European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 07, Issue 03, 2020

# Effect Of Pesticides On The Content Of Cytochrome P-450 Of The Monooxygenase System And On The Ultrastructure Of Hepatocytes In Rat Embryos

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***Abstract: Our results show that the pesticides butylcaptax, dropp and karate are highly toxic pesticides, when exposed to these pesticides, the activity of the enzyme of the P-450 monooxygenase system is disrupted. Also, the research results showed that when poisoning with the above pesticides, ultrastructural, and therefore functional changes in the subcellular components of embryonic hepatocytes occur. When using RAF (plant antioxidant factor), enzyme activity and other indicators are significantly restored, which indicates that RAF has antioxidant properties.***

***Keywords: pesticides, liver, embryo, antioxidant, RAF (plant antioxidant factor), P-450 enzyme, monooxygenase system, lipid peroxidation (LPO), malonic dialdehyde (MDA), ultrastructure, mitochondria, microsome.***

## 1. INTRODUCTION

The problem of environmental pollution is closely related to the dietary habits of the population, especially in industrialized countries. Indeed, the widespread use in agriculture and the food industry of various chemical compounds (pesticides, hormones, antibiotics, preservatives, dyes) significantly increases the degree of contamination of food products[5,13]. Entering the body in various ways, pesticides accumulate in the tissues of humans and animals, exerting a toxic effect on them. When intoxication with pesticides, all tissues and organs are affected, but the liver is most susceptible to their influence. The cells (mitochondria and microsomes) of this organ, actively participating in the metabolism of xenobiotics, become the main target of these compounds. Considering the important role of these organelles, it can be assumed that damage to their membranes is important in the overall chain of damage to the cell and the body as a whole. Considering the current situation, there is an acute issue of studying the effect of chemicals, in particular pesticides, on the human body.

Part of the pesticides that have entered the natural environment as a result undergo decomposition when interacting with microorganisms, either in the organisms of plants and animals, or under the influence of physicochemical processes. Moreover, decomposition can be accompanied by both detoxification of pesticides - the loss of the original substance of toxic properties, and toxicity - the formation of more toxic substances. At the same time, the results of toxicity are almost impossible to predict, since two or more pesticides can participate in this process. This is very similar to a "binary" chemical weapon, in which two relatively harmless chemicals, when combined, form a highly effective warfare agent. Chemical load also affects the course and nature of the operational processes of processes in the body[18]. Children are at greatest risk, since they are the ones that children eat, since they are the ones who eat a lot of fruits and vegetables.

The set of conditions in the Central Asian region contributes to the penetration of pesticides into the body in various ways (by increasing lung ventilation, through the skin, with water and food) [3,4,16].

## 2. MATERIALS AND METHODS

It is known that [12,2], despite the preventive measures taken, there are still some cases of acute and chronic poisoning with pesticides. In this regard, the study of the effect of pesticides on the qualitative and quantitative indicators of the metabolism of proteins, carbohydrates and lipids seems to be very relevant.

The reproductive function is carried out as a complex sequence of physiological processes in the body of the father, mother and fetus. Pesticides can have an adverse effect at any stage of the implementation of the function, manifesting themselves only after many months, and sometimes years, defects in conception, gestation, and intrauterine development of the fetus [6].

Literary data on the problem of environmental degradation and the results of pesticide pollution are mainly devoted to the description

In conditions of toxic effects, structures that detoxify xenobiotics deserve special attention. The most important organ that maintains homestasis and detoxifies the body is the liver. The main system involved in the processes of their detoxification in the liver is the monooxygenase system (MOS). In the microsomal oxidation system, the metabolism of steroid hormones, lipids (including enzymatic peroxidation of polyunsaturated acyl chains of membrane phospholipids), as well as various hydrophobic poisons, drugs, and carcinogenic substances takes place.

Microsomes are a membrane system that communicates channels, vacuoles and cisterns. They are a lipoprotein network that permeates the cytoplasm of the cell.

