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Influence Of Pesticides on Some Morpho-Biochemical Parameters of Liver Microsomes of Pregnant Rats and Their Embryos

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ABSTRACT

Poisoning of animals with pesticides - butylcaptax and Dropp causes pronounced dystrophic processes at the level of cells and subcellular structures of the liver. Along with slightly changed cells, there are heavily damaged ones. When inoculating pregnant rats with butylcaptax and Dropp, we found that in the liver microsomes of pregnant rats and their embryos, there is a tendency to a decrease in the content of PC, PE and the amount of phospholipids. In microsomal fractions, the level of LPL, FA and the ratio of CS / PL increases. However, these changes are more pronounced in poisoning on the 19th day of pregnancy, especially in experiments with butylcaptax. The results of studying the effect of butylcaptax and Dropp on the level of malondialdehyde showed that it leads to intensification of NADPH and ascorbate-dependent lipid peroxidation in the liver microsomes of the fetus and mother. The highest level of MDA with the introduction of butylcaptax and Dropp is in non-enzymatic lipid peroxidation. The content of cytochrome P-450 in microsomes is noted in case of poisoning with butyl captax on the 3rd day of pregnancy; the microsomal fractions of the liver of pregnant rats decrease. A more pronounced decrease in the content of this enzyme is observed in case of poisoning with butyl captax on the 3rd and 19th days of pregnancy

Keyword: *Pesticide, dropp, detoxification, rat, pregnancy, embryo, microsome, phospholipids, lipid peroxidation, enzyme, cytochrome P-450.*

1. INTRODUCTION:

Pesticides are poisons that poison target organisms; they also include sterilants (substances that cause infertility) and growth inhibitors. Pesticides are also called pesticides, since in general pesticides include a wide range of plant protection chemicals

They belong to inhibitors (catalytic poisons of biological enzyme catalysts). Under the influence of pesticides, some biological reactions stop occurring, and this makes it possible to fight diseases (antibiotics), store food longer (preservatives), destroy insects (insecticides), and destroy weeds (herbicides) [2, 6].

The United Nations Population Division estimates that the world's population will reach 9.7 billion by 2050, up 30% from 2017. Almost all of this demographic growth will occur in developing countries. The Food and Agriculture Organization of the United Nations (FAO) estimates that in developing countries, 80% of the increase in food production required by this population growth will come from increased yields and replanting of crops per field. Additional food production will be ensured by only 20% due to an increase in sown areas [7,8].

The use of pesticides prevents large-scale crop losses and therefore pesticides will continue to play a role in agriculture. However, the impact of pesticides on human health and the environment remains a matter of concern [2, 3, 4].

WHO and FAO jointly developed the International Code of Conduct for Pesticide Management. This voluntary code of practice was last published in 2014. It is intended for government regulators, the private sector, civil society and other stakeholders to provide information on best practices for managing pesticides at all stages of their life cycle, from production to disposal. [2, 3].

The Food and Agriculture Organization of the United Nations (FAO) estimates that in developing countries, 80% of the increase in food production required by this population growth will come from increased yields and replanting of crops per field. Additional food production will only be achieved by 20% through an increase in sown areas. The use of pesticides prevents large-scale crop losses and therefore pesticides will continue to play a role in agriculture. However, the impact of pesticides on human health and the environment remains a matter of concern.

The use of pesticides in food production, both for local consumption and for export, should be carried out in accordance with the principles of good agricultural practice, regardless of the economic situation of the country. Farmers should limit the amount of pesticides they use to the minimum necessary to protect their crops [3].

The use of pesticides is in demand by the commercial interests of industrial agricultural production, which is focused on such simple indicators as the durability and size of the crop, its storage and resistance to transportation. But the significant reduction in such qualities of the resulting products as microelement composition, usefulness and safety for consumer health is not taken into account.

Despite the large number of works in this area, the mechanisms and relationships between individual metabolic disorders under the influence of chemical environmental factors remain insufficiently studied. At the same time, in real conditions, the human and animal body is affected by various combinations of factors of varying intensity, which significantly affects its resistance to adverse effects.

Relevance of the work. Currently, assessing the health status of the population depending on the influence of chemical environmental factors is of particular relevance, which is associated with increasing public awareness of environmental issues, the development of a social movement, etc. At the Research Institute named after. A.N. **Sysin** of the Russian Academy of Medical Sciences has been developing research into the medical and biological study of the influence of chemical environmental factors on the body for a number of years [11]. The greatest attention is currently paid to the study of the main factors in the formation of pathology, the body’s resistance to adverse effects, taking into account the real situation, since there is no “pure” effect, but a combination, combination or influence of a complex of factors. In this case, it is necessary to take into account the specifics of the region, the priority of environmental pollution and other factors in the formation of pathology [1,6].

In particular, in the Central Asia region, pesticide pollution should be considered a priority, which is also relevant for other agricultural regions of the country. The currently existing GShK of chlorine and phosphorus organic pesticides (hexachlorane and phosphamide) are calculated without taking into account the real load on the body and require revision. In addition, an increase in injuries was detected among people employed in agricultural work and exposed to pesticides (organochlorine and organophosphorus nature). Chemical load also affects the course and nature of reparative processes in the body [9,10,14].

The problem of protecting the external environment from pollution by chemicals and protecting public health from their harmful effects has acquired particular relevance. Of primary importance is the impact of pesticides widely used in agriculture on future generations. This effect can be realized due to the mutagenic, embryotoxic and teratogenic effects of drugs that are able to penetrate the placenta. Among the approaches to deciphering the mechanism of the toxic action of chemicals, a major role belongs to biochemical studies at the subcellular level. In the analysis of the toxic effects of pesticides, an important place is occupied by their effect on the structure and function of the membranes of mitochondria and microsomes - their most likely targets.

According to literature data [1], in Uzbekistan, despite. the introduction of preventive measures when using pesticides in agriculture, isolated cases of acute and chronic poisoning by them continue to be observed. At the same time, significant shifts are noted in redox and other metabolic processes, which helps to reduce the overall reactivity of the body to adverse effects. Along with this, in particular, there are literary indications that the level of metabolic processes plays a great role in the recovery period of post-traumatic regeneration of damaged tissues [5,12,16]. Chemical load also affects the course and nature of regenerative processes in the body.

