UDC 616.8-008.6-053.1/.2-02:618.3-06:615.9]-092.9 DOI: 10.33273/2663-9726-2021-54-1-41-51

TESTING METHODS FOR THE ASSESSMENT OF CHEMICAL NEUROTOXIC EFFECTS ON THE DEVELOPING ORGANISMS IN PRE- AND POSTNATAL PERIOD

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ABSTRACT. Aim of the research. *Analysis of approaches to the assessment of neurotoxic effects of chemicals during ontogenesis. The dangerous tendency of the increase in the incidence of pathology of the nervous system in the child and the mother, who during pregnancy was exposed to neurotoxicants, necessitates the protection of the child's body from such a negative effect of chemicals. One of the possible preventive ways to solve this problem is screening of xenobiotics before their widespread application, as well as identification of their ability to cause neurotoxic effects on the body during its development, and banning substances, neurotoxic effects of which on the development of progeny are proven.*
Materials and Methods. *Detection of adverse effects at the stage of foetal development and then at the beginning of the functioning of a nervous system in the postnatal period requires complex experimental studies in laboratory animals, which are described in the recommendations of OECD guideline 426 (OECD Guideline for Testing of Chemicals; Guideline 426: Developmental Neurotoxicity Study, 2007). The OECD guideline 426 protocol provides for a wide range of methods for assessing sensory, motor, behavioural and cognitive functions.*
Conclusions. *Analysis of data given in publications and methodological approaches to research and evaluation of neurotoxic effects of chemicals on the developing organism showed that to obtain representative results it is important to take into account all factors that may affect the result, select adequate informative tests and comply with all requirements. In Ukraine, international methodological approaches to the study of neurotoxic effects of pesticides on the body at the stage of development in the process of ontogenesis are applied at the L.I. Medved's Research Center of Preventive Toxicology, Food and Chemical Safety, Ministry of Health, Ukraine (State Enterprise), Kyiv, Ukraine.*
Key Words: *nervous system, neurotoxic effects, OECD guideline 426, neurobehavioral tests.*

Introduction. It is known that the nervous system (NS) is one of the most complex systems in the body. It is responsible for the interconnected regulation of all parts of the body, as well as regulates reactions to changes in internal and external conditions. The nervous system (NS) of the body at the stage of development is more sensitive to chemicals than in adults. In the prenatal period, the NS of a foetal develops from ectodermal cells of the embryo, consisting of billions of cells that are precisely located, highly specialized and interconnected. In a normally developing brain, neurons move precisely along certain paths from their points of origin to their destination, communicating with other cells. All processes of brain development occur within a certain time interval, each stage is clearly planned and consistent. The effect of xenobiotics at any of the stages of brain development can lead to congenital morphological, structural or functional changes. If morphological and structural disorders of foetal development are developmental defects, which in most cases are incompatible with life, the functional disorders can occur at different stages of ontogenesis [1-6]. Analysis of many epidemiological studies indicates that there is a relationship between the effects of xenobiotics and the occurrence of NS pathology in children whose mothers were exposed to neurotoxicants during pregnancy [7-9]. The most common manifestations of such functional changes in children are autism, behavioural disorders, hyperactivity, inability to learn and various emotional problems [2, 3, 7-9].

Based on this, an important problem of modern preventive toxicology is the study of the possible impact of xenobiotics on the development of the nervous system in the pre- and postnatal periods.

The main source of information on the possible negative consequences of such exposure is the data obtained in experiments on laboratory biological models, which allow conducting a comprehensive assessment of the state of the nervous system and predicting adverse effects in children.

An important study aimed at identifying the adverse effects of xenobiotics in the development and onset of NS functioning in the postnatal period is an experimental study according to the OECD guideline 426 protocol (OECD Guideline for Testing of Chemicals; Guideline 426: Developmental Neurotoxicity Study, 2007). This protocol provides for a wide range of methods for assessing sensory, motor, behavioural and cognitive functions [10-12]. Carrying out such researches gives the chance to estimate comprehensively influence of pesticides on NS of progeny [2, 12-14].

Aim of the Research. Analysis of approaches to the assessment of neurotoxic effects of chemicals during ontogenesis.

