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To cite this article: L K Gerunova et al 2020 IOP Conf. Ser.: Earth Environ. Sci. 421 022072

View the article online for updates and enhancements.
Prenatal low-dose effects of pesticides and their long-term effects

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Abstract. Due to diffuse distribution in the environment and migration along the food chains, pesticides affect non-target organisms, including during embryonic development. The prenatal period is a “critical window” of development for the body when the basic organs and systems are laid and formed. Even a slight effect on the body of ecotoxics in this period can lead to developmental defects and further increases the risk of diseases and reproductive dysfunction. The studies examined regarding a low-dose, without visible clinical manifestations in mothers, prenatal exposure to pesticides, imitate the real conditions for the intake of toxicants in small quantities during pregnancy at different stages of embryonic development. The authors found that pesticides are capable of causing metabolic shifts and delayed behavioral changes in the offspring, which are a manifestation of the non-monotonous dose-response reaction associated with the presence of epigenetic mechanisms.

Pesticides, their biotransformation products and environmental degradation pose a serious danger during migration along trophic chains. According to environmental monitoring, in 2018, in 8 of the 38 examined constituent entities of the Russian Federation, soil pollution with pesticides was found to be higher than hygienic standards, in four of them, namely the Kursk, Orenburg, Penza and Samara regions, soil pollution with two or more types of pesticides was found [1]. Facts of the detection of high concentrations of pesticides in surface waters are known. For example, in 2017, in the Samara Region, during a planned study of water samples in the Chapaevka river (Volga tributary), an extremely high content of organochlorine pesticides (6 MPC) was recorded [2]. The State report of the Federal Service for Supervision of Consumer Rights Protection and Human Well-being “On the State of Sanitary and Epidemiological Well-being of the Population in the Russian Federation in 2018” indicates the presence of excess pesticides in food products from 2013 to 2018, except 2016 year [3].

It has now been proven that pesticides exhibit biological activity even in low doses because they interact with numerous enzymes, proteins, receptors, and transcription factors [4, 5]. This influence is especially dangerous during periods of “critical windows” of ontogenesis, such as embryonic development, pregnancy, reproduction. It is assumed that exposure to environmental pollutants affects offspring to a greater extent than adult organisms [6]. The effects of such influence on the fetus are difficult to predict, since they have complex formation mechanisms and depend on many factors, including the peculiarities of the influence of toxic substances on the mother’s body and the stage of fetal development [7, 8, 9].
The purpose of this review is to analyze the results of studies by authors of different countries on the problem of prenatal pesticidal intoxications and their long-term consequences in the offspring.

It was found that pesticides can affect the fetus, causing abnormalities in the placenta, as well as directly penetrating the placental barrier [10, 11].

Many authors attribute the effect of pesticides in the prenatal period to fetal growth retardation. It has been established that when pesticides are exposed to the mother's body at doses below the threshold level (NOAEL), offspring with lower body weight are possible [12, 13, 14].

Pesticide-induced changes in the placenta are manifested in the form of impaired microcirculation (blood supply) and oxidative stress. According to some authors, it is oxidative stress that occurs in the tissues of the placenta that can cause fetal growth retardation [13]. Then, the presence of a “catch-up period” can be observed, during which the progeny significantly increases body weight, up to obesity [15]. A similar effect was noted by T L Lassiter and S Brimijoin when exposed to chlorpyrifos. In their experiment, pregnant rats received chlorpyrifos daily at a dose of 2.5 mg/kg (from GD 7 to PND 21). Exposure to chlorpyrifos caused an increase in body weight in the offspring, starting from day 45 of the postnatal period, 73 days after birth, the weight of the experimental animals was 10.5% higher than in the control. At puberty, the experimental animals were 12% more in weight than the control. These data indicate the manifestation of a delayed effect of weight gain in animals treated prenatally with chlorpyrifos [16].

According to X. Liu with co-authors (2019), nonlinear changes in body weight of offspring when exposed to pesticides can be associated with impaired lipid metabolism [17]. Other authors associate similar nonlinearity effects with epigenetic changes [18, 19, 20], which represent hereditary disorders in gene expression that occur without changing the DNA sequence. Environmental factors can affect some epigenetic mechanisms, such as micro-RNA expression, DNA methylation, and histone modification. In vivo and in vitro studies have revealed several classes of pesticides that can modify epigenetic labels [21]. The defects arising in them, associated with pesticidal intoxication in the embryonic period, can sometimes be passed on to subsequent generations [19, 20, 22].

Epigenetic modifications due to intrauterine intoxication may underlie the process of obesity and other metabolic changes in developing offspring [20]. Similar mechanisms occur in other disorders caused by prenatal exposure to pesticides. For example, when the content of thyroid hormones in the offspring of zebrafish changes as a result of the influence of ecologically significant concentrations of fipronil [23], when changes in the pancreas occur in the offspring of mothers who received the metabolite of DDT during pregnancy [22], and with a change in the myelinating potential of oligodendrocytes in the brain when exposed to carbofuran [24].

It has now been established that there is a relationship between the prenatal exposure to pesticides and late neurological disorders in the offspring [25, 26].