In this regard, the purpose of this study was, on the basis of experimental data, to study the mechanisms of influence of pesticides on the body, using the example of butylcaptax and droppa, on the structural and biochemical parameters of liver microsomes of pregnant rats and their embryos, at different stages of pregnancy and embryonic development, and to develop on this basis diagnostic tests reflecting changes in the body's resistance to adverse effects.

Materials and methods. The objects of research were white female Wistar rats weighing 180-200 g. The experiments were carried out on the 3rd, 13th and 19th days of pregnancy, corresponding to the implantation period, organogenesis and the fetal period of embryonic development. To fertilize rats in the proestrus-estrus stage, they were placed overnight with males in a ratio of 3:1. The first day of pregnancy was considered the day sperm were detected in vaginal smears. Animals were primed with butylcaptax and dropp at a dose of 1/10 LD_{50} intragastrically with a special probe for 5 days. Animals were slaughtered on the 20th day of pregnancy, when the embryo reached a significant size, at the end of organogenesis and the beginning of the fetal period. Microsomes from the liver of embryos and the mother's body were used in the experiments.

Method for isolating microsomes. The microsomal fraction from the liver was isolated by differential centrifugation. First, the liver was removed from the glass, squeezed out on a gauze napkin, weighed and chopped with scissors. All procedures were carried out at 0-4°C. The liver was homogenized in a homogenizer with a Teflon pestle with 8-10 times the volume of the second isolation medium. The homogenate was centrifuged at 9000 q for 20 min. The supernatant was then centrifuged at 105,000 g for 60 min using a VAC-601 centrifuge. The resulting sediment was suspended with a syringe in a minimal amount of isolation medium [25].

Lipid extraction was carried out according to the Folch method [21,22]. Lipids from microsomes were extracted with a freshly prepared chloroform-methanol mixture [2:1].

Phospholipids were separated into fractions using thin layer chromatography [21,22]. The lipid extract was applied to an activated plate coated with a layer of KSK silica gel. The plate was placed in a chromatography chamber. The separation system consisted of a mixture of chloroform-methanol-acetic acid-water [65:43:1:4]. Identification of phospholipid fractions was carried out using witnesses and color reactions. Lipid phosphorus of individual fractions was determined according to Yu.A. Vladimirov [22], protein - according to O.N Lowry [23].

The activity of ascorbate-dependent and NADPH-dependent lipid peroxidation in microsomes was determined by the content of malondialdehyde [MDA]. MDA content was determined using 2-thiobarbituric acid. At wavelengths in the butanol layer, the intensity of lipid peroxidation processes was expressed in mol/min/mg of protein of the corresponding fraction.

To carry out the electron microscopy method, pieces of liver tissue were fixed with a 2.0% solution of glutaraldehyde in 0.1 M phosphate buffer, pH 7.4, followed by additional fixation with a 1.0% solution of osmium tetroxide in 0.1 M phosphate buffer, pH-7.4. Dehydration was carried out in alcohols of increasing concentration. The material was poured into a mixture of epon and araldite. Ultrathin sections obtained on an LKB-8800 ultratome (Sweden) were contrasted with a 2% aqueous solution of uranyl acetate and lead hydroxide according to Reynolds. Electron microscopy studies were carried out using an Hltachi-500 electron microscope.

Statistical processing of the data was carried out using the method of variation statistics. The probability of reliability of statistical indicators and the difference between them were determined using the Student's table.

Determination of cytochrome P-450 was carried out according to the method of T. Omuro, Sato [23], based on changes in the absorption value of the complex reduced with carbon monoxide.

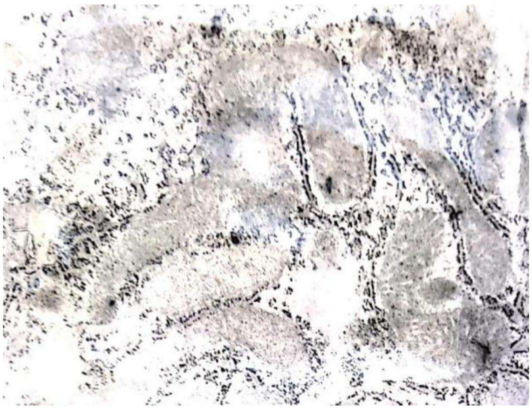
Experimental part. Many pesticides have a hepatotoxic effect. Liver cells, carrying out the metabolism of xenobiotics, become the target of the original drugs and the reaction of incapable metabolites [5,6].

According to numerous literature data, when pesticides act on the body, the most rapid and significant changes in structure and function are observed at the subcellular level (nuclei, mitochondria, microsomes). The degree of their severity depends on the dose and duration of poisoning, and their nature depends on the structural and functional characteristics of the organ (liver, heart).

Microsomes are a membrane system of communicating channels, vacuoles and cisterns. They represent a lipoprotein network that penetrates the cytoplasm of the cell. In microsomes, two types of endoplasmic reticulum (ER) are distinguished: rough, carrying ribosomes on its surface, and smooth, where systems of "multipurpose oxidases" are predominantly localized. Microsomes are associated with the cell membrane, mitochondria and lamellar complex.

We conducted morphological studies of the cytoultrastructure of hepatocytes during poisoning of the body with butylcaptax and dropp. Ultrastructural studies were carried out on pregnant rats and their embryos. Intact rats served as controls.

Administration of butylcaptax on the 3rd day of pregnancy causes changes in the structure of the endoplasmic reticulum. The amount of endoplasmic reticulum decreases, its definition becomes uneven. The number of free ribosomes and lisomes increases (Picture. 1 A).



