Morphofunctional changes in the organs of excretion and detoxification with pesticides prolonged low-dose exposure

L K Gerunova¹, E G Bardina²,³ and I V Sechkina²

¹ Omsk State Agrarian University named after P.A. Stolypin, 1 Institutskaya Ploschad, Omsk, Omsk region, 644008, Russia
² Omsk State Technical University, 11 Mira Ave., Omsk, Omsk region, 644050, Russia
³ E-mail: bardina0145@yandex.ru

Abstract. Many toxic substances in low doses daily enter the body of animals and humans with food. In this case, the main burden of the transformation and excretion from the body have the organs of excretion and detoxification. This review summarizes the results obtained on different experimental models and reflecting the impact of pesticides on the gastrointestinal tract, liver and kidneys at low doses chronic intoxication. It is established that, entering the body in low doses, pesticides cause a change in the morphological structure of the intestine and the enzymatic activity of the enterocytes, as well as help reduce the barrier function of the gastrointestinal tract and the development of dysbiosis. When exposed to pesticides there are also changes of biochemical processes in the liver and decrease its functional activity, impaired kidney structure. The original state of health and genetic features of stress-limiting systems determine the severity of the changes and level of post-toxic complications risk.

The continuous increase in the use of pesticides in world practice, as well as their persistence, which determines the time period necessary for the transformation and decomposition of active substances in the environment, represent real risks of accumulation of pesticide residues in natural objects, which threatens the animals and humans health [1, 2].

The most common route for the release of residual pesticides into the body is oral route [3, 4, 5]. Moreover, they are soon found in the largest number in the gastrointestinal tract [6], which becomes the first physical and biological barrier and, therefore, the first target of their action [2]. In general, the gastrointestinal tract is resistant to the daily forcing of chemicals to which it is exposed. But, nevertheless, many of these substances can affect various functions of the gastrointestinal tract, for example, the ability to absorb nutrients, secretory and contractile activity. In addition, some toxicants are able to act as transcriptional regulators and modulators of enzymes, altering the digestion process [7, 8].

Once in the body, pesticides are transformed by enzymes of the I and II phases of biotransformation to conjugation products, and then are excreted either by the renal or hepatic route [9, 10]. With an increase in the functional load, a structural reorganization of the excretion organs occurs, accompanied by a change in the biochemical status of the organism [11]. A wide range of possible functional and structural changes caused by the action of pesticides on the gastrointestinal
tract, liver and kidneys leads to the development of morphofunctional changes in other organs and systems of the body, forming a characteristic symptom complex of chronic intoxication.

The purpose of this review is to assess the role of prolonged low-dose exposure of pesticides in the development of pathology of the organs of excretion and detoxification in animals and humans.

Entering the body, pesticides do not always cause clinical signs of damage to the gastrointestinal tract. However, it is proved that they are able to exert a specific effect on the locomotor musculoskeletal activity. So, in experiments conducted in vitro, it was found that pesticides disrupt the motility of the gastrointestinal tract even in concentrations that are significantly lower than toxic doses. For example, incubation of rat jejunum in low concentration Roundup solutions caused a significant muscle relaxant smooth muscle response [11]. The reaction of the muscular wall of the jejunum to the glyphosate effect is biphasic, since initial relaxation is replaced by contraction [6]. It is important to note that changes in contractile activity of the intestine with a low-dose effect of the drug are reversible.

In addition to affecting the smooth muscle activity, pesticides can cause structural changes in the gastrointestinal tract. So, when conducting a histological study using a quantitative analysis of the morphological parameters of the intestine after the administration of low doses of Monocrotophos and Atrazine, a change in the length of the villi was revealed [12, 13], as well as the ratio of their height, total thickness of the mucous membrane and the depth of the crypts with a decrease in the height of epithelial cells [14].

Other changes in the structure of the intestine during chronic exposure to pesticides are characterized by the development of congestive and inflammatory processes [12, 15, 16]. Lipid metabolism in enterocytes may be impaired, which is accompanied by the accumulation of lipid drops in them. Similar changes were noted in the intestines of fish upon exposure to methylparathion [17].

Enterocytes abound in biotransformation enzymes and transport proteins, which often become targets of xenobiotics [10]. Even low doses of pesticides can cause an increase in the activity of K + - Na + - ATPase, intestinal disaccharidase, alkaline phosphatase and glycylglycine dipeptidase [12], a change in the activity of dehydrogenases [18], as well as enzymes of the antioxidant system [13, 19]. According to S. Agrahari and K. Gopal, a change in the activity of the main intestinal enzymes that play key physiological roles can disrupt the physiological state of the whole organism [20].

The gastrointestinal tract is inhabited by a huge number of microorganisms that play a role in the formation of the immune response, the regulation of homeostasis and the metabolic transformation of xenobiotics [21]. Intestinal microbiome also affects the kinetic characteristics of substances entering the body. This is due to the ability of microbiota to alter the expression of proteins that bind chemicals, or cell adhesion proteins that support the protective mucous layer. While the microbiome affects the metabolism of xenobiotics, xenobiotics also affect the balance and viability of the microbiome [22]. The composition of the microbiota can be changed under the influence of food components, drugs, as well as toxicants [2, 23]. With prolonged exposure, pesticides cause the development of dysbiosis [24], which is manifested by a change in the quantitative composition of the microbiota and phylogenetic diversity of the main intestinal microorganisms [16, 25].

