_3SiOCH_2CH_2N(C_2H_5)_2$	400	210
$(CH_3)_2Si[OCH_2CH_2N(C_2H_5)_2]_2$	720	64
$(C_2H_5)_2Si[OCH_2CH_2N(C_2H_5)_2]_2$	600	445
$CH_3Si[OCH_2CH_2N(C_2H_5)_2]_3$	600	385
$C_2H_5Si[OCH_2CH_2N(C_2H_5)_2]_3$	490	125
$C_6H_5Si[OCH_2CH_2N(C_2H_5)_2]_3$	560	—
$Si[OCH_2CH_2N(C_2H_5)_2]_4$	230	380
$HOCH_2CH_2N(C_4H_9)_2$	52	8
$(CH_3)_3SiOCH_2CH_2N(C_4H_9)_2$	640	600
$(C_2H_5)_3SiOCH_2CH_2N(C_4H_9)_2$	1650	2300
$(C_2H_5)_2Si[OCH_2CH_2N(C_4H_9)_2]_2$	2400	520
$(HOCH_2CH_2)_2NH$	1600	740
$[(CH_3)_3SiOCH_2CH_2]_2NH$	1250	380
$[(C_2H_5)_3SiOCH_2CH_2]_2NH$	1850	—
$(HOCH_2CH_2)_3N$	1450	110
$[(CH_3)_3SiOCH_2CH_2]_3N$	3500	1400
$[(C_2H_5)_3SiOCH_2CH_2]_3N$	4000	—
$(CH_3)_3SiOCH_2CH_2NC_5H_{10}$	400	—
$(C_2H_5)_3SiOCH_2CH_2NC_5H_{10}$	280	180
$(C_2H_5)_3SiOCH_2CH_2NHC_4H_9$	360	240
$(CH_3)_3SiOSi(CH_3)_3$	4500	

In the study of the effect of all the above aminoalkoxysilanes on the co-ordination of movement it was found that compounds of the type $(CH_3)_{4-n}Si[OCH_2CH_2N(C_2H_5)_2]_n$ with n = 1 and 2 are active at a dose smaller by a factor of 11–13 than the median lethal dose.

The data obtained convincingly demonstrate that the toxicity of 2-aminoethoxysilanes is scarcely due to the toxic effect of their hydrolysis products (one of these, hexamethyldisiloxane, for example, has LD_{50} = 4.5 g kg^{-1}) but is caused by the molecular structure as a whole. They also show that the high toxicity and physiological activity of 1-arylsilatranes cannot be attributed solely to the simultaneous presence in their molecule of the Si–aryl and Si–O–C–C–N bonds. Nor is it possible to explain the activity of 1-arylsilatranes by the presence in their molecules of the silatrane group $Si(OCH_2CH_2)_3N$, because 1-alkyl- and 1-alkoxy-silatranes are almost non-toxic. It might have been supposed that the physiological activity of 1-arylsilatranes is associated with the effect on the aromatic ring of the transannular co-ordinate bond Si ← N, which leads to an enhancement of its π-electron density and consequently its electron donor properties. However, the toxicity of 1-phenylgermatrane (smaller by a factor of 100 than that of 1-phenylsilatrane), which has a similar structure and dipole moment [358], suggests that the problem of the high physiological activity of 1-arylsilatrane still remains open, although it may be supposed that the much lower toxicity of 1-phenylgermatrane is due to its lower chemical stability.

The high physiological activity of 1-arylsilatranes suggested to us that other organosilicon compounds containing a nitrogen atom in the γ- or δ-position in relation to the silicon atom might be of definite interest in this respect. This was also indicated by a brief communication concerning the fairly high toxicity of compound (X):

$$(C_2H_5O)_2Si(CH_3)CH_2CH_2CH_2CH_2NH_2$$
(X)

(0.045 ml kg^{-1} when absorbed through the skin of the rabbit). [198,254]

Table 6. Acute toxicity (LD_{50}) of 3-aminopropylsilanes and dose which impairs the co-ordination of movements (ED_{50}) in white mice after intraperitoneal administration.

Compound	Formula	LD_{50}, mg kg^{-1}	ED_{50}, mg kg^{-1}
XI	$CH_3(C_2H_5O)_2Si(CH_2)_3\overline{N(CH_2)_4CH_2}$	6.6	8
XII	$CH_3(C_2H_5O)_2Si(CH_2)_3NH_2$	40	42
XIII	$CH_3(C_2H_5)_2Si(CH_2)_3NH_2$	47	—
XIV	$(C_2H_5)_3Si(CH_2)_3\overline{N(CH_2)_4CH_2}$	47	47
XIVa	$[(C_2H_5)_3Si(CH_2)_3\overline{NH(CH_2)_4CH_2}]Cl$	120	—
XV	$(C_3H_7)_3Si(CH_2)_3NH_2$	75	70
XVI	$CH_3(C_2H_5O)_2Si(CH_2)_3\overline{N(CH_2)_2OCH_2CH_2}$	86	40
XVII	$(C_2H_5)_3Si(CH_2)_3NH_2$	90	64
XVIII	$(CH_3)_3Si(CH_2)_3NH_2$	155	76
XIX	$C_2H_5(C_2H_5)_2Si(CH_2)_3NH_2$	120	100
XX	$(C_2H_5)_2C_6H_5Si(CH_2)_3NH_2$	140	62.5
XXI	$(C_2H_5)_3Si(CH_2)_3NHCH_2C_4H_3O$	185	280
XXII	$C_2H_5(C_2H_5O)_2Si(CH_2)_3NH_2$	215	130
XXIII	$(C_2H_5O)_3Si(CH_2)_3NH_2$	260	140
XXIV	$CH_3(C_2H_5O)_2Si(CH_2)_3\overline{N(CH_2)_2N(CH_2)CH_2CH_2}$	400	105
XXV	$CH_3(C_2H_5O)_2Si(CH_2)_3\overline{N(CH_2)_2SiCH_2CH_2}$	470	360
XXVI	$[(C_2H_5)_2SiCH{=}CHCH_2\overline{NH(CH_2)_4CH_2}]Cl$	110	31
XXVII	$[(C_2H_5)_2SiC{\equiv}CCH_2\overline{NH(CH_2)_4CH_2}]Cl$	195	80
XXVIII	$C_6H_4[Si(CH_3)_2CH_2CH_2CH_2NH_2]_2$-1,4	74	10
XXIX	$O[Si(CH_3)_2CH_2CH_2CH_2NH_2]_2$	80	60

To confirm this hypothesis, we investigated the toxicity and the effect on the co-ordination of movement of γ-aminopropyl substituted silanes and their unsaturated analogues. The data obtained (Table 6) show that, among compounds of this type, there are some fairly toxic [compound(XI) with LD_{50} = 6 mg kg^{-1}] and also compounds which fairly effectively reduce the motor activity and impair the co-ordination of movement [compounds (XXVI) and (XXVIII)] [294,298].

