

PRACA ORYGINALNA
ORIGINAL ARTICLE**EXPERIMENTAL STUDY ON THE CARCINOGENIC EFFECTS OF PESTICIDES WITH ASCERTAINED CARCINOGENIC ACTIVITY UNDER THE CONDITIONS OF ITS SIMULTANEOUS INFLUENCE ON THE ORGANISM OF LABORATORY ANIMALS****EKSPERYMENTALNE BADANIE KANCEROGENNEGO WPŁYWU PESTYCYDÓW NA ORGANIZM ZWIERZĄT LABORATORYJNYCH**Serhii Omelchuk¹, Alina Syrota¹, Olena Vavrinevych¹, Anna Blagaia¹, Viktoriia Lisovska², Olena Reshavska²¹BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE²L.I. MEDVED'S RESEARCH CENTER OF PREVENTIVE TOXICOLOGY, FOOD AND CHEMICAL SAFETY, MOH, UKRAINE, KYIV, UKRAINE**ABSTRACT**

Introduction: It is known that pesticides have both short-term and long-term effects of the action on the human body. Today, taking into account the growth rate of the agricultural crops protection means' market and the expansion of the range of pesticide mixtures and combined formulations, there is a need for a more in-depth study of its possible effects on the environment and the human body. Recently, a new fungicide containing a mixture of two active substances, benthialvalicarb isopropyl and folpet, was introduced for application in Ukraine. Considering the possible influence of both substances on the enzyme systems involved in the xenobiotic metabolism, potentiation of its carcinogenic action in the formulation can be expected. No genotoxic effect was revealed studying in vivo studies the mutagenic activity of both substances isolated. Therefore, both substances are epigenetic carcinogens with a promoter threshold mechanism of action. In this regard, the promoter action of these substances was studied by us in the mid-term test on a multi-organ model.

The aim: The purpose of our work was an experimental study of the carcinogenic action of benthialvalicarb-isopropyl and folpet – substances with ascertained carcinogenic activity, under the conditions of its simultaneous influence on the organism of laboratory animals (rats and mice).

Materials and methods: Toxicological, toxicometric (weight of animals, absolute, relative mass of internal organs) histological, microscopic, histochemical, and statistical methods were used in the study.

Results and conclusions: No combined action of folpet and benthialvalicarb-isopropyl on the proliferation of carcinogen-transformed hepatocytes and the formation of hyperplastic nodules expressing γ -glutamyltranspeptidases (γ -GTP) as markers of pre-tumor changes in hepatocarcinogenesis was revealed. This allows us to conclude that there is no modifying effect of the folpet on carcinogenicity.

KEY WORDS: carcinogenesis, benthialvalicarb isopropyl, folpet, combined action

Wiad Lek 2018, 71, 7, 1274-1280

INTRODUCTION

Due to the growing population of people in the world and, correspondingly, with the increasing need for food, every year more and more plant protection products are used to increase crop yields, protect from pests and obtain better products. However, scientists have found that the application of pesticides has a significant negative impact on the human body [1].

American scientists in the 6-year study found a link between the effects of pesticides used in private households and the incidence of cancer, including lymphomas (Hodgkin's, non Hodgkin's), soft tissue sarcomas. The study was performed in children under the age of 15, whose parents

used pesticides during the processing of agricultural lands. In the 252 cases of diagnosed cancer, a link was established between the pesticide application and the oncopathology (odd ratio - $\approx 3.7-4.0$) [2].

Scientists from the UK, based on a broad database from 1959 to 1997, also estimated the relationship between the sickness rates in children of farmers who lived near farms where the territory was treated with pesticides, with the possible development of diseases such as bone cancer in children, brain cancer, neuroblastoma (Wilms' tumor) and leukemia. A statistically significant increase in the incidence of kidney cancer was found in these children [3].

