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USSR Report

LIFE SCIENCES

AGROTECHNOLOGY AND FOOD RESOURCES

(FOUO 1/82)

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CONTENTS

 [III - USSR - 21n S&T FOUO]

ECOLOGICAL PROBLEMS

SEARCHING FOR SELECTIVELY ACTIVE INSECT ACARICIDES

Moscow INTENSIFIKATSIYA SEL'SKOKHOZYAYSTVENNOGO PROIZVODSTVA I PROBLEMY ZASHCHITY OKRUZHAYUSHCHEY SREDY in Russian 1980 (signed to press 31 Oct 80) pp 156-165

[Article by T.A. Mastryukova, Institute of Metallo-organic Compounds, USSR Academy of Sciences: "Methods for Searching for New Selective Phosphororganic Insect Acaricides Which Do Not Leave Harmful Residues in the Environment," from book "Intensification of Agricultural Production and the Problems of Environmental Protection," edited by T. I. Lipatova, Izdatel'stvo "Nauka", 500]

[Text] Agricultural production during the second half of the 20th Century has invariably been associated with the use of agents for protecting plants against weeds, pests and agricultural plant diseases. This leads to a disruption in the existing ecological balance in a given region and it naturally and necessarily serves to contaminate the surroundings [1].

Since we cannot cease our efforts directed against harmful organisms, we must employ preparations which, following the completion of their effective action, will disintegrate completely into non-toxic residues; on the other hand, the agents employed must be highly selective, destroying the harmful populations but not disrupting other ecological balances in the region.

If we look at pesticides -- the principal means for combating harmful organisms in agriculture, then it must be stated that first generation pesticides do not meet these requirements. They are highly toxic with regard to warm blooded animals and they are characterized by a broad spectrum of action, affecting both harmful and useful organisms and they are highly persistent, that is, they remain in the atmosphere for a long period of time.

The toxicity of such well known first generation phosphororganic insecticides as octamethyl, thiophos and systox, for warm blooded animals, was 1-7 mg/kg (such as LD_{50}), which is at the toxicity level for potassium cyanide (LD_{100} 2.5 mg/kg). Exactly the same high toxicity was possessed by the chlororganic derivatives, with the exception of DDT; their toxicity ranged from 7 to 40 mg/kg. It turned out later that they were especially toxic for fish (SK_{50} approximately 0.01 mg/kg). Their high persistence was extremely unpleasant; they could remain in the environment for years, circulating among the soil-water and food chains and eventually entering the human organism. At the present time, all of these pesticides are either completely prohibited by law or their use is strictly limited.

As a result of intensive studies carried out by firms and scientific institutes, the following pesticides have been obtained during the past few decades -- second and third generation pesticides which to a considerable degree lack the above shortcomings. Their toxicity for humans and animals has been lowered by tens and hundreds of times. It is sufficient to state that the average toxicity of preparations in use at the present time is on the order of 900 mg/kg. These preparations disintegrate rather rapidly in the environment. Thus, thiophos, a first generation preparation, disintegrates in the soil only 35 percent over a period of 2 weeks. This means that 90 percent of the thiophos decomposes roughly over a period of 3 months. Phosphamide decomposes in the soil two and a half times more rapidly. Many second and third generation phosphororganic preparations decompose by 90-95 percent in just 1-2 days.

Thus, considerable success has been achieved during the past decade in improving the chemical agents used for protecting plants. At the same time, the tasks for protecting the environment continue to advance newer and more strict requirements, which in turn stimulate a search for new pesticides. Here there are two principal tasks: first of all, a pesticide must break down in the environment and not leave harmful residues and, secondly, a pesticide must have high selective action as it affects definite harmful organisms. It must be non-toxic for other arthropods and certainly for humans and domestic animals.

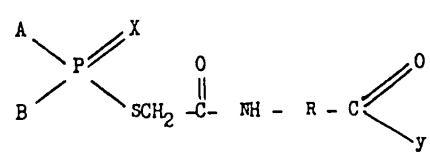
All successes achieved up until now in searching for second and third generation pesticides have been obtained as a result of tremendous research work, carried out using Ehrlich's "trial and error" method. This is a very laborious and costly path and with the passage of time it is becoming more difficult and more expensive. It is sufficient to state that during the past few years only one substance of more than 10,000 that have been synthesized and examined [2] has been introduced into agricultural practice.

Another method of specialized research is based upon a thorough study of the mechanism of the effect and metabolism of pesticides in various types of organisms.

Some results obtained from the second research method are set forth below. This method made it possible to find new pesticides which have a high level of selective action and which do not leave harmful residues in the environment.

Our work is based upon the following considerations. The absence of harmful residues in the environment can best be achieved if the preparation breaks up into fragments which are already present in abundance in the environment. The searches for selectivity are based upon differences in the metabolic changes of substances in various types of organisms. The substance is toxic for a given type if the metabolic activation "exceeds" the detoxication and conversely.

It was on this basis that we arrived at phosphororganic esters, which contain residues of acetylated amino acids in a side chain [3-5]

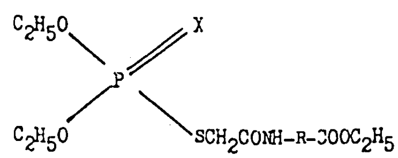


A, B = RO; CH_3, C_3H_7; X = S, O; Y = OR, OH, $NHCH_3$; R = CH_2, $CH(CH_3)$, $CH(C_3H_7$-iso), $CH(C_4H_9$-iso), $CH(CH_2C_6H_5)$, $CH(CH_2COOR)$, $CH(CH_2CH_2COOR)$, $CH_2CH_2SCH_3$ and others. For these compounds, extensive variations were noted both in the A and B substitutes in the phosphorus part of the molecule and in the amino acid residues. A high selective action was established for substances of this type for insects and mites on the one hand and warm blooded animals and arthropods on the other. Considerable importance is also attached to the fact that these compounds, upon decomposing in the environment, give off biogenic and non-toxic residues: amino acids, glycolic or thioglycolic acid and phosphoric acids. We studied the metabolism, toxicodynamics, anticholinesterase properties and the toxicity of the substances themselves and also their more important metabolites [6-8]. It was on this basis that we succeeded in developing a picture of the selective toxicity of the substances of this type.

By way of an example, let us examine the data obtained for certain dithiophosphates which we studied. A description of their physiological activity is furnished in Table 1.

