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**LIPOPHILIC PROPERTIES OF PESTICIDES:
BIOACCUMULATION AND BIOMAGNIFICATION IN ANIMALS,
THE TOXICITY FORECASTING**
(review)

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Abstract

The problem of pesticides contamination save actuality because of the growing demand for food and multi-factorial processes of their biotransformation and bioaccumulation in living organisms. As of July 11, 2023, more than 1,200 approved insecticides, acaricides and herbicides have been registered in Russian Federation (excluding fungicides, rodenticides, repellents, desiccants, plant growth regulators, microbiological and biological pesticides, etc.), many of them are included in the list of particularly dangerous according to PAN data, for example, diazinon, chlorpyrifos, dimethoate, imidacloprid, malathion, spinosad (PAN List of HHPs, 2021). Their uncontrolled using results the accumulation of parent compounds, metabolites and degradation products in soil, water, plants, and animals and the subsequent biomagnification of persistent pollutants at higher trophic levels (V.P. Kal-yabina et al., 2021; C.M. Volschenk et al., 2019; Z. Zhang et al., 2019). Pesticides have an adverse effect not only for target pests, but also on the crops, soil microbiota, natural ecosystems objects and humans. Biopesticides are safer, but at the same time, their high selectivity becomes a disadvantage in solving several agrotechnical objectives (W.-H. Leong et al., 2020; De O.H. Gomes et al., 2020). The absorption, distribution, and transport of pesticides in biological systems are determined by their lipophilicity (T. Chmiel et al., 2019; R. Beiras, 2018; S.-K. Kim et al., 2019). High lipophilicity generates conditions for high metabolic clearance of compounds. The biological activity of substances in the organism could be predicted by logP which describes their affinity for target proteins (T. Chmiel et al., 2019), where P is the distribution coefficient showing the ratio of the compound concentrations in two immiscible phases at equilibrium state. The extremely lipophilicity of pesticides (logP > 5) can result to their binding to hydrophobic targets, which provides non-selectivity and higher toxicity (C. Olisah et al., 2021). Insufficient data has been obtained on the metabolism and bioaccumulation of pesticides in farm animals and synergistic effects in real conditions by this time. The distribution of pesticides in soil, ground and surface waters depends not only on their lipophilicity, but on pH, temperature, the initial amounts of preparations, organic and inorganic substances content, solids sorption properties (S.D. Burlaka et al., 2019; S. Hintze et al., 2021; F.A.P.C. Gobas et al., 2018). The accumulation of pesticides in the soil results the decreasing of the involved in the circulation of elements and organic substances degradation soil microorganism activity and can be the biological indicator of ecosystems pollution. Generally, the levels of pesticide residues in environment are measured by gas, high-performance and ultra-high-performance liquid chromatography, enzyme immunoassay and capillary electrophoresis (A. Samsidar et al., 2018; S. Hintze et al., 2021; L. Fu et al., 2018). Gas chromatography is appropriate for volatile and thermally stable compounds, while high-performance liquid chromatography is more relevant for non-volatile and polar compounds. A combination of chromatographic separation with high-resolution mass spectrometry could be required for non-targeted analysis that allows the not detected in the target study compounds identification and determination. The search for safe plant protection substances and forecasting of their toxicity, bioaccumulation processes in environment and the transfer through food chains, is possible using a combination of two approaches.

These are «non-targeted search» and modern QSAR mathematical models. The «non-targeted search» allows both targeted and non-targeted analysis of pesticides and their metabolites, and QSAR models are based on the correlation of physicochemical, particularly lipophilic properties of molecules and their effects on living organisms (A. Speck-Planche, 2020; N.A. Ilyushina, 2019; O.G. Columbin, 2020).

Keywords: pesticides, lipophilicity, bioaccumulation, environmental pollution, toxicity, microbiome

The need for food is growing worldwide. According to UN forecasts, over the next 30 years the world's population will increase by 2 billion people, reaching 9.7 billion by 2050, and 11 billion by 2100 [1]. Despite growing organic agriculture, approximately a third of the world's crops are produced using pesticides [2].

