ORIGINAL ARTICLE

DERMAL ABSORPTION OF DIQUAT AND POTENTIAL OCCUPATIONAL RISK

DOI: 10.36740/WLek202007127

Tatyana O. Yastrub[1], Sergii T. Omelchuk[2], Andrii M. Yastrub[2]
[1] STATE INSTITUTION "KUNDIIEV INSTITUTE OF OCCUPATIONAL HEALTH OF THE NATIONAL ACADEMY OF MEDICAL SCIENCES OF UKRAINE", KYIV, UKRAINE
[2] HYGIENE AND ECOLOGY INSTITUTE OF BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

The aim: The toxicological-hygienic assessment of dermal absorption of diquat in terms of potential risk of its bioavailability in professional use.

Materials and methods: The object of the study was cutaneous exposure of diquat, determined in toxicological experiments of different duration (data of scientific literature) and at the stage of state testing of pesticide preparations based on diquat dibromide (data of a full-scale hygiene experiment, prognostic model of risk assessment), the technical concentrate of diquat dibromide (active substance content not less than 377 g / kg) contains relevant supplements, the content of which is regulated by the Food and Agriculture Organization.

Results and conclusions: Due to the high risk of the diquat adverse effects affecting the personnel, general public and environment, the European Union has introduced administrative decisions to forbid plant protection products containing the diquat. Fulfillment of the conditions of the Association Agreement between Ukraine and the European Union indicates the need to develop common regulations and risk assessment methods aimed at ensuring high level of protection of human health and the environment.

KEY WORDS: diquat, dermal absorption, occupational risk

Wiad Lek. 2020;73(7):1459-1464

INTRODUCTION

The research of dermal absorption (absorption through the skin) using standard experimental procedures is a mandatory step in testing of the active substance of the pesticide for its subsequent registration and application in the market of plant protection products [1-3].

Diquat is one of the pesticides with high risk of dangerous effects on health of workers, including dermal route of entry into the body. Acceptable operator exposure level (AOEL) was set at 0.0002 mg / kg bw by the European Food Safety Authority (EFSA), which is an order of magnitude lower than the acceptable daily intake (ADI) for the general public [2].

The AOEL value was justified on the basis of "no observed" NOEL level of 0.5 mg/ kg established in dog experiments while assessing chronic (within 1 year) toxicity of diquat, using an oral absorption factor of 0.04 and a coefficient of 100. This value is consistent with the results obtained in the short-term inhalation experiment in rats, based on the "No observed adverse effect concentration" (NOAEC) of 0.1 μg / l (equivalent to 0.02 mg / kg body weight) and the coefficient stock – 100 [2].

The high probability of negative effect of diquat on personnel penetrating the body through the skin is evidenced by a special mark, which was introduced when approving maximum permissible concentration (MPC) of pesticide in the working area air – 0.05 mg / m^3 as «dangerous for skin » [3].

Diquat was synthesized in the 1960s by Syngenta Crop Protection AG (Switzerland). The preparative forms such as water-soluble concentrates based on diquat dibromide, which are used for desiccation of crops of sunflower, soybean, peas, cereals, rapeseed, potatoes are registered in Ukraine [4].

Diquat is a non-selective contact herbicide and desiccant, belongs to the class of chemical compounds derived from bipyridylium. It is absorbed by leaves of the plants, spreads by the xylem and, due to its phytotoxic properties, leads to rapid drying of all green parts of the plant, thereby accelerating uniform maturation and early harvesting time in all weather conditions [5]. By mechanism or site of action on plants, bipyridylium derivatives are electron acceptors in photosystem 1 (FS1) of chloroplasts, leading to a significant increase in the content of super oxidant radicals and hydrogen peroxide, which, when reacting with each other, form a hydroxyl radical – a potential inducer of peroxidation reaction, factor of damage to membranes and destruction of photosynthetic apparatus [6].

Another representative of this class of chemical compounds is paraquat, which is prohibited for use in Ukraine and Europe due to its high toxicity (LD_{50} for experimental animals at oral admission is 30-50 mg / kg), environmental resistance, ability to cause pulmonary sclerosis and acute fatal poisoning in humans (lethal dose of paraquat for humans is 3-5 g).