TABLE 1

Physiological Activity of Certain Dithiophosphates -- Derivatives of Acetylated Amino Acids and Their R=O Metabolites, With the General Formula being



№	X	R	СК50		ЛД50 мг/кг (мыши) (3)	K_2 (л.·моль$^{-1}$·мин$^{-1}$)	
			(1) Тли	Клещи (2)		ХЭ тли	АХЭ (4)
Ш-I40	S	$-CH_2CH_2-$	0,0075	0,I4	2000	—	—
ЖШ-5	O	$-CH_2CH_2-$	0,0035	0,0095	250	2,3·I0^5	I,6·I0^3
Ш-I4I	S	$-CH_2$-C_3H_7-изо	0,I7	0,0027	90	—	—
Ш-I56	O	C_3H_7-изо	0,I0	0,0058	75	9,2·I0^3	3,6·I0^2
Ш-I20	S	$-CH_2-$	0,0I5	0,0I5	750		
Ш-I55	O	$-CH_2-$	0,0025	0,0052	75	I,22·I0^4	4,I3·I0^3
Ш-I22	S	$-CH_2$ CH_3-	0,0I8	0,004	I000	—	—
ЭГ-33	O	CH_3-	0,025	0,0023	290	7,5·I0^3	I,8·I0^3

Key:
1. Aphids
2. Mites
3. Lethal dose$_{50}$ mg/kg (mice)
4. Acetylcholinesterase

Here Ш-140 is the selective insecticide, Ш-141 is the selective acaricide and Ш-120 is the insecticide and acaricide of identical strength. At first glance, the data in the table present a rather complicated picture and yet can be understood provided one takes into account the simultaneous or consecutive flow of several biochemical processes, the presence of which is confirmed both by the data in this table and by special studies of the metabolism and toxicodynamics.

Precisely what changes are taking place in these substances?

First of all, there is the process of biochemical activation. It consists of the oxidation of the P=S groups of our insect acaricides into the P = O. Judging by the results of the study, it is dependent to only a slight degree upon the nature of the amino acid.

Secondly, the inhibiting of the cholinesterase P=O by the metabolites. Generally speaking, these are inhibitors of average strength. With regard to the AChE [acetylcholinesterase] of mammals, their activity depends very little upon the nature of the amino acid: the changes do not exceed one order. With regard to the ChE of aphids, to the contrary, an expressed selectivity is observed. For ZhSh-5 > Sh-155 > Sh-156 > EG-33, that is, the nature of the amino acid affects the inhibiting of the ChE of the aphids and in a manner such that the introduction of the α-branchings lowers the activity. Here we see an example of a different specificity in the AChE for mammals and the ChE for aphids.

Thirdly, there is carboxyesterase hydrolysis. This is the detoxication process. According to our data, the carboxyesterases in the homogenates of mites are more active than those in the homogenates of aphids.

With regard to the effect of the structure of an amino acid residue, it must be borne in mind that the hydrolysis of ethyl esters of carboxy acids slows down upon the introduction of the branchings to the α carbon atom of the acid, especially with the entry of the isopropyl group. Thus, our substances can be arranged in a series according to the speed of hydrolysis: derivatives β-alanine > glycine > alanine > valine. Moreover, in the case of mites the β-analine and glycine residues change in some areas

Fourthly, there is the inhibiting of carboxyesterase. As it turned out, the P=O metabolites of our substances inhibit the carboxyesterases. The valine derivative (Sh-156) shows the greatest inhibiting effect. It is obvious that the worse a substance with a carbalkoxy group is as a substrate for carboxyesterases, the stronger it will inhibit them.

Fifthly, there is carboxyamidase hydrolysis. This is also a process of detoxication which we did not study in particular, but judging by the metabolites revealed, it is taking place.

Let us examine the experimental data on toxicity. The β alanine derivatives represent the first pair of substances. Here, as already noted, Sh-140 is the selective insecticide. It hydrolyzes well in the liver of mice and in mites and thus its detoxication takes place more rapidly than its activation: thus Sh-140 is 8 times less toxic for mice than its P=O metabolite, 15 times for mites and only twofold for aphids. Owing to the fact that carboxyesterase activity is only weakly expressed in aphids, a good half of the Sh-140 is activated in the P=O metabolite, ZhSh-5 is a very strong anticholinesterase for aphids (10^5). It is precisely this which explains the high selective action of Sh-140 for aphids.

The second pair of substances -- valine derivatives. Sh-141 is a selective acaricide. Owing to the valine grouping, not only does its carboxyesterase hydrolysis take place in a slow manner, but the P=O metabolite (Sh-156) inhibits the carboxyesterases. Thus, oxidizing activation with the formation of Sh-156 is preferred for Sh-141 and once the Sh-156 forms it terminates further deactivation by inhibiting carboxyesterases. Hence the P=S compounds and their P=O metabolite are close in toxicity.

In a similar manner, it is possible to analyze the third pair of substances -- glycine derivatives. Here Sh-120 is an insecticide and acaricide of equal strength; in this instance the detoxication processes are expressed in aphids to a greater degree than with Sh-140 and in the case of mites -- to a lesser degree.

We are obviously aware that the interpretation cited above is sufficiently approximate and thus it can be utilized for predicting the selectivity of action for substances of related types and for planning further experiments.

If the substances or products of their activation are very strong anticholinesterases, then their carboxyesterase detoxication will not be very effective. This corresponds to the general rule of Unterstenhofer, according to which high activity is accompanied by a low selectivity. At the same time, this rule can be disrupted by a very high detoxication level.

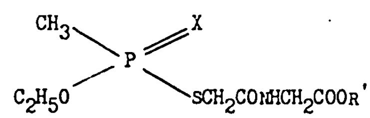
Allow me to cite data for a number of thiophosphonates (see Table 2), in which the COOR group radicals vary; X -- sulphur or oxygen. Here the phosphoryl compounds are strong and highly toxic acaricides which surpass the standard -- thiophos -- in terms of their action. With regard to the P=S compounds and with the exception of thiophos, they are strong insect acaricides and rather toxic for warm-blooded animals. However, NSh-8, an isobutyl ester, is detoxicated to a considerably stronger degree than lower homologs: its coefficients of detoxication for mice -- 6.6, for aphids -- 5.3 and for mites -- 5.7. Such strong detoxication is obviously associated with the ease in alkyl-oxygen disruption or the β elimination. As a result, we have a rather strong insect acaricide which is not inferior to thiophos, but which is at least 20 times less toxic than thiophos. This is an interesting observation and an equally interesting substance.

The effect of isobutyl protection is noted in other instances, for example, in the derivatives of the β-alanine, in which the monothioanalogs are strong anticholinesterases (10^5). Here the isobutyl derivative is the least toxic for mice.

The fact that in this effect we are dealing with hydrolytic detoxication based on a carboxyl group is revealed by examples in which the detoxication encounters very strong steric hindrance with the introduction of the isopropyl group (valine derivatives). The oxygen analogs of these substances are also strong anticholinesterases (10^5), but the substances themselves are not only poorly hydrolyzed by the carboxyesterases but in addition they are also strongly suppressed by them. Here there is no isobutyl effect whatsoever.