Among γ-aminopropylsilane derivatives, derivatives of bis-(3-aminopropylsilyl)benzene are of particular interest. For example, one of these [compound (XXVIII)] impairs the co-ordination of movement at a dose as low as 10 mg kg^{-1}, while at a dose of 4.8 mg kg^{-1} it reduces the body temperature by 3 deg.

It should be pointed out that the toxicity of the hydrochlorides of γ-aminopropylsilanes is reduced [compounds (XIV) and (XIVa)]. In the series of the hydrochlorides $[(C_2H_5)_3Si(CH_2)_nNH(CH_2)_4CH_2]Cl$ the toxicity decreases with increasing n. Thus for $n = 1$, 2, and 3, LD_{50} is respectively 60, 88, and 120 mg kg^{-1}.

We investigated the fungistatic and bacteriostatic activities of several dozen of nitrogen-containing organosilicon compounds of a wide variety of types [293,337]. Among these substances with a comparatively high activity were detected (Table 7).

Table 7. Minimum concentration (C) of nitrogen-containing organosilicon compounds suppressing the growth of micro-organisms.

Compound	Formula	Test microbe	C, mg ml^{-1}
XII	$CH_3(C_2H_5O)_2SiCH_2CH_2CH_2NH_2$	*Escherichia coli* 675	10.4
XV	$(n\text{-}C_3H_7)_3SiCH_2CH_2CH_2NH_2$	*Candida albicans* 67/846	41.7
		Epidermophyton Kaufmann Wolf 41	13.8
		Trichophyton gypseum 4/3	13.8
		Bac. mycoides 675	14.0
XXI	$(C_2H_5)_3SiCH_2CH_2CH_2NH$—	*Staphylococcus aureus haemolyticus* 209	10.4
		Bac. mycoides 675	10.4
XXX	$(CH_3)_2Si(CH_2Cl)CH_2CH(CH_3)CONH_2$	*Epidermophyton Kaufmann Wolf* 41	6.9
		Trichophyton gypseum 4/3	13.8

Although nitrogen-containing organosilicon compounds of a wide variety of structures have been investigated, only substances with the nitrogen atom in the γ-position in relation to the silicon atom proved to be active. Two of the compounds, listed in Table 7 [compounds (XV) and (XXX)], are only slightly inferior (by a factor of 1.8) in their fungistatic activity on *Trichophyton gypseum* to the fungicidal preparation nystatin widely used in clinical practice. Two other compounds effectively suppress gram-positive [compound (XXI)] and gram-negative [compound (XII)] bacteria.

There is no doubt that continued studies in this field will lead to the discovery of even more active organosilicon fungistatic and bacteriostatic substances which may find practical application, in particular for the formation of stable fungicidal and antibacterial coatings.

Thus we have shown that a wide variety of classes of nitrogen-containing organosilicon compounds containing both nitrogen and silicon atoms, separated from one another by three other atoms, exhibit useful and varied effects on the living organism. These are the most promising possible new silicon-containing medicinal preparations and pesticides. Nevertheless we discovered substances with a high physiological activity also among other classes of nitrogen-containing organosilicon compounds. For example, we found (together with D. P. Dremova) that compounds of the series $R_2NCH_2(CH_3)Si(OR')_2$ are insect repellents [335]. Some data on the activity of the compounds of this type are presented in Table 8.

We hope that further study of organosilicon insect repellents will make it possible to produce stable coatings with a similar property.

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The findings described above urgently necessitate development of a new branch of silicon chemistry—the chemistry, biochemistry, and pharmacology of biologically active organosilicon compounds, i.e. "bio-organosilicon chemistry". This should include a detailed study of the role of silicon in living organisms and the physiological processes and pathological and gerontological changes occurring in them, the search for compounds of this element with high and specific biological activity, and the study of the possible practical application of such compounds in medicine, veterinary practice, agriculture, and other branches of human activity.

Table 8. Repellent activity of $R_2NCH_2(CH_3)Si(OR')_2$ in relation to a culture of fleas *X. Cheopis* at a concentration of 20 g m^{-2}.

R	R'	Coefficient of repellent activity (after 24 h)
$n\text{-}C_4H_9$	$n\text{-}C_4H_9$	73.9
$n\text{-}C_4H_9$	$iso\text{-}C_4H_9$	80.7
C_2H_5	$n\text{-}C_6H_{13}$	70.0
C_2H_5	$CH_2(CH_2)_4CH$	79.9
C_2H_5	$n\text{-}C_8H_{17}$	77.9

In this connection we cannot fail to quote the prophetic lines written as early as 1878 by the French genius Louis Pasteur: "There is a great future for the therapeutic applications of silicon".

It is to be hoped that the time is near when, as a result of the combined efforts of chemists, biochemists, pharmacologists, physicians, biologists, and agronomists, a multiplicity of new synthetic and natural physiologically active organic compounds of silicon, which will prove as useful to man as silicates and silicones, will begin to be produced industrially.

REFERENCES

1. J. Kostiz, "Allgemeine Biochemie", VEB G. Fischer, Jena, 1963, pp. 28, 37.
2. V. I. Vernadskii, "Ocherki Geokhimii" (Outline of Geochemistry), ONTI, Moscow–Leningrad, 1934, pp. 89, 90, 128–131.
3. H. Schulz, Arch. Ges., Physiol., 84, 67 (1901).
4. F. Hoppe-Seyler and H. Tierfelder, "Handbuch der Physiologisch- und Patologisch-Chemischen Analyse", Springer Verlag., Vienna, 1953, Vol. V.
5. M. Nagata, Sci. Repts. Osaka Univ., 3, 53 (1954); Chem. Abs., 49, 14 110 (1955).
6. R. K. Iler, "Colloid Chemistry of Silica and Silicates" (Translated into Russian), Gosstroiizdat, Moscow, 1959, p. 261.
7. E. I. Parfenova and E. A. Yarilova, Pochvovedenie, No. 4, 38 (1956).
8. M. Kirchgessner, Z. Tierernähr. Futtermittelk., 12, 156 (1957).
9. F. Sauer, D. H. Laughland, and W. M. Davidson, Canad. J. Biochem. Physiol., 37, 1173 (1959).
10. S. Fregert, Acta Dermato-Venereologica, No. 42, Suppl., 39 (1959).

