

PROGRESS IN PESTICIDE TOXICOLOGY IN THE USSR

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ABSTRACT

In the USSR the study of pesticide toxicity and toxicodynamics began in 1932. All the compounds used are assessed; hygienic standards of acceptable concentrations in foods, working area air, atmospheric air, and water are calculated. The maximum acceptable daily intake of chemicals from all the media is tabulated and these data are examined for hygienic standardization. In the past toxicologists were engaged in the problem of prevention of acute and chronic poisoning, but for more than ten years already particular scientific attention has been paid to delayed effects (carcinogenicity, mutagenicity, embryotoxicity, etc.) Search is also made for alternative organotoxicity of pesticides and their allergenic properties. As pesticide circulation in the biosphere is unavoidable, in contrast to industrial effluents, pesticide selection assumes ever greater importance. Thus the hygienic classification of pesticides has been worked out. Highly toxic persistent and stable substances with adverse delayed effects are strictly forbidden. Hence, cyclodienes and other stable organochlorine substances, highly toxic systox, parathion, etc. are prohibited. Studies are carried out on the whole body, on isolated organs, and at cellular and subcellular levels. The correlation of pesticide effect with chemical structure is established. Some molecular structural peculiarities of organophosphate chemicals resulting in their hepatotropy (chlorine presence), embryotoxicity and teratogenicity (phthalimide group), and the morphological blood content effect (nitrophenol groups) are revealed. Distribution variations of organochlorine compounds in lipids are determined.

The highest levels of DDT and its metabolites are found in cholesterol ethers, lindane in glycerylates, and polychlorocamphene in phospholipids of the central nervous system. Prolonged exposure to small doses of DDT can change liver function and structure, increase susceptibility of the cardiovascular system to coronarospastic agents, and accelerate development of atherosclerosis and autoaggressive antihepatic and antierythrocytic antibodies. The adverse effect of DDT ingestion on pregnancy, delivery and posterity has been established. All these disturbances are based upon the disorder of mitochondria function, changes of cellular and intracellular membrane permeability, their bioelectric properties and intracellular regulatory mechanisms, and the alteration of catecholamine, serotonin and histamine metabolism. Studies of the physiological and biochemical modes of the action of pesticides facilitates elucidation of significant regularities.

Now and in the foreseeable future the leading role in the system for protecting plants from pests, diseases and weeds is played by chemical substances. The assortment and the amounts of pesticides are increasing, and new

chemicals are being produced every year. The rapid development of the production and use of pesticides stimulates research for studying the toxicity and toxicodynamics of various substances and classes of chemical compounds. The scope of research in many countries is extended from year to year.

The toxicology of pesticides as an independent branch of medical and biological sciences has already been established. The independence of toxicology in different countries is diverse. In many countries the toxicology of pesticides is a closed scientific discipline and it tries to decide the problems within the possibilities of toxicology. In these as well as in other countries researches are carried out rather in isolation for establishing toxicity parameters, and for investigating metabolism and the biochemical modes-of-action. This information is needed, but it serves only as a base for predicting potential hazards for the health of the people; it is not available for predicting actual ones.

The lack of distinct qualitative criteria of actual hazards for people and living creatures resulted in a number of countries allowing production of certain pesticides which can cause intoxications of people, animals and birds, and disturb the biocenotic equilibrium in nature. These pesticides are well-known now; they result from diene synthesis (aldrin, dieldrin, etc.), organochlorine compounds (DDT and others), carbamates (ziram, maneb), highly toxic organophosphorus (parathion, systox) and some other compounds. It was only after the passage of some years, when the damage for people's health and living creatures had become evident, that some of these chemicals were prohibited in some countries. Meanwhile if the actual danger had been predicted in time, dozens of hazardous chemicals would not have been permitted for use at all.