Research methods. Generalization of the main requirements and characteristics of the study of neurotoxic effects of xenobiotics on postnatal foetal development from the standpoint of modern preventive toxicology, set out in the recommendations of OECD guideline 426. This method may exist as a stand-alone study or be part of research on reproductive toxicity (OECD guideline 416 and 443) [15, 16].

1.1. Research principle

When studying the neurotoxic effects of chemicals on the body at the stage of development the following principles should be followed:

— choice of biological model and the possibility of reproducing the neurotoxic effect in the experiment on the selected species/line of laboratory animals;
— selection of the dose range and dependence of the effect on the dose with the ascertainment of the threshold of the neurotoxic effect for development;
— selection of a behavioural tests battery to assess the neurotoxic effects of chemicals based on the properties of the active substance: mandatory and additional research methods;
— extrapolation of the obtained experimental data on children who may be exposed to chemicals in low doses under real conditions in the periods of pre- and/or early postnatal development.

1.2. The necessity of the research

The research in accordance with the recommendations of the OECD guideline 426 should be conducted for:

— chemicals that exhibit a neurotoxic effect in experiments on adult laboratory animals;
— new pharmacological substances that can be prescribed to women during pregnancy and lactation.

1.3. Materials and test system

1.3.1. Selection of laboratory animals

Experimental, preventive and regulatory toxicology have a common goal – to protect human health, in particular of the most sensitive members of society – children. Therefore, the use of laboratory animals as biological models in the experiment is a necessary guarantee of the validation of the potential danger to humans and the reliability of preventive measures. The recommended biological test system is rats, given the short duration of pregnancy and fertility [17, 18]. It should also be noted that the placenta of rats, like the human placenta, belongs to the haemochorial type [19, 20]. The choice of other species of laboratory animals should be justified on the basis of toxicological and/or other characteristics.

1.3.2. Conditions for keeping animals

To obtain representative experimental data, animal husbandry conditions are important. The microclimatic conditions of the vivarium should be as follows: temperature (22±3)˚C, relative humidity – 30-70% (during the period of wet mopping 50-60%). Artificial lighting: 12 hours of light/12 hours of darkness. It is possible to change the lighting cycle before mating and during the study of behavioural indicators in the dark (with red light). Any changes in the lighting cycle should be long enough for the animals to adapt to the new lighting conditions. Premises where physiological experiments take place must be specifically arranged: without outside stimuli (light, sound, etc.), the air must not contain outside odours.

Animals are kept with free access to water and food. Animal cages must be made of a special material designed for such purposes and arranged so that the possible harmful effects associated with their movement are kept to a minimum. Experimental animals are kept individually or in small groups of the same sex. The mating procedure is performed in cages suitable for such purposes. Pregnant females must be sepa-

rated and provided with material for nest formation no later than on the 15th day of pregnancy.

1.3.3. Formation of experimental groups

Healthy, mature animals that have undergone an adaptation period in a vivarium should be selected for the research. Mating of P0 rat generation is carried out after the acclimatization period. Intact males are placed with females in a ratio of 1: 1 (1 male to 1 female); in females, vaginal swabs are taken daily until the fact of mating is established. The day of detection of sperm in a smear of the vaginal contents of the female or of vaginal copulatory tube is taken as the 0th day of pregnancy (DP). After establishing the fact of mating, the female is placed in a separate cage. Pregnant females are divided into groups. There should be 20 pregnant females in each experimental and control group.

1.3.4. Selection of doses

Three dose levels are usually used in the research (the highest, medium, and the lowest). The highest dose should be close to the maximum endurable for a pregnant female, due to the need to determine the maximum manifestation of the damaging potential of the test substance to establish harmful effects on the progeny. The average dose is necessary for the possible manifestation of adverse effects under the action of the test compound. The lowest dose should not cause toxic effects in pregnant and lactating females, nor affect the development and condition of their progeny.

Usually the highest dose is limited to 1000 mg/kg/day of body weight. Exceptions are cases where data on the effects of the test substance on humans indicate the need for higher dose levels.