11. A. I. Voinar, "Biologicheskaya Rol' Mikroelementov v Organizme Zhivotnykh i Cheloveka" (The Biological Role of Micro-elements in the Human and Animal Organism), Izd. Vysshaya Shkola, Moscow, 1960, p. 389.
12. V. Bažant, V. Chvalovsky, and J. Rathousky, "Silicones" (Translated into Russian), GKhI, Moscow, 1960, p. 401.
13. R. H. Monceaux, Prod. pharm., 15, 99 (1960).
14. I. F. Ponomarev, Khim. i Prakt. Prim. Kremneorg. Soed., 6, 227 (1961).
15. E. Knickmann, Landwirtsch. Forsch., 15, 130 (1962).
16. A. Duchaigne, Compt. rend. Congr. Soc. Savantes Paris Deot., Sect. Soc., 87, 1043 (1962).
17. H. Sticher and R. Bach, Schweiz. Landwirt. Forsch., 4, 352 (1965).
18. W. Pajor, Wszechświat, 4, 103 (1965).
19. W. Sedlak, Kosmos, A12, 497 (1963).
20. W. Sedlak, Kosmos, A14, 23 (1965).
21. W. Sedlak, "Rola Krzemu w Ewolucji Biochemicznej Zycia", PWN, Warszawa, 1967.
22. M. G. Voronkov, Khimiya i Zhizn', 2, 69 (1966); Problemy (Polska), No. 11, 667 (1967).
23. R. J. Fessenden and J. S. Fessenden, "Advances in Drug Research", Academic Press, London, 1967, Vol. 4, p. 95.
24. W. Heinen, Arch. Microbiol., 37, 199 (1960).
25. W. Heinen, Arch. Microbiol., 41, 229 (1962).
26. W. Heinen, Arch. Microbiol., 45, 145 (1963).
27. W. Heinen, Arch. Microbiol., 45, 162 (1963).
28. W. Heinen, Arch. Microbiol., 45, 172 (1963).
29. W. Heinen, Arch. Microbiol., 52, 49 (1965).
30. W. Heinen, Arch. Microbiol., 52, 69 (1965).
31. W. Heinen, Arch. Biochem. Biophys., 110, 137 (1965).
32. W. Heinen, Arch. Biochem. Biophys., 120, 86 (1965).
33. W. Heinen, Arch. Biochem. Biophys., 120, 93 (1967).
34. W. Heinen, Arch. Biochem. Biophys., 120, 101 (1967).
35. L. Holzapfel and W. Engel, Naturwiss., 41, 191 (1954).
36. L. Holzapfel and E. Richardson, Z. Naturforsch., 10b, 419 (1955).
37. M. A. Rouf, J. Bacteriol., 88, 1545 (1964).
38. Z. P. Tešič and M. S. Todorovič, Zemljište i Biljka, 7, 233 (1959); Chem. Abs., 54, 8980 (1960).
39. J. Coombs, W. M. Darley, O. Holm-Hansen, and B. E. Volcani, Plant Physiol., 42, 1601 (1967).
40. J. Coombs, P. J. Halicki, O. H. Hansen, and B. E. Volcani, Exp. Cell Res., 47, 302 (1967).
41. J. Coombs, P. J. Halicki, O. H. Hansen, and B. E. Volcani, Exp. Cell Res., 47, 315 (1967).
42. E. V. Grill and F. A. Richards, J. Marine Res., 22, 51 (1964).
43. R. C. Harriss, Nature, 212, 275 (1966).
44. F. P. Healey, J. Coombs, and B. E. Volcani, Arch. Microbiol., 59, 131 (1967).
45. E. G. Jørgensen, Physiol. Plantarum, 8, 840 (1955).
46. E. G. Jørgensen, Physiol. Plantarum, 8, 846 (1955).
47. J. C. Levin, Congr. intern. botan. Paris, Rap. et commun., 8, sect. 11/12, 111 (1954); Chem. Abs., 48, 10 851 (1954).
48. J. C. Lewin, J. Gen. Physiol., 37, 589 (1954).
49. J. C. Lewin, Plant Physiol., 30, 129 (1955).
50. J. C. Lewin, J. Gen. Physiol., 39, 1 (1955).
51. J. C. Lewin, Canad. J. Microbiol., 3, 427 (1957).
52. J. C. Lewin, B. F. Reimann, W. F. Bushby, and B. E. Volcani, "Cell Synchrony", 1966, p. 169.
53. B. E. F. Reimann, J. C. Lewin, and B. E. Volcani, J. Cell Biol., 24, 39 (1965).