In the USSR, as will be shown later, the toxicology of pesticides has achieved great success, and it is developing not independently but as an important part of a long established science—the *hygiene of pesticide use*. While hygiene is a science of people's health, its constituent—hygiene of pesticide use—is a science of methods, the ways and means of protecting people's health under extensive use of various chemicals for plant protection, their constant circulation in the environment, and their capacity for accumulation in environmental objects, including living organisms and human kind. The aim and tasks of the hygiene of pesticide use resolve themselves into the prevention of poisonings among people who use pesticides, into the prevention of excessive contamination of foodstuffs of plant and animal origin, of water reservoirs, atmospheric air and soil. It is quite obvious that the possibility of poisoning at work depends not only upon the toxic properties of a substance, but also and mainly upon the conditions of use (ground or air application, hand spraying or by means of the ancillary equipment, etc.). Hygiene studies the sources of danger under working conditions and it plans protection.

It is clear from the above that the hygiene of pesticide use is a complex discipline elucidating problems of work hygiene, food hygiene, water, air and soil hygiene.

In agriculture all the problems are mutually involved; therefore more effective decisions are possible when taking into account the role of each environmental link in the life activity of living beings.

To decide the task of protecting the health of people and living creatures it is necessary to know the physicochemical properties, the toxicity and other characteristics of each pesticide. Even a highly toxic compound which decomposes quickly into non-toxic components under natural conditions may be less dangerous than a slightly toxic compound which remains unchangeable for years.

From these considerations it is apparent that many problems concerning the task of protecting people's health are out of the toxicological sphere; they refer to the competence of hygiene. That is why the toxicology of pesticides in the USSR originated and developed under the beneficent influence of hygiene and by means of its (toxicological) methods, steadily improving them, it controls the tasks put forward by hygiene.

Solving the problems suggested by the hygiene toxicology of pesticides at the same time occupies the clinic. Data obtained by toxicology on physiological and biochemical modes-of-action of each chemical substance on an animal organism are used by clinical workers for understanding the processes of intoxication and for solving the problems of diagnostics and treatment.

Toxicology began the first investigations on pesticides in the USSR in 1932. Since 1937 new pesticides have been thoroughly tested before introduction into general use. From that time the use of each new pesticide in agriculture has been possible only after official permission by the Ministry of Public Health of the USSR, which is only forthcoming after the many-sided toxicological and hygienic investigations provided for predicting the actual hazards for people's health. These investigations are carried out in laboratories and under field conditions. While before the introduction of precautionary sanitary inspection the toxicological researches were mostly perceptual, after that time the responsibilities of scientific workers have increased and the researchers have become more purposeful and more practical. Any wrong decision may lead to tragic results. In the case of an unsubstantiated prohibition of an effective chemical, when hazards are exaggerated, definite economic damage is possible. Otherwise, when permission for use is given without taking account of actual hazards, the health of people and living creatures is damaged in essence. The first and the second are inadmissible. For taking substantiated decisions, appropriate methodological approaches and adequate methods are needed as well as quantitative criteria for predicting potential and actual hazards. Hence, from the first days of pesticide toxicology, the Soviet scientists have been working to improve both research methods and quantitative criteria.

In the course of developing the hygiene of use of pesticides and of pesticide toxicology four periods are marked more or less distinctly and each subsequent period originates and grows from the previous one.

The first period includes researches in 1932-1937. In 1932 the first laboratory of pesticides was organized at the Kiev Institute of Work Hygiene and Professional Illnesses headed by Professor G. L. Shkavera—a pupil of N. P. Kravkov. During that period the toxicity and toxicodynamics of formulations of arsenic, copper, fluorine and various other compounds used in agriculture were studied by methods of industrial toxicology and pharmacology; the method of isolated organs, in particular, was widely used. It was proved that pesticides should be studied before their use in agriculture.

The second period began in 1937 after the introduction of precautionary sanitary inspection. New pesticides, such as organomercury compounds for seed dressing and some others, were then studied before being recommended for practical use. While studying sanitary-hygienic conditions of work a method of instrumental-laboratory researches was used and toxicological experiments were carried out under conditions imitating those found in practice. For the first time the concentration of organomercury compounds in the working atmosphere during seed dressing were defined. On the basis of hygienic and experimental-toxicological researches, the maximum allowable concentrations for use in the working atmosphere were first recommended. Research results and preventive recommendations were published¹.