It should also be noted that non-compliance to the proper

conditions for the storage and application of pesticides leads to pollution not only of the environment, but also the possible contamination of the agro-industrial complex workers' habitats. For example, in a survey conducted in Oregon, USA (1997), where most farm workers formed families of migrants from Latin America who are low in acquaintance with Good Agricultural Practice (GAP) rules, there is an increased risk for the health of their families' members, as they borne the residual amounts of pesticides from work to home on clothing, skin, hair, tools and vehicles, thereby endangering themselves and their relatives [4].

Studies in Sweden, Denmark and Finland indicate that more than 60% of breast cancer-related diseases in women are due to environmental contamination with organic solvents and pesticides. Provocative effects of pesticides on the development of breast cancer have been shown in experiments on rats. Pesticides accelerated the growth of tumors and had a genotoxic effect. These chemicals have been classified as triggering tumors (mutagens, or genotoxic), or tumor promoters (endocrine disruptors), thus, they may affect any of the stages of breast cancer development [5].

It is known that pesticides have both short-term and long-term effects of the action on the human body. The United Nations registers more than 2 million poisonings and thousands of deaths annually caused by pesticides. Concerning the long-term effects of pesticides, they include increasing the risk of cancer, disorders of nervous, immune, reproductive systems. An analysis of the studies' results indicated the relationship between certain types of cancer with particular pesticides [6]. Today, taking into account the growth rates of the agricultural crop protection means market and the expansion of the range of mixed and combined pesticides, there is a need for a more in-depth study of its possible effects on the environment and the human body.

Recently, a new fungicide, which is a mixture of two active substances, namely, benthialavicalarb isopropyl and folpet was introduced for application in Ukraine [7]. Benthialavicalarb isopropyl is a new fungicide in Ukraine recommended for application as a part of mixture in crop protection products. Both active substances are studied according to international requirements and are registered in a number of countries. In accordance with the existing regulations, hygienic norms and safe application regulations are separately substantiated for both pesticides. As a result of these studies, the carcinogenic effect of folpet observed in mice and benthialavicalarb isopropyl – in rats and mice. The mechanism of carcinogenesis of benthialavicalarb isopropyl is epigenetic, promoter, but according to the US EPA experts is not clear enough. In view of the above-mentioned, it can be predicted that a mixture of these substances can modify its carcinogenic effect due to the influence of benthialavicalarb-isopropyl on the system of multipurpose oxidases, and the folpet on the content of glutathione [7-11]. Taking into account the possible influence of both substances on the enzyme systems involved in the xenobiotic metabolism, potentiation of its carcinogenic

action in the pesticide formulation can be expected.

The research of mutagenic activity of both substances revealed no genotoxic effect in the *in vivo* studies. Therefore, both substances are epigenetic carcinogens with a promoter threshold mechanism of action [7-13]. In connection to this, we studied the promoter action of these substances in the mid-term test on a multi-organ model [14].

THE AIM

Aim of the work: experimental study on the carcinogenic effects of pesticides with ascertained carcinogenic activity under the conditions of its simultaneous influence on the organism of laboratory animals (rats and mice).

MATERIALS AND METHODS

Combined fungicide contains 17.5 g/kg of benthialavicalarb isopropyl (1.75%) and 500.0 g/kg of folpet (50%) [12].

Experiments were performed on 45 male Wistar Han, SPF rats weighing 130 ± 5.9 g, obtained from the "L.I. Medved's Research Center of Preventive Toxicology, Food and Chemical Safety, MoH, Ukraine" nursery.

After randomization, animals were divided into three groups: 1 group (negative control) received water with OP-10 (wetting agent 0.05% technical preparation), group 2 received an aqueous suspension of OP-10 with a combined preparation, group 3 received aqueous a suspension of OP-10 with triadimefon, which is a hepatocarcinogen, and showed a positive effect in the mid-term test [14].

As a multiorgan initiator of carcinogenesis, the combined effect of N-nitrosodiethylamine (NDEA) (100 mg/kg b.w. per day), N-methyl-N-nitrosourea (MNU) (20 mg/kg b.w. per day), N-nitroso-bis 2-hydroxypropylamine (NDHPA) (3.7 mg/kg b.w. per day) on male Wistar Han rats was used. Initiation of carcinogenesis was activated by sequential administration to rats. The dose of the combined preparation according to the protocol of the experiment (0.05% of the diet) was determined at the level of 100.0 mg/kg [14].

