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# CHARACTERIZATION OF CUMULATIVE EXPOSURE AND RISK ASSESSMENT OF SPECIFIC EFFECTS OF PESTICIDE IMPACT ON THE NERVOUS SYSTEM DURING THEIR SIMULTANEOUS INTAKE WITH APPLES INTO THE HUMAN BODY

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**Key words:** *pesticides, neurotoxic effects, residues in food products, cumulative dietary risk*
**Ключові слова:** *пестициди, нейротоксичний вплив, залишки в харчових продуктах, кумулятивний аліментарний ризик*

**Abstract. Characterization of cumulative exposure and risk assessment of specific effects of pesticide impact on the nervous system during their simultaneous intake with apples into the human body. Yastrub A.M., Zhminko P.H., Yastrub T.O.** *The purpose of the study is to characterize the cumulative exposure and quantify the risk of specific effects of insecticidal pesticides of different chemical classes on the nervous system when they enter the body simultaneously with apples at the level of approved maximum residue levels. By literature data, inactive and minimal dose levels of abamectin, emamectin benzoate, milbemectin, alpha-cypermethrin and acetamiprid for their specific effects on the nervous system were established. Domestic reference values – acceptable daily doses, maximum residue levels of insecticides in apples were studied and their comparative characteristics were carried out with those established in the European Union. A comparative characteristic for the daily exposure of the studied insecticides in apples when they enter the children and adults' bodies according to the scenario of maximum residue levels is carried out. It was found that acetamiprid (0.00026/0.0001 mg/kg bw (body weight) for children 2-6 years/adults, respectively) is characterized by the highest level of exposure for which the maximum residue level is approved – 0.05 mg/kg. The greatest contribution to the risk of cumulative alimentary effects is made by abamectin (65.8-66.4%), for which the lowest permissible daily dose (0.0002 mg/kg) is justified. The determined risk parameters from cumulative alimentary exposure are within accep table values (hazard index <1, total exposure margin >100). It was found that the cumulative effect per unit of body weight for children is higher compared to adults. It is shown that the effect of a mixture of the studied substances when they are taken with apples in the maximum permissible quantities will not lead to adverse health consequences for different age groups of the population (adults and children 2-6 years), in particular, the effect on nervous system. The results obtained indicate that the reference values of the studied insecticides approved in Ukraine will ensure safety for the health of consumers when they enter the body with apples. Recommendations are given on the need to take into account processing factors in food production technology and baby food hygiene.*

**Реферат. Характеристика сукупної експозиції та оцінка ризику виникнення специфічних ефектів впливу пестицидів на нервову систему при їх одночасному надходженні з яблуками до організму людини. Яструб А.М., Жмінько П.Г., Яструб Т.О.** *Мета дослідження – характеристика сукупної експозиції та кількісна оцінка ризику виникнення специфічних ефектів впливу пестицидів інсектицидної дії різних хімічних класів на нервову систему при їх одночасному надходженні з яблуками до організму на рівні затверджених максимально допустимих рівнів. За даними літератури встановлені недіючі та мінімальні рівні доз абамектину, емамектину бензоату, мілбемектину, альфа-циперметрину та ацетаміприду за їхніми специфічними ефектами впливу на нервову систему. Досліджено вітчизняні референтні величини – допустимі добові дози, максимально допустимі рівні інсектицидів у яблуках та проведено їх порівняльну характеристику зі встановленими в Європейському Союзі. Проведена порівняльна характеристика денної експозиції досліджуваних інсектицидів у яблуках при їх надходженні до організму дітей та дорослих за сценарієм максимально допустимих рівнів.*

*Установлено, що найвищим рівнем експозиції характеризується ацетаміприд (0,00026/0,0001 мг/кг м.т. для дітей 2-6 років/дорослих відповідно), для якого затверджений максимально допустимий рівень – 0,05 мг/кг. Найбільший внесок щодо небезпеки сукупного аліментарного впливу робить абамектин (65,8-66,4%), для якого обґрунтована найнижча допустима добова доза (0,0002 мг/кг). Визначені параметри ризику від кумулятивного аліментарного впливу лежать у межах допустимих величин (індекс небезпеки <1, загальний запас експозиції >100). Установлено, що сукупний кумулятивний вплив на одиницю маси тіла дітей є вищим порівняно з дорослими. Показано, що вплив суміші досліджених речовин при їх надходженні з яблуками в максимально допустимих кількостях не призведе до несприятливих наслідків для здоров'я різних вікових груп населення (дорослі та діти 2-6 років), зокрема впливу на нервову систему. Отримані результати свідчать, що затверджені в Україні референтні величини досліджених інсектицидів забезпечать безпеку для здоров'я споживачів при їх надходженні з яблуками до організму. Надано рекомендації щодо необхідності врахування факторів переробки в технології виробництва харчової продукції та гігієни дитячого харчування.*