Diquat is less toxic than paraquat, but mortality from poisoning can be as high as 50% [7]. Basically, poisoning is observed in the inhalation and oral routes of penetrating the body. The potential effect of diquat on personnel is

Table I. Acute toxicity of diquat and diquat of dibromide for rats

Toxicometric parameter	Indicator value	
	diquat ion [10]	diquat dibromide [11]
Acute oral toxicity, LD_{50}*, mg / kg	214 (♂), 222 (♀)**	1009 (♂), 1047 (♀)
Acute dermal toxicity, LD_{50}, mg /kg	> 424 (♂;♀)	> 2000 (♂;♀)
Acute inhalation toxicity, LC_{50}, mg / l	0,121 (♂); 0,132 (♀)	0,8 (♂); 1,09 (♀)

Note: * LD50 (LC50) – median lethal dose (concentration); ** ♂ / ♀ – males / females, respectively

Table II. In vitro dermal absorption of diquat in human and in rat

Dilution, mg / ml	Application rate, mg / cm^2	Dermal absorption rate, mcg / cm^2 / year	Absorbed dose, % (in 24 h)
Human skin			
1	0.1	0.06	1.44
5	0.5	0.18	0.86
50	5.0	0.98	0.47
Skin of rats			
1	0.1	0.23	5.52
5	0.5	1.01	4.85
50	5.0	9.55	4.58

observed at inhalation of the aerosol during spraying of plants. Irritation of the mucous membranes of the eyes, nose, and upper respiratory tract is possible; acute poisoning can lead to serious lung disorders. However, due to its low volatility (vapor pressure <10-8 kPa at 25 °C), its flow into the working zone in dangerous concentrations is restricted [2]. Oral poisoning is more common than inhalation. The symptoms of intoxication are nausea, vomiting, chest pain, development of cardiogenic shock, toxic effects on the liver and kidneys. The lethal dose of diquat dibromide for humans is 6-12 g. Deaths after swallowing 20 ml and 50 ml of Reglon (diquat dibromide, 200 g / l) have been reported [8].

Diquat and its preparations have a mild irritant effect on the skin and mucous membranes of the eyes. Prolonged single or multiple exposures with concentrated solutions of diquat led to severe skin and nail damage in personnel [9]. The high prooxidant activity of diquat, which leads to a cytotoxic effect, makes it potentially dangerous when penetrating through the skin.

THE AIM

The toxicological-hygienic assessment of dermal absorption of diquat in terms of potential risk of its bioavailability in professional use.

MATERIALS AND METHODS

The object of the study was cutaneous exposure of diquat, determined in toxicological experiments of different duration (data of scientific literature) and at the stage of state testing of pesticide preparations based on diquat dibromide (data of a full-scale hygiene experiment, prognostic model of risk assessment).

The methods of expert-analytical study of scientific information on the toxicological properties of diquat, its bioavailability at transdermal admission to the body; and the prognostic model of determination of dermal absorbed dose of diquat for the assessment of the risk of adverse effects on employees are used in the work.

The technical concentrate of diquat dibromide (active substance content not less than 377 g / kg) contains relevant supplements, the content of which is regulated by the Food and Agriculture Organization (FAO), namely: 2,2'-bipyridyl (exhibits mutagenic and teratogenic activity) – not more than 0.75 g / kg, ethylenedibromide (genotoxic action, carcinogenic activity) – not more than 0.01 g / kg, total terpyridine (high toxicity) – not more than 0.001 g / kg.

RESULTS AND DISCUSSION

The toxicological profile of diquat and diquat dibromide is widely reported in the scientific literature [10,11]. The parameters of acute toxicity to rats with different routes of exposure are shown in table I.

As can be seen from the data table, the substance of toxicity is diquat ion. Clinical pattern of laboratory animals acute poisoning is characterized by decrease in motor activity, impaired coordination of movements, with introduction of lethal doses – hypersalivation, hemorrhagic discharge from the eyes and nose, difficult breathing, death of animals occurs on the 3rd -7th days associated with pulmonary

insufficiency. The toxic effect is manifested in changes in the redox enzymes activity, an increase in the number of erythrocytes, leukocytes and reticulocytes, hemoglobin content and sulfhydryl groups of whole blood [10].