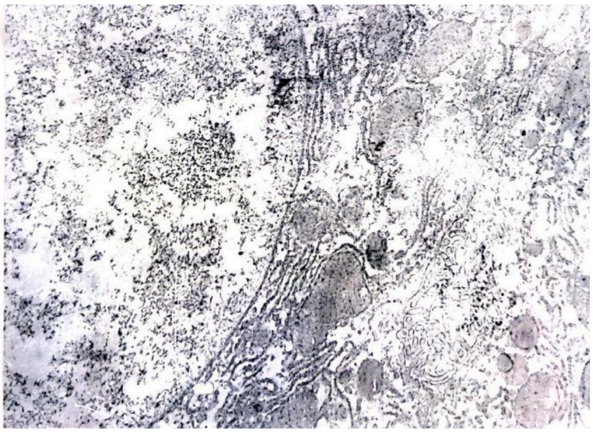
A

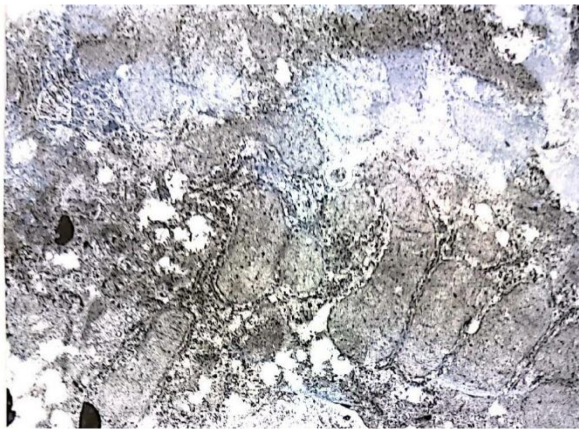
A B

Picture.1. Ultrastructure of a hepatocyte of a pregnant rat poisoned with butylcaptax (A) and dropp (B) on the 3rd day of pregnancy. Inc:30000X

In cases of dropp poisoning, on the 3rd day of pregnancy, maternal hepatocytes exhibit sharp focal hyperplasia of the granular reticulum (Picture. 1B), and its detachment from the mitochondrial membrane. There are single lysosomes with heterogeneous contents.

On the 13th day of pregnancy, when poisoned with butylcaptax, the following was noted in the hepatocytes of rats. In some places, there is an accumulation of granular reticulum in the form of elongated tubules. Their fragmentation also occurs. Focal hyperplasia of the granular reticulum persists. The microvilli of the bile capillaries are densely located (Picture. 2 A).





A B

Picture 2. Ultrastructure of a hepatocyte of a pregnant rat poisoned with butylcaptax (A) and dropp (B) on the 13th day of pregnancy. Inc:30000X

When intoxicated with droppa, on the 13th day of pregnancy, reticulin fibrils and membrane formations appear in maternal hepatocytes. The endoplasmic reticulum is moderately developed, with a uniform distribution of ribosomes on its membranes, and unevenly scattered throughout the cytoplasm. (Picture. 2 B).

On the 19th day of pregnancy, with butylcaptax poisoning, changes in hepatocytes are less pronounced. Fragmentation of the endoplasmic reticulum is observed. Lipid dropps are available. Inside the cell, the number of filamentous formations increases, and single lysosomes are found. The karyolemma is uneven, thickened and compacted.

With droppo intoxication during this period of pregnancy, the following is also observed. The profiles of the granular reticulum are elongated. Lipid dropplets appear in large quantities. There are many secondary lysosomes at the biliary pole. In the bile capillaries, the microvilli are tall and dense.

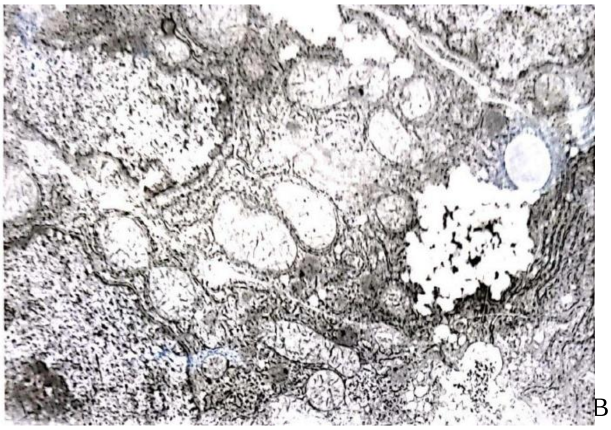
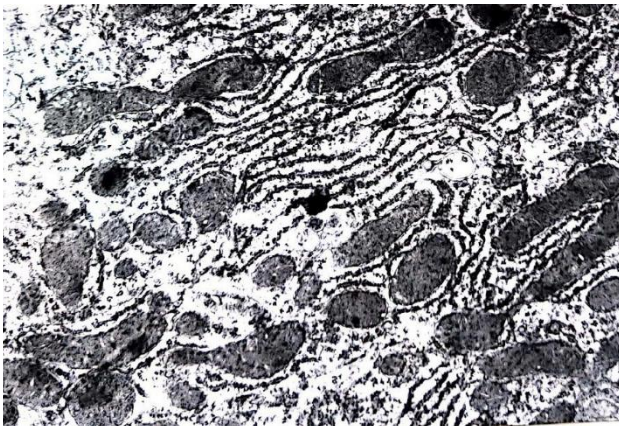
Thus, the pesticides butylcaptax and dropp cause a number of ultrastructural changes in the liver of pregnant rats, characterized by lipidation of the cytoplasm, some qualitative and quantitative changes in the cytoplasmic and nuclear structures.

In hepatocytes of embryos, when seeded with butylcaptax, on the 3rd day of postembryonic development, lipid dropplets appear, their structure similar to neutral fats. Many dropps are located at the sinusoidal pole.

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

Structureless zones appear in the cytoplasm of hepatocytes. There are many informationosomes in the karyoplasm (they may be delayed). The chromatin is blurry. Deep invaginant karyolemmas appear, containing vesicles with electron-dense contents (Picture. 3 A).

When intoxicated with droppa, on the 3rd day of embryonic development, accumulations of a granular network in the form of elongated tubules are detected. Some of them are fragmented and densely strewn with ribosomes. The number of polysomes is moderately increased (Picture 3 B).