Features of use of plant protection products (PPP), which mean their regular and purposeful introduction into the environment, as well as an increase in the range of mixed formulas can lead to simultaneous pollution with two or more active substances (AS) of various environmental objects (water, air, food). This makes it necessary to conduct scientific studies to assess the potential combined effects of their complex impact on human health [1, 2, 3].

The issue of quality and safety of agricultural products is relevant, which in relation to the residues of PPP AS in food products involves taking into account cumulative effects when using different products with the content of one AS or a specific food product with the content of several AS (multiple residues) [4, 5]. In the context of this issue, cumulative effects are considered as the combined effect of several active substances with a common mechanism of toxic action through the alimentary route of exposure [6].

The analysis results about the food samples, which are periodically (every three years) published in the reports of the European Food Safety Agency (EFSA) as part of monitoring programs, show a certain frequency of multiple residues in some types of products [7, 8, 9]. Thus, the EFSA report for 2022 provides the results of the analysis of 11,727 samples, of which 32% (3,760 samples) contained quantified residues of more than one AS. The products with the highest percentage of leftovers (10%) were apples, peaches, tomatoes, and lettuce [10]. Content of AS did not exceed the limit of the quantitative determination method and was within the established maximum residue levels (MRLs). However, the cases of multiple residues cause public concern, and the scientific community is encouraged to look for an answer to the question: can any AS enhance the effects of other substances, cause additive or synergistic effects?

Risk assessment from acute and chronic alimentary exposure to multiple PPP AS residues in food products is carried out in accordance with the methodology of grouping substances into cumulative assessment groups (CAG) according to the general mechanism of toxic action [1, 11]. Such groups are created for substances based on their effect on the nervous system (NS), thyroid gland, inhibition of acetylcholinesterase (AChE) activity, and their ability to cause craniofacial malformations [12, 13, 14, 15].

Of all possible effects on NS, five specific evaluation criteria for the classification of substances in CAG were selected: inhibition of AChE in the brain and/or red blood cells, functional changes in NS parts, histological pathological changes in nerve tissues, neurotoxicity for the development of offspring (developmental neurotoxicity (DNT)), and cognitive effects [16]. According to [17] 47 substances are included in CAG inhibition of AChE in the brain and/or red blood cells, 119 – in CAG functional changes in the motor part of the NS, 101 – in CAG functional changes in the sensory and autonomic parts of the NS, 19 – in CAG histological pathological changes in nerve tissues [17]. Information on the combined effects of AS on DNT and cognitive effects is not yet sufficient to create appropriate CAGS.

All substances included in CAG were characterized by dose levels at which no harmful effects were observed (no observed adverse effect level, NOAEL). NOAEL values were obtained from available information on toxicological studies conducted on laboratory animals in accordance with international testing protocols.

A known or suspected neurotoxic mechanism of action is characterized by PPP, which exhibit insecticidal properties and belong to chemical classes of compounds: avermectins (abamectin, emamectin benzoate), milbemycin (milbemectin), neonicotinoids (acetamiprid), synthetic pyrethroids (alpha-cypermethrin).

On the basis of these active substances, both single-component and mixtures of PPP are registered in Ukraine, which are used to protect various agricultural crops, orchards and vineyards [18].

The aim of this study is to characterize exposure and quantify the risk of specific effects of insecticides of various chemical classes on the nervous system when they enter the body with apples at the level of approved maximum residue levels.

**MATERIALS AND METHODS OF RESEARCH**

The object of research was insecticides: abamectin, emamectin benzoate, milbemectin, acetamiprid, alpha-cypermethrin, which are used in Ukraine on apple trees. The general mechanism of their insecticidal action according to the classification developed by the Insecticide Resistance Action Committee (IRAC) is shown in Table 1 [19].