In the mode of short-term and long-term exposures, hepatotoxic, nephrotoxic and cataractogenic effects are the main ones in the toxic action of diquat.

The cumulative properties of the diquat are not expressed. The plasma half-life period is 4 hours; more than 90% of the absorbed dose is excreted in urine and bile during 96 hours. The highest content of diquat is in the kidneys, gastrointestinal tract, lungs, and liver, in small amounts it is found in the lens [2].

The absorption of diquat at low concentrations penetration is negligible and it is: in the gastrointestinal tract – 4%, through the skin – 1-2%. The effect of high concentrations, which can exert local irritant effect, increases the degree of absorption. Absorption of diquat from the lungs is more effective (about 70% of the respiratory fraction of the aerosol particles), which results in its high inhalation toxicity.

The literature provides data on the study of penetration of diquat through the skin in vitro using diffusion chambers and isolated skin of rats and humans; and in vivo – studies in rats and volunteers [2,10,12-14].

In studies conducted by Scott R.C. and Corrigan M.A. (1990) using diffusion chambers, diquat was applied to human and rat skin in a volume of 0.1 ml / cm^2 at various concentrations: 1 mg / ml, 5 mg / ml and 50 mg / ml (skin scraps were taken after death) from the abdomen and the dorsal part of the rat body). A measured volume of 0.9% saline was placed into the receptor chamber. Samples of 50 µl were taken from the receptor chamber at different time intervals and the content of the diquat was also estimated. The uptake period (delay time) was about two hours for rat skin and 15 hours for human skin [12, 13]. A steady state absorption rate was calculated for each dilution as shown in Table II.

As can be seen from the data of table 2, penetration of diquat through human skin is slower, and the percentage of absorbed dose increases towards less concentrated solutions. The total absorption of diquat through human skin at 24 hours was (0.47-1.44)%, through the skin of rats – (4.58-5.52)% of the exposure dose.

According to other data [2,10] dermal absorption of diquat through human skin (in vitro data) from concentrated aqueous solutions of preparative forms (diquat content of dibromide – 200 g / l) was (0.2-0.5)%, from diluted solutions (1 + 100 dilution; 1 + 200 and 1 + 250) – 0.5%, 2% and 8%, respectively.

Dermal absorption of diquat in vivo was investigated in rats with single application of 0.05% aqueous solutions of skin; 0.5; and 5.0 mg of ^{14}C-diquat (skin exposure – 24 hours). After 24 hours, systemic absorption of diquat was found to be 2.5%, 2.1%, and 3.4% of the applied dose, respectively [10].

In studies conducted by Feldmann R.J. and Maibach H.I. (1974) on human volunteers, single diquat was applied to the forearm area in the amount of 4 mg / cm^2 [14]. Urine specimens were collected for 5 days (at 4 and 12 hour intervals on the first day and every 24 hours in the following days) and analyzed for the content of diquat. The total excretion of diquat with urine was 0.3 ± 0.1% of the applied dose, which indicates the bioavailability of diquat when it gets on the skin. When assessing the parameters that affect absorption, it was noted that occlusion increases absorption 3.5 times (up to 1.4%), and damaged skin – 9.5 times (up to 3.8%).

Diquat penetrates cell membranes, mainly due to diffusion, which is known to be facilitated with the ability of the substance to dissolve in lipid and aqueous phases. Diquat, as a highly charged cation, is practically insoluble in the lipid phase (partition coefficient in the n-octanol / water system: $\log K_{o/w} = -3.45$ at 22 ° C) [2], and therefore it penetrates slowly through membranes. Binding to the anionic sites of different substrates also limits its systemic bioavailability. However, the ability of diquat to activate free radical lipid peroxidation (LPO) causes damage to biological membranes and cell death, which form a barrier to the entry of toxicants into the body (alveoli, mucous membrane of the gastrointestinal tract).