A  B 

Picture.3. Ultrastructure of an embryo hepatocyte poisoned with butylcaptax (A) and dropps (B) on the 3rd day of development. Inc:30000X

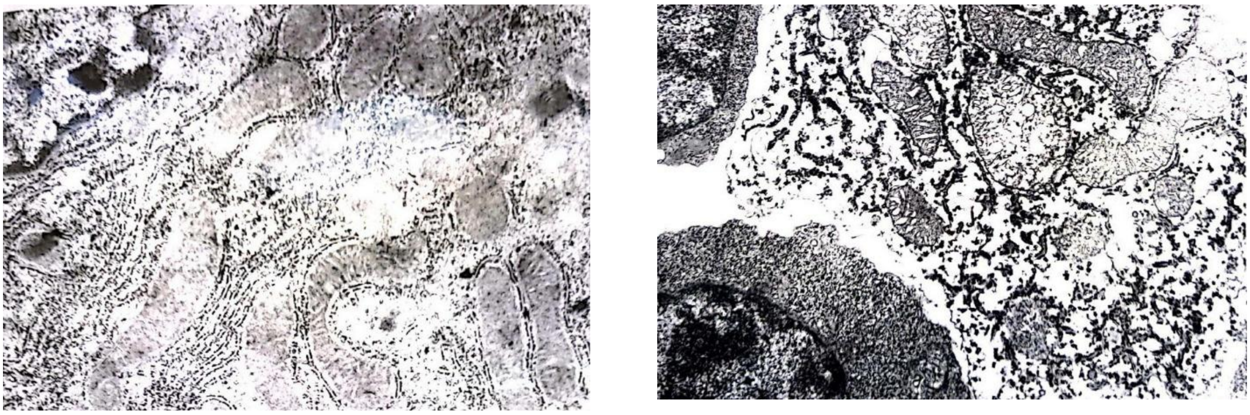
When intoxicated with droppa, on the 3rd day of embryonic development, accumulations of a granular network in the form of elongated tubules are detected. Some of them are fragmented and densely strewn with ribosomes. The number of polysomes is moderately increased (Picture 3 B).

Mitotic figures are found among hepatocytes. The intercellular gaps are widened and destructured in places. Membranous formations are visible in the cracks.

In case of butylcaptax poisoning, on the 13th day of embryonic development, an elongation of the profile of the granular reticulum is observed, densely dotted with ribosomes.

Microvilli in the bile capillaries are enlarged and more densely located. There are vesicles and microbodies around the capillaries, but there are fewer vesicles compared to the 3-day period. Lipid dropplets appear in large quantities in individual hepatocytes. The number of secondary lysosomes and polysomes also remains increased (Picture. 4 A).

When priming with dropp on the 13th day of embryonic development, lipid dropplets are visible in embryonic hepatocytes, and the formation of membrane structures is enhanced (Picture. 4 B).



A B

Picture.4. Ultrastructure of an embryonic hepatocyte induced by butylcaptax (A) and dropps (B) on the 13th day of development. Inc:30000X

When exposed to butylcaptax on the 19th day of development, the endoplasmic reticulum is fragmented. The number of ribosomes and polysomes is increased. The intercellular gaps widen, and there is a moderate amount of fat dropplets in the cytoplasm.

During dropp intoxication, on the 19th day of development, the endoplasmic reticulum is fragmented. The bile capillaries are destructured, their walls are smoothed, and there are many different plasma-type structures in the lumen.

Consequently, by the 19th day of embryonic development, embryonic hepatocytes are not normalized. More profound changes are caused by bile capillaries, which indicates violations of the external secretory functions of the liver during intoxication with pesticides.

Based on electron microscopic studies, it can be concluded that exposure of animals to pesticides - butylcaptax and dropp - causes pronounced degenerative processes at the level of cellular and subcellular structures of the liver. The greatest structural changes in the ultrastructure of hepatocytes are observed at the early stage of embryogenesis (on the 3rd day of embryonic development). The severity of damage in the mother's liver varies. In the thickness with little changed cells there are severely damaged ones.

Changes in the physicochemical properties of the lipid bilayer of various membranes, especially in the microenvironment of enzyme systems, affect the activity of enzyme complexes, possibly due to changes in the conformational characteristics and mobility of enzyme components. The next series of experiments included a study of the lipid composition of liver microsomes of pregnant rats and embryos when they were primed with butylcaptax and dropp in doses of 1/10 LD_{50} at various stages of pregnancy (Tables 1–4).

Table 1 Effect of butylcaptax on the phospholipid composition of liver microsomes in pregnant rats, % of total lipid phosphorus (n=7)

Phospholipid fraction	**Control**	**Gestation period, days**		
		3	**13**	**19**
Phosphatidylcholines (PC)	37,5 ± 2,1	36,0 ± 2,7	37,2 ± 3,0	37,4 ± 3,2
Phosphatidylethanoamine (PE)	22,3 ± 1,6	21,3 ± 1,5	19,0 ± 1,1	18,1 ± 0,82**
Phosphatidylserine (PS)	10,9 ± 0,78	11,1 ± 0,74	12,3 ± 0,68	10,4 ± 0,91
Phosphatidylinositol (PI)	7,2 ± 0,56	7,0 ± 0,56	7,8 ± 0,51	7,3 ± 0,62
Phosphatidyc acid (PA)	3,5 ± 0,18	4,6 ± 0,21	5,5 ± 0,28	4,4 ± 0,15***
Sphingomielin (SPH)	16,0 ± 1,1	15,2 ± 0,96	13,4 ± 0,72	16,5 ± 0,85
Lisophospholopids (LPL)	2,1 ± 0,13	2,9 ± 0,12	4,6 ± 0,21	5,8 ± 0,18***

Phospholipid (PL), mkMol	16,5 ± 0,91	14,2 ± 1,1	14,0 ± 1,0	13,8 ± 0,65**
Cholesterol (ChL), mkMol	7,01 ± 0,44	6,1 ± 0,31	6,0 ± 0,27	6,4 ± 0,44
ChL/PL	0,425	0,429	0,428	0,450

*Notes. *P < 0,05; ** P < 0,02; *** P < 0,001*

In the microsomal fractions of the liver of pregnant rats, as in other membrane formations, the bulk of the phospholipid components are in the PC, PE and SPH fractions. When considering them from the point of view of percentage, no significant changes were found under the influence of pesticides. However, when recalculating the content of these phospholipid fractions into lipid phosphorus, there is a tendency for their level to decrease relative to the control. At the same time, the content of the PE fraction decreases by more than 30%, and the PC fraction by 2.5%. A decrease in the level of these phospholipids leads to a dropp in the content of the total phospholipid fraction by the 19th day of pregnancy by 15%. It should be noted that the decrease in the level of phospholipids without sudden jumps.

When primed with butylcaptax, a decrease in the level of the ФС fraction of liver microsomes of pregnant rats is also observed. Its content by the 19th day of pregnancy decreases by 20%, although these changes are not detected in percentage terms. As in the mitochondrial fraction, the level of phospholipid lysoproducts increases in the lipid composition of microsomes. By the 19th day of pregnancy, their content increases 2.3 times in terms of lipid phosphorus and almost 3 times as a percentage.