When using a solvent (emulsifier) it is necessary to take into account its toxicological characteristics (absorption, metabolism, interaction with the test substance, etc.). Animals in the control group are administered distilled water with emulsifier in equivalent amounts.

1.3.5. Exposition

The test substance should be administered by the most probable route of entry into the human body, taking into account available toxicological and kinetic data. Particular attention is paid to oral exposure (can be performed with a metal probe, given with food or water). The choice of other routes of administration of the test substance (inhalation, etc.) must be justified.

Usually the exposure is carried out once a day, at the same time, the time of administration of the test substance should not lead to a shift in circadian rhythms of activity of animals. Accidental and systematic errors associated with the administration of the substance should be minimized.

The sensitivity of the foetus to the neurotoxic effects of chemicals depends on the stage of development. But it should be borne in mind that the foetus, which is in the developmental stage, may differ in sensitivity to the action of substances of different structure. The exposure period of the test substance should last from the 6th day of pregnancy to the 21st day of lactation. In the absence of a potential effect of the test substance on the implantation process, the administration of the test substance may begin from the 0th day of pregnancy.

The amount of test substance exposed is calculated individually based on the body weight of the animal. Particular care should be taken when calculating the dose during the last third of pregnancy. No exposure is held on the day of delivery.

It is assumed that in the postpartum period, the effect of the test substance on the progeny will occur through breast milk, but in the absence of such data, the direct introduction of the test substance to the progeny is possible.

When using other species of laboratory animals, the duration of administration of the test substance should be adjusted to observe the manifestation of its neurotoxic effects in all periods of NS development, which will correspond to prenatal and early postnatal development of human NS.

1.4. Conduct of an experiment

OECD guideline 426 provides for two stages of research with a wide range of modern methods for assessing the toxic effects of chemicals on the body of a pregnant female and their neurotoxic effects on the foetus at the stages of pre- and postnatal development. At the first stage, the toxic effects of chemical compounds on the body of pregnant and lactating females are investigated.

1.4.1. Study of the effects of chemicals on pregnant and lactating females (P0 generation)

The change in body weight and weight gain are evaluated as integral indicators of the toxic effect of the test substance. Weighing of animals is carried out at least twice a week, on the day of the expected date of birth and on the day of birth, as well as on the 21st day of lactation. The duration

of pregnancy (duration of gestation) should be fixed. The day of birth is taken as the 0th day of lactation (DL) for females and the 0th day of postnatal development (DPN) for progeny. During the experiment, feed and water consumption are studied.

Assessment of the clinical condition of pregnant and lactating females usually includes (but is not limited to) indicators of general activity, the presence of neurological symptoms, changes in higher nervous activity, impaired coordination/muscle tone, vegetative changes, etc. [21].

After euthanasia, females undergo macroscopic examination of internal organs; the number of implantation sites is estimated. If it is expedient, clarification of additional parameters is possible.

1.4.2. Study of the effect of chemicals on progeny (F1 generation)

The second stage of the research in accordance with the requirements of OECD guideline 426 is to study the effects of chemical compounds on the body at the stage of its development. It should be noted that the test substance may affect several target organs/tissues under different mechanisms of action. Therefore, it is necessary to use a standard battery of neurobehavioral tests, which are stated in the OECD guideline 426, if necessary – additional.

According to the protocol after birth the sex of rats is determined, the weight and size of the litter, the number of live and dead new-borns, and the number of individuals of different sexes are calculated, and the survival index is calculated according to the following formula [22, 24]:

$$\text{Survival index} = \frac{\text{Number of live pups}}{\text{Overall number of pups}} \times 100$$

The litter is balanced on the 4th DPN [25, 26]. After that, the size of the litter should not exceed 8-12 individuals and contain an equal number of females and males (as far as it is possible). Animals from each group are divided into research cohorts so that males and females of each litter are included in all cohorts where necessary. F1 generation animals that were not distributed among the cohorts are euthanized. An example of the distribution of animals into cohorts and control research indicators monitoring scheme are presented in table. 1.