54. L. Walter-Lévy and R. Strauss, Compt. rend., 239, 897 (1954).
55. E. Drechsel and H. Winogradow, Zentr. Physiol., 11, 361 (1897).
56. C. Cerny, Z. physiol. Chem., 62, 296 (1909).
57. M. L. Issacs, Bull. Soc. Chim. biol., 6, 157 (1924).
58. J. T. Fallon, Canad. Med. Assoc. J., 36, 223 (1937).
59. P. Ohlmeyer and V. Olpp, Z. physiol. Chem., 281, 203 (1944).
60. L. Holzapfel, Naturwiss., 30, 185 (1942).
61. L. Holzapfel, Kolloid. Z., 100, 380 (1942).
62. L. Holzapfel, Arbeitsmedizin, 21, 79 (1942).
63. L. Holzapfel, Z. ver deut. Ing., 87, 605 (1963).
64. L. Holzapfel, Staub-Heft, 21, 141 (1944).
65. L. Holzapfel, Naturwiss., 34, 189 (1947).
66. L. Holzapfel, Kolloid. Z., 115, 137 (1949).
67. L. Holzapfel, Angew. Chem., 63, 286 (1951).
68. L. Holzapfel, Z. Elektrochem., 55, 577 (1951)
69. L. Holzapfel and I. Kerner-Esser, Naturwiss., 31, 386 (1943).
70. L. Holzapfel and P. Fahrnlaender, Naturwiss., 35, 314 (1948).
71. L. Holzapfel and W. Engel, Naturwiss., 36, 375 (1949).
72. E. J. King, U. Gilchrist, and S. Rae, J. Plant Bacteriol., 59, 324 (1947).
73. A. Policard, Presse Med., 19, 213 (1947).
74. P. F. Holt and D. M. Yates, Biochem. J., 45, 32 (1949).
75. P. F. Holt and D. M. Yates, Biochem. J., 54, 300 (1953).
76. A. O. Voinar and V. N. Galakhova, Sbornik Nauch. Trud. Stalingrad. Med. Inst., 12, 7 (1958).
77. M. Chvapil, E. Heleckova, B. Cmuchalova, V. Kobrle, and J. Hurych, Exp. Cell. Res., 26, 1 (1962).
78. H. Kahle and Rossle, München. med. Woch., 61, 752 (1914).
79. R. Kobert, "Ueber Kieselsaurehaltige Heilmittel", Rostock, 1918.
80. J. Boudard, "La Silice, son role biologique, ses applications therapeutiques", Thesis Toulouse, 1919.
81. Anon, Chem. Ztg., 45, 249 (1921).
82. E. Kadisch, Beitr. Klin. Tuberk., 53, 111 (1922).
83. Chevalier, Soc. Therapeut, No. 4, 129 (1927).
84. B. N. Dolgov, "Khimiya Kremneorganicheskikh Soedinenii" (The Chemistry of Organosilicon Compounds), ONTI, Leningrad, 1933, pp. 183–186.
85. G. Lavalle, J. Sci. Liege, 1935.
86. H. Braun, Süddeut. Apoth.-Ztg., 79, 786 (1939).
87. R. Schwarz, Fortschr. Therap., 16, 182 (1940).
88. F. Mattausch, München. med. Woch., 1037 (1940).
89. K. Stejskal, Wien. med. Woch., 93, 402 (1943).
90. A. Bauer, Zentr. allg. Path. path. Anat., 86, 67 (1950).
91. L. Vaumier, Homeopathie franc., 26, 502 (1950).
92. G. Glimm, Zentr. Chir., 77, 1187 (1952).
93. B. Kober, München. med. Woch., 97, 767 (1955).
94. R. Moncraux, L'Hopital, 690 (1959).
95. W. N. Mann, Guy's Hosp. Repts, 87, 151 (1937).
96. C. J. Tidmarsh and R. G. Baxter, Canad. Med. Assoc. J., 39, 358 (1938).
97. M. Kraemer and A. Aaron, Amer. J. Digestive Diseases, 7, 57 (1940).
98. D. Wyllie, Edinburgh Med. J., 47, 336 (1940).
99. R. R. Heffner, R. O. Page, and A. Frey, Amer. J. Digestive Diseases, 8, 219 (1941).
100. R. C. Page, R. R. Heffner, and A. Frey, Amer. J. Digestive Diseases, 8, 13 (1941).
101. J. Armstrong, A. S. Beidas, D. J. Craik, and W. H. Stephenson, J. Pharm. Pharmacol., 7, 862 (1955).