The endoplasmic reticulum of the liver contains a system of biological oxidation of xenobiotics and endogenous substrates, which is physiologically important in the sense of "protecting the internal environment of the body". Most of the metabolic transformations that foreign compounds undergo in the body are provided by enzymes localized in the membranes of the endoplasmic reticulum of liver cells.

Microsomal enzymes catalyze hydroxylation reactions of compounds foreign to the body, as well as important endogenous substrates (saturated and unsaturated fatty acids, phospholipids, etc.)

Recently, questions of enzymatic activity in complex membrane-bound systems have attracted more and more attention of researchers in connection with the elucidation of not only the structural, but also the functional role of the phospholipid component of biological membranes. Chemical modification of biomembranes with toxic products of lipid peroxidation disrupts protein-lipid interaction. Mambran-bound enzyme complexes are inactivated, membrane permeability increases, intracellular compartmentalization is

disturbed, which leads to profound changes in cell metabolism and, as a result, to its degradation [4, 1, 15].

Of great interest is the effect of pesticides on intrauterine development, their teratogenic and embryotoxic properties. The action of teratogens can manifest itself at different levels of organization of a living organism, in changing various aspects of the metabolism of liver cells [11].

About 30 enzymes are involved in the metabolism of xenobiotics. Most often, metabolism occurs in the presence of functional groups in a xenobiotic molecule, it can immediately undergo conjugation [3,13] The most important is the P-450 system localized mainly in the membranes of the endoplasmic reticulum (EPS), called the microsomal metabolic system or the monooxygenase system [3 , 4,6,13]. The important advantages of the system are localization and high power on the main routes of xenobiotic entry into the body and a variety of metabolic pathways. In this system, the key enzyme is cytochrome P-450 [3,6]. The main function of the enzyme is to catalyze the process of hydroxylation of various chemical compounds, xenobiotics. It acts as one of the components of hydroxyl systems with different substrate specificities. The cytochrome P-450 system is involved in the oxidation of numerous compounds, both endogenous and exogenous. Enzymes of this group play an important role in the metabolism of steroids, bile acids, unsaturated fatty acids, as well as in the neutralization of xenobiotics.

## 3. DISSCUSSION

In order to reduce the toxic effect of xenobiotics on the body, in particular on the liver, a plant antioxidant factor (RAF) has been developed at the Department of Botany of the Tashkent State Pedagogical University [19]. According to the developers of the antioxidant, RAF helps to normalize the biochemical processes of the liver, poisoned by the pesticide in rats. This, in turn, became a prerequisite for research into its influence at the embryonic level.

Since MOS and in its composition cytochrome P-450 is a detoxifying complex of liver microsomes, we had to study the effect of some pesticides (karate, butylcaptax, and dropp), widely used in agriculture, on the detoxification function of the liver of rat embryos. The aim of this work was to investigate the effect of the above pesticides on the content of cytochrome P-450, which is involved in the detoxification of foreign chemicals and in combination with the plant antioxidant factor (RAF), also on LPO of microsomal membranes and on the ultrastructure of rat embryonic liver hepatocytes.

In connection with the above, we were faced with the following tasks:

- To study the effect of pesticides butylcaptax, dropp, karate and plant antioxidant factor (RAF) on the content of cytochrome P-450 in rat embryonic liver microsomes;
- To investigate the effect of the above mentioned pesticides on lipid peroxidation of membranes of microsomes of the liver of rat embryos;
- To study the effects of pesticides butylcaptax and droppa on the ultrastructure of rat embryonic liver hepatocytes.

Clinically healthy intact female and male rats of reproductive age were used in the experiments, the weight of the animals was 180-200 g. The number of animals in each experiment was 50 individuals, 10 in each group: 1 - control group, 2 - group poisoned with butylcaptax, 3 - group poisoned with dropp, 4 - group poisoned with karate and 5 - group poisoned with karate and injected with the antioxidant RAF rats. Mating was carried out at the end of the working day, while males were attached to females in a ratio of 1: 2 or 1: 3. The first day of pregnancy was established based on the detection of spermatozoa in a vaginal smear in normally circulating females.