The research was performed on a multi-organ model, which is used in the study of carcinogenicity of chemicals as a pre-screening test, as well as to study the mechanism of carcinogenic action of chemicals [15-16]. The administration of NDEA-MNU-NDHPA carcinogens to rats led to the initiation of carcinogenesis in many organs: the liver, lungs, thyroid gland, esophagus, stomach, small and large intestine, pancreas, kidneys, prostate, bladder. The subsequent administration of studied pesticides to the animals allows determining its promoter activity in the development of tumors in these organs. Since the animals have previously received a complex of carcinogens, the doses of these substances, which should not cause toxic effects, are usually 0.05% of the diet [14].

Scheme of administration of carcinogens and test substances is presented in Fig.1.

The purpose of the second experiment was to study the effect of benthialavicalarb-isopropyl on the folpet induction of cytotoxic and proliferative changes as potential pre-tu-

weeks			
0	2	4	24
↓▼▼▼▼			
Group 1	***	Water+OP-10	
↓▼▼▼▼			
Group 2	***Combined fungicide+OP-10.....	
↓▼▼▼▼			
Group 3	***Tridimephon+OP-10.....	

Footnotes: ↓ - intraperitoneal injection of 100 mg/kg DENA;
▼ - intraperitoneal injection of 20 mg/kg MNU twice a week;
*** - adding 0.01 % NDHPA solution to drinking water;
..... - intragastric administration of test substance.

Figure 1. Scheme of the experiments

mor conditions in the duodenum in mice. Substances were admixed to the diet in a ratio close to the content in the formulation and fed. 30 sexually mature male mice CD-1, SPF (from the same nursery), with a body weighing 23.0 ± 1.1 g were used in the experiment. They were divided into three groups after randomization: 1 group - control; Group 2 received folpet (purity 94%); Group 3 received folpet (purity 94%) and benthiavalicarb isopropyl (purity 97.64%).

Substances were administered with diet at concentrations similar to its contents in the formulation: 700 ppm (folpet) to mice of group 2 and 80 ppm (benthiavalicarb isopropyl) and 700 ppm (folpet) to mice of group 3. Approximately, it corresponded to doses of 80 mg/kg and 3.5 mg/kg. Control animals received only feed. The substances were admixed to chopped diet daily and administered on an empty stomach for 28 days. After the animals ate food with substances additional to the diet feed added in the feeder. Experimental research meets the requirements of the Bioethics Commission on Humane Animal Treatment [17].

The animals were euthanized in a special chamber by inhalation flow of carbon dioxide, in compliance with the rules of humane treatment of animals, in accordance with the requirements of the European Convention for the Protection of Experimental Animals, EC 86/609 [14]., CO₂-box for euthanasia was used for this purpose.

All animals were subjected to an autopsy with compulsory macroscopic examination for the presence of visible gross lesions of the internal organs and tissues. Before the autopsy, at the external examination of the animal, all deviations from the norm were recorded. A registration, description, count of all changes and tumors with different

localization in all, without exception, laboratory animals were carried out.

The samples of stomach, and duodenum were taken for histological examination, the absolute and relative mass of the thyroid gland, liver and kidneys were determined in the mice. The samples from the liver, as well as organs and tissues with detected pathological changes were taken in the rats. The same localization of excision was followed in all animals.