When primed with butylcaptax, a decrease in the level of the PS fraction of liver microsomes of pregnant rats is also observed. Its content by the 19th day of pregnancy decreases by 20%, although these changes are not detected in percentage terms. As in the mitochondrial fraction, the level of phospholipid lysoproducts increases in the lipid composition of microsomes. By the 19th day of pregnancy, their content increases 2.3 times in terms of lipid phosphorus and almost 3 times as a percentage.

Table 2. Effect of butylcaptax on the phospholipid composition of liver microsomes in rat embryos, % of total lipid phosphorus (n=7)

Phospholipid fraction	**Control**	**Duration of embryonic development, days**		
		3	**13**	**19**
Phosphatidylcholines (PC)	34,1 ± 2,20	34,5 ± 2,85	34,8 ± 1,95	34,1 ± 2,0
Phosphatidylethanoamine (PE)	22,3 ± 0,91	21,8 ± 1,91	19,4 ± 1,84	18,5 ± 0,97*
Phosphatidylserine (PS)	14,5 ± 0,71	15,1 ± 1,0	15,7 ± 1,3	13,1 ± 0,65
Phosphatidylinositol (PI)	7,6 ± 0,53	7,5 ± 0,51	7,8 ± 0,46	8,3 ± 0,71
Phosphatidyc acid (PA)	5,2 ± 0,28	5,9 ± 0,40	5,4 ± 0,36	7,1 ± 0,56**
Sphingomielin (SPH)	14,8 ± 0,65	14,1 ± 1,1	14,5 ± 1,0	15,1 ± 0,92
Lisophospholopids (LPL)	1,2 ± 0,05	2,2 ± 0,14	2,4 ± 0,11	3,8 ± 0,27***
Phospholipid (PL), mkMol	14,3 ± 0,70	12,0 ± 1,0	12,5 ± 1,22	12,8 ± 0,81
Cholesterol (ChL), mkMol	4,87 ± 0,20	4,14 ± 0,35	4,48 ± 0,41	4,67 ± 0,28
ChL/PL	0,337	0,345	0,358	0,365

*Notes: *P < 0,05; ** P < 0,02; *** P < 0,001*

When studying the lipid composition of embryonic liver microsomes after inoculation with butylcaptax, the following picture was revealed (Table 2). In the lipid composition of microsomes of embryonic hepatocytes, as in the maternal body, there is a tendency to decrease the content of PC, PE and SPH fractions. However, changes in the level of the last two phospholipids are unreliable. Perhaps, as in the case of the mitochondrial fraction of hepatocytes, this is due to the age characteristics of the embryos. However, it should be noted that the formation of lysoproducts in this case increases almost 3 times. The effect of dropp on the microsomal fraction of the liver of pregnant rats and their embryos at various stages of development is reflected in Table. 3 and 4.

Table 3. Effect of droppa on the phospholipid composition of liver microsomes of pregnant rats, % of total lipid phosphorus (n=7)

Phospholipid fraction	Control	Gestation period, days		
		3	13	19
Phosphatidylcholines (PC)	37,5 ± 2,1	37,2 ± 1,6	36,5 ± 2,5	36,9 ± 1,8
Phosphatidylethanolamine (PE)	22,3 ± 1,6	21,4 ± 1,1	20,5 ± 0,95	19,3 ± 0,64
Phosphatidylserine (PS)	10,9 ± 0,78	9,6 ± 0,68	11,5 ± 1,0	11,9 ± 0,75
Phosphatidylinositol (PI)	7,2 ± 0,56	7,9 ± 0,61	7,6 ± 1,2	7,0 ± 0,89
Phosphatidyc acid (PA)	3,5 ± 0,18	3,0 ± 0,15	4,7 ± 0,21	4,1 ± 0,34*
Sphingomielin (SPH)	16,0 ± 1,1	17,5 ± 1,2	15,6 ± 0,87	16,5 ± 0,91
Lisophospholopids (LPL)	2,1 ± 0,13	3,0 ± 0,11	3,5 ± 0,18	4,3 ± 0,14***
Phospholipid (PL), mkMol	16,5 ± 0,91	14,6 ± 1,20	14,5 ± 1,15	13,7 ± 0,85**
Cholesterol (ChL), mkMol	7,0 ± 0,44	6,3 ± 0,41	6,2 ± 0,38	6,3 ± 0,32
ChL/PL	0,425	0,431	0,437	0,456

*Notes. *P < 0,1; ** P < 0,05; *** P < 0,001*

The table shows that in case of poisoning with this pesticide, a similar trend is observed in changes in the phospholipid composition of microsomes. In the liver microsomes of pregnant rats, the content of ФХ, ФЭ and СМ fractions of phospholipids decreases, which causes a decrease in the level of the total ФЛ fraction against the background of an increase in the content of ФЛ lysoproducts, the FA fraction and the ХС/ФЛ ratio.

This trend persists in the lipid composition of embryonic liver microsomes. However, changes in the content of lipid fractions both in percentage terms and in absolute values of lipid phosphorus are unreliable. The exception is the increase in lysophospholipid levels on the 13th day of embryonic development.

Table 4. Effect of dropp on the phospholipid composition of liver microsomes in rat embryos, % of total lipid phosphorus (n=7)

Phospholipid fraction	Control	Duration of embryonic development, days		
		3	13	19
Phosphatidylcholines (PC)	34,1 ± 2,2	35,1 ± 2,6	34,8 ± 1,85	34,6 ± 3,0
Phosphatidylethanolamine (PE)	22,3 ± 0,91	20,6 ± 1,7	20,6 ± 1,2	19,5 ± 0,85*
Phosphatidylserine (PS)	14,5 ± 0,71	13,2 ± 1,2	12,7 ± 1,0	13,6 ± 0,96
Phosphatidylinositol (PI)	7,6 ± 0,53	7,8 ± 0,47	8,0 ± 0,22	8,3 ± 0,26
Phosphatidyc acid (PA)	5,2 ± 0,28	5,7 ± 0,41	5,5 ± 0,35	5,2 ± 0,21
Sphingomielin (SPH)	14,8 ± 0,65	15,6 ± 1,2	15,2 ± 1,1	14,9 ± 0,79
Lisophospholopids (LPL)	1,2 ± 0,05	1,9 ± 0,77	2,8 ± 0,12	3,8 ± 0,16**
Phospholipid (PL), mkMol	14,3 ± 0,70	12,3 ± 0,91	13,0 ± 0,68	13,5 ± 0,57