Up until 1945 research was carried out at one laboratory only, and between 1945 and 1954 this number rose to six. In the researches on the toxicological and hygienic estimation of new pesticides the methods of conditioned and unconditioned reflexes, giving integral data of poison effect on an animal organism, were widely used. The experiments reproduced conditions similar to the occupational ones, and biochemical research methods were more widely applied, as well as the method of electrocardiographia, investigations on chemoreceptors and other methods providing good information on the toxicodynamics of preparations studied.

The research became regular and the design of scientific work became a constituent part of animal husbandry problems and themes in a number of scientific institutes. Scientific personnel were trained and improved their skill by devoting their creative activity to development of the hygiene of pesticide use and of pesticide toxicology.

First, some original methods and experimental equipment for scientific investigations (camera for studying conditioned reflexes on cats, camera for toxic dusts, etc.) were designed. The creative links between hygienists and scientific workers of other disciplines were developed and strengthened.

The third period of development of research on pesticide toxicology was between 1955 and 1964. Whereas before 1955 research on the hygiene and toxicology of insectofungicides was carried out by individual scientific bodies, since 1955 it has been conducted as a part of a common State plan and this is a scientific-organizational characteristic of the third period.

In 1955 attached to the Ministry of Public Health of the USSR the Committee for the Study and Regulation of Pesticides was organized. This Committee directs all the researches and approves the recommendations on each pesticide. The personnel of the Committee include hygienists, toxicologists, chemists synthesizing new pesticides, entomologists, representatives of the Ministry of Public Health and of the Ministry of Agriculture in the USSR.

By 1957, some 22 scientific-hygienic institutions were already engaged in the work.

An appreciable raising of the experimental-theoretical level of research work was of major importance for its further development. The problem of the unification of research methods had arisen by then. On 23 February 1957 the Ministry of Public Health of the USSR approved the *Methodical Instructions on Hygienic and Toxicological Assessment of New Pesticides, Recommended for Use in Agriculture*.

The toxic properties of all the pesticides permitted for agricultural use in the USSR and hygienic conditions of pesticide use were studied. To prevent the accumulation of poisons in foodstuffs use regulations for all the pesticides were formulated. For most of the pesticides, hygienic norms of their concentration in the working atmosphere and in foodstuffs were approved.

The toxic properties of about 500 chemical substances recommended for agricultural use were studied. Many of those which did not conform to the hygienic standards were forbidden.

Of great theoretical importance was the establishment of the dependence of toxic properties upon the chemical structure of organochlorine, organophosphorus, organomercury, dinitrophenolic and other compounds; it helped chemists to seek out compounds of slight toxicity.

The initial modes-of-action and toxicodynamics of organomercury, organophosphorus, arsenic-containing and some other compounds were determined. This promoted development of specific antidotes for the treatment of pesticide intoxications and of effective prophylactics.

On the basis of steady improvement of the hygienic requirements and for the sake of strict scientific objectives in the hygienic assessment of new chemicals, a classification of pesticides in accordance with their toxicity, physicochemical and other properties was formulated. Four groups were proposed:

- (i)—deadly poisons, LD_{50} below 50 mg/kg;
- (ii)—highly toxic, LD_{50} from 50–200 mg/kg;
- (iii)—moderately toxic, LD_{50} from 200–1000 mg/kg;
- (iv)—slightly toxic, LD_{50} above 1000 mg/kg.

Analyses of poisonings showed that 60 per cent of all cases were caused by compounds of the first group, 20–25 per cent by the second and less than ten per cent by the third group of compounds. Poisonings by slightly toxic compounds are registered infrequently and then only under specific conditions.

Apart from toxic action the persistence of pesticides under natural conditions is of primary importance for their assessment. Persistent pesticides can collect in soil, water and foodstuffs and may circulate for a long time in the biosphere. A number of compounds cumulate in environmental objects and biological systems. For instance, DDT concentration increases 1000 times in the system: water–plankton–fish–birds.

According to stability, pesticides are to be classified again under four headings:

- (a)—highly persistent, the degradation period more than two years;
- (b)—persistent, the degradation period from six months to two years;
- (c)—moderately persistent, decomposing during one vegetative period, say in six months;
- (d)—unstable, decomposing in one month.