Pesticides can have adverse effects not only on target pests, but also on crops themselves [3] and on soil microbiota [4]. Farm animals are exposed to pesticides through contaminated feed and water [5-7] and through direct contact, e.g., through inhalation of polluted air near agricultural land. Thereof, even low concentrations of chlorpyrifos, dichlorophenyl dimethylurea and their mixtures negatively affected the physiological and biochemical parameters of chickens [8]. There was a decrease in acetylcholinesterase activity, changes in the content of liver biomarkers (alkaline phosphatase, aspartate aminotransferase and alanine aminotransferase) and renal biomarkers (total protein, creatinine, uric acid and urea). The consumption of poultry meat in the world is steadily growing, and the accumulation of toxicants in livestock products can pose a threat to human health [6, 8, 9]. Pollution of environment with pesticides also concerns plant-pollinating insects [10, 11], including honey bees (*Apis mellifera*), which provide a significant increase in crop yields [12-14].

With prolonged use of pesticides, pests are able to develop resistance to their active ingredients [15-17]. In addition to the increase in the number of resistant arthropod species, there is the development of multiple resistance to toxicants of different chemical classes [18]. Excessive use leads to the accumulation of these compounds, their metabolites and decomposition products in soil, water, plants and the body of farm animals. Possible negative effects of bioaccumulation include the development of cancer pathologies [19], reproductive dysfunction, immunological, endocrine, neurodegenerative disorders [20, 21], birth defects and respiratory disorders [22-24].

In the Russian Federation, state registration of pesticides and agrochemicals is currently governed according to the approved procedure (Order of the Ministry of Agriculture and relevant administrative regulations No. 442 dated July 31, 2020, as amended on January 19, 2022). State registration includes tests of a pesticide or agrochemical, an examination of regulations for use, state registration and issuance of the certificate, inclusion in the State Catalog of Pesticides and Agrochemicals approved for use in the Russian Federation. At the beginning of 2020, the state catalog contained 652 drugs (separate and mixed according to the active ingredients) [25]. As of July 11, 2023, more than 1,200 approved insecticides, acaricides, and herbicides (excluding fungicides, rodenticides, repellents, desiccants, plant growth regulators, microbiological and biological pesticides) have been registered [26]. Moreover, as of March 2021, some of them according to the criteria of the Pesticide Action Network were included in the PAN International List of Especially Hazardous Pesticides, e.g., diazinon, chlorpyrifos, dimethoate, imidacloprid, malathion, spinosad, etc. [27].

The purpose of this review is to analyze the properties of pesticides that determine their sorption, distribution, bioaccumulation and toxicity for biological systems, stability and biodegradation in the environment, in order to predict the biological activity of drugs developed on their basis.

The most dangerous organochlorine pesticides for living beings, e.g.,

dichloro diphenyl trichloromethyl methane (DDD), hexachloro cyclohexane (HCH), aldrin, hexachloro benzene, endrin, heptachlor, chlordane are prohibited in Russia, as in most countries of the Northern Hemisphere. However, they continue to be used in Southeast Asia and, due to their extreme persistence, are capable of migrating to other regions by water circulation and sea currents. In the work of V.Y. Tsygankov [28], HCH isomers, DDD and its metabolites were detected in all marine organisms collected in the Sea of Japan, Bering and Okhotsk from 2000 to 2017.

The two main groups of pesticides are chemicals and biopesticides [19]. Chemicals are mainly synthetic compounds. Biopesticides are produced from natural sources (animals, plants, bacteria, some minerals) [2]. Chemical pesticides, based on their origin, are divided into a large number of groups and subgroups. The most common are organochlorines (OCs), organophosphates (OPs), carbamates, pyrethroids, benzimidazoles and triazoles. Biopesticides are divided into microbiological (bacteriophages, bacteria, yeast and fungi; *Bacillus thuringiensis* is most often used); biochemical (natural non-toxic substances, for example sex pheromones of insects, plant extracts) and built-in plant protection agents produced by plants [19]. Biopesticides are safer for animals and selective to target pests, which is both their advantage and disadvantage when solving several agro-technical problems simultaneously [19, 29].