TABLE 2

Physiological Activity of Certain Methyldithiophosphonates -- Derivatives of Acetylated Glycine and Their Monothioanalogs, With the General Formula Being:

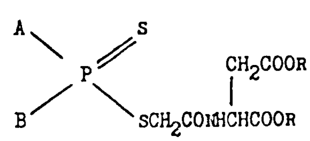


№	R'	X	ЛД50, мг/кг, Мыши (1)	СК50 (2) Тли	(3) Клещи
НШ-I	CH_3	S	I25	0,0005	0,000I5
НШ-3	CH_3	0	I,7	0,0025	0,0003
ЭГ-20	C_2H_5	S	I40,0	0,0005	0,0003
ЭГ-I3	C_2H_5	0	3,3	0,00I	0,0004
НШ-2	C_3H_7-изо	S	22,0	0,00I2	0,000I5
НШ-4	C_3H_7-изо	0	I,5	0,0007	0,00035
НШ-8	C_4H_9-изо	S	370,0	0,003	0,002
НШ-9	C_4H_9-изо	0	5,6	0,00056	0,00035
$K_{детоксикации}$ (4)			66,0	5,3	5,7
	Тиофос (5)		9-25	0,00I-0,008	0,003-0,006

Key:
1. Lethal dose$_{50}$ mg/kg, mice
2. Aphids
3. Mites
4. $K_{Detoxication}$
5. Thiophos

The same is observed in a number of methionine derivatives. And here the α branching (introduction of the $CH_2CH_2SCH_3$ group) lowers the possibility of effective detoxication.

More complicated results ensue from the introduction--into the position alpha to the carboxyl--of groupings capable of carboxylesterase hydrolysis, for example, the COOR groups, such as takes place in the derivatives of aspartic acid:



Here, on the one hand, there is an α substitute which hinders carboxylesterase detoxication but, on the other hand, a second carbalkoxy group appeared which is capable of detoxication. The introduction of the second carbalkoxy group lowers the toxicity for mice and leaves an overall strong insect acaricide effect. We obtained similar results from a series of derivatives containing residues of glutamic acid.

Subsequently, the effect of carboxylesterase detoxication was employed for lowering the toxicity of such well known first generation insect acaricides as timet, M-74 and Niagara 1240. The introduction of carbalkoxy groups into the side chair led to a reduction of 100-250 times in the toxicity of compounds for warm blooded animals. Several dozens of substances were synthesized and tested in these series of compounds and it turned out that many of them were stronger than thiophos and were considerably less toxic for warm blooded animals. A number of preparations from this series were tested in the field.

Thus the introduction into the molecule of a well known insect acaricide of groupings which promote selective detoxication but which do not inhibit their interaction with the "target" among insects and mites, can serve as still another method for searching for new and highly selective preparations.

Nor were the above methods for searching for selectivity of action the only ones analyzed. We also studied stereochemical selectivity of action, using as an example the derivatives of methylphosphonic acid, which contain residues of acetylated amino acids. Examples were found in which the optical antipodes differ by one order or more.

Other methods are possible when there are many metabolic changes in the phosphor-organic substances in live organisms, for example the use of phosphatase hydrolysis, regroupings and a number of others.

These studies are the result of work carried out by a large inter-departmental collective, organized by Academician M.I. Kabachnik. The following individuals participated in this work: A.E. Shipov, E.B. Gorbenko, M.S. Vaysberg, G.V. Zhdanova, M.V. Markova, V.A. Sergeyev and Ye.M. Piskunova (INEOS [Order of Lenin Institute of Metallo-organic Compounds] of the USSR Academy of Sciences); M.Kh. Berkhamov, Z.K. Yemkuzheva and L.G. Grineva (KBGU [Kabardino-Balkarian State University]); A.P. Brestkin, I.L. Brik, Yu.Ye. Mandetl'shtam and A.N. Fedin (IEFB imeni I.M. Sechenova of the USSR Academy of Sciences); M.P. Chabanova, O.V. Sundukov, K.N. Savchenko, I.N. Sazonova, A.A. Rakitin and S.G. Zhukovskiy (VIZR [All-Union Institute for the Protection of Plants] of VASKhNIL [All-Union Academy of Agricultural Sciences imeni V.I. Lenin]); Yu.S. Kagan, Ye.A. Yershova and M.A. Klisenko (VNIIGINTOKS of the USSR Ministry of Public Health); S.A. Roslavtseva, N.A. Guseva, T.N. Kaluzhina, N.G. Rozhkova and A.S. Sedykh (VNIIKhSZR [All-Union Scientific Research Institute of Chemicals Used for Plant Protection]); S.A. Zhuravskaya (IZiP of the UzSSR Academy of Sciences).

In conclusion, it should be mentioned that the developed system of views is making it possible to carry out a purposeful synthesis of insect acaricides. This is not meant to imply that it is possible to write a formula for an ideal preparation in advance (this would be utopia). However, it does mean that it is possible to select effectively classes of substances, among which there is a higher probability of finding preparations which satisfy the high modern requirements.

Summary

In the interest of finding selectively acting insect acaricides which are of low toxicity with regard to warm blooded animals and do not leave harmful residues in the environment, a basic principle was proposed according to which the molecules of new pesticides must form from fragments disseminated naturally in nature. A group of esters and methylamides of amino acids containing the residues of esters of dithionic acids of phosphorus was synthesized. A study of anticholinesterase properties, metabolism, toxicodynamics, toxicity for warm blooded animals and entomological properties has made it possible to uncover factors which determine the selective action of synthesized compounds. It was found that in the case of the leading anticholinesterase type of action, an important role is played by carboxylesterase and carboxylamidase hydrolysis and by the ability of substances to suppress carboxylesterases.

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INDUSTRIAL TOXICOLOGY

PRINCIPAL TASKS ASSOCIATED WITH SEARCH FOR NEW PESTICIDES

Moscow VESTNIK AKADEMII NAUK SSSR in Russian No 5, May 81 pp 44-53

[Article by N.N. Mel'nikov, corresponding member of USSR Academy of Sciences: "Principal Tasks in Field of Searching for New Pesticides"]

[Text] Pesticides usually include all chemical compounts used for combating various harmful organisms in the environment. This includes -- substances for destroying weeds, pests and the causative agents of diseases in useful plants, carriers of infectious diseases of man and animals and animal ectoparasites and also for combating biological damage to metallic and non-metallic materials and undesirable harmful organisms in industry (for example, mucous formation in the paper industry, algae in water cooling systems and so forth), for preventing ships from becoming fouled with barnacles and for many other similar purposes. In addition, pesticides include insect sterilizers, preparations of hormonal action and plant growth regulators, which in low concentrations are usually growth regulators and in high concentrations -- herbicides.

The use of pesticides in the national economy produces very great economic results. It is sufficient to state that during the tenth five-year period the use of means for protecting plants against pests, diseases and weeds produced more than 7 billion rubles worth of additional output annually. These measures ensured an additional increase of approximately 12 percent in overall farming output, against expenditures of approximately 1.2-1.3 billion rubles annually.

The use of pesticides is also promoting improved labor productivity in agriculture -- both in tending the plantings and in harvesting the crops, especially cotton.

It is appropriate to point out that the use of pesticides makes it possible to reduce by almost fourfold the energy expenditures required per ton of agricultural output (taking into account the energy expended for producing the pesticides themselves).

Great importance is attached to pesticides for preventing damage to metallic and non-metallic materials and products, caused by various harmful organisms.

The data furnished below provides some insight into the scale to which pesticides are being produced throughout the world.