1.4.2.1. Physical and sexual development

Physical development is one of the integrative indicators of biological maturity of all body systems. It affects the body formation rate, muscular and mental performance [28, 29]. At least 1 male and 1 female shall be selected from each litter to assess physical development where possible. During postnatal development, the dynamics of ear separation, the appearance of primary hair, eruption of incisors, eye opening, and testicles descent/separation of the prepuce/opening of the vagina are studied [30-34].

1.4.2.2. Motor-sensory function.

The study of motor-sensory function, which includes a battery of functional tests, expands the scope of diagnosis of possible functional disorders in litter and allows tracing the appearance, development, duration and reversibility of neurotoxic effects of chemicals taking into account its intensity [6, 35-37]. The choice of a battery of functional tests in neurotoxic studies should be based, on the one hand, on the recommendations of the OECD guideline 426, on the other – on data on the specific effects of the chemical on motor and/or sensory function [38].

To assess the motor-sensory function of the litter different physiological tests are used:

— rate of formation of reflexes;
— neuromuscular function;
— sensory reactivity to different modality stimuli (sound, visual, pain).

It is possible to conduct additional functional tests (for example, in the study of pharmacological drugs – pain syndrome, etc.) [39].

While performing testing, it is necessary to strictly adhere to the conditions of functional studies, as the results largely depend on the "readiness" of animals to perform them, which is affected by even minor changes in experimental conditions, including sound level, abrupt changes in temperature, relative humidity, light, odour, the use of a conventional animal cage or a new test cage, etc. [40].

In rare cases, animals showing signs of toxicity that have a significant effect on the results may be excluded from functional tests, but this should be a reasonable decision and recorded in the protocol of the study.

1.4.2.3. Behavioural reactions.

Behavioural reactions of animals are a sensitive indicator of higher nervous activity of animals, which allows determining the presence, nature and extent of its toxic lesion [41-44].

Table 1

Example of distribution of animals into cohorts and control research indicators monitoring scheme

Indicators	Research period	
	early postnatal period (0-21 DPN)	postnatal period (21-70 DPN)
Body weight and weight gain	at least once a week	at least once every two weeks
Physical and sexual development	if necessary[a]	
Sexual development	—	males from 21 DPN [b]/30 DPN [c] females from 28 DPN
Motor-sensory function	at least once per period	once per period
Behavioural reactions	1-3 times [d]	at least once per period [d]
Memory and ability to learn	—	2 times per period (25 ± 2) DPN and 60-70 DPN)
Additional behavioural tests	if necessary[e]	
Morphometric parameters	22 DPN[f]	at the end of the study
Neuropathology		
Clinical observations	at least once a day[g]	

Notes:
[a] — change in the timing of physical development is associated with body weight. Body weight and weight gain can be an indicator of the level of physical development of an individual. Based on this, the ascertainment of the terms of physical development should be carried out in the case of confirmation of the influence of the test substance on them [25, 27];
[b] — in the study of testicles descent;
[c] — at research of the separation of the prepuce;
[d] — information is provided in 1.4.2.3;
[e] — neurobehavioral function tests (sexual behaviour, social behaviour, etc.) are if necessary, while not violating the integrity of the basic design of the experiment;
[f] — the study of morphometric parameters of the brain and neuropathology can be conducted at an earlier stage of postnatal development (for example, at 11 DPN);
[g] — information is provided in 1.5.

At least 1 male and 1 female shall be selected from each litter for their assessment where possible. According to the recommendations of the OECD guideline 426, studies are conducted during lactation (13, 17, 21) and on DPN 60-70 [38]. If necessary, they are performed more often.

Behavioural responses can also be monitored using an automated recording device that will detect both increase and decrease (the activity of the animal in the open field in this case should not be so low as to exclude the possibility of detecting a decrease and not so high as to prevent fixation of the increase in this activity). Each device before use is checked by standard procedures to ensure reliable operation for a certain period of the study.

When studying the behavioural reactions of animals, it is also necessary to strictly adhere to the conditions of the experiment (paragraph 1.4.2.2).

1.4.2.4. Memory and ability to learn

Tests aimed at studying cognitive function are usually performed in the post-lactation period (for example, DPN (25 ± 2) days, DPN 60 and older).