Statistical data were calculated by Excel 2010 software package, "Statistica 6.0, Stat Soft 31415926535897"

RESULTS AND DISCUSSION

According to the literature, benthiavalicarb isopropyl has been tested for the presence of carcinogenic properties in chronic experiments in two species of animals [7, 8]. Findings indicated the following: experimental groups of mice received benthiavalicarb isopropyl per os with diet for 78 weeks in the dose range of 2.7-927.8 mg/kg b.w.; rats received the substance with diet for 104 weeks in the range of 2.5-649.4 mg/kg b.w. An increase in the incidence of liver and thyroid tumors was observed in mice in high doses. An increase in the incidence of tumors was not observed at doses of 13.7 mg/kg b.w. in males and 18.6 mg/kg b.w. in females. An increase in the incidence of liver tumors and tumors of the uterus was observed in male and female rats received high doses of benthiavalicarb-isopropyl, correspondently. Tumor growth was not observed at doses of 2.5 mg/kg b.w. in males and 3.2 mg/kg b.w. in females.

The genotoxic activity of benthiavalicarb-isopropyl in

Table I. Average number and area of hyperplastic nodules in the liver of rats

Statistic parameters	Square ² of the nodules, mm ² /cm ²	Number ³ of nodules/cm ²	Average square of nodules, mm ²
Group 1. Negative control (n = 9)			
M±SD	0,76±0,67	93,34±68,81	0,007±0,003
Mediana	0,64	76,08	0,007
Group 2. Preparation (n = 10)			
M±SD	0,812±0,64	94,68±72,06	0,008±0,002
Mediana	0,600	79,42	0,008
% of mean out of control	82	89	113
% of mediana out of control ²	81	88	112
P	0,13 ³	0,34 ³	0,22 ⁴
Group 3. Positive control, Triadimefon (n = 10)			
M±SD	1,42±0,88	134,53±71,90	0,0102±0,002
Mediana	1,27	126,87	0,0103
% of mean out of control	187	144	151
% of mediana out of control	199	167	151
p	0,13 ³	0,34 ³	0,01 ⁴

Footnotes: M – arithmetic mean; n – number of test animals; SD – standard deviation ;

1 – % of mean values in experiment/negative control;

2 – % mediana values in experiment/negative control;

3 – Kruskal–Wallis test;

4 – Mann-Whitney U Test.

the study of its mutagenicity in the set of standard tests was not detected. Mechanisms of carcinogenic action are epigenetic - promoter. Beniavalicarb isopropyl induces liver and thyroid gland tumors by phenobarbital mechanism, as an inducer of cytochrome P-450. The mechanism of uterine tumors formation is not clear enough. EPA experts have classified benthiavalicarb isopropyl as a potential carcinogen for humans.

Folpet has been studied in chronic experiments on rats and mice. Oncogenic effect was revealed only in mice. An increase in the incidence of malignant tumors of the duodenum was observed in doses higher than 47 mg/kg b.w., and pre-tumor changes in the mucous membrane were observed at doses higher than 16 mg/kg b.w.

The main pathway for the metabolism of benthiavalicarb isopropyl is via glutathione conjugation, followed by the formation of mercapturic acid and methyl sulfides.

The mechanism of toxic, including carcinogenic, effect of folpet is due to the interaction of this substance with SH-groups of cell biosubstrates, resulting in a sharp decrease of glutathione content in tissues. Given that glutathione is necessary for the detoxification of benthiavalicarb-isopropyl, reducing its concentration in tissues can inhibit the excretion of the latter from the body. In addition, glutathione plays an important role in carcinogenesis [15].

Thus, simultaneous administration of both substances with a molar ratio of 1:36 in the formulation can change its toxic, including carcinogenic effect.

Effect of folpet on hepatocarcinogenicity of benthiavalicarb-isopropyl in the formulation.

No mortalities occurred during the experiment in the control and experimental groups. No treatment-related clinical signs were observed. Behavior, appearance, motor activity of rats in all groups during the experiment did not change. Feed and water consumption was not affected. No symptoms of toxic effects of the preparation were detected.

Macroscopic examination revealed no treatment-related gross lesions. Summarized data on histochemical studies are presented in the table I.

The research was conducted on the model proposed by Ito [14, 18], which is based on the initiation of hepatocytes by carcinogens, resulting in their transformation into tumor cells. Preneoplastic locuses are formed in the liver tissue when proliferated carcinogen-transformed cells, and subsequently – hyperplastic nodules.