*Table 1*

**Classification of the studied active substances by the mechanism of insecticidal action**

| Trivial name of the AS | The main group and the main action site | Class of compounds |
|---|---|---|
| Abamectin | Group 6: Allosteric modulators of glutamate-dependent chloride channels. Acts on the nerves and muscles of insects | Avermectins |
| Emamectin benzoate | | |
| Milbemectin | | Milbemycins |
| Acetamiprid | Group 4: Competitive nicotinic acetylcholine receptor (nAChR) modulators. Decreased nervous activity | Neonicotinoids |
| Alpha-cypermethrin | Group 3: Modulators of sodium channels. Acts on the nerves, ataxia | Synthetic pyrethroids |

The subject of the research was the cumulative risk of the studied active substances when they simultaneously enter the human body with apples. The research materials included reports from EFSA, The World Health Organization (WHO), scientific information on the study of the mechanism of insecticide toxic action, and the determination of NOAEL by their specific effects on NS [12, 16, 17]. Theoretical studies of national regulatory legal acts on reference values – acceptable daily dose (ADD), MRL in apples and their comparison with those established in the European Union [20, 21] were conducted. The main parameters for characterizing the acute alimentary cumulative effect of AS residues in apples were calculated for two age groups of the population (adults and children aged 2-6 years), taking into account the daily rate of apple consumption (J, kg/person/day): for adults J=0.125, for children – 0.082 [22].

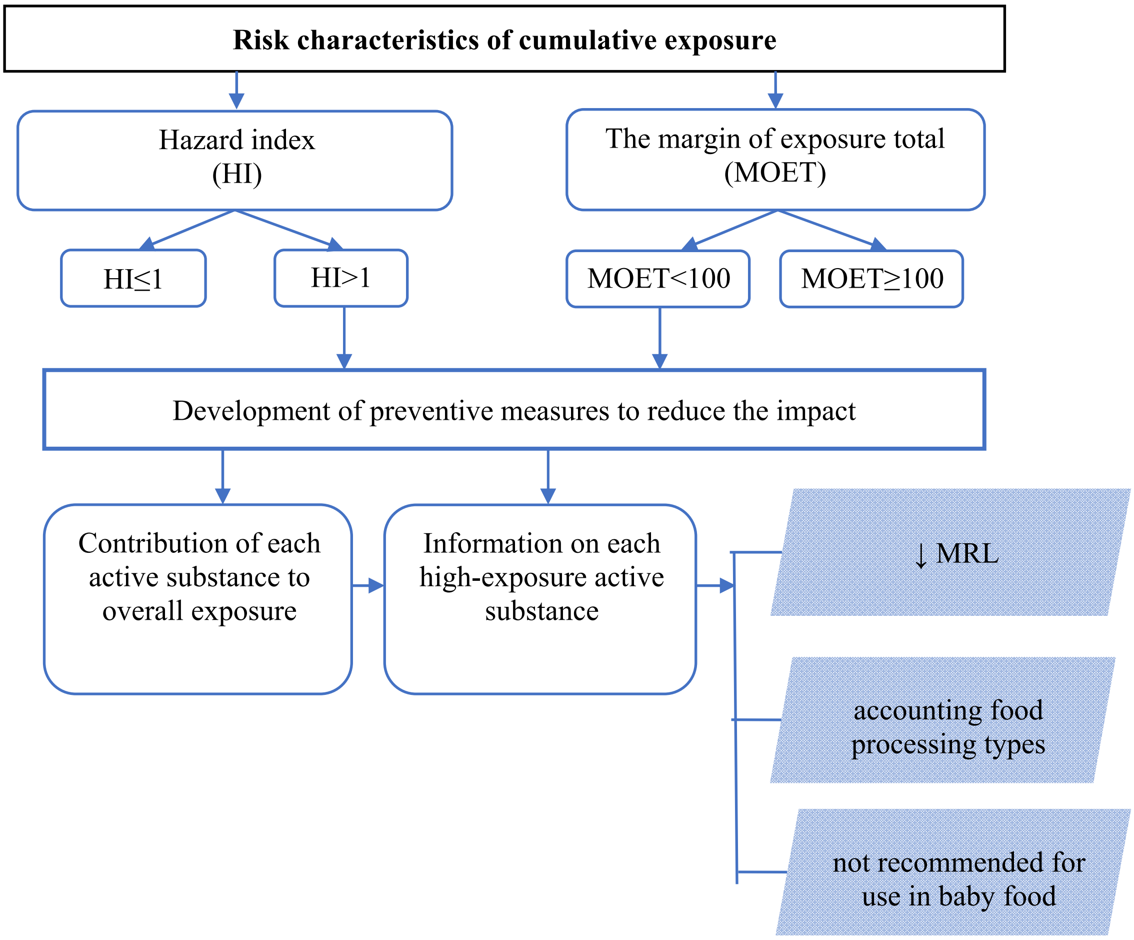
The daily exposure dose of residues of each AS ($E_i$, mg/kg body weight/day) was determined as the ratio of the product of the daily apple consumption rate (J, kg/person/day) and MRL of AS in a food product (mg/kg of the product) to body weight (bw) (M – 60 kg for an adult, 15.6 kg – body weight of children aged 2-6 years) [23]): $E_i = J \times MRL : M$.