Based on the target organism, pesticides are classified as herbicides (kill plants), insecticides (kill insects), fungicides (kill fungi), zoocides (kill warm-blooded animals), nematicides (kill nematodes), molluscicides (kill shellfish), algacides (kill algae), bactericides (kill bacteria, although they are generally considered among fungicidal agents) [30, 31]. The first three groups are the most representative; within them, there are additional subgroups.

The World Health Organization (WHO) classifies pesticides according to the acute toxicity value (LD_{50} , peroral, mg/kg), Ia stands for extremely dangerous (< 5), Ib for very dangerous (5-50), II for moderately dangerous (50-2000), III for slightly dangerous (> 2000), IV for unlikely to pose a danger (5000 or more) [19, 32]. The United States Environmental Protection Agency (EPA) identifies four hazard classes [20]. The hygienic classification of drugs adopted in the Russian Federation includes four hazard classes by average lethal dose when administered into the stomach (mg/kg), the extremely dangerous (≤ 50), highly dangerous (51-200), moderately dangerous (201-1000) and low hazardous (> 1000) [33]. In addition, not only acute toxicity are taken into account, but also allergenicity, teratogenicity, embryotoxicity, reproductive toxicity, mutagenicity and carcinogenicity, as well as persistence in soil.

It is not possible to prevent pesticides from getting into the soil, water, air and plants, so a search is underway for new, effective, safe for humans, environmentally friendly plant protection products, and responsible handling of pesticides of earlier generations is being practiced [2, 3, 16, 34].

Properties of pesticides that determine sorption, distribution, bioaccumulation and toxicity for biological systems. Metabolism, biological activity and bioaccumulation of pesticides in the organs and tissues of farm animals are primarily determined by their structure and, thereof, by physicochemical properties. Pesticides in the body bind to plasma proteins, blood cells, lipids and are distributed in various organs and peripheral tissues [35]. The absorption, distribution, and movement of chemical compounds in biological systems depend on their lipophilicity [35-38]. Lipophilicity determines the ability of xeno- and endobiotics to undergo metabolic transformations and the affinity to target proteins [36]. The biological activity and toxicity of compounds depends on their lipophilic properties [35, 39]. Accordingly, their optimization in the

new pesticide formulations can help in identification of structures that determine toxicity and biodegradation potential.

The soil is capable of retaining pesticides, as a result, the correct biochemical pathways in biogeochemical soil cycles is disrupted and the activity of microorganisms that play a key role in the cycling of elements and the decomposition of organic matter is reduced [17]. The enzymatic activity of soils, which characterizes its biological activity, is highly sensitive to external influences. A decrease in the activity of soil microorganisms can serve as a biological indicator of ecosystem pollution [4].

Soil microflora is highly sensitive to triazoles; the maximum toxic effect occurs in the initial period after their application; recovery can take up to 10 weeks [40]. A toxicity study of malathion (organophosphorus pesticide, OPP) demonstrated inhibition and reduction in the number of *Bacillus* spp., *Pseudomonas* spp., *Arthrobacter* spp., *Azotobacter* spp., *Flavobacterium* spp. and *Penicillium* spp. already at 1PC (pesticide concentration) used, at 2PC, *Pseudomonas* spp. and *Bacillus* spp. become dominant species, and at 5PC the death of the entire microenvironment occurs [41]. The negative effect of the insecticide is associated with the phosphorus and sulfur atoms, and with the morphological features and susceptibility of microorganisms.

Lipophilicity, namely the degree of hydrophobicity, determines the distribution of compounds between the aqueous and organic phases. It is characterized by the separation (distribution) coefficient P which shows the ratio of the concentrations of a compound in two immiscible phases at equilibrium. However, other solubilizing media, such as biomembranes, can also participate in this distribution [36, 37]. The logP value predicts the biological activity of substances in the body because it describes their affinity to target proteins [36].

The metabolism of pesticides, like other xenobiotics, may involve one or two stages. In the first stage, a polar group is introduced into the molecule with the participation of predominantly cytochrome P450-dependent monooxygenases and, to a lesser extent, flavin-containing monooxygenases and hydrolases [36]. In the second stage, when uridine-5-diphosphate glucuronosyltransferase, sulfotransferase and glutathione-S-transferase introduce much larger substituents (sugars, sulfates or amino acids), a significant increase in water solubility of the compound occurs [36]. Enzyme binding sites are primarily lipophilic and readily accept lipophilic pesticide molecules.