According to the guiding principles of OECD guideline 426, recommended test method(s) are based on its/their sensitivity to this class of compounds, if such information is available in the publications. In its absence, test(s), which combine(s) the assessment of at least one of the types of memory and the ability of animals to learn, are performed [38].

Examples of tests used to assess the effects of chemicals on the cognitive function of laboratory animals:

— ***The Morris Water Maze.*** This test is used to study the effect of xenobiotics on the functioning of the CNS of animals, namely: the ability of animals to form spatial concepts, the functioning of short- and long-term memory. The results obtained in the "Morris water maze" on laboratory animals are used to extrapolate data on the effects of chemicals on people with Alzheimer's disease, autism, various brain injuries [45-49].
— ***Barnes Maze.*** As a less stressful, it can be used as an alternative to Morris test. The results of this testing are used to extrapolate the effects of chemicals on people with different types of neuronal diseases, including Alzheimer's disease, to study the effect of the test substance on spatial memory [50-52].
— ***Cincinnati Water Maze.*** The method is used to assess cognitive and orientation abilities of animals, their ability to learn, short- and long-term memory [53].
— ***T-maze/Y-maze.*** The test allows the study of the effect of the test substance on spatial and working memory. Various modifications of these labyrinths can be used (for example, a combination of the T-maze and the Morris water maze) [54-57].
— ***Radial arm maze.*** The method is used to study different types of stress disorders, as well as to study the effect of the test substance on working and spatial memory [58-60].

If during testing the chemical affects the cognitive function of the test animals, additional tests may be used to exclude alternative interpretations based on changes in sensory, motivational and/or motor activity.

1.5. Clinical observations

During the experiment the clinical condition of females and progeny is assessed to identify possible symptoms of intoxication. Along with the assessment of the general condition of the animals during the exposure period it is necessary to conduct (at least twice) a more detailed clinical examination of pregnant and lactating animals using at least ten females per dose level. At careful clinical examination of the progeny, where it is possible, at least 1 male and 1 female are selected from each litter.

A detailed clinical examination should include, inter alia, the determination of general activity, the presence of neurological symptoms, changes in higher nervous activity and vegetative disorders. The study is conducted by a qualified specialist outside the cage, in a special arena or in the «open field» [21, 61].

The results of the examination must be carefully recorded using a calculation system that provides criteria or quantitative scales for each measurement in the study. The criteria or scales used must be clearly defined by the testing laboratory.

1.6. Necropsy

The morphometric parameters of the brain and histological parameters of central and peripheral NS of the progeny are evaluated.

To study the morphometric parameters after euthanasia, decapitation is performed and the brain is removed from the skull. Immediately after that (to prevent brain drying), the absolute and relative masses of the brain are examined. The relative mass of the brain is calculated according to the following formula [62]:

$$\text{Relative brain mass} = \frac{\text{Animal's brain mass}}{\text{Animal's body weight}} \times 100$$

When evaluating neuropathological studies:
— parts of the nervous system that show neuropathological changes are identified;
— types of neuropathological changes that occurred under the influence of the test substance are identified;
— range and severity of neuropathological changes are determined.

Samples of brain tissue are taken from all major departments (e.g., olfactory bulbs, cerebral cortex, hippocampus, basal ganglia, thalamus, hypothalamus, midbrain, pons Varolii, medulla, and cerebellum). It is important that the brain sections of all animals are selected in the same plane.

At the end of experimental studies in F1 generation adults, representative sections of the spinal cord and peripheral nervous system are taken. Areas of study include: eye with optic nerve and retina, spinal cord of cervical and lumbar parts, dorsal and ventral nerve roots, proximal sciatic nerve, proximal tibial nerve (in the knee joint) and branches of the tibial nerve of the calf muscle. Sections of the spinal cord and peripheral parts of the NS should include both transverse and longitudinal sections. Neuropathological evaluation includes the detection of signs of NS disorders in addition to cellular disorders (e.g., vacuolisation, degeneration, neuronal necrosis) and histological changes (e.g., hemo- and plasmorrhagia, gliosis, leukocyte infiltration, cystic for-

mations). It is important to distinguish between effects due to the exposure to the test substance and changes associated with euthanasia.