Total exposure ($E_{total}$, mg/kg bw/day) was defined as the sum of the products and the relative potential factor ($RPF_i$) of each active substance from the related group: $E_{total} = \sum E_i \times RPF_i$. $RPF_i$ is defined as the ratio of the NOAEL index compound (IC) to the NOAEL of the individual AS ($RPF_i = NOAEL_{ic} : NOAEL_i$). Exposure was evaluated using the hazard index (HI) as the sum of the hazard ratios of each active substance: $HI = \sum HQ_i$ ($HQ_i = E_i : ADD_i$). The risk is considered acceptable at $HI \leq 1$. The connection between the dose and effect allows us to establish the margin of exposure total (MOET) [22]. This value is defined as the ratio of $NOAEL_{ic}$ obtained in a toxicological experiment on animals to $E_{total}$: $MOET = NOAEL_{ic} : E_{total}$. Margin of exposure is considered acceptable at $MOET \geq 100$.

Risk characteristics of the cumulative alimentary influence according to the scenario of maximum residue levels and development of appropriate recommendations for its reduction was carried out by the algorithm (Fig.) [25].

The research was conducted without involving humans or animals. The study uses biblio-semantic, systematic, analytical methods, normative search and comparative analysis, and a semi-quantitative method of risk assessment. The calculation of RPF, HI, MOET values was performed using the cumulative risk assessment methodology recommended by the Scientific Panel on Pesticides and the EFSA Scientific Committee [11, 24]. The research results were subjected to statistical processing using the IBM SPSS Statistics Base V. 22 and Microsoft Excel 2010 statistical software package.

All planned studies were reviewed and approved by the Commission on Ethics of Medical and Biological Research of L.I. Medved's Research Center of Preventive Toxicology, Food and Chemical Safety, Ministry of Health of Ukraine (Protocol No. 35 of 04.03.2025).




**The algorithm for risk characteristics and development of recommendations for minimizing cumulative alimentary impact according to the scenario of maximum residue levels**

**RESULTS AND DISCUSSION**

According to the literature [16, 17, 26, 27, 28, 29, 30, 31] the main criteria for evaluating and indicators of the specific effects of the studied insecticides on NS were established (Table. 2).

As can be seen from the data shown in Table 2, all the studied insecticides affect the motor part of the NS, causing such specific effects as tremor, ataxia, decreased motor activity, and impaired coordination of movements. These effects were observed in experiments on studying acute neurotoxicity on rats, sub-chronic and chronic toxicity on dogs.

Neurotoxicity of macrocyclic lactone insecticides – abamectin, emamectin benzoate, milbemectin is also manifested by functional changes in the sensory and vegetative parts of the NS (reduced extension reflex, hyperreactivity, salivation, mydriasis). Neuropathological effects in the form of degeneration of nerve axons and myelin were observed in dogs with sub-chronic and chronic exposure to emamectin benzoate at doses of 0.5 mg/kg and higher. This substance is a specific toxicant for the optic nerves and retinal tissues. Neurotoxicity for the development of offspring was found in experiments on rats under the influence of emamectin benzoate, alpha-cypermethrin and acetamiprid.

The reference values (ADD, MRL), NOAEL for the effect on NS and RPF of each AS in relation to IC (emamectin benzoate) are shown in Table 3.