Transformed cells express the γ -glutamyltranspeptidase enzyme (γ -GTP), which is a histochemical marker of preneoplastic changes. The presence, number and size of hyperplastic γ -GTP positive nodules in the liver tissue are the main criteria for determining the promoter activity of the test compound [14, 19, 20].

A statistically significant increase by 51% of the average area of nodules positive for γ -glutamyltranspeptidase was found in animals receiving hepatocarcinogen triadimefon ($p \leq 0,01$).

The total specific area of nodules per cm² and the specific number of nodules per cm² have not changed significantly, but were increased by 99% and 67%, respectively. The obtained data can be the evidence to the adequacy of the chosen model. Against the background of these results, the

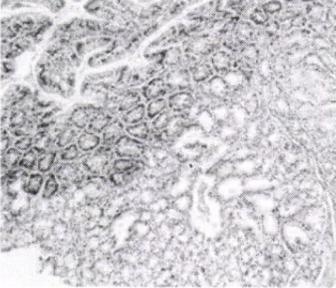
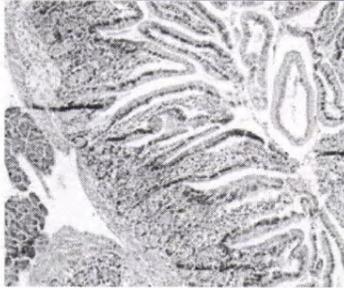
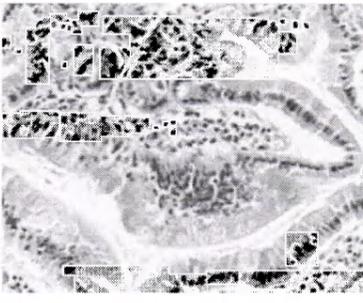
Animal group	Morphological and histological changes	
Group 1 – negative control (Water per os)	No changes observed	
Group 2 (folpet, 80 mg/kg)		
	Dilatation of duodenal glands, 200x	Hypertrophy of the duodenal villi, 200x
Group 3 (folpet 80 mg/kg + benthiavaliarb-isopropyl 3 mg/kg)		
	Hypertrophy of the duodenal villi, 200x	Hypertrophy and hyperplasia of the villi of the duodenum, 400x

Figure 2. Histomorphological changes in the duodenum. Staining with hematoxylin and eosin. №№2.1-2.3 200x, №2.4 – 400x.

values of the above indicators did not differ from the negative control in animals that received a combined pesticide. The total specific area of nodules per cm² and the specific number of nodules per cm² were not statistically significantly changed and were reduced in comparison with the control by 18% and 12%, respectively. At the same time, a statistically significant increase by 12% in the average area of γ -glutamyltranspeptidase positive nodules was detected.

Thus, a fungicide with two active substances did not induce an increase in the number and the size of GTP nodules, which suggests that folpet has no modifying effect on the carcinogenicity of the benthiavaliarb isopropyl in the formulation.

The obtained results showed that administration of the mixture of benthiavaliarb-isopropyl and folpet in the preparation to rats for 24 weeks did not cause changes in the general condition of the organism and death of animals, as well as statistically significant unidirectional changes in the average body weight and its growth. Autopsy of the

rats and the macroscopic examination of the body and internal organs in most animals revealed no pathological abnormalities.

Influence of benthiavaliarb-isopropyl on induction of the pre-tumor conditions in the duodenum by folpet.

No treatment-related death of animals and clinical manifestations of toxic effects during the experiment were observed when benthiavaliarb-isopropyl with folpet administered with feed, as well as folpet alone. Behavior, appearance, motor activity in all groups during the experiment did not change. Animals eagerly ate feed and water consumption was not affected.

No changes in the body weight found in test animals compared with the control.

Administration of benthiavaliarb-isopropyl and folpet to the mice during the experiment in the studied doses did not cause systemic toxic effects on the organism.

Animals were euthanized on day 29 of the experiment. All animals were subjected to an autopsy with compulsory mac-

roscopic examination for the presence of visible pathological changes of the internal organs and tissues. No differences in the appearance, shape and color of the internal organs and tissues were revealed in the external examination and autopsy of both control and experimental animals.