In 1978, the average cost for 1 kilogram of pesticide was approximately $3.49 and this figure allows one to evaluate the overall tonnage of the preparations being produced. It is noted that from a cost standpoint the world production of pesticides at the present time is commensurate with the production of mineral fertilizers and reflects a tendency towards further growth.

World Production of Pesticides in 1978 and Forecast for 1984
(millions of dollars in 1978 prices)*

Pesticide Groups	1978	1984
Herbicides	3716.4	4792.3
Insecticides and acaracides	3028.4	3821.7
Fungicides	1538.8	1965.1
Fumigants	168.2	228.9
Defoliants and desiccants	96.8	146.9
Pesticides of other groups	120.5	155.9
Total	8669.1	11110.8

* See: FARM CHEMICALS, No. 9, 1979, pp 61-64

Data on pesticide production in the USSR testifies to the fact that over the past 20 years it has increased by a factor of more than 9 (in a computation for 100 percent active agent). However the rapidly increasing requirements of agriculture for these substances are still not being satisfied fully.

Pesticide Production in the USSR From 1960 To 1970
(thousands of tons)

Method of Measurement	1960	1965	1970	1975	1979
In standard units	61.4	197.8	289.7	438.3	474.7
In a computation for 100% active agent	30.6	108.3	163.8	264.08	284.3

In connection with the fact that pesticides are physiologically active compounds and the scales of their use, as evident in the data cited above, are rather high, a problem has arisen with regard to protecting the environment and ensuring their safe practical use. This problem is truly an urgent one, since the initial pesticides used on a rather large scale (for example, compounds of arsenic, lead and mercury) were stable and capable of being accumulated in surrounding objects. The second generation pesticides are also stable preparations; they include DDT and a number of other chloroorganic compounds. Their accumulation is conditioned to a considerable degree by the tremendous scales of their use, which is continuing at the present time in a number of countries (in particular, over the past 20 years approximately 4.5 million tons of DDT were employed throughout the world).

The capability of pesticides to accumulate has raised the need for increasing the requirements for introducing new preparations into operational practice and for studying their behavior in various surrounding objects. At the present time, the following principal requirements can be imposed with regard to new pesticides:

...moderate persistence in surrounding objects within a given climatic zone;

...as low a toxicity as possible for man, animals and other useful organisms, including hydrobionts;

...relatively rapid disintegration in soil, water, the atmosphere and in the organisms of warm-blooded animals, with the formation of products deemed safe for man, animals and cultivated plants;

...the absence of an accumulation of these preparations in the organism of man, animals, birds and hydrobionts;

...a maximum high effectiveness in combating harmful organisms, with reduced expenditures of the preparation per unit of area treated;

...sufficiently high economic effectiveness of use in agriculture and in other branches;

...absence of remote adverse consequences for man, animals and other living organisms, as a result of the systematic and extended use of the preparations;

...the possibility of alternating the preparations from various classes of compounds in order to avoid the harmful organisms from becoming accustomed to them and also the accumulation of the preparations in surrounding objects;

...the absence of undesirable effects in the object being protected;

...adequate stability of the preparations during storage and low degree of aggressiveness with regard to the equipment used for employing the preparations;

...accessibility of the raw materials required for producing the preparation and the possibility of production on the scales required.

Constant increases in the requirements lowers the output from suitable preparations when searching for them and raises the cost for developing one preparation. Based upon the data cited here, it is apparent that over a period of 25 years the number of compounds that had to be synthesized and studied, in order to obtain one preparation of practical value, increased by a factor of almost 8.

Number of Compounds Subjected To Screening In Order To Find One Preparation Suitable For Introduction Into Practice

	1956	1964	1967	1970	1973	1977	1980
Number of compounds, in thousands	1.8	3.6	5.8	7.4	10.2	12	14

We have estimated that there are presently 20 large firms in economically developed countries which are annually spending approximately 500 million dollars for scientific-research work in the field of pesticides. Some idea as to the structure of these expenses can be obtained from an analysis of the pertinent expenditures of 37 firms in the particular branch of the chemical industry of the U.S.A. during

19/7, the total amount of which was 250 million dollars. Of this amount, 41 percent was expended for the synthesis and screening of chemical compounds and for developing the forms for their use and the creation of a production technology (usual items of expense for NIR [scientific research work] in the chemical industry) and 42 percent was spent for determining the toxicity of the preparations, for field testing them, for studying the metabolism and determining the residues, that is, the entire complex of ecological studies. In the process, 65 percent of all funds was spent searching for new pesticides and 35 percent -- for work associated with preparations created earlier.

The creation and study of pesticides involves the participation of specialists representing various disciplines, including chemist-synthesis specialists, analysts and technologists, biochemists, entomologists and phyto-toxicologists, toxicologists, physicists, mathematicians, biologists of various specialties and many others.

The principal method of search is that of "trial and error" (screening), however with a definite direction in mind. This matter of direction is borne out by data on the number of patents published during the 1976-1978 period for new pesticides by classes of chemical compounds.

It is apparent from the data cited that organic compounds of phosphorus and heterocyclic compounds of various ranks and also various derivatives of carboxylic acids are being studied most intensively for pesticide activity. In recent years the derivatives of cyclopropane carboxylic acid, which is close in structure to chrysantheminic acid, have been studied intensively as insecticides.

The intensive search for pesticides in the mentioned classes of compounds derives from the fact that recently the greatest number of active preparations have been found among these compounds. Attempts to predict pesticide activity for substances through the analysis of physical-chemical and other properties in the new classes of chemical compounds, using electronic computers, have still not produced reassuring results. Success has been achieved in predicting the presence of pesticide activity only in those classes of compounds in which the biological properties of at least two of the substances are known. However, in such instances the predictions are purely qualitative in nature. This is associated to a considerable degree with the insufficient volume of studies of the manner in which the various classes of chemical compounds act upon the harmful and useful organisms, the metabolism and other changes in the chemical compounds in surrounding objects.

One of the most important tasks is that of creating the scientific principles for the directed synthesis of pesticides having a given physiological activity, persistence and other properties which satisfy the modern requirements. Towards this end, a requirement exists for setting up all-round fundamental studies involving the participation of specialists representing various fields of knowledge. Only such an overall approach will make it possible to achieve a rapid solution for the task of directed synthesis of new pesticides having the given properties.

By way of an example of such an approach, permit me to cite studies carried out on the metabolism of DDT and some of its analogs (particularly methoxychlor, methylchlor and methylthiochlor) in various surrounding objects.