It was found (Table 3) that the lowest ADD values are characterized by substances from the avermectin class – abamectin (0.0002 mg/kg), emamectin benzoate (0.001 mg/kg) and milbemectin (0.003 mg/kg). These substances are inhibitors of GABA receptors, an amino acid that acts as a neurotransmitter. A characteristic feature of avermectins is the blocking of chloride tubules, increasing the permeability of membranes for chloride ions, which leads to neurotoxic effects.

The potential danger of avermectins is also associated with a high risk of embryotoxic and teratogenic effects when administered to pregnant animals, effects on reproductive function and development. These effects are taken into account in additional safety factors when justifying ADD.

*Table 2*

**Main evaluation criteria and indicators of specific effects of the studied insecticides on the nervous system**

| Active substance | Evaluation criteria | NOAEL, mg/kg | LOAEL*, mg/kg | Indicator of a specific effect | Type of research, animals |
|---|---|---|---|---|---|
| Abamectin | Acts on the motor part of the NS | 1.5 | 6.0 | Ataxia | Acute neurotoxicity, rats |
| | | 0.25 | 0.5 | Ataxia, tremor | Sub-chronic toxicity, dogs |
| | Acts on the sensory part of the NS | 0.5 | 1.5 | Reduced extension reflex | Acute neurotoxicity, rats; chronic toxicity, dogs |
| Alpha-cypermethrin | Acts on the motor part of the NS | 2.3 | 6.8 | Ataxia | Sub-chronic toxicity, dogs |
| | Neurotoxic effect on the offspring's development | <0.25 | 2.0 | Clinical features in joeys | DNT, rats |
| Acetamiprid | Acts on the motor part of the NS | 10.0 | 30.0 | Reduced motor activity | Acute neurotoxicity, rats |
| | Neurotoxic effect on the offspring's development | 2.5 | 10 | Suppression of the acoustic starter response without neuropathology | DNT, rats |
| Emamectin benzoate | Acts on the motor part of the NS | 5.0 (1.0)** | 10 | Tremor | Acute neurotoxicity, rats |
| | | 0.25 (0.05)** | 0.5 | Tremor | Chronic toxicity, dogs |
| | Acts on the sensory part of the NS | 0.5 (0.1)** | 0.75 | Hyperreactivity | |
| | Acts on the vegetative part of the NS | 0.5 (0.1) | 0.75 | Mydriasis | |
| | Neuropathological effect | 0.95 | 4.74 | Histological changes in the brain, spinal cord, sciatic nerve, skeletal muscles | Subacute (14 days) neurotoxicity, rats |
| | | 0.25 | 0.5 | Degeneration of central and peripheral nervous tissue, optic nerve, myelin | Sub-chronic, chronic toxicity, dogs |
| | Neurotoxic effect on the offspring's development | 0.6 | 2.5 | Tremor, extension of the hind limbs, decreased motor activity and sensorimotor reflexes, neuron degeneration | DNT, rats |
| Milbemectin | Acts on the motor part of the NS | 10.0 | 30.0 | Unsteady gait, tremor | Sub-chronic toxicity, dogs |
| | Acts on the vegetative part of the NS | 3.0 | 10.0 | Salivation, vomiting | |

**Notes:** * – LOAEL (lowest observable abverse effect level) – the minimum dose level at which toxic effects are observed; ** – additional factor 5 was introduced through a small dose interval and a steep "dose-response" curve.

*Table 3*

**The reference values (ADD, MRL) and the output values (NOAEL, RPF) to assess the risk of cumulative alimentary effect**

| Active substance | ADD, mg/kg | MRL, mg/kg | NOAEL, mg/kg | RPF |
|---|---|---|---|---|
| Abamectin | 0.0002 | 0.01 | 0.25 | 0.200 |
| Alpha-cypermethrin | 0.005 | 0.02 | 0.25 | 0.200 |
| Acetamiprid | 0.01 | 0.05 | 2.5 | 0.020 |
| Emamectin benzoate IC | 0.001 | 0.01 | 0.05 | 1.00 |
| Milbemectin | 0.003 | 0.02 | 3.0 | 0.017 |

For the synthetic pyrethroid alpha-cypermethrin and neonicotinoid acetamipride, the limiting effect in hazard assessment is the neurotoxic effect on development.