The pesticides butylcaptax, dropp, and karate were administered once at a dose of 1/10 LD50 orally to females on the 3rd, 13th and 19th days of pregnancy.

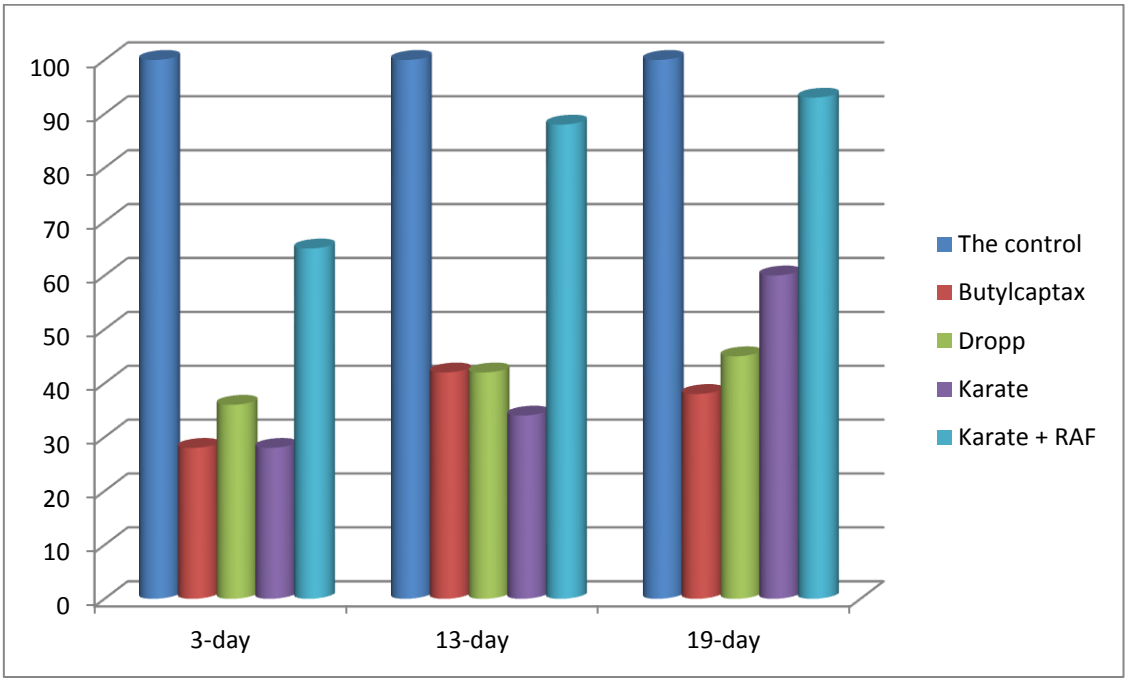
Butylcaptax - 2-Butylthiobenzothiozole, a benzothiazole derivative. LD50 - 1300 mg / kg.
Dropp - Thidiosuron, a urea derivative. LD50 - 4000 mg / kg.
Karate - λ-cyano phenoxybenzyl 3- (2 chloro-3,3,3-trifluoroprol-1-ethyl) -2,2-dimethylcyclopropanecarboxylate. LD50 - 1180 mg / kg.
The studies were carried out on the 21st day of pregnancy by decapitation of pregnant females and subsequent extraction of embryos.
In the experiments, we used a liver homogenate of rat embryos isolated in a cold room.
Protein concentrations were determined by the Lowry method [20].
The activity of the cytochrome P-450 enzyme was determined by the spectrophotometric method of T. Omuro and R. Sato [21], based on the change in the absorption of the complex reduced by carbon monoxide.
The activity of NADP.H-dependent and ascorbate-dependent lipid peroxidation in microsam was determined by the content of malondialdehyde (MDA) using 2-thiobarbituric acid [14].
The ultrastructure of embryonic liver hepatocytes was investigated by electron microscopy on a Hitachi-500 electron microscope.
As shown by the research results (Table 1), in the microsomal fractions of the liver of rat embryos poisoned with pesticides, the content of cytochrome P-450 decreased. When rats were poisoned with butylcaptax on the 3rd day of pregnancy, the enzyme content decreased by 72%, on the 13th day - by 58%, and on the 19th day - 62%. In case of poisoning with dropp at the same time, the content of the cytochrome P-450 enzyme decreased by 64%, 58% and 55%, respectively.
In case of karate pesticide poisoning, a decrease in the content of cytochrome P-450 is also observed. The content of this enzyme decreased by 72%, 66%, and 40%, respectively.