Organochlorine pesticides are highly lipophilic, persistent, toxic, and bioaccumulative [42]. The most dangerous are 4,4-dichlorodiphenyl trichloromethylmethane (DDT) and γ -hexachlorocyclohexane (γ -HCH, lindane), logP 6.91 and 3.72, respectively [43]. They can persist in soils for many years, are resistant to degradation, have estrogenic and carcinogenic properties, and are banned for use in most countries [2, 44]. Organophosphate pesticides, carbamates and pyrethroids are now more widely used due to their lower persistence than in organochlorines. However, they cannot be unambiguously classified as low-hazard compounds, since some of them form highly toxic products during transformation, such as 3,5,6-trichloro-2-pyridinol in the case of chlorpyrifos [4, 7, 45].

Through risk assessment and review of short- and long-term effects, many of the registered pesticides are classified as prohibited. For example, in 2018, it was shown that the use of sulfoxaflor (registered in 2007, a group of sulfoximines), as well as some members of the neonicotinoid group (imidacloprid, thiamethoxam and clothianidin) [13, 29, 46] leads to a decrease in the number of pollinating bees [47]. Chlorpyrifos, cypermethrin, and thiacloprid have been shown to cause endocrine disruption in honey bees [48]. Chlorpyrifos causes the strongest expressional changes, i.e., the induction of marker genes for MRJP2 (*mrjp2*), MRJP3 (*mrjp3*) (major royal jelly proteins), ILP1 (*ilp1*) (insulin-like peptide), HBG3 (*hbg3*) (alpha-glucosidase) and Sima (*sima*), and down-

regulation of *buffy*.

Many factors influence the persistence and biodegradability of pesticides in ecosystems. The distribution in soil, groundwater and surface water depends on the soil characteristics, the content of organic and inorganic substances and the sorption properties of solid particles [3, 36, 49], the structure of the compound which determines its water solubility, pH, temperature, and the amount of applied preparations (in accordance with the seasonality of agricultural activities) [35, 50, 51]. The distribution of compounds between the water environment and soil, as well as bioaccumulation, depends on lipophilicity (hydrophobicity) [35, 36, 51]. The increase in phytotoxicity of pesticides depends on the soil water regime which determines the migration of compounds deeper into soil horizons [3].

It is known that OC pesticides are more stable in an acidic environment than in an alkaline environment, and the organic compounds present in the soil bind most pesticides into water-insoluble forms, so they are not hydrolyzed and become practically inaccessible to microorganisms [3, 49, 52]. For example, a study of the prohibited γ -HCH using the C¹⁴-lindane model showed that the amount of the bound form in the soil increases over time, and the bulk is localized mainly in the 0-3 cm upper layer [3]. The accumulation of pesticides that are resistant to decomposition in the reproductive organs of plants leads to their entry into beekeeping products with nectar and pollen [9]. The use of surface water for agricultural purposes (irrigation and livestock farm water supply) can also facilitate recycling of pesticides.

When pesticides are washed out of the soil and from the surface of treated plants, they enter water sources which negatively affects the condition of living organisms [11, 24, 53]. Fish can be a bioindicator of pollution [53]. Bioaccumulation of glyphosate and its metabolite aminomethylphosphonic acid (AMPA), bifenthrin, azoxystrobin and cyproconazole has been observed in fish living in water in rice fields [54]. Bifenthrin was detected in all fish after fumigation, it has the greatest bioaccumulation potential of the four compounds studied, is stable and is characterized by high persistence and bioavailability. For lipophilic OC pesticides, species-specific accumulation in fish organs and tissues was observed, correlating with lipid content [42]. However, bioaccumulation is influenced by metabolic processes. Detoxification of pyrethroids occurs through oxidation by cytochrome P450 and subsequent hydrolysis catalyzed by carboxylesterase [54]. The presence of aromatic amino acids in the active site of acetylcholinesterase creates a hydrophobic region, and due to the lipophilicity of pyrethroids, they can interact with the active site, causing inhibition of enzymatic activity. Aquatic organisms lack the carboxylesterase, so the destruction and excretion of pyrethroids in fish is reduced. Acetylcholinesterase activity in fish brain was significantly reduced, and although it is considered a specific neurotoxic biomarker of PO pesticides and carbamate exposure, several studies have reported similar effects for triazoles, pyrethroids, and glyphosate [54].