Cholesterol (ChL), mkMol	4,8 ± 0,20	4,1 ± 0,17	4,6 ± 0,25	4,9 ± 0,24
ChL/PL	0,337	0,340	0,356	0,362

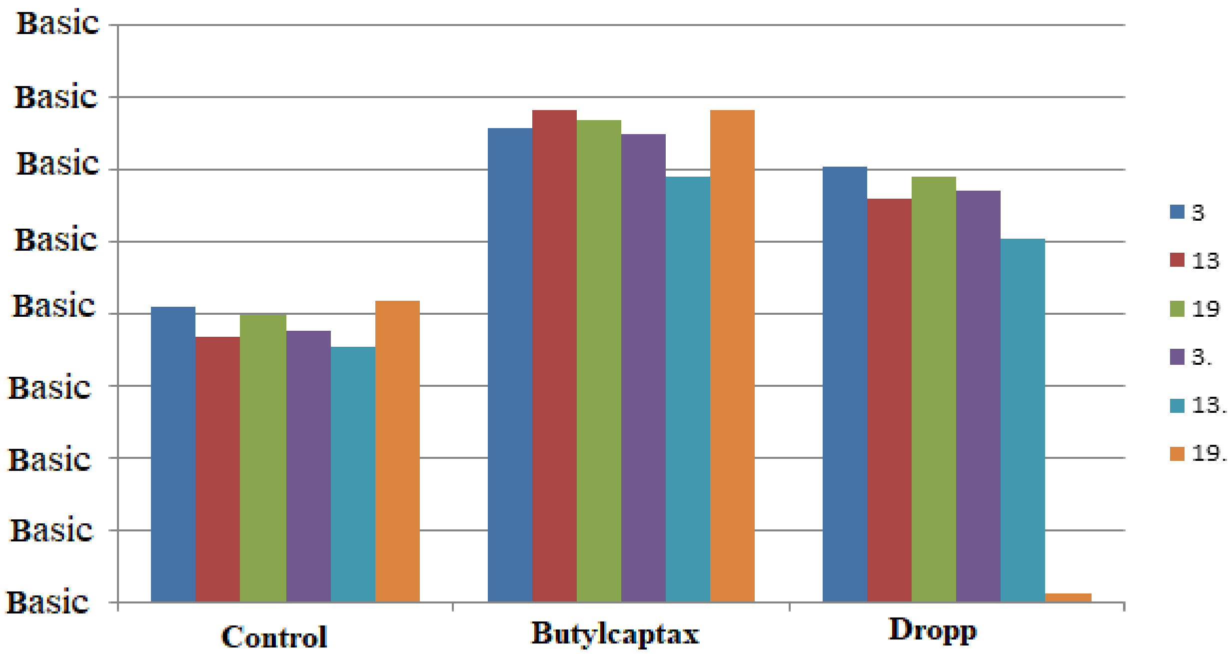
*Notes: *P < 0,05; ** P < 0,001*

The discovered trend in changes in the phospholipid composition of liver microsomes of pregnant rats and their embryos when primed with butylcaptax and dropp indicates a general mechanism of action of pesticides, in which the processes of lipid peroxidation and the activity of lipolytic enzymes play a key role. The microenvironment of enzyme systems contains phospholipids containing more unsaturated acyl radicals. They promote the mobility of components of enzyme systems and increase their conformational capabilities, while the rest of the lipid matrix consists of lipids with more saturated acyl chains. A decrease in the content of PE and PS fractions of phospholipids in liver microsomes, as well as an increase in the microviscosity of the lipid bilayer, was discovered during priming with pesticides, due to a decrease in the content of these fractions and an increase in the ratio ChL/PL, possibly affects the activity of cytochrome P-450. Lyso derivatives PL exhibit detergent properties, which probably causes further degradation of microsomal membranes and, as a result, affects the activity of enzyme complexes. However, it is possible that transacylation processes, in particular the transformation PS, PE and SPH as well as a compensatory increase in the level of cholesterol in the microsomal fraction of the liver under the influence of pesticides somewhat inhibit degradation processes and maintain the functional properties of microsomal membranes at the required level.

By their structure, unsaturated fatty acids of phospholipids of biological membranes are optimal substrates for peroxidation. In recent years, the LPO of biological membranes has been assigned a special role in the pathogenesis of various diseases. With the advanced process of lipid peroxidation in the phospholipids of biomembranes, the amount of unsaturated fatty acids decreases while the amount of saturated fatty acids increases. We studied the effect of butylcaptax and droppa on the content of MDA, one of the end products of LPO, in the liver of pregnant rats and their embryos (Tables 5 and 6).

Table 5. Content of lipid peroxidation products in liver microsomes of pregnant rats under the influence of butylcaptax and droppa (mgmol/mg protein)

NADP.H-dependent sex			Ascorbate-dependent sex		
Days of Pregnancy					
3	13	19	3	13	19



It was found that with the introduction of butylcaptax on the 3rd day of pregnancy, NADPH and ascorbate-dependent lipid peroxidation in pregnant rats, the content of lipid peroxidation products in the microsomal fraction increases by 60 and 72%. Priming animals with this pesticide on the 13th day of pregnancy also enhances enzymatic and non-enzymatic LPO.