102. B. Keeler and S. A. Lovelace, J. Exp. Med., **109**, 601 (1959).
103. J. Krantz and C. J. Carr, "The Pharmacologic Principals of Medical Practice", Williams and Wilkins Co., Baltimore, 1961, p. 386.
104. H. J. Dauer, Medizinische, 689 (1955).
105. B. Fox, Hippokrates, **33**, 947 (1962).
106. G. Grundmann, Zentr. Chir., **75**, 158 (1950).
107. H. F. Kamp and J. O. Watts, S. African Med. J., **41**, 651 (1967).
108. H. E. Reed, J. Amer. Inst. Homeop., **59**, 142 (1966).
109. T. N. Robinson and W. W. Robinson, Milit. Med., **130**, 1082 (1965).
110. F. E. Kurkudym, Symposium, "Lechebnye Mineral'nye Vody i Gryazi USSR" (Medicinal Mineral Waters and Mud Baths In the Ukrainian SSR), Izd. Zdorov'e, Kiev, 1965, pp. 18–23.
111. Anon, Pharm. Ztg., 66, 1012 (1921).
112. H. Zeller, "Therapie der Gegenwart", 1922; Chem. Zentr., I, 892 (1922).
113. E. Klimesch, Wiener Klin. Wschr., **36**, 799 (1923).
114. A. Flaskämper, Z. Tuberk., **39**, 257 (1924).
115. A. Freund, "Therapie der Gegenwart", 1924; Chem. Zentr., I, 551 (1925).
116. G. I. Pfalz, Mediz. Klinik, No. 28 (1926); Chem. Zentr., II, 2200 (1926).
117. G. Worth, Klin. Woch., **30**, 82 (1952).
118. H. Kaufman, DDR P. 528 988 (1928); Chem. Abs., **25**, 5177 (1931); French P. 684 814 (1930); Chem. Zentr., II, 2957 (1930); Austrian P. 121, 578 (1931); Chem. Zentr., I, 2933 (1931).
119. H. Kaufman, Klin. Woch., **14**, 1420 (1935).
120. H. Kaufman, Ber., **69**, 2685 (1936).
121. H. Kaufman, DDR P. 641 075 (1936); Chem. Zentr., I, 2817 (1937).
122. E. Hesse, Klin. Woch., **18**, 502 (1939).
123. E. Hesse and G. Meissner, Deut. med. Woch., **66**, 407 (1940).
124. G. Klein and H. Nienburg, German P. 637 532 (1936); Chem. Zentr., I, 1014 (1937).
125. Anon, Pharm. Ztg., 49, 137 (1904).
126. H. Weyland, German P. 272 338 (1914); Chem. Zentr., I, 1385 (1914).
127. Menzel, Pharm. Zentr., **63**, 579 (1922).
128. Lecinwerk Dr. E. Laves, German P. 323 596 (1920); Chem. Zentr., IV, 491 (1920); German P. 337 796 (1922); 348 411 (1923); 349 384 (1923); 351 732 (1923); 351 734 (1923).
129. F. A. Wülfing, German P. 439 043 (1927); Chem. Zentr., I, 1750 (1927).
130. Gesellschaft für Chemische Industrie in Basel, Swiss P. 107 202 (1924); Chem. Zentr., I, 1130 (1925).
131. M. Świetlikowski, Wiad. Parazyt., **7**, (2), 337 (1961).
132. I. Skards, Symposium, "Revmatizm" (Rheumatism), "Zvaigzne" Riga, 1966, p. 135.
133. I. Skards, Symposium, "Revmatizm" (Rheumatism), "Zvaigzne" Riga, 1966, p. 145,
134. I. Skards, Symposium, "Revmatizm" (Rheumatism), "Zvaigzne" Riga, 1966, p. 151.
135. M. Gonnermann, Z. physiol. Chem., **99**, 255 (1917).
136. M. Gonnermann, J. Chem. Soc., **112**, 494 (1917).
137. A. Kühn, Süddeutsch. Apoth. Ztg., **78**, 142 (1938).
138. M. Roberg, Pharm. Zentral-halle, **84**, 196 (1943).
139. A. Charnot, Maroc. med., **32**, 589, 597 (1953).
140. R. H. Monceaux, Sem. Therap., **35**, 148 (1959).
141. A. Kalvelis and M. Zile, See Ref. 132, p. 167.
142. A. Viehoever and S. C. Prusky, Amer. J. Pharm., **110**, 99 (1938).
143. C. H. J. Gueyne and M. I. Duffaut, French P. 1069 M (1960).
144. J. Loeper and C. Paule, Compt. rend. Soc. Biol., **151**, 263 (1957).
145. J. Loeper and J. Loeper, Compt. rend. Soc. Biol., **152**, 563 (1958).
146. J. Loeper and J. Loeper, Compt. rend. Soc. Biol., **155**, 468 (1961).
147. J. Loeper, J. Loeper, and A. Lemaire, Clin. Med., **47**, 595 (1966).
148. J. Loeper, J. Loeper, and A. Lemaire, Presse Med., **74**, 865 (1966).
149. J. Loeper and J. Loeper, Compt. rend. Soc. Biol., **161**, 589 (1967).
150. P. Gendre, Compt. rend. Soc. Biol., **161**, 2177 (1967).
151. J. M. Merrill and F. Golland, Circulation, **18**, 488 (1958).
152. C. H. J. Gueyne and M. I. Duffaut, French P. 1 234 213 (1959); Chem. Abs., **57**, 4698 (1962).
153. J. Gueyne, N. Duffaut, and R. Quilichini, Therapie, **17**, 549 (1962).
154. C. R. Rager, Urgence médicale et chirurgicale, **2**, 443 (1962).
155. C. R. Rager, Agressologie, **8**, 69 (1967).
156. J. Janet, Soc. Sc. Phys. Nat. Bordeaux, P.-V., 143 (1967).
157. J. Janet, Soc. Sc. Phys. Nat. Bordeaux, P.-V., 163 (1964).
158. S. A. Braley, Trans. Amer. Soc. Artif. Intern. Organs, **10**, 240 (1964).
159. S. A. Braley, Amer. Chem. Soc., Div. Org. Coatings, Plastics Chem., Preprints, **24**, 189 (1964).
160. S. A. Braley, Trans. Penn. Acad. Ophthal., **18**, 73 (1965).
161. A. Danek, Polski Tygodnik lek., **11**, 1887 (1956).
162. W. Eichler, Z. Ges. Hyg., **13**, 746 (1967).
163. H. Goodman, Amer. Prof. Pharmacist, **21**, 129 (1955).
164. Goodman, Amer. Prof. Pharmacist, **21**, 172 (1955).
165. S. Hohnjec and B. Žlof, Farm. Glasnik, **18**, 107 (1962).
166. J. P. W. Hughes, J. Ind. Nurses, No. 3 (1957).
167. G. Kaiser, Deut. Gesundheitswesen, **12**, 830 (1957).
168. V. Kyral, K. Swehla, and Z. Faix, Čas. Lek. Cesk., **105**, 310 (1966).
169. H. Lehmann, Schweiz. Apth.-Ztg., **93**, 459 (1955).
170. F. Leiss and K. H. Peter, Arzneimittel-Forsch., **4**, 571, 614, 664 (1954).
171. M. A. Lesser, Drug. and Cosmetic Ind., **72**, 616, 688 (1953).
172. H. L. Levin, Milit. Med., **121**, 397 (1957)
173. R. Levin, Manufact. Chemist, **26**, 157 (1955).
174. R. Levin, "Pharmacy of Silicones and Their Uses in Medicine", London, 1958.
175. R. R. McGregor, "Silicones in Medicine and Surgery", Michigan, 1957.
176. Midland Silicones Ltd., Hopkin and Williams, Ltd., "Silicones for Use in Medicine", London, 1962.
177. R. Müller, Pharmazie, **9**, 949 (1954).
178. A. Murgia, Minerva chir. (Torino), **9**, 1132 (1954).
179. H. Reuther, Pharm. Zentralhalle, **100**, 265 (1961).
180. O. Saiko, Österr. Apoth.-Ztg., **9**, 361 (1955).
181. D. M. E. Thomas, The Alchemist, 21 (1954).
182. R. Blocksma and S. Braley, Plast. Reconstr. Surg., **35**, 366 (1965).
183. Dow Corning Center for Aid of Medical Research, Rubber World, **143**, 67 (1961).