In the course of qualitative and quantitative neuropathological analysis, histological preparations from groups of animals that were exposed to the highest dose of the test substance are compared to the data of the control group. In the absence of neuropathological changes in these animals, no further analysis is performed.

1.7. Assessment of Results

The study in accordance with the requirements of the OECD guideline 426 is aimed at identifying the negative effects of xenobiotics on the morphological and functional state of the NS during ontogenesis. Because the study evaluates the effects of chemicals on two biological systems (the body of a pregnant female and the foetus at the developmental stage), the emphasis is on both general toxicity and neurotoxicity endpoints. The obtained results allow differentiating neuropathological phenomena in progeny that occur in the absence of general maternal toxicity and are manifested only at those dose levels that are also toxic to maternal animals.

When interpreting the results it is necessary to take into account all the data obtained and include expert assessment. It is necessary to take into account the patterns of behavioural or morphological results, if they occur, as well as to establish a "dose-effect" relationship. Data from all studies, including epidemiological observations and/or clinical cases, results of experiments in various biological test systems, information on the structural activity of the chemical compound, etc., can be included in the report, which also provides an analysis of the relationship between doses of test substance and the presence of or lack of exposure, as well as the degree of any neurotoxic effect for each sex. Evaluation of results should include a discussion of both biological and statistical values.

The report can substantiate the specific or non-specific action of the test substance. The test substance is considered neurotoxic to the body at the stage of development, if there are one or more types of effects on the functional state or morphological changes of the progeny. To be classified as a neurotoxicant with a specific action, the drug must directly cause functional or morphological changes at the stage of development of the foetus/new-born. These changes should not be secondary (nonspecific) manifestations due to the toxic effect in the body of pregnant and lactating females. To assess the possible relationship/absence between the toxic effect in the body of a pregnant and lactating female and the manifestation of the neurotoxic effect in the progeny, it is necessary to analyse the data of the control group of animals; historical control (data of researches carried out in the same conditions of one laboratory for the three-year period, on the same line of animals); the presence of toxic effects on the mother and neurotoxic manifestations in the progeny.

Statistical analysis should be seen as a tool that guides but does not determine the interpretation of data. The lack of statistical significance cannot be the only justification for the absence of a corresponding effect of the test substance. The analysis should include the relationship, if any, between neuropathological and behavioural effects. The choice of a parametric or non-parametric method of analysis must be justified taking into account factors; including natural data, their distributions in particular. The relative stability of the selected statistical analysis should also be taken into account. In the case of deviations of the distribution law from the normal (heterogeneous), statistical processing of the results is carried out using Fisher, Wilconson. The choice of statistical analysis method and study scheme must be justified in order to minimize Type I (false test results) and Type II (false negative test results) errors.

In accordance with the requirements of OECD guideline 426, to study the neurotoxic effects of pesticides on the developing organism, it is necessary to scientifically substantiate the value of the level at which there is no effect (no-observed-effect-level - NOEL) [38]. The NOEL value of the neurotoxic effect for this organism is taken into account when setting the allowable daily dose (ADD) for humans.

Conclusions. Analysis of data given in publications and methodological approaches to research and evaluation of neurotoxic effects of chemicals on the body at the stage of development showed that to obtain representative results it is important to take into account all factors that may affect the result, select adequate informative tests and comply with all requirements. In Ukraine, international methodological approaches to the study of neurotoxic effects of pesticides on the body at the stage of development in the process of ontogenesis (OECD

guideline 426 Developmental Neurotoxicity Study) have been brought into laboratory practice at the L.I. Medved's Research Center of Preventive Toxicology, Food and Chemical Safety, Ministry of Health, Ukraine (State Enterprise), Kyiv, Ukraine.