The effects of toxicants, including pesticides, on the microbiome are localized not only in the intestine, but also spread to other systems and organs [21, 26]. When studying the effect of low doses of Chlorpyrifos in mice, the presence of correlation between the broken intestinal microbiome and the composition of metabolites in the urine formed during the biotransformation of amino acids, short chain fatty acids, phenyl derivatives and bile acids was established [16]. Intestinal microbiota plays an important role in endocrine-depleting substances-induced dysregulation of carbohydrate metabolism and the development of hyperglycemia [27]. It has been established that the intake of low doses of Chlorpyrifos in the body promotes the development of obesity and insulin resistance in mice by acting on the intestines and intestinal microbiota [2].

Chronic intoxication is characterized by a long period of compensation, during which a gradual biotransformation and removal of pesticides and their metabolites from the body occurs. At the same time, the main burden of neutralizing and removing toxic products falls on the liver and kidneys.
During intense metabolism, a change in the functioning and / or damage of individual structures of these organs occurs. Chronic exposure to pesticides leads to a subtle biochemical rearrangement of the liver, which is sometimes difficult to detect [28].

Liver cells synthesize a large number of compounds necessary for the body in the process of life. A change in the level of synthesis of these substances indicates a change in the state of the liver and the organism as a whole. The most informative indicators are the levels of alanine aminotransferase (ALAT), aspartate transaminase (ASAT) and alkaline phosphatase (ALP) in serum. These indicators are overly sensitive biochemical markers of liver dysfunction [29].

In most cases, with chronic exposure to pesticides, there is an increase in the activity of ALAT, ASAT, and alkaline phosphatase in the blood serum of animals. An elevated level of hepatic enzymes reflects a violation of biochemical processes in the liver and a loss of structural integrity of hepatocytes. This pattern has been deeply studied with prolonged exposure to organophosphorous compound and chlororganic compound even in doses comparable to the acceptable level [30, 31, 32, 33]. However, in chronic intoxication with synthetic pyrethroids at low doses, the levels of ALAT and ASAT sometimes do not increase [34].

According to A.F. Hernandez et al. the most important diagnostic criterion for chronic pesticide poisoning is serum cholinesterase. The level of this enzyme can vary in different directions. Under the action of organophosphorous compound in low doses, cholinesterase activity decreases by more than 25% of the baseline value [31]. Administration of pyrethroids to animals, on the contrary, increases the level of cholinesterase [34].

In chronic pesticide intoxication, a decrease in the protein-forming function of the liver occurs. As a result, there is a decrease in the content of total protein and, in particular, albumin in the blood serum of experimental animals. In this case, the production of cholesterol and triglycerides may decrease [33], which indicates impaired hepatocyte function. A sharp decrease in cholesterol indicates diffuse damage to the hepatic parenchyma [35].

The increased levels of bilirubin on the background of chronic intoxication by pesticides occurs only with a toxic agent sufficiently long exposure. For example, A. M. Khasawinah and J. F. Grutsch noted the increased levels of bilirubin in the blood serum of rats in 30-months use of a diet with a content of 25 ppm Chlordane [36]. Hyperbilirubinemia may be a manifestation of hepatic cholestasis, developing in violation of the transport system of hepatocytes [37].

Prolonged exposure to pesticides may increase the liver [29, 32, 36] with the development of stagnation, focal inflammation [38], and focal necrosis [39].

Ultrastructural changes are characterized by an increase of hepatocytes [29], deposition of lipids within cell structures [40], the mitochondrial swelling and expansion of the reticuloendothelial system [30, 41]. Such injuries indicate the initial stages of liver dysfunction as a result of prolonged exposure to low doses of pesticides [30].

In chronic pesticidal intoxications, a change in carbohydrate metabolism occurs with a predominance of catabolic processes. Moreover, the glycogen content in the liver decreases [34] up to its complete absence [41].

The kidneys are actively involved in the disposal and removal of xenobiotics entering the body [42]. However, intense renal blood flow and hypersensitivity to hypoxia make the organ vulnerable to chemical stressors. The process of lipid peroxidation and damage to cell membranes that develops in this case causes a violation of the structure and / or function of the kidneys [43]. Most often, a change in renal function in chronic pesticidal toxicosis is manifested as a decrease in glomerular filtration rate. In this case, there may be an increase in the level of creatinine, urea and / or uric acid in the blood plasma [31, 34, 44], and fractional excretion of potassium may also increase [45]. Clinical signs of renal failure with low-dose exposure to pesticides are usually absent, but in almost all cases structural changes in the body are revealed in the form of renal glomerular dystrophy [39], renal connective tissue fibrosis, and proximal tubular epithelial necrosis [44].
Thus, an analysis of the results of studies of many authors indicates that the organs of excretion and detoxification are overly sensitive to low-dose exposure to pesticides. The severity of morpho functional changes developing in them with prolonged contact with a chemical stressor depends on the initial state of health, which determines to a large extent the body’s resistance to the action of damaging factors. The probability of developing these disorders is determined mainly by the genetically determined and / or altered state of stress-limiting systems and their reactivity during the course of life. Prevention of violations of the barrier functions of the body is of paramount importance in a systematic approach to maintaining the health of animals and humans.

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