184. Dow Corning Center for Aid to Medical Research, Rubber and Plastics Age, 42, 292 (1961).
185. S. Fomon and J. W. Bell, Arch. Otolaryng., 84, 514 (1966).
186. H. A. Zarem, Surg. Clin. North Amer., 48, 129 (1968).
187. C. Ramel, Praxis, 55, 1302 (1966).
188. M. T. Alyushin, Gigiena Truda i Prof. Zabol., No. 9, 54 (1967).
189. C. P. McCord, W. G. Frederick, and S. Stolz, J. Lab. clin. Med., 23, 278 (1937).
190. J. A. Kasper, C. P. McCord, and W. G. Frederick, Bur. Ind. Hyg. and Bur. Labs., Dept. Health. Detroit, 14 (1937); Ind. Med., 6, 660 (1937).
191. H. F. Smyth and J. J. Seaton, J. Ind. Hyg. Toxicol., 22, 288 (1940).
192. Anon, J. Amer. Med. Assoc., Queries and Minor Notes, 118, 857 (1942).
193. Anon, Chem. Eng. News, 24, 1690 (1946).
194. A. Badinand and M. Barlier, Arch. malad. profes., 9, 558 (1948).
195. C. P. Carpenter, H. F. Smyth, and U. C. Pozzani, J. Ind. Hyg. Toxicol., 31, 343 (1949).
196. H. F. Smyth, C. P. Carpenter, and C. S. Weil, J. Ind. Hyg. Toxicol., 31, 60 (1949).
197. H. F. Smyth, C. P. Carpenter, C. S. Weil, and U. C. Pozzani, Arch. Ind. Hyg. Occup. Med., 10, 61 (1954).
198. Union Carbide Corporation, Silicones Division Bulletins X1901, X1902.
199. V. K. Rowe, H. C. Spencer, and S. L. Bass, J. Ind. Hyg. Toxicol., 30, 332 (1948).
200. H. Taylor, Brit. Med. Bull., 7, 15 (1950).
201. U. C. Pozzani and C. P. Carpenter, Arch. Ind. Hyg. Occup. Med., 4, 465 (1951).
202. J. Vrba, Pracovni Lékařstvi, 8, 210 (1956).
203. J. V. Klauder, Arch. Environmental Health, 1, 407 (1960).
204. A. A. Kanarevskaya, Toksikol. Novykh Prom. Khim. Veshch., 3, 5 (1961).
205. S. N. Kremneva, Toksikol. Novykh Prom. Khim. Veshch., 3, 18 (1961).
206. N. K. Kulagina, A. I. Korbakova, and E. A. Korlyakova, Toksikol. Novykh Prom. Khim. Veshch., 3, 10 (1961).
207. N. K. Kulagina, A. I. Korbakova, and T. A. Kochetkova, Toksikol. Novykh Prom. Khim. Veshch., 3, 81 (1961).
208. D. W. Fasset, "Industrial Hygiene and Toxicology", Intersc. Publ., New York, 1962, Vol. 2, p. 1933.
209. H. F. Smyth, C. P. Carpenter, C. S. Weil, U. C. Pozzani, and J. A. Streigel, Amer. Ind. Hyg. Assoc. J., 23, 95 (1962).
210. I. F. Zapalkevich and S. I. Murav'eva, Gigiena Truda i Prof. Zabol., 7, No. 11, 35 (1963).
211. N. K. Kulagina and T. A. Kochetkova, Toksikol. Novykh. Prom. Khim. Veshch., 5, 192 (1963).
212. A. I. Korbakova, Vestnik Akad. Med. Nauk, SSSR, 19, No. 7, 17 (1964).
213. N. K. Kulagina and T. A. Kochetkova, "Toksikologiya i Gigiena Vysokomolekuyarnykh Soedinenii i Khimicheskogo Syrya Ispol'zovannogo dlya Ikh Sinteza, Materialy II Konferentsii" (The Toxicology and Hygiene of High-Molecular Compounds and the Chemical Raw Materials Used for Their Synthesis, Proceedings of the Second Conference), Moscow, 1964, p. 61.
214. M. K. Kulagina and T. A. Kochetkova, Toksikol. Novykh Prom. Khim. Veshch., 6, 95 (1964).
215. M. K. Kulagina and T. A. Kochetkova, Toksikol. Novykh Prom. Khim. Veshch., 6, 109 (1964).
216. N. V. Lazarev, "Vrednye Veshchestva v Promyshlennosti" (Harmful Substances in Industry), Izd. Khimiya, Moscow–Leningrad, 1965, Part II, pp. 325–331.
217. N. K. Kulagina, T. A. Kochetkova, and V. B. Losev, Okhr. Truda i Tekh. Bezop., Ochistka Stochnykh Vod. i. Otkhod. Gazov i Khim. Prom., 2, 15 (1966).
218. E. G. Rochow, "Introduction to the Chemistry of the Silicones", New York, 1949, p. 60.
219. R. F. Keeler and S. A. Lovelace, J. Exp. Med., 109, 601 (1959).
220. H. D. Cogan and C. A. Sotterstram, Chem. Eng. News, 2499 (1946).
221. E. N. Pomerantseva, "Instruktsii to Okazaniyu Pervoi Pomoshchi pri Ostrykh Intoksikatsiyakh Alkyl(aril)khlorsilanami i Tri- i Tetraetoksisilanami" (First-Aid Instructions for Acute Intoxication with Alkyl(aryl)chlorosilanes and Tri- and Tetraethoxysilanes), Moscow, 1961.
222. A. L. Klyashchitskaya and E. N. Elkhovskaya, "Toksikologicheskaya Kharakterestika Monomernykh Kremniiorganicheskikh Soedinenii i Epoksidnykh Smol" (Toxicological Characteristics of Monomeric Organosilicon Compounds and Epoxy-Resins), NIITEI, Moscow, 1966.
223. N. K. Kulagina, T. A. Kochetkova, and V. B. Losev, Gigiena Truda i. Prof. Zabol., 12, No. 5, 42 (1968).
224. N. K. Kulagina and V. B. Losev, Plast. Massy, No. 10, 51 (1968).
225. International Labour Office, Occup. and Health., 2, 841 (1934).
226. P. Zeglio, Med. Lavoro, 33, 184 (1942).
227. N. I. Sax, "Handbook of Dangerous Materials", New York, 1951.
228. A. Badinand, Bull. soc. pharm., Bordeaux, 90, 289 (1952).
229. M. L. Rylova, Farmak. i. Toksikol., 15, No. 5, 46 (1952).
230. O. N. Syrovadko, "Tezisy Dokladov Konferentsii Molodykh Nauchnykh Rabotnikov" (Abstracts of Reports of the Young Scientists Conference), Izd. Inst. Gigieny Truda i Prof. Zabol. Akad., Med. Nauk SSSR, Leningrad, 1957, p. 3.
231. S. F. Belova and E. A. Korlyakova, Giegiena. i Sanit., 23, No. 9, 72 (1958).
232. N. K. Kulagina and A. I. Korbakova, Prom. Toksikol., 106 (1960).
233. N. K. Kulagina, Toksikol. Nov. Prom. Khim. Veshch., 3, 73 (1961).
234. E. A. Korlyakova, Toksikol. Nov. Prom. Khim. Veshch., 3, 23 (1961).
235. N. K. Kulagina and A. I. Korbakova, Toksikol. Nov. Prom. Khim. Veshch., 3, 33 (1961).
236. N. K. Kulagina and A. I. Korbakova, Toksikol. Nov. Prom. Khim. Veshch., 3, 48 (1961).
237. N. K. Kulagina and A. I. Korbakova, Toksikol. Nov. Prom. Khim. Veshch., 3, 61 (1961).
238. I. V. Sanotskii, Toksikol. Nov. Prom. Khim. Veshch., 2, 75 (1961).
239. A. A. Golubei and E. N. Lyublina, "Materialy Nauchnoi Sessii, Posvyashchennoi Itogam Raboty Instituta za 1959–1960 gg." (Proceedings of the Scientific Session Devoted to the Results of the Work of the Institute in 1959–1960), Izd. Leningrad. Inst. Gigieny Truda i Profzabol., Leningrad, 1961, p. 107.
240. A. A. Golubev, Prom. Toksikol. i Klinika Prof. Zabol., 76 (1962).