The brain develops over a long period of time, during which it is highly sensitive to environmental influences and endogenous hormones that modulate the plasticity and properties of the brain. Even a low-level effect of neurotoxic chemicals that does not cause clinical signs during this period can disrupt the development of the brain and subsequently affect the behavior and learning process of offspring [18, 27, 28].

Studies using the elevated cruciform labyrinth test showed anxiety behavior in rat offspring (PND 21) when mothers were exposed to low doses of chlorpyrifos (GD 14-20) [29]. Depressively similar behavior was detected in a forced swimming test in adult rats (PND 60) obtained from mothers exposed to subchronic glyphosate (from GD 5 to PND 60) [30]. In rats treated with prenatally dichlorvos (DDVP) at a dose of 8 mg/kg, at the age of three weeks and in adults, the Open Field test showed a decrease in motor activity and an increase in the period of immobility [31].

Exposure of methoxychlor to mothers leads to dulling of fright reactions and avoiding salamander in hatching larvae [32]. Zebrafish fry obtained from mothers exposed to fipronil in environmentally significant concentrations also showed a decrease in swimming speed [23].
The authors attribute such deviations in the behavior of offspring to changes in the neurotransmitter systems that regulate locomotor activity and cause anxiety arising from exposure to low doses of pesticides [31, 33].

It should be noted that behavioral changes after prenatal exposure to pesticides, as a rule, are delayed [29, 30, 31] and can manifest themselves in the process of growing up or even aging [18, 25, 34]. According to V.P. Eroshenco et al., With the widespread use of pesticides, changes in group behavior can affect population dynamics and survival of pesticide-exposed species [32].

In addition to behavioral changes, in the offspring after contact with pesticides in the prenatal period, there is a subsequent decrease in learning ability and memory deficit [24, 31, 35, 36]. Violation of the learning process and memory may be associated with functional and morphological changes in the hippocampus that occur during intoxication during embryonic development. Along with neurotransmitter changes in the hippocampus, oxidative stress, astrocyte dysfunction, impaired proliferation, maturation and differentiation of oligodendrocytes, their apoptosis and myelination defects are often noted [24, 30, 36].

Sexual differences play a role in the manifestation of prenatal toxicity of pesticides [29, 37]. This is due to the processes of sexual differentiation of the brain during early development with the help of male and female gonads [9].

The organizational hypothesis of sexual development states that gender differences are formed in two stages. At the first stage, fetal hormones prepare tissues for reaction to gonad hormones in later periods of development. At the second stage, an increase in the level of hormones in the puberty period activates the prepared masculinized or feminized substrates during the growing period. The effect of sex hormones on an adult organism depends on the level of prenatal exposure to these hormones. Experiments on rodents confirmed this hypothesis and showed that sexual dimorphisms in sexual behavior are formed neonatally and are activated in adulthood [20].

Puberty is a process regulated by the endocrine system, the physiological mechanisms of which are not well understood. Factors that can lead to disruption of this system can seriously affect the development of reproductive function. Changes in puberty may be a nonspecific consequence of general toxicity to offspring, however, some toxicological studies indicate the potential for reproductive toxicity [9, 38]. In particular, pesticides exhibiting anti-estrogenic, antiandrogenic activity or interacting with the hypothalamus-pituitary-gonadal axis may have such selective action.

Endocrine disruptors during fetal development are of particular danger [39]. So, for example, the prenatal effect of synthetic pyrethroid phenvalerate leads to a delay in puberty in female rats, disruption of the estrous cycle and a change in the mass of the uterus in different phases of the estrous cycle. The authors attribute these adverse effects to the antiestrogenic effect of fenvalerate during critical periods of the sexual organization of the female body [40].

Similar changes were noted in mice under the influence of cypermethrin. The drug even in low doses provokes a delay in puberty in females, leading to a decrease in the number of estrous cycles in offspring [41].

A prospective cohort study in Japan revealed the effect of low doses of organochlorine pesticides during prenatal development on testosterone, cortisone, and cortisol levels in boys [42]. Immunohistochemical studies of other authors showed a significant decrease in the activity of enzymes related to the production of testosterone, as well as a decrease in the content of mRNA encoding these enzymes in male offspring of rats treated with oral linuron (GD 13 - GD 18). The data obtained indicate a high risk of sexual development disorders in males when exposed to linuron due to its direct effect on testosterone production in the fetus and in the postpartum period in male offspring [43].

The observed effect of pesticides on reproductive processes can have long-term effects on fertility, which poses a threat to individual populations and entire species [20].

Thus, the mechanism of prenatal toxicity of pesticides involves a combination of various endocrine, metabolic and epigenetic changes that develop at the cellular and molecular levels. The presence of a non-monotonic dose-effect relationship and the delayed manifestation of changes
complicate the assessment of the risk of prenatal contact with pesticides. For an objective judgment on the potential danger of ecotoxicants, long observation intervals are necessary taking into account the characteristics of critical periods of development and gender differences in response. Promising is the study of compensatory mechanisms with low-dose prenatal exposure to pesticides and other environmental toxicants.

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