## 4. MAIN PART

A large difference in the content between the cytochrome P-450 microsomes of the liver of control embryos and those poisoned with the pesticide karate when using RAF is reduced by an average of 20%. (figure. 1)
Our findings indicate that the pesticides studied above have a toxic effect on the organism of rat embryos, passing through the placental barrier.
Table 1
Content of cytochrome P-450 in liver microsomes of embryos poisoned with pesticides of pregnant rats and after administration of the antioxidant RAF (nmol / mg protein)

| Options | Terms of poisoning and pregnancy (days) | | |
|---|---|---|---|
| | 3 - day | 13 – day | 19 – day |
| The control | 1,001 ± 0,080 | 1,001 ± 0,080 | 1,001 ± 0,080 |
| Butylcaptax | 0,270 ± 0,035 | 0,340 ± 0,042 | 0,380 ± 0,037 |
| Dropp | 0,360 ± 0,045 | 0,420 ± 0,035 | 0,455 ± 0,045 |
| Karate | 0,273 ± 0,035 | 0,343 ± 0,045 | 0,601 ± 0,043 |
| Karate + RAF | 0,654 ± 0,042 | 0,883 ± 0,051 | 0,933 ± 0,038 |

The toxicity of the above pesticides is expressed in the inhibition of the activity of the key MOS link - the cytochrome P-450 enzyme. This occurs, apparently, as a result, to a varying degree, of the destructive effect of pesticides butylcaptax, droppa and karate on biological membranes, which leads to the accelerated formation of free radicals, causing a change in the lipid composition of membrane structures [1]. As a result of LPO in microsomes, the dissociation of ribosomes, inhibition of protein synthesis and microsomal oxidation processes occur [5.]




Picture 1. Effect of pesticides on the content of cytochrome P-450 in liver microsomes of rat embryos and with subsequent administration of the antioxidant RAF (%)

As can be seen from the above data, the degradation of cytochrome P-450 and a decrease in microsomal oxidation confirm the disruption of LPO processes in microsomal membranes and, in our opinion, plays an important role in the mechanism of pathology development.

In recent years, LPO of biological membranes has played a special role in the pathogenesis of various diseases. At the same time, everyone knows that microsomes are well protected from the harmful effects of exogenous and endogenous toxic substances due to the double lipoprotein membrane, but the non-exaggerated structure of the phospholipids of biological membranes makes them the optimal substrate for free radical peroxidation. Apparently, the mechanism of the effect of these pesticides is based on the enhancement of free radical LPO [14].

A characteristic feature of the organization of microsomal membranes is a high content of polyunsaturated fatty acids in them, which are capable of undergoing intense oxidation by the free radical peroxide mechanism. The process of formation of lipid peroxides has a free radical chain mechanism similar to the reactions of oxidation of organic compounds with molecular oxygen. This process can begin if there are free radicals in the system.

At the early stages of ontogenesis, the rate of non-enzymatic and enzymatic LPO noticeably increases in liver microsomes. The rate of ascorbate-dependent LPO reaches maximum values in liver microsomes of 2.5-month-old rats. The rate of enzymatic LPO in microsomal liver fractions during ontogenesis changes extremely and reaches a maximum level in the liver of 2-month-old rats (an increase of almost 20 times compared to the liver of newborns) [13, 15].

Based on the above, we set ourselves the following task - to investigate the effect of the studied pesticides on LPO of membranes of rat embryo liver microsomes.