241. E. A. Peregud and B. S. Boikina, Gigiena i Sanit., No. 6, 49 (1962).
242. O. N. Syrovadko, Gigiena Truda i Prof. Zabol., **6**, No. 4, 22 (1962).
243. N. K. Kulagina and T. A. Kochetkova, Toksikol. Nov. Prom. Khim. Veshch., **5**, 149 (1963).
244. N. K. Kulagina and T. A. Kochetkova, Toksikol. Nov. Prom. Khim. Veshch., **5**, 165 (1963).
245. N. K. Kulagina and T. A. Kochetkova, Toksikol. Nov. Prom. Khim. Veshch., **5**, 173 (1963).
246. N. K. Kulagina and T. A. Kochetkova, Toksikol. Nov. Prom. Khim. Veshch., **5**, 182 (1963).
247. E. Holstein, "14th International Congress on Occupational Health, Madrid, 1963"; Chem. Abs., 64, 20510 (1966).
248. A. A. Golubev, Gigiena Truda i Prof. Zabol., **9**, No. 9, 27 (1965).
249. J. M. Barnes and L. Magos, Organomet. Chem. Rev., **3A**, 137 (1967).
250. Y. Henderson and H. W. Haggard, "Noxious Gases", Reinhold Publ. Corp., 1943, p. 99.
251. W. Jaross, Deut. Gesundheitswesen., **21**, 1141 (1966).
252. A. J. Lanza and J. A. Goldberg, "Industrial Hygiene", New York, 1939, p. 508.
253. B. Malis, Kozarstvi, **14**, 289 (1964).
254. C. Eaborn, "Organosilicon Compounds", London, 1960, p. 473.
255. W. Noll, "Chemie und Technologie der Silicone", Verlag Chemie, Weinheim, 1968, p. 448.
256. A. L. Klyashitskaya, G. N. Krasovskii, and S. A. Fridlyand, "IV Konferentsiya po Khimii i Primenenii Kremniiorganicheskikh Soedineii, Tbilisi, Tezisy Dokladov" (The IVth Conference on the Chemistry and Applications of Organosilicon Compounds, Tbilisi Abstracts of Reports), NIITEI, Moscow, 1968, p. 105.
257. N. K. Kulagina and T. A. Kochetkova, Toksikol. Nov. Prom. Khim. Veshch., **5**, 214 (1963).
258. E. A. Peregud and B. S. Boikina, Gigiena i Sanit., **23**, 66 (1958).
259. V. D. Topolyanskii, Farmakol. i Toksikol., 309 (1968).
260. T. Adamczak, I. Kasprzycka, S. Maciejczyk, J. Sadowski, and J. Zareba, Pol. Tyg. Lek., **15**, 659 (1960).
261. J. M. Andrews, Plast. Reconstr. Surg., **38**, 581 (1966).
262. K. Anborger, Farm. Rev., **53**, 50 (1954).
263. R. R. Barondes, W. D. Judge, C. G. Towne, and M. L. Baxter, Milit. Surgeon, **106**, 379 (1950).
264. N. Ben-Hur and Z. Neuman, Israel Med. J., **22**, 15 (1963).
265. I. A. Boyd and C. L. Pathak, Scot. Med. J., **9**, 345 (1964).
266. S. Byczkowski, R. Piekoś, A. Radecki, T. Mincer, and K. Wrześniowa, Pozn. Tow. Przyj. Nauk Wydz. Lekar. Prace Kom. Farm., **4**, 141 (1966).
267. S. Carson, M. S. Weinberg, and B. L. Oser, Proc. Sci. Sect. Toilet Goods Assoc., **45**, 8 (1966).
268. C. P. Child, H. D. Paquin, and W. B. Deichmann, Arch. Ind. Hyg. Occup. Med., **3**, 479 (1951).
269. W. C. Cutting, Stanford Med. Bull., **10**, 21 (1952).
270. L. T. Fairhall, Ann. Rew. Med., **3**, 265 (1952).
271. A. Gancberg, Ind. Chim. Belge, **24**, 1486 (1959).
272. General Electric Co., Silicone Polymer Toxicological Data Sheet, AD-28B (1953).
273. C. Gloxhuber and G. Hecht, Arzneimittel-Forsch., **5**, 10 (1955).
274. H. J. Horn, D. J. Kilian, and R. A. Smith, Amer. Med. Assoc. Arch. Ind. Health, **15**, 63 (1957).
275. W. C. Hueper, J. Nat. Cancer Inst., **33**, 1005 (1964).
276. S. F. Kern, R. C. Anderson, and P. N. Harris, J. Amer. Pharm. Soc., **38**, 575 (1949).
277. W. E. McDonald, G. E. Lanier, and W. B. Deichman, Amer. Med. Assoc. Arch. Ind. Health, **21**, 514 (1960).
278. J. D. B. MacDougall, Nature, **172**, 124 (1953).
279. R. Magimel, P. Freour, M. Serise, and J. Plantie, J. Méd. Bordeaux, **133**, 1196 (1956).
280. M. Meijst, Pharm. Weekblad, **90**, 869 (1955).
281. G. Polemann, Klin. Woch., **33**, 1011 (1955).
282. G. Polemann and G. Froitzheim, Arzneimittel-Forsch., **3**, 457 (1953).
283. W. A. Reed and C. F. Kittle, Amer. Med. Assoc. Arch. Surg., **78**, 220 (1959).
284. T. D. Rees, J. Platt, and D. L. Ballantyne, Plast. Reconstr. Surg., **35**, 131 (1965).
285. V. K. Rowe, H. C. Spencer, and S. L. Bass, Arch. Ind. Hyg. Occup. Med., **1**, 539 (1950).
286. R. W. Thomassen, J. P. Howbert, D. F. Winn, and S. W. Thompson, J. Thor. Cardiov. Surg., **41**, 611 (1961).
287. J. Baltkajs, M. G. Voronkov, and G. Zelcans, Ind. Akad. Nauk. Latv. SSR, Ser. Khim., No. 2, 102 (1964).
288. M. G. Voronkov and G. Zelcans, "IX Mendeleevskii S'ezd po Obshchei i Prikladnoi Khimii; Sektsia Khimii i Tekhnologii Lekarstvennykh Veshchestv, Referaty Dokladov i Soobshchenii" (IXth Mendeleev Congress on General and Applied Chemistry; Section on the Chemistry and Technology of Medicinal Substances—Abstracts of Reports and Communications), Izd. Nauka, Moscow, 1965, p. 10.
289. Anon, Chem. Eng. News., **43**, No. 51, 31 (1965).
290. M. G. Voronkov, Pure Appl. Chem., **13**, 35 (1966).
291. M. G. Woronkow, G. I. Seltschan, A. Lapsina, and W. A. Pestunowitsch, Z. Chem., **8**, 214 (1968).
292. G. Zelcans, "Silatrany" (Silatranes), Candidate's Thesis, Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga, 1967.
293. Z. Atare, N. G. Voronkov, S. Gutberga, G. Zelcans, A. Zile, A. Kimenis, L. Kruzmetra, and E. Lukevics, "Kremniiorganicheskie Soedineniya, Trudy Soveshchaniya" (Organosilicon Compounds. Conference Proceedings), Moscow, 1966, Vol. 4, p. 25.
294. E. Lukevics, M. G. Voronkov, A. E. Pestunovich, A. Kimenis, S. Gutberga, and Z. Atare, Izv. Akad. Nauk. Latv. SSR, No. 4, 93 (1968).
295. E. Lukevics, S. Gutberga, L. Liberts, A. Kimenis, and M. G. Voronkov, Izv. Akad. Nauk. Latv. SSR, No. 8, 60 (1969).
296. E. Lukevics, L. Liberts, and M. G. Voronkov, Zhur. Obshch. Khim., **39**, 1784 (1969).
297. E. Lukevics, L. I. Liberts, and M. G. Voronkov, "II Symposium internat. sur la Chimie des composes organiques de Silicium, Bordeaux, 1968", p. 123.
298. E. Lukevics, A. E. Pestunvich, E. A. Reshetilova, and M. G. Voronkov, "IV Konferentsiya po Khimii i Prakticheskomu Primeneniyu Kremniiorganicheskikh Soedinenii, Tbilisi, Tezisy Dokladov" (The IVth Conference of the Chemistry and Practical Applications of Organosilicon Compounds, Tbilisi, Abstracts of Reports), NIITEI, Moscow, 1968, p. 48.
299. A. Kimenis, R. Vitolin, E. Lukevics, L. Liberts, and M. G. Voronkov, Izv. Akad. Nauk. Latv. SSR, (in the press).
300. Anon, Chem. Eng. News, **42**, No. 37, 60 (1964).