Histomorphological studies of thyroid gland, liver, kidney, stomach, duodenum and cecum were performed (Figure 2).

No proliferation of carcinogen-transformed cells observed and the formation of hyperplastic nodules expressing the γ -glutamyltranspeptidase enzyme (γ -GTP), which is a histochemical marker of pre-tumor changes, has not been revealed under the influence of the mixture of benthiavalicarb-isopropyl and folpet on the body of rats in the liver tissues. The total specific area of nodules per cm^2 and the specific number of nodules per cm^2 were not statistically significantly changed, and were reduced by 18% and 12%, respectively, compared with negative controls. However, the average area of γ -glutamyltranspeptidase positive nodules increased by 12% ($p \geq 0.05$). These rates were significantly higher in animals from the positive control group who received hepatocarcinogen triadimefon.

According to literature, it is known that benthiavalicarb-isopropyl administered via single intragastric injection at a dose of 2000 mg/kg did not initiate hepatocarcinogenesis in rats on the model of "NDEA-hepatectomy" [8].

An increase in the proliferative activity of rat liver cells was observed at the benthiavalicarb-isopropyl administration in doses higher than 10 mg/kg b.w. for 7 days (cumulative dose – 70 mg/kg b.w.) [8]. Chronic administration of this substance to rats was only 2 mg/kg b.w. (cumulative dose – 240 mg/kg m.t.) in our experiment; therefore the increase in the size of the node was not statistically significant. However, it was found that captan, a substance similar to folpet by the mechanism of action, caused a positive effect in rats on the model of "NDEA-hepatectomy" hepatocarcinogenesis. Therefore, one should expect an increase in the size of nodules when animal organism exposed to the combined fungicide.

Absolute and relative weight of the liver of rats receiving a mixture of benthiavalicarb-isopropyl and folpet was not different from that of control animals, which also confirms the above data on the absence of promoter effect.

No changes in the absolute and relative mass of the brain, thyroid gland, kidneys, spleen, or the heart of animals receiving a combined fungicide have been observed. These animals have a statistically significant increase in the absolute and relative mass of the adrenal glands, as well as insignificant – pancreatic and prostate glands, which indicates their functional tension.

The revealed pathological changes in other organs were isolated incidents in all groups. Among the revealed pathology of other localization, it should be noted, first, single tumors in the duodenum and small intestines, as well as seminal vesicles, found in animals receiving a combined preparation. However, it should be mentioned that the neoplasm of such localization is also found in the rats of the positive control group. Such type of pathology has not been

observed in animals from the group of negative control. Therefore, these results may indicate a weak, non-specific promoter effect of fungicide.

Studying the effect of benthiavalicarb isopropyl on the induction of the pre-tumor state in the duodenum by folpet, mice did not show any toxic effects during the experiment and no mortalities observed. Folpet administered to mice in a dose close to the minimum active one. The dose of benthiavalicarb isopropyl was picked up taking into consideration the ratio of it in the combined fungicide.

During examination and macroscopy of the internal organs of the mice no pathological abnormalities were revealed.

Absolute and relative weights of organs target to benthiavalicarb isopropyl and folpet toxic effects on the mice organism – liver and kidney – did not change, while the mass of thyroid gland decreased by 19% and 22%, respectively. It is known that benthiavalicarb-isopropyl disrupts homeostasis of thyroid hormones, which results in the formation of adenomas in mice. The same decrease in this index, found in animals receiving folpet only, eliminates the effect of benthiavalicarb-isopropyl. Consequently, the revealed changes in the mass of the thyroid gland under the influence of folpet are functional.