We studied the effect of butylcaptax and droppa on the content of small dialdehyde (MDA), one of the end products of lipid peroxidation, in the liver of rat embryos (Table 2).

It was found that when butylcaptax was administered on the 3rd day of embryonic development, NADP.H- and ascorbate-dependent LPO in embryonic liver microsomes increased by 74 and 47%. In case of poisoning with dropp on the 3rd day of embryonic

development, enzymatic and non-enzymatic LPO in microsomes of the liver of embryos also increased by 60 and 50%. At the same time, the content of enzymatic and non-enzymatic LPO was significantly lower than in the lesion with butylcaptax (Figure. 2).

table 2

Effect of pesticides butylcaptax and droppa on LPO of rat embryo liver microsome membranes (μmol / min / mg protein)

| Options | OVER.H- - dependent sex | Ascorbate - dependent sex |
|---|---|---|
| | Development day | |
| | 3rd day | 3rd day |
| The control | 0,308 ± 0,032 | 0,328 ± 0,038 |
| Butylcaptax | 0,537 ± 0,075 | 0,482 ± 0,054 |
| Dropp | 0,436 ± 0,052 | 0,438 ± 0,048 |

The high content of enzymatic LPO in microsomes can be explained by the fact that in the case of NAD.H- - dependent LPO, the substrate in microsomes is polyunsaturated fatty acids localized near the components of the electron transport chain, and in the case of ascorbate-dependent LPO - other fatty acids [15].

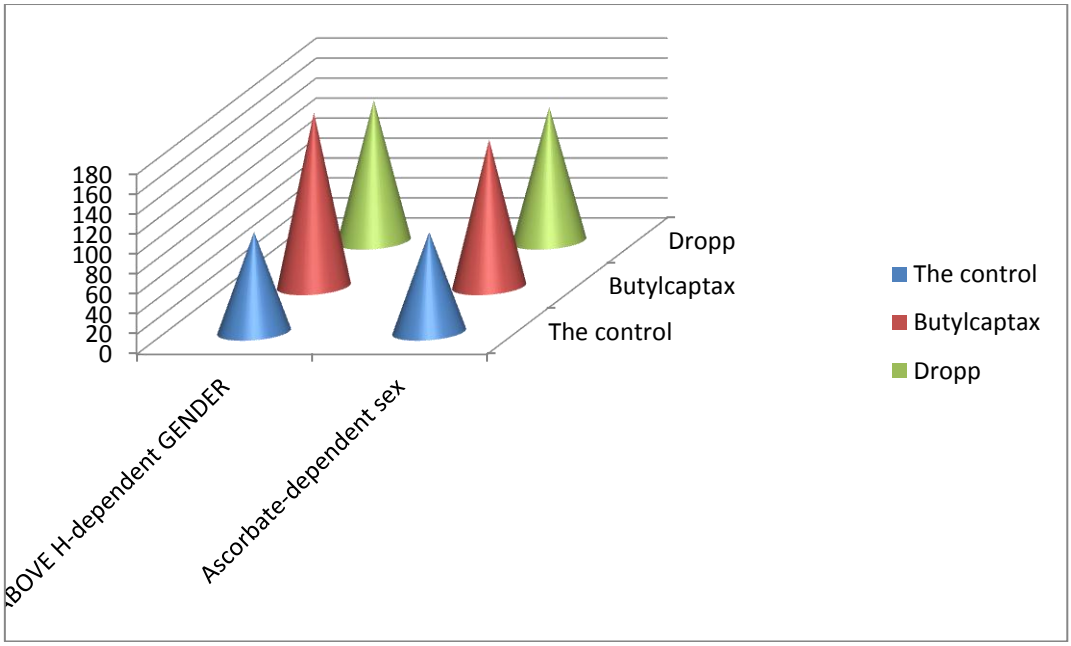



Figure-2. Effect of pesticides butylcaptax and droppa on MDA levels in liver microsomes of rat embryos (%)

Thus, the oxidation products of butylcaptax and droppa stimulate peroxidation reactions in the membranes of the embryonic liver microsomes, which leads to their damage, and these damage can be seen in the ultrastructure of the embryonic liver hepatocytes.