When xenobiotics enter the animal's body with feed and water, the intestinal epithelial membrane serves as the main physiological barrier to transport the toxicant into the bloodstream [36]. Passive transport by diffusion across lipid membranes in transcellular and paracellular mechanisms is the dominant route for lipophilic molecules. Penetration of xenobiotics into the central nervous system also occurs through passive diffusion, and, as a rule, higher lipophilicity allows for easier passage of the blood-brain barrier. Too high a lipophilicity ($\log P > 2.8$), on the contrary, can lead to increased nonspecific binding to plasma proteins (36). Compounds that are excessively lipophilic ($\log P > 5$) tend to bind to hydrophobic targets, increasing the risk of nonselectivity and toxicity [39].

As already noted, OC pesticides are stable and capable of bioaccumulation; they are cytotoxic to both higher animals and microorganisms. Despite the ban on their use, their circulation in agroecosystems continues. According to research by the Institute of Water and Environmental Problems of the Siberian Branch RAS (Barnaul), in areas of former storage and use of pesticides in the Altai Republic, there are pockets of intense contamination with DDD and HCH of soils and associated natural environments (surface waters, bottom sediments and plants) [55]. Moreover, in feed and food plant and animal products from contaminated areas, residual pesticide contents exceeding their maximum permissible levels (MPL) are sometimes still found. In addition, OC pesticides are capable of being transported over unlimited distances with air and water, and their transfer to higher trophic levels leads to biomagnification [56-58]. Wild animals also suffer from contamination from organochlorine compounds used in agriculture [29, 58, 59]. The use of lipid reserves leads to the redistribution of toxicants in the body of migratory birds and has a negative effect during the breeding season [29, 59]. The biomagnification of OC pesticides is due to their high lipophilicity. When additional links are included in the food chain, such as predatory fish, carnivorous mammals, or humans, the dose of pesticides entering the body can increase many times over [35, 60].

The metabolism and bioaccumulation of pesticides in the body of farm animals, as shown by an analysis of the literature for 2017-2022 (PubMed, PubChem, ScienceDirect and eLibrary), is not given enough attention, and only a few works are devoted to the effects of their combinations [61]. The results of in vivo studies on laboratory animals (mice, rats, dogs, rabbits) and in vitro on lymphocyte cell cultures (human and animal), L8824 (grass carp liver hepatocytes), Neuro-2a (mouse neuroblastoma) and C6 (rat glioma induced in vivo by N-nitrosomethylurea) [62-64]. Synergistic interactions between pesticides and the possible increase in toxicity for living organisms when combined, even if the current standards for each of them separately are not violated, are also not sufficiently studied at present. For example, for bees, existing risk assessment procedures are designed primarily for individual compounds and do not take into account real-world exposure to multiple pesticides simultaneously. Typically, this involves the use of fungicides and insecticides, most often combinations of triazoles or PO pesticides with pyrethroids [12, 47]. Data obtained from single studies have shown that the combined effects of pesticides on *Apis mellifera* in natural conditions can cause serious damage from additive, antagonistic and synergistic interactions. It has been established that activation of PO pesticides by cytochrome P450 can lead to a decrease in the ability to detoxify pyrethroids due to the inhibitory effect of PO pesticides on esterases. A similar mechanism has been noted for tetraconazole (triazole) in combination with pyrethroids [12]. There are not enough studies of synergy in real conditions yet. This requires a cumulative risk assessment rather than summing the effects of individual compounds [35].