It is considered here that decomposition to non-toxic components is complete.

A classification of pesticides according to the cumulation coefficient is suggested:

- (1)—very rapid cumulation, coefficient below 1;
- (2)—rapid cumulation, coefficient 1–3:

(3)—moderate cumulation, coefficient 3–5;

(4)—slight cumulation, coefficient above 5.

This classification takes account of volatility and the ability of pesticides to penetrate into the organism. To study cumulative properties, investigations on low-level doses and concentrations similar to practical levels are required.

The fourth period should be regarded as beginning about 1964–1966, when the All-Union Scientific Research Institute of Hygiene and Toxicology of Pesticides, Polymers and Plastics was established (1964). It was affiliated to the Problem Committee of the Academy of Medical Sciences of the USSR dealing with the scientific principles of the hygiene and toxicology of pesticides (1966), and it now coordinates the research work of more than 50 scientific institutions of the USSR.

Prior to 1964 the problems of work hygiene and food hygiene had been well developed, investigations on the sanitary protection of water reservoirs had begun and some investigations on soil had been carried out. But no attention had yet been paid to investigations on the pesticide contamination of atmospheric air. Toxicological investigations had so far been focused chiefly on the prophylaxis of acute and chronic poisonings.

It is well known that pesticides may enter man's organism with food, water and air and, as a rule, in very small quantities, which need not produce immediate pathological effects. But entering the organism for a long time, they accumulate in it and generally may cause pathological symptoms. However, hygienic dosages had been formulated for separate media, not taking account of the total intake of pesticides from all the media.

For elucidating delayed effects (cancerogenicity, mutagenicity, embryotoxicity, etc.) only some individual researches had been carried out up to that time.

The scientific workers of the new institute in cooperation with scientists of other institutions began extensive researches on the above-mentioned problems. New instruction methods were worked out ('Some Methodical Instructions on Hygienic Assessment of New Pesticides') and approved by the Ministry of Public Health of the USSR in 1969.

These instructions are characterized with a common hygienic approach to the assessment of pesticides having regard to all the possible pathological effects caused by the pesticides. They list all the compulsory toxicological and hygienic researches and the time they should be performed. Such unification of methodical approaches promotes the collection of similar information available for generalization and evaluation. The unification of approach is evidently only the necessary minimum and it must not restrain the investigator's creative initiative.

The collection of informative evidence on toxicity and the accumulation of pesticides as well as on the levels of hygienic norms^{2,3} facilitated the application of methods of correlative and regressive analysis for establishing the relationship between these parameters.

Strong and mean correlative relations were determined between LD₅₀ and MAC, LD₅₀ and AR*, cumulative coefficients and reserve coefficients for

* AR denotes allowable residues in mg/kg of fresh product, while MAC indicates mean accumulation coefficient.

establishing MAC, threshold doses and the values of hygienic norms in air and foodstuffs.

Equations of rectilinear and curvilinear regression were derived, permitting approximate estimation of the values of MAC and AR for pesticides on the toxicity and cumulation data. Regression levels have also been derived, reflecting the multifarious dependence of MAC and AR upon the toxicity and cumulation rate.

One of the tasks of pesticide toxicology is to elucidate the regularities, basing the dependence of biological activity and primarily the toxicity of chemical substances on their chemical structure.

The present study of this problem is designed to determine the quantitative relationship between the structure of reacting molecules and the rate constants of their reactions or the constants of chemical equilibria. The problem becomes complicated because many substances, before reaching the target areas, are converted into more or less active compounds, and their effect depends upon the actions of several new compounds. Among the organophosphorus insecticides there are compounds with very different toxicity. Obviously, the toxicity of organophosphorus compounds depends mainly upon the structure of the molecule as a whole and is not associated with the toxicity of elementary phosphorus⁴; this is, however, quite different in the case of organomercury compounds. Investigations on the toxicity of a number of compounds of this group⁵ showed that whatever the structure, their toxicity (LD_{50}) varied within a narrow range. These data indicate that the toxicity of organomercury compounds is determined, first of all, by an available molecule of elementary mercury; the structure of the molecule influences the toxicity only within definite limits. This is also confirmed by similarity of modes-of-action of mercury vapours and organomercury compounds, by symptoms of poisoning from them, and by information obtained in special experimental investigations showing that organomercury compounds, as well as mercury, blockade the SH-groups of enzymes. The differences in their action are more quantitative than qualitative and associated with peculiarities of their distribution and penetration into the central nervous system, etc.