According to the specific effects of the studied substances on NS, the lowest NOAEL values obtained in studies on rats and dogs from the most sensitive evaluation criterion were determined: for abamectin – 0.25 mg/kg (rats, motor part – ataxia, tremor), alpha-cypermethrin – 0.25 mg/kg (rats, DNT – clinical signs in joeys), acetamiprid – 2.5 mg/kg (rats, DNT – suppression of acoustic starter reaction without neuropathology), emamectin benzoate – 0.05 mg/kg (rats, motor part – tremor), milbemectin – 3 mg/kg (dogs, vegetative part – salivation, vomiting).

Emamectin benzoate was selected as the index compound by the completeness of toxicological data, the ability to cause neurotoxic effects in acute, subchronic, chronic exposure regimens, DNT studies, and the lowest level of NOAEL – 0.05 mg/kg.

To compare the NOAEL values, the $RHF_i$ value was calculated for each studied substance. For emamectin benzoate IC the RHF value was taken as one, while for other substances, the RHF value ranges from 0.017 (milbemectin) to 0.2 (abamectin, alpha-cypermethrin).

The assessment of exposure and the main parameters of the cumulative alimentary effect of insecticides of various chemical classes when they enter the body of children and body of adults with apples are shown in Tables 4 and 5.

*Table 4*

**Cumulative alimentary effect of active substances when they enter the body of children aged 2 to 6 years with apples**

| Active substance | Daily exposure, mg/kg bw/day | | Hazard quotient (HQ) | % from ADDIC |
|---|---|---|---|---|
| | Ei | Ei × RPFi | | |
| Abamectin | 0.000053 | 0.000011 | 0.265 | 9.0 |
| Alpha-cypermethrin | 0.000110 | 0.000022 | 0.022 | |
| Acetamiprid | 0.000260 | 0.000005 | 0.026 | |
| Emamectin benzoate IC | 0.000053 | 0.000053 | 0.053 | |
| Milbemectin | 0.000110 | 0.000002 | 0.037 | |
| $E_{total}$ =0.00009 mg/kg bw/day | | | | |
| HI =0.403 – acceptable risk (H<1) | | | | |
| MOET =556 – exposure margin within acceptable values (MOET>100) | | | | |
| IC – index compound | | | | |

*Table 5*

**Cumulative alimentary effect of active substances when they enter the body of adults with apples**

| Active substance | Daily exposure, mg/kg bw/day | | Hazard quotient (HQ) | % from ADDIC |
|---|---|---|---|---|
| | Ei | Ei × RPFi | | |
| Abamectin | 0.000021 | 0.000004 | 0.105 | 3.6 |
| Alpha-cypermethrin | 0.000042 | 0.000008 | 0.008 | |
| Acetamiprid | 0.000100 | 0.000002 | 0.010 | |
| Emamectin benzoate IC | 0.000021 | 0.000021 | 0.021 | |
| Milbemectin | 0.000042 | 0.000001 | 0.014 | |
| Etotal =0.00004 mg/kg bw/day | | | | |
| HI=0.158 – acceptable risk (H<1) | | | | |
| MOET =1250 – exposure margin within acceptable values (MOET>100) | | | | |
| IC – index compound | | | | |

It was found (Table 4) that according to emamectin benzoate IC the total exposure ($E_{total}$) of residual amounts of AS when apples are consumed by children aged 2 to 6 years old is determined at 0.00009 mg/kg bw/day and is 9.0% of the ADD is (ADD of emamectin benzoate – 0.001 mg/kg).

$E_{total}$ for adults (Table 5) is 0.00004 mg/kg bw/day and doesn't exceed the reference IC value (3.6% ADD).

The total effect of multi-residues in apples on the level of MRL with simultaneous intake of AS into the body was 0.403 for children of 2-6 years old and 0.158 for adults, which makes it possible to assess the risk as acceptable (HI<1).

When combined with GABA receptor agonists, alpha-cypermethrin and acetamipride, MOET for children of 2-6 years is 2500, adults – 4167, which indicates a sufficient margin of exposure.