Modern methods for determining the content of pesticides and their metabolites. Prediction of biological activity of new drugs. When choosing a method for determining the content of pesticides, their volatility, thermal stability and polarity are most important. Pesticides are mostly determined by classical analytical methods, e.g., gas chromatography (GC), high-performance and ultra-high-performance liquid chromatography (HPLC and UHPLC), enzyme-linked immunosorbent assay (ELISA) and capillary electrophoresis (CE) [2, 6, 19, 50, 65]. GC is typically used for volatile and thermally stable compounds, HPLC for nonvolatile and polar compounds [15, 19, 66]. Modern chromatographic methods serve as the gold standard in determining the content of pesticides and their metabolites. They are selective and highly sensitive due to

the combination of GC and HPLC with mass-spectrometric detection in MS/MS mode and HRMS (high resolution mass spectrometry) [5, 15, 67, 68]. Currently, UHPLC and HPLC–HR-MS have become the most effective tools for monitoring the residual content of pesticides and their metabolites in environment and food products [69].

The presence of pesticide metabolites in the environment and livestock products poses a risk due to their possible toxicity and quantities exceeding the residual content of the parent compounds, as is the case with DDT and its metabolites dichlorodiphenyldichloroethane (DDD) and dichlorodiphenyldichloroethylene (DDE). DDT is metabolized and accumulated in high-fat foods. In eggs, the total concentrations of DDD and DDE may exceed the DDT initial concentration [70]. Analytical techniques are targeted at the most relevant, frequently detected and well studied metabolites, while other presumed transformation products in food samples are underestimated. Moreover, when assessing health risks, the ability of a chemical to transform into more toxic products is one of the main criteria for identifying priority chemicals unintentionally present in foods [71].

In the environment, pesticides can undergo degradation, that is, metabolic degradation by microorganisms, plants and animals and abiotic degradation in chemical reactions such as hydrolysis and photodegradation. Thereof, thousands of new compounds with unknown toxicity, stability, or bioaccumulation susceptibility may be generated [72]. For example, in Russia, 12 drugs are registered for the treatment and prevention of varroaosis of honey bees, containing amitraz as active ingredient [73]. Such drugs are not approved for use in Switzerland. Amitraz degrades very quickly, and three major degradation products identified are N-(2,4-dimethylphenyl)-N-methylformamide, N-(2,4-dimethylphenyl)-formamide, and 2,4-dimethylaniline [74]. In particular, (+)-trans-chrysanthemum acid (the main metabolite of λ -cyhalothrin), 2-hydroxy-4-methoxybenzophenone (a metabolite of deltamethrin), methylmethoxylic acid (a metabolite of metalaxyl), and 3-phenoxybenzoic acid (metabolite of λ -cyhalothrin and deltamethrin) were detected in crops treated with pesticides [72]. 2,4-Dimethylaniline is highly toxic to aquatic organisms [75]. Some neo-nicotinoid metabolites have also been found to exhibit toxicity equivalent to or greater than that of the parent compound [76, 77].

HPLC–MS/MS is primarily suitable for targeted analysis because the spectral information is relevant only for analytes within the scope of a particular technique. Non-targeted analysis detects compounds not identified in a targeted study. Untargeted analysis by HPLC–MS/MS is only possible if the number of analytes is small. The combination of chromatographic separation with HRMS is a better tool for a non-targeted approach, as it provides a complete mass spectrum with m/z peaks for all analytes in the sample. Developed “untargeted search” techniques allow simultaneous targeted and untargeted analysis of samples to identify both pesticides and their metabolites [72, 78-81].

Sample preparation is the most important and limiting stage of analysis when quantifying pesticides and their metabolites due to the differences in physicochemical properties of the substances. The least labor-intensive procedure for complex matrices (plant and livestock products, soil) remains the QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe) dispersive solid-phase extraction method [19, 23, 42, 69, 82]. In addition, analytical tasks, for example, monitoring a specific object such as water, air, soil, food raw materials or finished food products, risk assessment, control of wastewater treatment plants, toxicological examination, arbitration analysis to confirm a previous semi-quantitative result, determine the methods for preparing samples and their examination [14, 23, 66, 83, 84]. Screening methods are useful for a large set of routine samples, but detection of a pesticide will require quantitative confirmation.