The embryonic liver is predominantly glycolytic tissue, and lactate, which is accumulated in the liver and blood serum, is transported through the maternal bloodstream, where it is further metabolized. In the embryonic liver of rats, the endoplasmic reticulum is represented mainly by a rough subfraction. At the beginning, it looks like bubbles, which then turn into cisterns. Smooth membranes appear in the postnatal period. There is very little endoplasmic reticulum in the third phase of pregnancy, its monooxygenase activity is very low. In significant

numbers, the granular endoplasmic reticulum appears at the age of one week. On the 20th day of gestation, cytochrome P-450 was not detected spectrophotometrically in the embryonic liver of intact rats. In the following days, until the moment of delivery, the concentration of hemoprotein gradually increases. The peak of the differential spectrum of cytochrome P-450 during these periods was stably fixed at a wavelength of 450-450.5 nm [15].

Many pesticides are hepatotoxic. Liver cells, carrying out the metabolism of xenobiotics, become the target of the parent drugs and reactive metabolites. According to numerous literature data, under the action of pesticides on the body, the fastest and most significant changes in structure and functions are observed at the subcellular level (nucleus, mitochondria and microsomes). The degree of their severity depends on the dose and duration of the poisoning, and the nature - on the structural and functional features of the organ (liver, heart).

In the following experiments, we carried out morphological studies of the cyto-ultrastructure of hepatocytes of the liver of embryos in case of poisoning of the body with pesticides - butylcaptax and dropp on 3 days of embryonic development.

Lipid drops appear in hepatocytes of embyrons in case of poisoning with butylcaptax on the 3rd day of postembryonic development, which are similar in structure to neutral fats. Many drops are located in the sinusoidal pole. Mitochondria are swollen, no pronounced polymorphism was found. The mitochondrial matrix is light, but the cristae are deformed.

The granular network is poorly expressed, its vesiculation is noted, and a flocculent material is seen in the vesicles. Vesicles are located mainly in the biliary pole of the hepatocyte. The granular network that envelops the mitochondria has close contact with them.

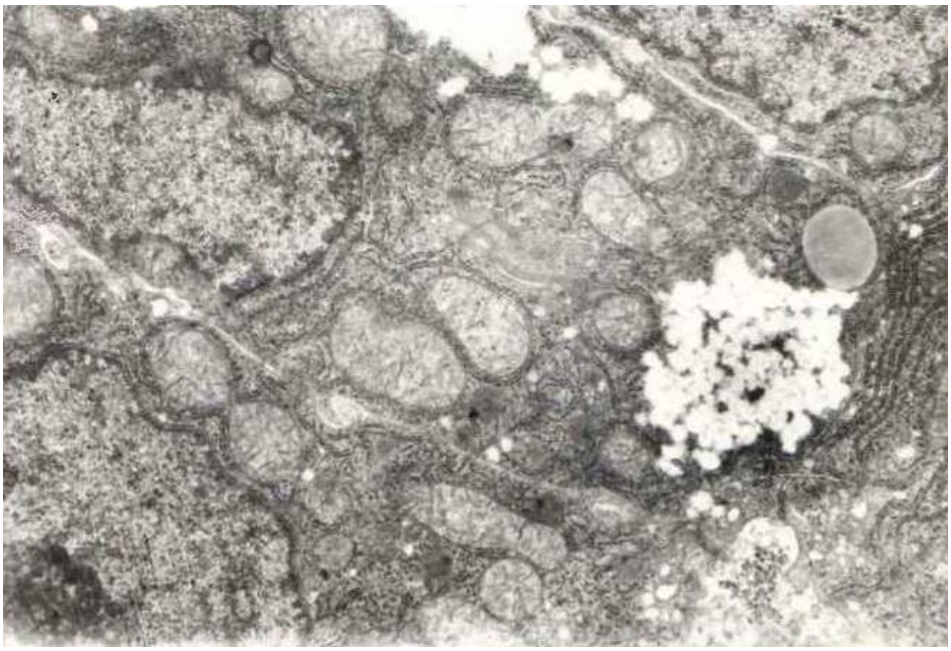


Figure -3. Electron micrographs of an ultrathin section of the liver tissue of embryos on the 21st day of embryonic development, poisoned with butylcapx on the 3rd day of development.