The bioavailability and systemic toxicity of diquat at its long cutaneous exposures is confirmed by the results of toxicological studies obtained in the subacute studies of rats and rabbits [13].

When the authors applied to the skin of Sprague-Dawley rats (12 animals in each group) diquat dibromide (20.64% diquat-ion) at doses of 5, 20, 40, 80 mg-ion / kg bw for 21 days, systemic toxic effects included mortality in groups of animals treated with 20, 40, and 80 mg-ion / kg bw (1/12, 5/12, and 11/12) starting at 18, 8, and 6 days, respectively. Changes in hematological and biochemical parameters associated with dehydration and malnutrition, impaired renal, hepatic and cardiac function have been found in the maximum dose surviving animal. Local manifestations of diarrhea occurred in all experimental groups and included skin irritation (erythema, edema, atony, desquamation) and tissue destruction (necrosis, scab). The frequency and severity of these effects were directly proportional to the dose applied. NOEL for systemic effects made up 5 mg-ion / kg bw, NOEL for local effects hasn't been not established.

In experiments with rabbits (10 animals in each group), when we applied to the skin diquat dibromide at doses of 3.1; 6.3; 12.5 and 25 mg / kg bw, animal mortality was observed in all experimental groups within 20 days: at the highest dose, mortality was 100% (first death was recorded on day 4), at a dose of 12.5 mg / kg – 90% (first death on day 3), dose of 6.3 mg / kg – 20% (first death at day 7), dose of 3.1 mg / kg – 10% (death reported at day 10). The manifestations of systemic effects, the intensity of which depended on the dose applied to the skin, were ulcers of the gastric mucosa, degenerative changes in the convoluted tubules of the kidneys, bleeding in the thymus, plethora of the lungs. The locally marked redness and swelling of the skin were noted as well as with the highest dose introduced – large areas of epidermis necrosis. No invalid level was found during the exploratory study of diquat.

Table III. Estimation of dermal exposure by diquat

Indicator	Value		
Production cycle: mixing / filling (preparation of working solutions)			
Container size / neck tube diameter, l / mm	10 / 45		
The contamination level of the skin (of the hands) during work, ml	0.1		
The consumption rate of the drug, l / ha	2.5		
The maximum cultivated area, ha	50 ra		
Number of work operations per shift	13		
The contamination level of the skin (of the hands) per shift, ml / day	1.3		
Use of personal protective equipment	gloves		
Transfer to skin,%	5		
Dermal exposure to the drug, ml / day	0.065		
Production cycle: Desiccation with a barrel sprayer with hydraulic nozzles			
The flow rate of working fluid, l / ha	300		
The level of contamination by the working solution, ml / h	10		
Distribution of pollution by localization (%)	D_{hand} (65)	D_{body} (10)	D_{leg} (25)
Use of personal protective equipment	gloves	uniform	working shoes
Transfer to skin,%	10	5	15
Dermal exposure to working solution, ml / h	0.65	0.05	0.375
Total dermal exposure to working solution, ml / day	6.45		

Table IV. Assessment of skin-absorbed dose of diquat

Indicator	Production cycle	
	Mixing / filling	Desiccation
Dermal exposure to the drug and working solution, ml / day	0.065	6.45
The concentration of diquat in the preparation and working solution, mg / ml	200	1.667
Dermal exposure to diquat, mg / day	13	10.75
Dermal absorption of diquat,%	0.5	8
Skin absorbed dose, mg / day	0.065	0.86
Total absorbed dose, mg / kg bw / day	0.0154	

Thus, the results of the study of subacute dermal toxicity of diquat confirm its ability to exhibit a cytotoxic effect, thereby increasing the bioavailability and skin-resorptive toxicity.

Simple calculations using the oral absorption factor of 0.04 [2] for diquat give reason to claim that the dose of the toxicant that entered the bloodstream and caused the death of 50% of laboratory animals is 8.56 mg / kg (4% of a single dose of 214 mg / kg administered to rats). When applied on the skin of rats in the subcutaneous experiment mode, a dose of 40 mg / kg, starting from the 8th day of the experiment, resulted in the death of almost half of the experimental animals (42%) that is the total dose of diquat absorbed through the skin under these experimental conditions was 7 mg / kg.