Nonspecific morphostructural changes in the tissues of the thyroid gland, liver, kidneys, stomach, duodenum and cecum were found in both the experimental and control animals according to the results of histological studies. Dilatation of duodenal glands (Fig. 2.1); lymphoid leukocyte infiltration of the mucous membranes and hypertrophy of villi (Fig. 2.2) was revealed in the part of mice receiving folpet. Several animals receiving folpet and benthiavalicarb isopropyl showed both hypertrophy and hyperplasia of the villi of the duodenal mucosa (Fig. 2.3, 2.4). And if hypertrophy of villi is noted in some cases, but in all groups, including control, then hyperplasia was revealed only in animals receiving folpet and benthiavalicarb isopropyl. However, insignificant severity and low incidence (in 2 out of 10 animals) do not allow them to be unambiguously associated with the combined effect of benthiavalicarb-isopropyl and folpet.

CONCLUSIONS

1. The carcinogenic action of benthiavalicarb isopropyl and folpet was studied on a multiorgan model of NDEA-MNU-NDHPA in rats at simultaneous administration to animals in doses that could really affect the human body under conditions of the combined fungicide application.
2. No combined action of folpet and benthiavalicarb-isopropyl on the proliferation of carcinogen-transformed hepatocytes and the formation of hyperplastic nodules expressing γ -glutamyltranspeptidases (γ -GTP) as markers of pre-tumor changes in hepatocarcinogenesis was revealed. This allows us to conclude that there is no modifying effect of the folpet on carcinogenicity
3. An increase in the total number of single tumors of different localization can be estimated as a non-specific promoter action of the combined fungicide.

4. The combined effect of benthiavalicarb isopropyl on induction of the pre-tumor states in the duodenal mucosa in mice by folpet was not observed under the conditions of the performed experiment.

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Authors' contributions:

According to the order of the Authorship

Conflict of interest:

The Authors declare no conflict of interest

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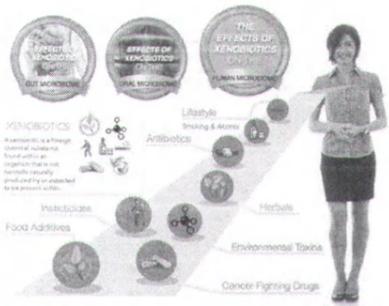
Received: 10.06.2018

Accepted: 08.09.2018



FEATURES OF THE MODERN PESTICIDES MODES OF ACTION ON THE THYROID GLAND FUNCTIONALITY (review)

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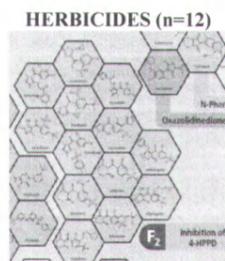
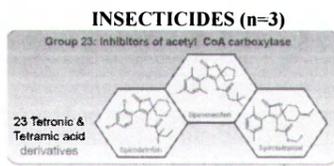
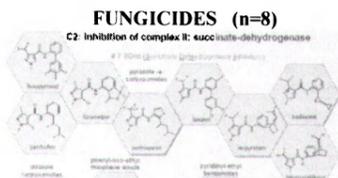
A large number of xenobiotics, entering the human body from the environment, may disrupt normal functioning and contribute to the development of various diseases of the thyroid gland.

The relevance of our study is confirmed by the joint report of WHO and UN on Feb. 19, 2013 in Geneva and the Report of WHO National Experts in Ukraine, October 15-16, 2018, on the results of negative effects on the people's health of the so-called endocrine disruptors study.



The purpose of our work was expert-analytical study of pesticides (as chemical environmental factor) mechanisms of action on the functioning of the thyroid gland