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МЕТОДИ ОЦІНКИ НЕЙРОТОКСИЧНОГО ВПЛИВУ ХІМІЧНИХ РЕЧОВИН НА РОЗВИТОК ОРГАНІЗМУ В ПРЕ- І ПОСТНАТАЛЬНОМУ ПЕРІОДАХ

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РЕЗЮМЕ. Мета. *Аналіз підходів щодо оцінки нейротоксичної дії хімічних речовин у період онтогенезу. Небезпечна тенденція до зростання патологій нервової системи у дитини, матір якої під час вагітності зазнала впливу нейротоксикантів, обумовлює необхідність убезпечення дитячого організму від такої негативної дії хімічних речовин. Одним з можливих профілактичних шляхів вирішення цієї проблеми є скринінг ксенобіотиків ще до їхнього широкого упровадження у практику, а також виявлення здатності спричиняти нейротоксичну дію на організм у період його розвитку, необхідність заборони речовини, нейротоксичний вплив на розвиток потомства яких доведений.*
Матеріали та методи. *Виявлення несприятливих ефектів на стадії розвитку плода, а потім на початку функціонування нервової системи в постнатальному періоді потребує складних експериментальних досліджень на лабораторних тваринах, які зазначені в рекомендаціях OECD guideline 426 (OECD Guideline for Testing of Chemicals; Guideline 426: Developmental Neurotoxicity Study, 2007). Протокол OECD guideline 426 включає широкий спектр методів для оцінки сенсорних, моторних, поведінкових і когнітивних функцій.*
Висновки. *Аналіз даних літератури та методичних підходів щодо дослідження й оцінки нейротоксичного впливу хімічних речовин на організм, що знаходиться на стадії розвитку, показав, що для отримання репрезентативних результатів важливим є врахування всіх факторів, що можуть вплинути на результат, вибір адекватних інформативних тестів і дотримання всіх вимог їх проведення. В Україні в лабораторну практику впроваджені міжнародні методичні підходи щодо вивчення нейротоксичного впливу пестицидів на організм на стадії розвитку в процесі онтогенезу в ДП «Центр превентивної токсикології, харчової та хімічної безпеки імені академіка Л.І. Медведя Міністерства охорони здоров'я України».*
Ключові слова: *нервова система, нейротоксичний вплив, OECD guideline 426, нейроповедінкові тести.*

МЕТОДЫ ОЦЕНКИ НЕЙРОТОКСИЧЕСКОГО ВЛИЯНИЯ ХИМИЧЕСКИХ ВЕЩЕСТВ НА РАЗВИТИЕ ОРГАНИЗМА В ПРЕ- И ПОСТНАТАЛЬНОМ ПЕРИОДАХ

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РЕЗЮМЕ. Цель. *Анализ подходов к оценке нейротоксического действия химических веществ в период онтогенеза. Опасная тенденция роста патологий нервной системы у детей, матери которых во время беременности подвергались влиянию нейротоксикантов, обусловливает необходимость принятия мер, направленных на защиту детского организма от нейротоксического воздействия химических веществ. Один из возможных профилактических путей решения этой проблемы – скрининг ксенобиотиков еще до их широкого внедрения, а также определение способности вызывать нейротоксическое действие на организм во время его развития, необходимость запрета веществ, для которых доказано нейротоксическое действие на развитие потомства.*
Материалы и методы. *Для выявления неблагоприятных эффектов на стадии развития плода, а затем в начале функционирования нервной системы в постнатальном периоде требуется проведение сложных экспериментальных исследований на лабораторных животных, которые отражены в рекомендациях OECD guideline 426 (OECD Guideline for Testing of Chemicals; Guideline 426: Developmental Neurotoxicity Study, 2007). Протокол OECD guideline 426 включает широкий спектр методов для оценки сенсорных, моторных, поведенческих и когнитивных функций.*
Выводы. *Анализ данных литературы и методических подходов к исследованию по оценке нейротоксического воздействия химических веществ на развивающийся организм показал, что для получения репрезентативных результатов важно учитывать все факторы, которые могут повлиять на результат, выбор адекватных информативных тестов и соблюдение всех требований их проведения. В Украине в лабораторную практику внедрены международные методические подходы к изучению нейротоксического воздействия пестицидов на развивающийся организм в процессе онтогенеза в ГП «Научный центр превентивной токсикологии, пищевой и химической безопасности имени академика Л.И. Медведя Министерства здравоохранения Украины».*
Ключевые слова: *нервная система, нейротоксическое воздействие, OECD guideline 426, нейроповеденческие тесты.*

Received November 18, 2020