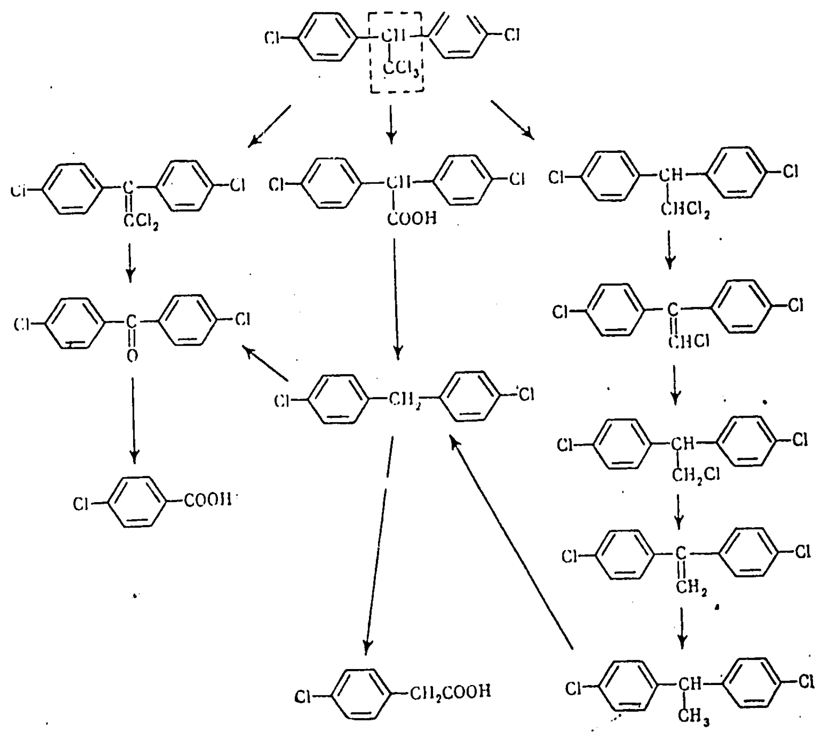
PATENTS PUBLISHED DURING 1976-1978 PERIOD

Class of Compounds or Purpose	Number of Patents	Class of Compounds or Purpose	Number of Patents
Forms of use	202	Derivatives of urea and thiourea	216
Preparations based upon mixtures of several agents	126	Mercaptans, sulfides, sulfones and related compounds	50
Hydrocarbons of various series	15	Derivatives of sulfo acids	136
Halogen derivatives of an aliphatic series	24	Derivatives of hydrazine and azo compound	70
Halogen derivatives of an alicyclic series	20	Organic compounds of mercury	3
Halogen derivatives of an aromatic series	21	Organic compounds of tin, lead, silicon, antimony and bismuth	44
Nitro compounds of various series	26	Organic compounds of phosphorus	892
Amines and their derivatives	165	Organic compounds of arsenic	11
Alcohols, phenols and simple ethers	279	Five-membered heterocycles with one heteroatom	162
Aldehydes, ketones and quinones	114	Six-membered heterocycles with one heteroatom	201
Aliphatic carboxylic acids and their derivatives	419	Five-membered heterocycles with two heteroatoms	375
Alicyclic carboxylic acids and their derivatives	208	Six-membered heterocycles with two heteroatoms	298
Derivatives of cyclopropane carboxylic acid	173	Five-membered heterocycles with three or more heteroatoms	175
Aromatic carboxylic acids and their derivatives	158	Six-membered heterocycles with 3 or more heteroatoms	175
Aryloxyalkane carboxylic acids and their derivatives	95	Antibiotics	73
Derivatives of carbonic acid	31	Inorganic compounds	4
Derivatives of carbamic acid	246	Total	5365
Derivatives of thio and dithio-carbamic acid	158		

The principal directions in the metabolism of DDT are presented in Diagram 1 and for its analog methoxychlor -- in Diagram 2.

It is apparent from Diagram 1 that the metabolism for DDT proceeds with the formation of hydrophobic compounds which accumulate in the lipoids. When a definite level of DDT content is reached in an organism, undesirable consequences and even a fatal outcome may ensue. Meanwhile, the closest DDT analogs, particularly methoxychlor, form hydrophilic products during metabolism, products which are easily withdrawn from vertebrate organisms, do not accumulate and hence cannot cause undesirable consequences. Actually, in studying the appearance of chlororganic pesticides in the milk of cows, it turned out that even in the case of a large amount of methoxychlor in the feed, considered to be impossible for actual use conditions, its relative content in the milk (with regard to the feed) was less by a factor of 100 than in the case of DDT, as can be seen in Table 1.

DIAGRAM 1



The KBD's [koeffitsiyent biodegradatsiya; coefficient of biodegradation] for DDT (first line) and its analogs in a water ecological system, expressed in relative units, are furnished in Table 2. The KBD is a value that is proportional to the speed of disintegration of a preparation in a definite ecological system. The data in the table reveals that even among the closest analogs of DDT, compounds may be found which disintegrate in the surrounding environment 100 times more rapidly than does DDT.

Such an approach to solving the task of searching for new pesticides and acaricides is already being employed in the USSR Academy of Sciences by a large group of scientists under the direction of Academician M.I. Kabachnik. In addition to the institutes of the USSR Academy of Sciences, this work also involves participation by the institutes of VASKhNIL [All-Union Academy of Agricultural Sciences imeni V.I. Lenin], VUZ's and also by VNIIKhSZR [All-Union Scientific Research Institute of Chemicals Used for Plant Protection].

The author of the present report made a suggestion regarding the high and diverse physiological activity of organic compounds of phosphorus having an asymmetric atom of phosphorus:

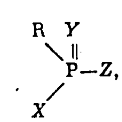
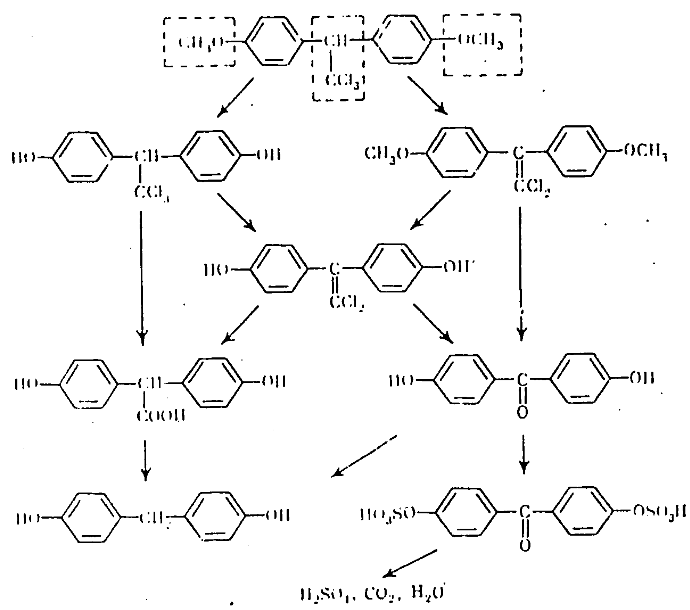


DIAGRAM 2



where R is the substituted or unsubstituted hydrocarbon radical, X = S or O and Y and Z -- very different chemical groups.

As a result of having synthesized and studied a large number of such compounds, success was achieved in finding a number of practically valuable substances such as trichlormetaphos-3, isophos-3, heterophos, etaphos and some others. At the present time, a number of compounds of the indicated structure have entered into practical use both in the USSR and abroad.