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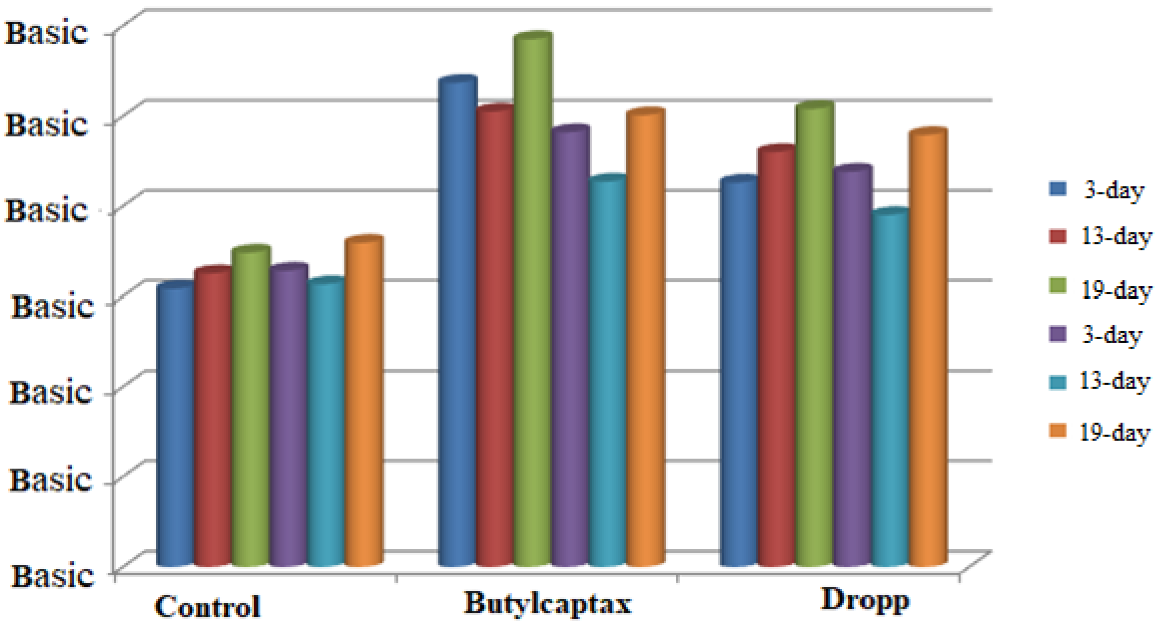
Table 6.Content of lipid peroxidation products in embryonic liver microsomes under the influence of butylcaptax and droppa (mgmol/mg protein)

NADP.H-dependent sex	Ascorbate-dependent sex
Development days	



In microsomes, NADP-H-dependent LPO increases by 75%, and ascorbate-dependent LPO by 66%, but these figures are lower than when primed on the 3rd day. A similar picture is observed in case of poisoning on the 19th day of pregnancy. Intensification of NADPH and ascorbate-dependent lipid peroxidation in microsomes - 67 and 62%. Consequently, in microsomes the process of formation of lipid peroxidation products is much more intense.

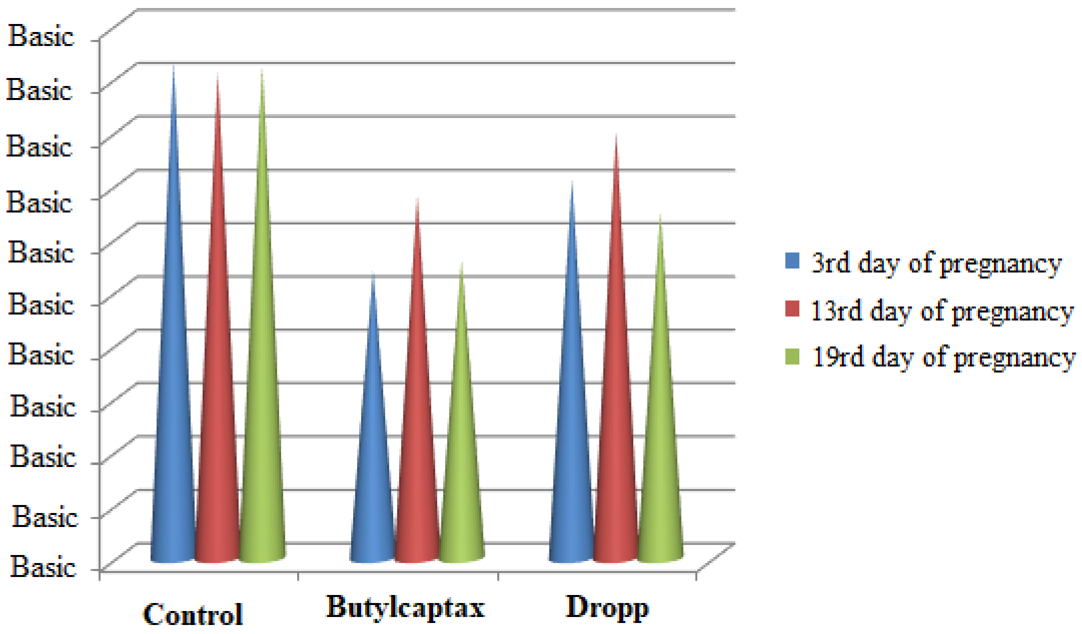
The same picture was revealed in embryos on the 3rd, 13th and 19th days of their development. In particular, when priming on the 3rd day, the intensification of NADPH and ascorbate-dependent in microsomes is 74 and 47%. When primed on the 13th day of development, the level of MDA increased by 55 and 36%, respectively, in microsomes. On the 19th day, enzymatic and non-enzymatic lipid peroxidation also increased by 54 and 39%. The high content of enzymatic LPO in liver microsomes can be explained by the fact that in NADPH-dependent LPO, the substrate in microsomes is polyunsaturated fatty acids - phospholipid acyls, localized near the components of the electron transport chain, and in ascorbate-dependent - other fatty acids.

The effects of butylcaptax and droppa were studied at the same periods of pregnancy and embryonic development. On the 3rd day of pregnancy in rats, an increase in enzymatic and non-enzymatic lipid peroxidation in microsomes was observed by 60 and 50%, respectively. Poisoning of rats on the 13th day of pregnancy led to an increase in the MDA content in microsomes by 50 and 37%, respectively. when priming pregnant rats on the 19th day of pregnancy, the level of MDA in microsomes was 47 and 45%. Similar changes in the level of oxidation products were noted in the liver microsomes of embryos poisoned with Dropp on the 3rd, 13th and 19th days of development (see Table 7).

.On the 3rd day of development, the level of enzymatic and non-enzymatic lipid peroxidation in microsomes is 60 and 50%. On the 13th day it increased by 44 and 37%. On the 19th day, enzymatic lipid peroxidation in microsomes increased by 47%, and ascorbate-dependent lipid peroxidation by 3%. Thus, the oxidation products of butylcaptax and droppa stimulate peroxidation reactions in the liver microsomal membranes of the maternal organism and the embryo, which leads to their damage.

At high concentrations of xenobiotics, i.e. When cytochrome P-450 is completely saturated with substrates, mitochondrial oxidation is inhibited and the prerequisites arise for the regulatory switching of the flow of reduced equivalents from mitochondria to the ER. In this case, cytochrome P-450 is activated and detoxification of foreign substances occurs faster.