The results obtained in the study highlighted a number of issues for discussion. Thus, the exposure assessment under the MRL usage scenario showed that the higher the MRL, the higher the level of exposure. MRL ranges from 0.01 mg/kg (abamectin, emamectin benzoate) to 0.05 mg/kg (acetamiprid). Daily exposure to acetamiprid was highest: $E_i$ =0.00026/0.0001 mg/kg bw/day for children/adults, respectively. For the most dangerous substances abamectin and emamectin benzoate, the lowest MRL is approved, which is usually used for baby food products. However, even at low levels of residues, it is possible to exceed the ADD value established for infants and young children at the level of 0.0005 mg/kg of body weight [32]. This is confirmed by the results of the study and literature data: the cumulative effect per unit of body weight of children is higher compared to adults [33, 34].

It was found that HQ values increase with decreasing ADD. Thus, with the same MRL (0.01 mg/kg) for abamectin, which has the lowest ADD (0.0002 mg/kg), HQ is 0.265/0.105 respectively for children of 2-6 years old/adults, for emamectin benzoate (ADD – 0.001 mg/kg), HQ is 0.053/0.021.

The contribution of each AS to the danger of total alimentary effect, which is characterized by the value of HI, is determined. Abamectin (65.8-66.4%) and emamectin benzoate (13.2-13.3%) make the greatest contribution to HI. The contribution of milbemectin is 8.9-9.0%, acetamiprid – 6.3-6.5% and alpha-cypermethrin – 5.1-5.5%.

The domestic reference values of the studied insecticides are compared with those established in the EU. For abamectin, the acceptable daily intake (ADI) accepted in the EU is higher than the domestic standard (0.0012 mg/kg and 0.0002 mg/kg, respectively). At the same time, the safe maximum residue limit (MRL) in apples is set at 0.006 mg/kg (the lower limit of analytical determination) against 0.01 mg/kg approved in Ukraine. For milbemectin, the value of ADI is an order of magnitude higher than ADD, while the residue levels in apples are the same – 0.02 mg/kg [20, 21, 35]. For alpha-cypermethrin, acetamiprid, and emamectin benzoate, ADI is 0.00125 mg/kg, 0.005 mg/kg, and 0.0007 mg/kg, respectively, and is lower than domestic ADDs. These values were determined based on the results of a toxicological assessment conducted by EFSA experts, taking into account the effects of neurotoxicity on development [30, 31, 36]. At the same time, the maximum levels of alpha-cypermethrin, acetamiprid and emamectin benzoate residues accepted in the EU in apples are higher than domestic ones and amount to 1.0 mg/kg, 0.07 mg/kg and 0.02 mg/kg, respectively [35].

It should be noted that technological ways of processing raw materials can reduce the residual amount of pesticides or, conversely, contribute to their concentration in the final food product.

The analysis of the EU authorized database on processing factors (PF) [37] showed that only acetamiprid has known PF values for various technological ways of apple processing. It is shown that acetamiprid residues in various types of apple juice are reduced compared to the raw product (PF=0.47-0.88). At the same time, pesticide residues accumulate in dried apples (PF=3.1) and apple cake (PF=1.3).

Therefore, taking PF into account reduces uncertainty in the quantitative assessment of the risk of alimentary effects and is important information that needs to be taken into account in the production of food products and baby food hygiene.

## CONCLUSIONS

1. Based on the results of the scientific information analysis on the toxic action mechanism of insecticides: abamectin, emamectin benzoate, milbemectin, alpha-cypermethrin and acetamiprid, inactive and minimum active dose levels were established according to the evaluation criteria and indicators of their specific effects on the nervous system.
2. A comparative characteristic of the daily exposure of the studied insecticides in apples when they enter the body of children and adults is carried out. It was found that the highest level of exposure is characterized by acetamiprid (0.00026/0.0001 mg/kg bw/day for children of 2-6 years old/adults, respectively), for which the maximum residue level is approved – 0.05 mg/kg.
3. The greatest contribution to the risk of cumulative alimentary effects is made by abamectin (65.8-66.4%), for which the lowest permissible daily dose (0.0002 mg/kg) is justified.
4. The quantitative parameters of risk from cumulative alimentary exposure are determined within the permissible values (hazard index <1, total exposure margin >100). It is shown that the effect of a mixture of the studied substances when they are taken with apples in the maximum permissible quantities will not lead to adverse health consequences for different age groups of the population (adults and children of 2-6 years old), in particular, the effect on NS.

**Contributors:**

Yastrub A.M. – conceptualization, methodology, working with data, research, writing;

Zhminko P.H. – project administration, resources;

Yastrub T.O. – formal analysis, verification, visualization.

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