The principal work concerned with the synthesis of new pesticides is being carried out in the USSR at the following institutes of the USSR Academy of Sciences: at the Institute of Organic Chemistry imeni N.D. Zelinskiy, Institute of Hetero-Organic Compounds imeni A.N. Nesmeyanov, Institute of Organic Chemistry of the Siberian Branch of the USSR Academy of Sciences, Institute of Physiologically Active Substances, Institute of Organic Chemistry of the UkSSR Academy of Sciences, Institute of Organic Synthesis of the Latvian SSR Academy of Sciences, at VNIIKhSZR and at a number of others. Interesting work on insect feromones and hormones is being carried out at the Institute of Bioorganic Chemistry imeni M.M. Shemyakin of the USSR Academy of Sciences and at certain other organizations. At the present time, a number of new preparations are undergoing field testing in various regions of the country.

For the successful development of the production of new pesticides, special importance is attached to developing methods for obtaining the semi-finished products and expanding their assortment. The development of studies in this area is of great importance to other branches of fine organic synthesis.

TABLE 1

Passage of Certain Chlorine-Containing Insecticides into the Milk of Cows

Insecticide	Content of Insecticide, in milligrams per kilogram		Ratio of Content in Milk To Content in Feed
	In Feed	In Milk	
Aldrin	40	16.1	0.4
	10	3.42	0.34
	1	0.41	0.41
Dildrin	10	1.78	0.18
	0.3	0.015	0.05
	0.05	0.002	0.4
DDT	200	6	0.03
	25	2.29	0.092
	10	0.63	0.063
	0.3	0.007	0.023
Methoxychlor	7000	2.14	0.00032
	1000	0.19	0.00019
	600	0.13	0.00016

Extreme importance is also attached to the development of biochemical studies which are of primary importance not only with regard to searching for new pesticides, but also for introducing already developed preparations into agricultural practice, since knowledge of their behavior in surrounding objects is the basis for their correct, safe and effective use. Microbiological studies play a very important role in this regard.

In view of the tremendous number of harmful organisms which are causing considerable damage to agricultural production, the efforts of researchers must be directed mainly to studying those harmful organisms which are inflicting the greatest amount of economic damage. Studies must be launched on the biochemistry of both useful and harmful organisms, particularly their fermentive systems, for the purpose of finding the differences in their structures and creating the prerequisites for the directed syntheses of the pesticides. Considerable importance is also attached to studies of the cometabolism of pesticides with soil microorganisms, which determine to a considerable degree the persistence of the pesticides in the surrounding environment. In addition, an important problem is that of studying the "ecology of pesticides" in agrocenosis, in conformity with the various climatic zones.

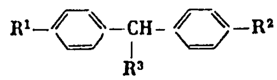
In order to accelerate thework of creating new pesticides and developing the scientific principles for the directed synthesis of compounds having a prescribed physiological activity, it would be advisable to examine the question of creating inter-departmental collectives which operate not on the basis of formal coordinated plans but rather in close creative collaboration and under a common management, similar to the collective headed by Academician M.I. Kabachnik. This collective needs to be expanded. When effort is concentrated on solving definite problems under a common management, more complete and practically important results can ensue.

In conclusion, I would like to mention several problems the solutions for which would promote improved labor productivity and energy savings in agriculture.

TABLE 2

Coefficients of Biodegradation (KBD) for DDT and Its Analogs in a Water Ecological System

Common formula for compounds:



R^1	R^2	R^3	КБД
Cl	Cl	CCl_3	0,015
Cl	Cl	$HCCl_2$	0,054
CH_3O	CH_3O	CCl_3	0,94
CH_3	CH_3	CCl_3	7,14
CH_3S	CH_3S	CCl_3	47,0
Cl	CH_3	CCl_3	3,43
CH_3	C_2H_5O	CCl_3	1,2
CH_3O	CH_3S	CCl_3	2,75
CH_3O	CH_3O	$C(CH_3)_3$	1,04
Cl	Cl	$HC(CH_3)NO_2$	3,27

First of all, it will be necessary to supply agriculture with an optimum variety of herbicides for such crops as corn, sunflowers, sugar beets, cotton, potatoes, soybeans, grain crops and a number of others. Despite the fact that there are satisfactory preparations for the mentioned crops in the international assortment, each one of them is marked by certain shortcomings.

The creation of effective and safe defoliants is required for the purpose of mechanizing the laborious work of cotton harvesting and also growth regulators for accelerating the ripening of the cotton and some other crops. The latter is of particular importance for grain crops grown in northern regions where the growing season is short. Great importance is attached to creating systemic fungicides for combating cotton wilt and other similar diseases.

An important task in the area of insecticides and acaricides is that of combating arthropods which possess a resistance to the usual preparations.

An attempt must also be made to reduce the amount of time between the synthesis of a preparation and its introduction into operational practice. This is associated to a considerable degree with rationalization of the processes for studying the effect of new preparations on various biological objects.

* * *

During a discussion of the scientific report by N.N. Mel'nikov, a speech was delivered by Academician G.K. Skryabin. He directed attention to the recent appearance of a large amount of data testifying to the fact that quite often, as a result of the effect of microorganisms and also various physical-chemical environmental factors on non-toxic or low toxicity pesticides in the soil or water, products of the disintegration of these substances are formed which are considerably more dangerous to man and the biosphere than the initial pesticide. For example, studies carried out on the herbicide Ordran at IBFM [Institut biokhimii i fiziologii mikroorganizmov AN SSSR; Institute of Biochemistry and the Physiology of Microorganisms of the USSR Academy of Sciences] in Pushchino revealed that this preparation disintegrates under natural conditions with the formation of partially oxidized products, which are retained in water for a very long period of time and which are highly toxic.

Another example -- an entire series of pesticides, mentioned in particular in the above report, which contain a molecule of nitrogen in their structure. Some of the nitrogen-containing pesticides disintegrate in the natural environment with the formation of nitro compounds which even in insignificant quantities are highly carcinogenic.

Thus a requirement exists for the study of and control over the toxicity and mutagenic and carcinogenic activity not only of the pesticides themselves but also of the intermediate products of their disintegration directly under natural conditions.

Subsequently, G.K. Skryabin discussed one effective variety of chemical agents for protecting plants -- feromones. Unfortunately, up until now these compounds have been extremely expensive and their production extremely complicated.

Recently a basically new and extremely effective and very cheap method for obtaining reproductive feromones was developed at IBFM. At the present time, the institute has four expeditionary detachments operating in different regions of the country. Without losing any time and under field conditions, these detachments are carrying out checks on the biological activity of the feromones obtained by this method. Reports have already been received confirming the high quality of all of the preparations tested.

In 1981, jointly with Glavmikrobioprom of the USSR Council of Ministers, the institute intends to prepare a sufficient number of preparations not only for carrying out extensive field tests but also for employment as effective agents for protecting plants in the economic work of kolkhozes and sovkhozes.

In conclusion, G.K. Skryabin emphasized that the DDT problem continues to be an extremely important one. Its use is actually being continued in a large number of countries and in those areas where its use is forbidden, its content in the soil in many regions remains rather high since this compound disintegrates extremely slowly. Thus a requirement exists for developing studies aimed at finding effective methods for its disintegration.