301. R. Fessenden and M. D. Coon, J. Medicin. Chem., 7, 561 (1964).
302. R. J. Fessenden, J. G. Larsen, M. D. Coon, and J. S. Fessenden, J. Medicin. Chem., 7, 695 (1964).
303. R. J. Fessenden and M. D. Coon, J. Medicin. Chem., 8, 604 (1965).
304. R. J. Fessenden and M. D. Coon, J. Medicin. Chem., 9, 262 (1966).
305. M. G. Voronkov and B. N. Dolgov, Izv. Akad. Nauk SSSR, Otd. Khim. Nauk, 1128 (1957).
306. M. G. Voronkov, Izv. Akad. Nauk SSSR, Otd. Khim., Nauk, 517 (1957).
307. H. S. Booth and C. F. Swinehart, J. Amer. Chem. Soc., 54, 4750 (1932).
308. Anon, J. Amer. Med. Assoc., 124, 268 (1944).
309. Anon, J. Ind. Hyg. Tox., 26, 118 (1944).
310. H. S. Booth and A. A. Schwartz, J. Amer. Chem. Soc., 68, 2662 (1946).
311. R. K. Ingham, S. A. Rosenberg, and H. Gilman, Chem. Rev., 60, 459 (1960).
312. P. L. De Benneville and M. J. Hurwitz, U. S. P. 2 876 209 (1959); Chem. Abs., 53, 12 321 (1959).
313. M. G. Voronkov, "Composés du silicium biologiquement actifs, II Symposium-international sur la chimie des composés organiques du Silicium, Bordeaux, 1968", Pure Appl. Chem., 19 (1969).
314. M. Frankel, M. Broze, D. Gertner, A. Rotman, A. Shenhar, and A. Zilkha, J. Medicin Chem., 11, 857 (1968).
315. I. Belsky, D. Gertner, and A. Zilkha, J. Medicin Chem., 11, 92 (1968).
316. I. Belsky, D. Gertner, and A. Zilkha, J. Medicin Chem., 11, 451 (1968).
317. E. A. Brown and I. Laos, Belgian P. 668 903 (1966); Chem. Abs., 65, 7238 (1966).
318. E. A. Brown and R. A. Mikulec, U. S. P. 3 300 523 (1967); Chem. Abs., 66, 115 877w (1967).
319. E. Chang and V. K. Jain, J. Medicin Chem., 9, 433 (1966).
320. S. Fregert and H. Rorsman, Nature, 192, 989 (1963).
321. P. T. Henderson, E. J. Ariens, B. W. J. Ellenbroek, and A. Simonis, J. Pharm. Pharmacol., 20, 26 (1968).
322. I. Belsky, D. Gertner, and A. Zilkha, J. Medicin Chem., 11, 448 (1968).
323. R. J. Fessenden and R. Rittenhouse, J. Medicin. Chem., 11, 1070 (1968).
324. M. Ya. Marova, M. G. Voronkov, and B. N. Dolgov, Zhur. Prikl. Khim., 30, 650 (1957).
325. L. S. Moody, U. S. P. 2 567 742 (1951); Chem. Abs., 47, 145 (1953).
326. D. L. Bailey and R. M. Pike, U. S. P. 2 957 781 (1961); Chem. Abs., 55, 5426 (1961).
327. R. L. Metcalf and T. R. Fukuto, J. Econom. Entomol., 58, 1151 (1965).
328. E. L. Morehouse, U. S. P. 2 938 046 (1961); Chem. Abs., 55, 1066 (1961).
329. G. B. Sterling and C. E. Pawloski, U. S. P. 3 256 308 (1966); Chem. Abs., 65, 7217 (1965).
330. C. H. Richardson and F. R. Du Chanois, J. Econom. Entomol., 44, 997 (1951).
331. A. R. Gilbert, U. S. P. 2 768 193 (1956); Chem. Abs., 51, 5816 (1957).
332. H. Hartmann, German P. 1 061 322 (1959); Chem. Abs., 55, 6500 (1961).
333. D. A. Kochkin and I. N. Azerbaev, "Olovo- i Svinetsorganicheskie Monomery i Polimery" (Organotin and Organolead Monomers and Polymers), Izd. Nauka, Alma-Ata, 1968, p. 175.
334. Z. I. Shabarova and M. G. Voronkov, Izv. Akad. Nauk. Latv. SSR, Ser. Khim., 321 (1967).
335. V. P. Dremova, E. Lukevics, and M. G. Voronkov, Izv. Akad. Nauk. Latv. SSR, Ser. Khim., No. 12 (1969).
336. L. K. Maslii, V. T. Osipyan, B. V. Aleksandrov, V. B. Kazhdan, and T. P. Razbegaeva, USSR P. 180 015 (1963); Byull. Izobret., No. 6, 107 (1966).
337. M. G. Voronkov, L. N. Alekseeva, B. Brizga, A. Zile, L. Kruzmetra, V. P. Kozyukov, E. Lukevics, I. L. Lyashenko, V. F. Mironov, and N. S. Fedotov, Khim. Farm. Zhur., No. 5, 26 (1967).
338. E. A. Mason, B. P. 964 182 (1964); Chem. Abs., 61, 9366 (1964).
339. A. Kaller, DDR P. 45 885 (1966); Chem. Abs., 65, 9661 (1966).
340. Midland Silicones Ltd., B. P. 778 272 (1957); Chem. Abs., 52, 429 (1958).
341. T. H. Porter and W. S. Shive, J. Medicin. Chem., 11, 402 (1968).
342. J. L. Speier, U. S. P. 2 611 776 (1952); Chem. Abs., 47, 11 244 (1953).
343. Dow Corning Corp., B. P. 630 952 (1949); Chem. Abs., 44, 4491 (1949).
344. Q. F. Soper, C. W. Whitehead, O. K. Behrens, J. J. Corse, and R. G. Jones, J. Amer. Chem. Soc., 70, 2849 (1948).
345. T. M. Voronkina, I. T. Strukov, and M. F. Shostakovskii, Zhur. Obshch. Khim., 34, 1464 (1964).
346. G. E. Ham, U. S. P. 3 243 429 (1966); Chem. Abs., 65, 3908 (1966).
347. L. F. Cason and J. R. Rhone, U. S. P. 2 789 122 (1957).
348. R. L. Merker, French P. 1 403 705 (1965); Chem. Abs., 63, 13 973 (1965).
349. J. K. Leasure and D. R. Mussell, U. S. P. 3 183 076 (1965); Chem. Abs., 63, 3558 (1965).
350. J. K. Leasure and J. L. Speier, J. Medicin. Chem., 9, 949 (1966).
351. G. E. Bennet and W. W. Lee, U. S. P. 2 887 371 (1959); Chem. Abs., 53, 19 883 (1959).
352. E. Lukevics and M. G. Voronkov, Zhur. Obshch. Khim., 38, 2325 (1968).
353. R. J. Fessenden and C. Ahlfors, J. Medicin. Chem., 10, 810 (1967).
354. J. Paul and W. F. R. Pover, Arch. Biochem. Biophys., 87, 312 (1960).
355. R. R. McGregor, Dow Corning Center for Aid to Medical Research, The Bulletin, 2, No. 4, 15 (1961).
356. E. D. Green, Thesis, San Jose State Coll., California, 1965.
357. M. G. Voronkov, Vestnik. Akad. Nauk SSSR, No. 10, 48 (1968).
358. M. G. Voronkov, G. Zelcans, V. F. Mironov, J. Bleidelis, and A. Kemme, KhGS, 227 (1968).

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