Table 7 Effect of pesticides butylcaptax and droppa on cytochrome content P-450 in microsomal fractions of the liver of pregnant rats, nmol/mg protein.



Microsomal monooxygenase, characterized by broad specificity due to the existence of multiple forms of cytochrome P-450, has the ability to oxidize hundreds of substances of various chemical natures, preventing the accumulation of toxic hydrophobic compounds in the body.

The total content of the hemoprotein cytochrome P-450 in the liver microsomes of pregnant rats is significantly higher than that of non-pregnant rats.

Among membrane structures, lipid peroxidation processes in the endoplasmic reticulum are the most effective. Damage to its membranes increases in parallel with the development of lipid peroxidation [20]. The processes of peroxidation in microsomes are closely related to the metabolism of xenobiotics. They can compete for reducing equivalents and oxygen. In addition, xenobiotics and their metabolites can have direct antioxidant or prooxidant effects [13,17,19].

Activation of lipid peroxidation processes causes degradation of cytochrome P-450 and weakening of microsomal oxidation processes. Metabolic activation of xenobiotics, leading to the formation of free radicals, occurs in the electron transport chain of the ER. Cytochrome P-450 plays a key role in this [20].

The enzyme system of microsomal oxygenases plays an important role in the metabolism of chemical carcinogens. The terminal site of this system is the enzyme cytochrome P-450, which plays a major role in the biotransformation of foreign substances.

The changes we discovered in the lipid matrix of microsomal membranes under the influence of pesticides suggest changes in the properties of the cytochrome P-450 enzyme complex. The effect of butylcaptax and droppa on the content of cytochrome P-450 in the microsomal fraction of the liver of pregnant rats was studied.

When butylcaptax was administered to pregnant rats on days 3, 13, and 19 of pregnancy, the content of cytochrome P-450 in the microsomal fractions of the liver decreased. When rats were poisoned with butylcaptax on the 3rd day of pregnancy, the content of cytochrome P-450 decreased by 42%, on the 13th day by 25%, and on the 19th by 36%. When poisoned with dropp at the same time, the content of this enzyme decreased by 24, 13 and 23%, respectively. As can be seen from the above data, activation of LPO causes degradation of cytochrome P-450 and a decrease in the processes of microsomal oxidation. Inactivation of cytochrome P-450 confirms the disruption of lipid peroxidation processes in microsomal membranes and, in our opinion, plays a leading role in the mechanism of pathology development.

The results of electron microscopic studies allow us to judge the degree of toxic effect of the pesticides butylcaptax and droppa on liver tissue. It has been established that in case of pesticide poisoning, disturbances are observed in the structure of the endoplasmic reticulum and in the cell as a whole. Fragmentation of the granular reticulum, its sharp focal hyperplasia, and an increase in the content of free ribosomes and polysomes are also observed. These disorders indicate low activity of the organelle

When priming pregnant rats with butylcaptax and dropp, we found that in the liver microsomes of pregnant rats and their embryos, when priming with butylcaptax and dropp, there is a tendency towards a decrease in the content of PC, PE and the amount of phospholipids. In microsomal fractions, the level of LPL, PA and the ChL/PL ratio increases. However, these changes are more pronounced in case of poisoning on the 19th day of pregnancy, especially in experiments with butylcaptax. Possessing a high degree of unsaturation, the fatty acid chains of microsomal phospholipids serve as potential substrates for FR LPO (Free radicals) processes. The main factors determining the lipid composition of membrane formations are the state of lipid metabolism, the activity of lipolytic enzymes and LPO. The results of studying the effect of butylcaptax and droppa on the level of malondialdehyde (one of the end products of LPO) showed that it leads to the intensification of NADP.H and ascorbate-dependent LPO in microsomes of the fetal and maternal liver. The highest level of MDA during non-enzymatic lipid peroxidation in microsomes was observed during butylcaptax poisoning on the 3rd day of pregnancy. During this period, an increase in MDA through the enzymatic pathway of lipid oxidation was also established. Apparently, under the influence of these pesticides, significant disturbances in the structural arrangement of microsomal membranes occur, which create conditions for intense oxidation of membrane lipids. The increase in NADP.H-dependent liver lipid peroxidation in the early stages of embryogenesis is probably due to the fact that during these periods the content of the oxidation substrate, PUFA, increases in the microsomes of the liver of embryos. In the liver of adult rats, the level of NADP.H-dependent LPO is higher than in embryos. Activation of lipid peroxidation processes causes degradation of cytochrome P-450 and weakening of microsomal oxidation processes. Metabolic activation of xenobiotics, leading to the formation of free radicals, occurs in the electron transport chain of the endoplasmic reticulum. Cytochrome P-450 plays a key role in this. When butylcaptax and droppa are administered, the content of cytochrome P-450 in the microsomal fractions of the liver of pregnant rats decreases. A more pronounced decrease in the content of this enzyme is observed in case of butylactic acid poisoning on the 3rd and 19th days of pregnancy. In this regard, our data are consistent with the results of earlier studies, according to which the processes of microsomal oxidation and LPO are alternative: activation of one of them leads to suppression of the other.

Thus, the pesticides butylcaptax and dropp cause significant structural and functional changes in the subcellular components of hepatocytes of pregnant rats and embryos. These changes reduce the protective and adaptive capabilities of the entire organism. It is necessary to develop measures to protect people, especially women and children, from pesticides.

Based on the above, the following conclusions were made:

- Butylcaptax and Dropp, when baited on the 3rd, 13th and 19th days of pregnancy, cause disturbances in the ultrastructure of rat hepatocytes and their embryos. The greatest changes are observed with poisoning on the 3rd day of pregnancy.

- When baited with pesticides, an intensification of NADPH- and ascorbate-dependent lipid peroxidation is observed both in the mitochondria and in the liver microsomes of pregnant rats and their embryos. The MDA level is higher with butylcaptax poisoning on the 3rd day of pregnancy.

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- When pesticides are introduced, the activity of polyenzyme systems of the mitochondrial respiratory chain is inhibited. The deepest inhibition is observed in the NADH oxidase branch during butyl captax poisoning on the 19th day of pregnancy.

- When butyl captax and dropp are introduced, the content of cytochrome P-450 in the microsomal fraction of the liver of pregnant rats decreases. This decrease is more pronounced during butyl captax poisoning on the 3rd and 19th days of pregnancy

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