Academician Ye.N. Mishustin emphasized in his speech the tremendous importance attached to expanding the variety of pesticides being produced in the USSR. At the present time, the number of types of pesticides being produced in our country is several times less than the number in such countries as the U.S.A. and Japan. It is because of this fact that a number of preparations must be procured abroad.

Meanwhile, a situation is developing at the present time wherein, for failing to treat the plantings with the required pesticides, the use of fertilizers is not only just slightly effective but in fact it may even lower the cropping power of some crops, for example soybeans, since fertilizers, especially nitrogen and phosphate fertilizers, are actively utilized by weeds which subsequently choke out the principal crop.

In recent years, the Academy of Sciences has devoted a great amount of attention to the problem of creating new pesticides. In particular, in the Committee on Scientific Principles of Agriculture of the Presidium of the USSR Academy of Sciences, a great amount of work was carried out in connection with composing an overall plan for chemical and biological studies in the area of creating pesticides. Computations were carried out on the capital investments required. In the absence of capital investments being allocated, it would be very difficult to ensure the required assortment of pesticides. However, this problem has still not been solved. It is obvious that the program must include the most important directions to be followed in carrying out studies and such studies must be properly financed.

One of the main difficulties associated with the creation of new preparations -- the need for testing a tremendous number of chemical compounds, as mentioned by the speaker. At the present time, our volume of such tests is completely inadequate. But, in addition to intensifying the screening volume, a requirement also exists for a more intensive search for a scientific approach for directed synthesis. Special attention should be given to this problem.

Importance is also attached to taking into account the climatic conditions under which the pesticides are used, since the processes of pesticide disintegration in the soil may be completely different depending upon these conditions. In a number of instances, an unforeseen formation of toxic and not easily disintegrated forms may occur.

In particular, mention should be made of the Hungarian experience, where several years ago, having established the norms adopted in the U.S.A., simasine was employed on an extensive scale. However, owing to the different climatic conditions, this preparation did not disintegrate in the Hungarian soils and the following year the grain crop yield obtained from fields treated with simasine was considerably lower. It is obvious that in the USSR, where the differences in natural conditions by regions are tremendous, such problems are especially urgent and thus appropriate studies must be carried out on an extensive scale. Such studies are being carried out at the Institute of Agrochemistry and Soil Science of the USSR Academy of Sciences in Pushchino, under the direction of M.S. Sokolov. Valuable results have been obtained and yet this is only the beginning.

In conclusion, Ye.N. Mishustin directed attention to the need for increasing organizational support for work concerned with the creation and checking upon the effectiveness of new pesticides in the USSR Academy of Sciences.

M.S. Sokolov (Institute of Agrochemistry and Soil Science of the USSR Academy of Sciences) discussed in his speech the ecological aspects of the use of pesticides and the problems concerned with evaluating and forecasting the consequences of their use. This is extremely important for those regions of the country where pesticides are employed more intensively, primarily in the regions of the Azov-Black Sea and Aral-Caspian Sea basins -- in the Uzbek, Tajik, Azerbaijan and Moldavian SSR's. Here their application dosages per hectare of arable land exceed the all-union indicators by a factor of 10-15.

Successful work is being carried out in this area jointly with the institutes of the republic academies of science and interesting results have been obtained within a relatively brief period of time. For example, an inspection of the territory of Azerbaijan revealed that for a generally high level of pesticide use, their content in the soil, even on plantings of the same crop, changes in the various regions by a factor of 10 or more. The reason -- specific soil, hydrothermal and microbiological conditions, as mentioned in particular during earlier speeches. Once again we are able to take all of these factors into account to only a weak degree and, as a rule, we pay no attention to them when planning the use of certain preparations.

If appropriate studies are not developed and if an ecological evaluation of the consequences of using the new preparations is not furnished, then we will be constantly forced into examining their assortment and introducing more strict limitations upon their use. The development of a uniform method for conducting such an evaluation is extremely necessary for our country.

In summarizing the results of the discussion, the President of the USSR Academy of Sciences, A.P. Aleksandrov, commented upon the need for preparing recommendations on the further development of studies concerned with the more urgent problems touched upon in the scientific report by N.N. Mel'nikov.

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DIMETHYL PHOSPHITE PURIFICATION BY VACUUM DISTILLATION IN FILM ROTOR EVAPORATOR

Moscow KHIMICHESKAYA PROMYSHLENNOST' in Russian No 9, Sep 79
pp 33-34

[Article by V. V. Degtyarev, A. M. Kukushkin, Ye. A. Vinnikov, V. V. Khlynov and L. G. Loskutov]

[Text] Among the organic phosphorus compounds with pesticidal properties, chlorofos and vinifos are of great practical importance, and the output thereof is constantly increasing. Production of these agents is based on interaction of dimethyl phosphite with chloral and acetophenone [1]. It has been determined [2] that at least 94% concentration of dimethyl phosphite is required to obtain high-grade products.

Most methods of producing dimethyl phosphite that are described in the literature [3-6] are purely preparative, and the main constituent in the synthesized product ranges from 80-90%. There are no data concerning production of dimethyl phosphite in over 90% concentration.

Since the boiling point of impurities contained in dimethyl phosphite (mainly monomethyl phosphite) is above its boiling point, one can remove the impurities that subsequently contaminate chlorofos and vinifos by means of distillation. However, distillation of dimethyl phosphite under industrial conditions presents considerable difficulty because of its thermolability at temperatures close to the boiling point (loss of product and contamination of heat-transmitting surface). Purification of dimethyl phosphite in still-type circulating apparatus did not yield good results when tested under industrial conditions. The proposed chemical methods of neutralizing impurities (ammonia and soda) were found to be ineffective and time consuming [3].

We have studied the possibility of using a thin-film rotor evaporator to purify raw dimethyl phosphite. The diagram of the unit is illustrated in Figure 1.

The original industrial dimethyl phosphite containing up to 85% of the main constituent was loaded into tank *1*, from which it was delivered by vacuum to the top part of the evaporator *2*. A type VN-2MG vacuum pump was used to create vacuum in the system. Delivery of raw material was dispensed by rotameter *3*. The vapor of volatile components was condensed in a tubular condenser cooled by brine at a temperature of -10°C. The condensate then drained into a collecting tank and the unvaporized part passed into apparatus *7*.

A casing was placed on the evaporator (Figure 2), which had an area of 0.0628 m^2, for heating by the steam. The flared top part of the apparatus served to separate splashes from the vapor phase. There was a rotor with four hinged blades within the housing. The rotor shaft turned in two ball bearings installed in the lid of the apparatus and a sliding bearing in the bottom part of the evaporator. An end gasket was placed into the unit of the top bearing to seal the place where the shaft exited into the evaporator lid.

Vacuum in the evaporator was monitored by a U-shaped pressure gauge, and vapor pressure was controlled by means of valves, with monitoring by pressure gauge *8*.

Dimethyl phosphite content in products of distillation of the industrial product was determined by potentiometric titration with an alcohol solution of alkali.