In the cytoplasm of hepatocytes, structureless zones appear, there are many informosomes, and their delay is possible. Invaginations of the nuclei are visible, the clear contour of the nuclear envelope is lost. Chromatin is vague, deep invaginating karyolemmas appear, in which vesicles with electrodense contents are located (Figure. 3).

## 5. RESULT

With dropp intoxication on the 3rd day of embryonic development, mitochondrial polymorphism is manifested. They are mainly dumbbell-shaped, elongated and spherical in shape and of various densities. Most of the mitochondria are moderately swollen, the matrix is cloudy, the contours of the mitochondrial membranes and their cristae are indistinct. Mitochondria are usually located near the nuclear zone. There are cases of myelination. In places, accumulations of a granular network in the form of elongated tubules are found. Some of them are fragmented and densely strewn with ribosomes. The number of the policy has been moderately increased.

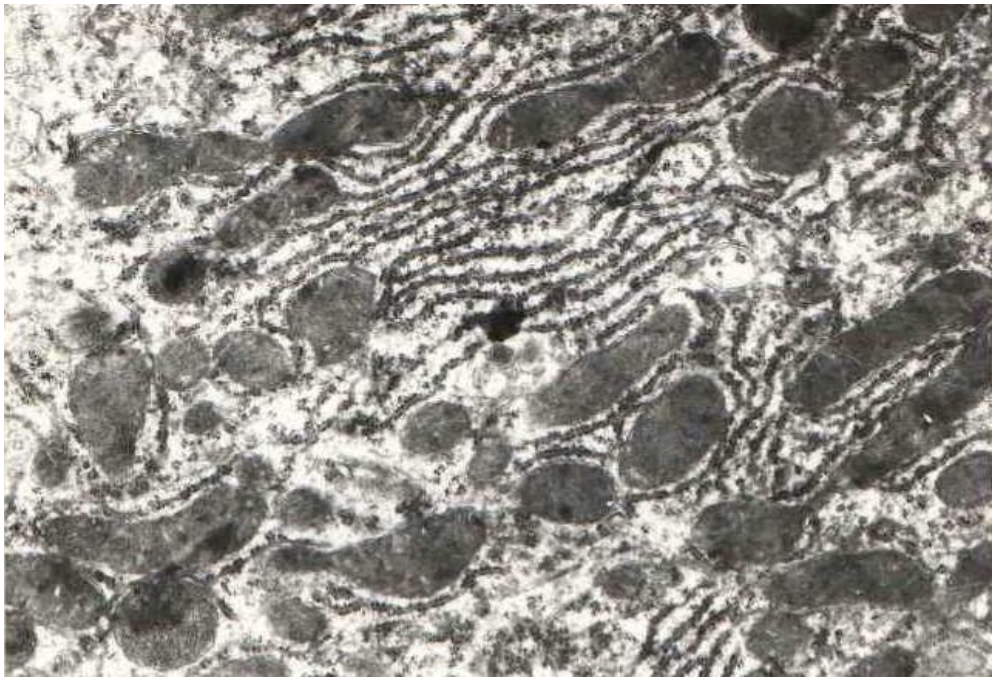


Figure- 4. Electron micrographs of an ultrathin section of the liver tissue of embryos on the 21st day of embryonic development, poisoned with dropp on the 3rd day of development.

The bile capillaries are somewhat dilated, but destructed, the number of microvilli is sharply reduced. The walls of the bile capillaries are almost smooth. Nuclei euchromatization is observed. The nucleoli are located under the karyolemma. The porosomes are enlarged.