While studying the toxicity and toxicodynamics of chemicals, revealing the dependence of their action upon the chemical structure and some other factors, in the USSR much attention is paid to predicting their delayed effects, such as mutagenic, embryotropic, gonadotropic and blastomogenic. Considering possible entry of pesticide residues into the organism with foodstuffs, the study of delayed effects is particularly realistic.

At present, the influence of chemical compounds on gonadal function is being studied. A selective effect on reproductive function of an organism is observed under contact with sevin, granosan, ziram, captan and some other pesticides⁶.

Special attention is paid also to studies of the mutagenic properties of the chemicals widely used in agriculture. Choice of the best models and methods is of great importance for substantiated genetic-hygienic estimation. In recent years some success has been achieved which is, in particular, associated with unification of methods technology and the objects of the investigations

(cytogenic study of somatic cells in animals and humans). In tests on experimental animals (mice, rats, rabbits) work has been done to determine the cytogenetic activity of some organochlorine pesticides—DDT, aldrin, hexachlorane, heptachlor, sevin and granosan; herbicides of the triazine and 2,4-D groups; fungicides of dithiocarbaminic acid derivatives group—TMTD, ziram, maneb and others.

Cytogenetic action of dithiocarbamates (ziram, maneb and editone) has been studied on human cells in leucocyte culture of peripheral blood and increased aberration frequency has been revealed in persons in contact with ziram, TMTD and polychlorocamphene⁷.

Results of the studies demonstrated a potential genetic hazard of some pesticides and this became a reason for revising the assessment of these compounds and for changing the hygienic regulations and hygienic norms. Further work is to be done to establish methods and criteria to predict the actual danger.

The lack of a precise correlation between chemical structure and the blastomogenic activity of substances calls for study of the blastomogenicity of almost every pesticide. From this point of view a number of pesticides have already been assessed. Thus, investigations of possible blastomogenicity in a series of pesticides, carried out on inbred animals, have revealed some pesticides without blastomogenic properties (lindane) and some (zineb, ziram, maneb, TMTD) with only slight blastomogenic activity. Potential blastomogenic activity has been also found in some herbicides (monuron, diuron, cotoran). The experience of recent years puts forward further new problems to be solved. The main one is to produce the actual risk for people while using substances with slight blastomogenic activity and it is evident that account should be taken not only of the quantity and quality of developing tumours, but also of the duration of their latent period.

Comparison of intensity and the pattern of changes caused by pesticides with the results of cytologic, cytogenic and histological investigations makes it possible to come to some tentative conclusions.

In the organism of people in many countries DDT and some other pesticides are found. People have become the carriers of synthesized compounds foreign to human nature. The problem of the influence of absorption of DDT upon human health has been discussed widely and different points of view are suggested. We supposed, *ab initio*, that absorption of DDT may be harmful for health. The investigations carried out at our institute have proved that prolonged exposure to DDT in doses close to those which enter man's organism with foodstuffs causes disturbances of the functional and morphological state of liver (impairment of detoxication, carbohydrate, enzymatic-synthetic and other functions), leads to the development of pathologic antigens, which induce autoaggressive antihepatic and antierythrocytic antibodies, increases susceptibility to coronary-spastic agents, and promotes myocardium infarction in animals.

Significant disturbances of energy-producing systems appear, and the ATP synthesis and the pyridine nucleotide content decrease. Under the influence of DDT, swelling of the hepatic mitochondria increases and their protein content changes. The content of one of the most important bioactive substances—serotonin—in blood and brain changes too.

Female carriers of DDT have more frequent complications during pregnancy and delivery.