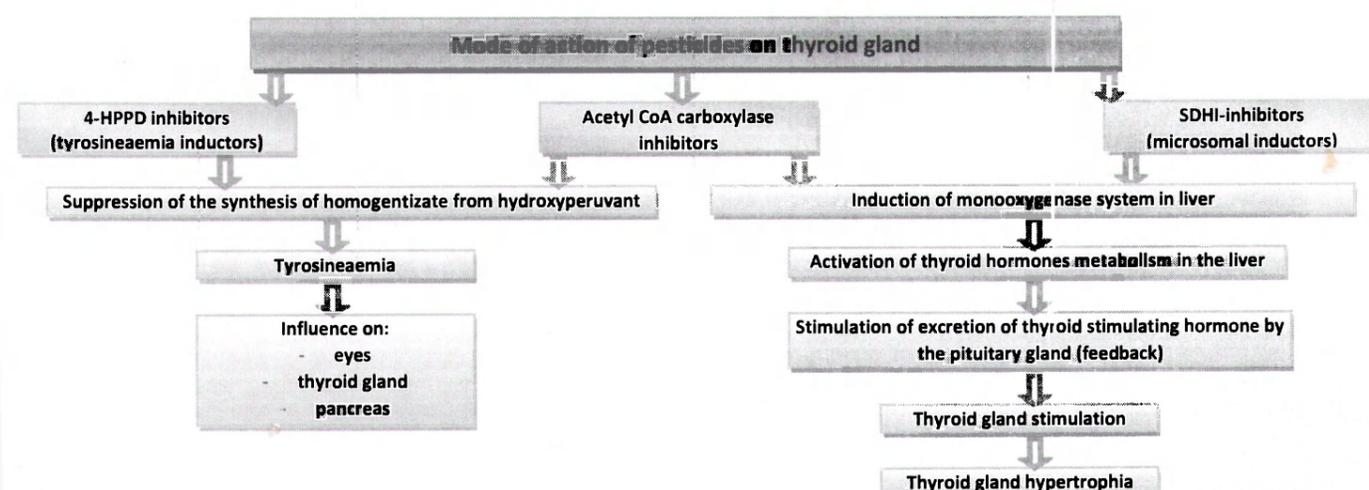
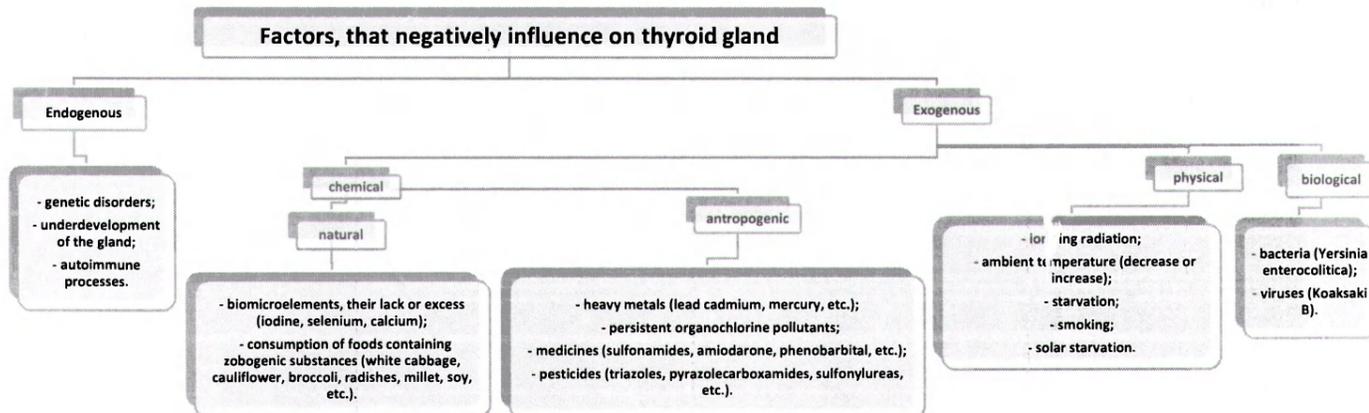
Material and methods.



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The methods of empirical and theoretical research of scientific information, namely analysis, synthesis, induction, deduction and systematization were used. The sources of information were EPA US, EFSA, WHO, IUPAC, research articles on the topic etc.

Results.



Conclusions: The analysis of pesticides mechanisms of action on the thyroid gland allowed to establish two main ways of its hypertrophy development: 1) inhibition of hydroxyypyruvate transformation, and 2) activation of the monoxygenase system in the liver. The obtained data should be taken into account when substantiating the possibility of these pesticides application on territories with radiation load or industrial regions that are subject to additional chemical contamination.