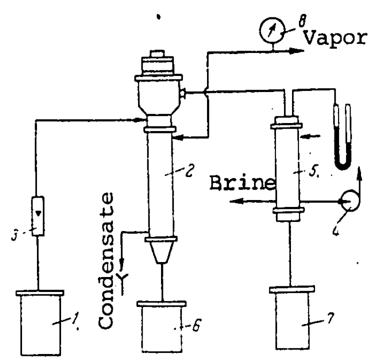

Figure 1.
Diagram of experimental apparatus

1) tank with initial product
2) evaporator
3) rotameter
4) vacuum pump
5) condenser
6,7) collectors for still residue and distillate, respectively
8) pressure gauge

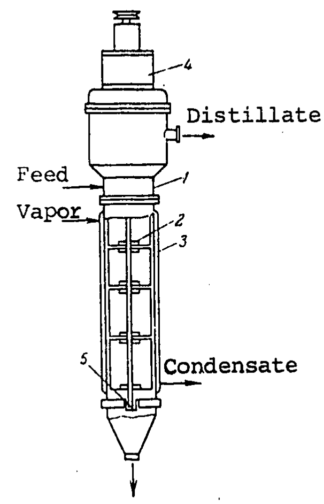

Figure 2.
Diagram of film rotor evaporator

1) housing
2) rotor
3) casing [jacket]
4) top bearing
5) bottom bearing

Dimethyl phosphite breaks down when heated, so that we used the maximum permissible temperature of 143°C for the heating agent. The mixture was delivered into the evaporator starting with 19.1 kg/(m^2•h), which is the minimal amount with which uniform distribution of film on the wall was obtained. With increase in delivery there is increase in distillate output of the apparatus (Figure 3) due to agitation of the draining film of fluid.

As can be seen in Figure 4, maximum extraction of dimethyl phosphite constitutes 97% with a load of about 200 kg/(m^2•h). With further increase in load there is a decrease in extraction, apparently due to an increase in share of heat-exchange surface involved in heating the initial mixture to the boiling point.

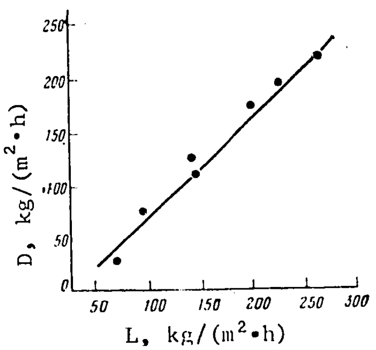

Figure 3.
Distillate yield as a function of load of nitial product

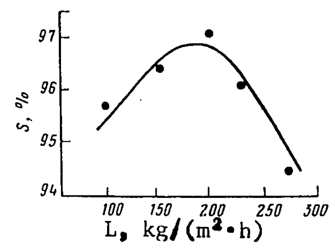

Figure 4.
Degree of extraction of dimethyl phosphite as a function of load of initial product at residual pressure of 100 mm Hg and excess pressure of heating steam of 2.8 kgf/cm^2

The esults of the experiments revealed that, even with small loads and residual pressure of 100-150 mm Hg one can recover distillate containing 90-94% dimethyl phosphite. Let us mention that, in some of the experiments, there was an increase in dimethyl phosphite during distillation, which could be attributed to disproportionate amounts of monomethyl phosphite in dimethyl phosphite and phosphorous acid. The results of potentiometric titration of fractions obtained with distillation of raw dimethyl phosphite were indicative of presence of the latter.

In the course of the studies, we noticed that if the heat-carrier temperature exceeded 145°C the apparatus became less productive and the quality of the distilled product was poorer. These parameters are influenced by residual pressure also. Optimum results are obtained at pressure of 100-150 mm Hg.

Thus, our results are indicative of the existence of an optimum mode of distillation, with which one can obtain a 97% yield and 95-97% level of dimethyl phosphite in the distillate.

The statistical method of planning the experiment [7] was used to find the optimum mode of operating the film evaporator with hinged blades. On the basis of data obtained from a passive experiment, we took as optimization parameters the dimethyl phosphite concentration in distillate Y_1 and degree of extraction of dimethyl phosphite Y_2. Working pressure in the apparatus X_1, heat-carrier pressure X_2 and load X_3 served as independent variables.

The optimization parameters as a function of parameters of the process were determined in the form of a complete quadratic equation of relationship:

$$Y_{1,2} = b_0 + \sum_1^n b_i x_i + \sum_1^n b_{ij} x_i x_j + \sum_1^n b_{ij} x_i^2 \quad (1)$$

where i and j are factor numbers, n is the number of factors taken into consideration and b_i are coefficients of regression. An orthogonal first order, type 2^3 matrix was used to determined the coefficients of equation (1).

	X_1, mm Hg	X_2, kgf/cm^2	X_3, ℓ/h
Main level	100	2.3	7.5
Variation interval	50	0.9	5
Maximum level	150	3.2	12.5
Minimum level	50	1.4	2.5

The Table lists the main level and intervals of variation of the variables selected on the basis of the results of the passive experiment. The intervals of variation and central point of the plane were chosen so as to have the experiment cover a significant part of the factor space and to adhere to conditions of symmetry and of normal operation of equipment. Estimates of b_i and b_{ij} were obtained by the least squares method. Accuracy of approximation of response surface was evaluated by dispersion of equivalence [adequacy]:

$$\sigma^2_{eq} = \frac{\Sigma(\hat{x}_{yi} - x_{yi})^2}{N - m} \qquad (2)$$

where $\hat{x}_{yi}$ are estimated values, x_{yi} are measured values, N is the number of measurements, m is the number of found (significant) coefficients b_i and b_{ij}.* Error of reproducibility σ_r was calculated from the results of experiments conducted in the center of the plane. A comparison of estimates of dispersion for first order and quadratic models revealed that there is appreciable increase in approximation of response surface with addition of quadratic terms.

Using a previously described method [8], the following equations of regression were obtained from the experimental data:

$$Y_1 = 96{,}07 + 0{,}093X_1 - 0{,}366X_2 + 0{,}682X_3 - 1{,}398X_1^2 + 0{,}784X_2^2 - 0{,}890X_3^2 - 0{,}067X_1X_2 - 0{,}639X_1X_3 - 0{,}524X_2X_3 \qquad (3)$$

$$Y_2 = 96{,}0 - 0{,}09X_1 + 13{,}1X_2 - 2{,}04X_3 + 4{,}8X_1^2 - 12{,}95X_2^2 - 2{,}83X_3^2 - 3{,}29X_1X_2 - 6{,}80X_1X_3 + 0{,}41X_2X_3 \qquad (4)$$

A check revealed that all of the coefficients of the equations are significant. Equivalence of obtained equations was checked with the criterion of Fisher.

Processing of equations (3) and (4) revealed that the following parameters must be maintained for the process in order to obtain a product with at least 96% dimethyl phosphite: pressure of heating vapor (excess) 2.8 kgf/cm^2, residual pressure 100 mm Hg, load 190 kg/(m^2•h).

The obtained mathematical model can serve as the basis of an algorithm for control of the technological process of distilling raw dimethyl phosphite in vacuum in a film rotor evaporator.

*Subscript "y" refers to yield.

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