Among the hepatocytes, mitotic figures are found. The intercellular gaps are widened, in places destructed. Membrane formations are visible in the cracks (Figure. 4).

Thus, the pesticides butylcaptax and dropp cause ultrastructural and, consequently, functional changes in the subcellular components of rat embryonic hepatocytes. These changes, in turn, reduce the protective and adaptive capabilities of the whole organism.

Metabolic activation of xenobiotics, leading to the formation of free radicals, is carried out in the electron transport chain of the endoplasmic reticulum. Cytochrome P-450 plays a key role in this. With the introduction of butylcaptax and dropp, the content of this enzyme in the microsomal fractions of embryos is observed in case of poisoning with butylcaptax on the 3rd day of embryonic development. In this respect, our data are consistent with the results of earlier studies, according to which the processes of microsomal oxidation and LPO are alternative: the activation of one of them leads to the suppression of the other [8].

The problem of protecting the external environment from pollution by chemical substances and protecting public health from their harmful effects is of particular relevance. Of paramount importance is the question of the impact of widely used pesticides in agriculture

on the future generation. These influences can be realized due to the microgenic, embryotoxic and teratogenic effects of preparations that are able to penetrate the placenta.
Among the approaches to deciphering the mechanism of the toxic action of chemicals, an important role belongs to electron microscopic and biochemical studies at the subcellular level. In the analysis of the toxic effect of pesticides, a special place is occupied by their influence on the structure and function of microsomal membranes - their most likely targets.
The results of electron microscopic studies make it possible to judge the degree of toxic effects of pesticides butylcaptax and droppa ns liver tissue. It was found that in case of poisoning with pesticides, there are disturbances in the structure of the endoplasmic reticulum and in the cell as a whole, characterized as polymorphism of mitochondria, phroagmentation of the granular reticulum, sharp focal hyperplasia of it, an increase in the content of free ribosomes and polysomes. These violations indicate a low activity of the organelle. A large number of lipid drops appear in the cytoplasm of hepatocytes as a result of metabolic disturbances of LPO. Other qualitative and quantitative changes in cytoplasmic structures were also noted. The most profound disturbances in hepatocytes of embryos under the influence of pesticides are observed with poisoning with butylcaptax on the 3rd day of pregnancy.
The results of studying the effect of butylcaptax and droppa on the level of malondialdehyde showed that it leads to the intensification of enzymatic and non-enzymatic LPO in microsomes of embryos. The highest level of MDA in non-enzymatic LPO in liver microsomes with butylcaptax poisoning on the 3rd day of development. During this period, an increase in MDA was also established along the enzymatic pathway of lipid oxidation. Apparently, under the action of these pesticides, significant disturbances in the structural arrangement of microsome membranes occur, which create conditions for intensive oxidation of membrane lipids. An increase in liver LPO in the early stages of embryogenesis is likely. It is connected with the fact that during these periods in the microsomes of the liver of embryos the content of oxidation substrate - polyunsaturated fatty acids - increases.

## 6. CONCLUSION

Activation of LPO processes causes degradation of cytochrome P-450 and weakening of microsomal oxidation processes. With the introduction of butylcaptax and droppa, the content of cytochrome P-450 in microsomal fractions of the liver of embryos decreases. The most pronounced decrease in the content of this enzyme is observed in case of poisoning with butylcaptax on the 3rd day of development.

Also, the pesticide karate, like other pesticides, has a toxic effect on the body of the embryo, its toxicity is expressed in the inhibition of the activity of the cytochrome P-450 enzyme. The functional disorders of the integrity of the hepatocyte membranes obtained as a result of pesticide poisoning can be corrected by administering antioxidant drugs. In this case, the plant antioxidant factor we used in the experiment gave positive results, which affected both the structure of the liver and the activity of cytochrome P-450.

Thus, the pesticides butylcaptax, dropp and karate cause ultrastructural and, consequently, functional changes in the subcellular components of embryonic hepatocytes. These changes reduce the protective and adaptive capabilities of the whole organism.

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