Due to the growing need for novel pesticides with less toxicity and potential danger to farm animals and humans, various mathematical models are increasingly being used that are based on the relationship between biological activity and physicochemical properties of compounds and prediction of their toxicological parameters and effects. An example is mathematical models QSAR (quantitative structure-activity relationship, quantitative structure-property relationship). S. Hansch [36] was the first to use mathematical methods for correlation studies of the physicochemical properties of molecules and their biological activity. QSAR modeling has found widespread application in biomedical chemistry [85-87]. Models with different lipophilicity descriptors have been developed to address biological, pharmaceutical, and environmental applications [36, 88]. Most of these include lipophilicity expressed as logP. Recently, several but still very few reports were published, including in Russia, on screening and predicting the toxicity of pesticides [89-91]. A preliminary study of a non-experimental (based on previously described data) screening model for lipophilicity, water solubility, toxicity, bioavailability and mutagenicity using the example of 490 pesticides and their active ingredients revealed a satisfactory agreement (83-94%) between previously described experimental parameters and calculations using QSAR models [91].

Stability and biodegradation of chemical pesticides. The stability of pesticides in soil varies and is determined, in addition to hydrophobicity and polarity, by many factors (pH, microbial activity, humidity and temperature). The time for decomposition into non-toxic components can range from several weeks to tens of years [92]. Organochlorine pesticides are resistant to decomposition in soil, which increases their accumulation in pollen and nectar of honey plants and transfer to beekeeping products (honey, royal jelly, beebread, bee pollen), although the residual quantities may not exceed the MPL [9]. Triazole derivatives can persist in soil for one year [40]. Glyphosate (a PO pesticide) quickly loses activity, and its half-life, depending on the type of soil, is from 2 to 197 days, the typical half-life in field conditions is 47 days [93], the most up-to-date information was obtained in 2010. However, the half-life of its metabolite aminomethyl phosphonic acid (AMPA) in soil ranges from 119 to 900 days [22].

Pesticide degradation occurs through hydrolysis, photolysis, and biodegradation [24]. Biodegradation can also be affected by environmental conditions, such as soil moisture. It determines not only the ratio of bound and hydrolyzed forms of compounds, but also the diversity of soil microorganisms and their activity [17, 94, 95]. The main groups of bacteria involved in biodegradation are *Bacillus*, *Pseudomonas*, *Klebsiella*, *Actinomycetes*, *Nocardia*, *Streptomyces*, *Thermoactinomycetes*, *Micromonospora*, *Mycobacterium*, *Rhodococcus*, *Flavobacterium*, *Comamonas*, *Escherichia*, *Azotobacter* and *Alcaligenes* [95]. Generally, aerobic microbial activity increases with soil moisture until it reaches a maximum and then decreases. Low soil water content reduces microbial activity, which may promote longer sorption of pesticides and less degradation in arid regions [94].

The use of old-generation chemical pesticides which are persistent and toxic to the agroecosystem requires the effective methods for their detoxification. Among the biological methods for detoxifying pesticides in soil, the stimulation of its own microbiota is still the most accessible [4, 34]. The specialized microorganisms selected from the natural environment or bred by genetic engineering are promising in laboratory testing but can cause unpredictable environmental consequences [34, 96]. In some cases, metabolization of xenobiotics may produce more toxic intermediates [35, 36, 45].

Thus, lipophilicity determines the sorption of pesticides, their distribution and toxicity to biological systems. Excessively high lipophilicity ($\log P > 5$) entails the binding of pesticides to hydrophobic targets, resulting in non-selectivity and

higher toxicity. Lipophilic properties are considered decisive in bioaccumulation and biomagnification of pesticides in farm animals, and in further degradation of these compounds. Based on lipophilic properties, bioactivity of drugs under development may be predicted. Currently, drugs that are effective, safe for non-target organisms and easily decompose in the environment are of interest. It is also important to improve analytical methods for monitoring pesticide residues. The combination of non-target screening of pesticides and their metabolites in soil, water, animals and livestock products using UHPLC–HR-MS and QSAR modeling (for preliminary toxicity assessment) can become an effective tool for assessing the risk to animal and human health and ensuring food safety.

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