Some other clinical data confirm the harmful influence on the organism of small doses of stable organochlorine pesticides, especially DDT. That is why, in the USSR, DDT was prohibited in livestock husbandry in 1962 and in field husbandry in 1970. DDT is excluded from the list of pesticides permitted for use in Russian agriculture.

While in the first period of development (1932–1937) of pesticides toxicology investigations were carried out only at one scientific institution for determining the toxicity parameters for the needs of work hygiene, in the second period (1937–1955) the investigations were already carried out at six scientific institutions where not only the toxicity but some physiological and biochemical modes-of-action, working conditions of the use of pesticides and amount of pesticide residues in foodstuffs were studied as well. In that period, the hygienic determination of pesticide dosage in foodstuffs and in the working atmosphere began.

In the third period (1955–1964) of investigation, 27 scientific institutions were cooperating. The scope of research and their experimental-theoretical level was enhanced. The hygienic investigations were the most important, but as the pesticide synthesis was perpetually increasing, the study of separate substances began to lag behind and their introduction in agriculture was retarded. In order to do away with such a situation, it was decided in 1964 to organize in Kiev the All-Union Scientific-Research Institute of Hygiene and Toxicology of Pesticides, Polymers and Plastics, and in 1966 working from the Institute the Problem Committee was organized, the main task of which is to plan and coordinate all the researches in this field. From that time the most fruitful period began.

Investigations on hygiene and toxicology of pesticides are carried out now at 45 scientific institutions. During the period from 1932 to 1965 in the USSR the toxicity of about 500 chemicals, proposed as pesticides, was studied; and from 1965 till 1974 at the All-Union Scientific-Research Institute of Hygiene and Toxicology of Pesticides, Polymers and Plastics 540 pesticides were investigated. Like numbers can be given from other USSR institutions.

During the last ten years chemical substances have been studied toxicologically twice as much as in the previous 32 years.

The toxicology of pesticides is improving steadily and has already achieved a high level of development. It serves actively for the prophylaxis of acute and chronic intoxications, but the methods of toxicology do not provide for predicting delayed effects. Study of chemical cancerogenicity, mutagenicity and embryotoxicity, etc. requires special scientific workers and adequate methods. At great institutes special laboratories for studying delayed effects are created where investigations are carried out in cooperation with toxicologists. Researches are also carried out on revealing the specific organotoxicity of different chemical compounds.

As a result of continuous development we have formulated an experimental pathology of chemical aetiology including and combining the research work of toxicologists, biochemists, physiologists, pathomorphologists and histochemists, specialists of chemical, cancerogenicity and mutagenicity, and other experts.

The task of the experimental pathology of chemical aetiology involves various information for predicting any pathological effect. No animal experiment can be available for answering all the questions.

At our institute researches on the clinical pathology of chemical aetiology are organized. They are carried out at the clinic for 130 patients, and a polyclinical study of people's health in regions with different conditions of use of pesticides has been set up. Attention is focused on revealing pre-nosological (latent) forms of diseases of chemical aetiology. Complex hygienic experimental and clinical investigations have appeared to be rather fruitful. This is a single proper way for solving the problems of protecting people's health in relation to environmental contamination with chemical substances. Our principal achievements, as we consider, are:

- (1) A common plan for the whole country providing for investigations according to the climatic-geographic peculiarities of different regions.
- (2) Unification of research methods providing for the combination of hygienic experimental and clinical investigations.
- (3) Establishing of quantitative criteria for predicting hazards for people's health and living creatures (hygienic classification of pesticides).

Of significant advantage is the rational, from a hygienic point of view, selection of pesticides. Over the whole period more than 1500 chemical substances synthesized in the USSR and partly in other countries and proposed as pesticides have been studied. Of this number only 200 pesticides are permitted for use and occupational examination.

In the whole world some 900 chemical substances are used (according to the active agent). Almost all of them have been studied by the hygienists and toxicologists of the USSR and most of them were given negative estimation. The fact that in our country hundreds of pesticides, which have caused tragic situations in the countries where they have been used, are forbidden—we consider to be our great achievement.

Study of the medical aspects of pesticide use in the USSR is of a new qualitative level permitting the recommendation for use of less hazardous pesticides contributing to efficient economics and without danger for people's health.

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