To sum up, it is especially important to emphasize the repeated impact. Despite the moderate risk of single skin application, repeated and prolonged, low-dose cutaneous exposures occurring under real pesticide conditions can impair skin barrier function and increase the risk of skin resorption.

The confirmation of this conclusion was expressed in the working studies under the real agricultural modeled situations [15]. To predict and quantify the occupational risk of dermal exposure to diquat, which the operator may experience during mixing / filling (preparation of working solutions) and plant spraying phases, we determined cutaneous exposure doses and dermal absorption values using the main predictive exposure provisions [16].

The calculation was performed for a typical formulation on the basis of diquat dibromide: soluble concentrate, the content of diquat dibromide in the formulation – 200 g / l, the consumption rate of the drug – 2.5 l / ha, the size of the container – 10 l, the diameter of the neck of the container – 45 mm.

According to [2], the AOEL of diquat is 0.0002 mg / kg, dermal absorption from concentrated formulation solutions – 0.5%, from dilute aqueous solutions – 8% (dilution 1 + 250).

Estimated values of dermal exposure to diquat at different stages of production of the pesticide are shown in table III.

The calculations showed that if personal protective equipment is used, the predicted cutaneous exposure dose of diquat for a shift (6 hours) will be: 0.065 ml at the mixing / filling stage (preparation of working solutions), 6.45 at the spraying (desiccation) stage of the plants, ml.

The data of the absorbed dose of diquat are shown in table IV.

As can be seen from Table 4 data, the total dose of diquat absorbed through the skin, including all production cycles, is 0.0154 mg / kg bw / day, exceeding the allowable level (AOEL) by 77 times.

The results suggest that the risk of adverse effects of diquat exerted on personnel is considered to be extremely high, even without an inhalation component, which requires appropriate management decisions to be taken to ensure high level of the human health and environment protection.

In this regard, it should be noted that such a decision has already been taken in the European Union. Thus, in accordance with the EU Regulation No 2018/1532 of 12 October 2018, the marketing authorization for an active substance of diquat has not been renewed and amendments are made to Regulation (EU) No 541/2011 on the conditions for the approval of diquat and the forbidding use of plant protective products (PPPs) with it [17].

The rationale for this decision is confirmed high risk of diquat for operators, observers and residents, which was calculated using validated risk assessment models for all pesticide use conditions. In addition, a high risk of diquat for birds was identified.

In accordance with the Art. 46 of Regulation (EU) No 1107/2009 of the European Parliament and of the Council, the Member States have time period until 4 February 2020 to cancel authorizations for plant protection products containing diquat.

In Ukraine, the decision on the registration of PPPs is made by the relevant state bodies, in compliance with the basic principles of protection against toxic effects of pesticides. The EU-Ukraine Association Agreement requires adoption of common rules and methods for risk assessment in order to preserve human health and protect the environment.

CONCLUSIONS

1. Diquat is a non-selective contact herbicide and desiccant, it belongs to the class of chemical compounds derived from bipyridylium with high pro-oxidant activity and cytotoxic effect.
2. According to the results of empirical and theoretical research of scientific information, the value of dermal absorption of diquat was estimated in various toxicological experiments. Repeated and prolonged, low-dose cutaneous exposures occurring in the actual pesticide application can impair skin barrier function, increase bioavailability and potential occupational risk of skin and resorptive action of diquat.
3. Due to the high risk of adverse effects of diquat on the personnel, general public and environment in the European Union, management decisions have been introduced to forbid the use of plant protection products based on it. The fulfillment of the conditions of the Association Agreement between Ukraine and the European Union indicates the need to develop common regulations and risk assessment methods aimed at ensuring high level of the human health and environment protection.

REFERENCES

1. Buist H., Craig P., Dewhurst I., et al. 2017. Guidance on dermal absorption. EFSA Journal. 2017;15(6):4873. https://doi.org/10.2903/j.efsa. 2017.4873
2. European Food Safety Authority. Conclusion on the peer review of the pesticide risk assessment of the active substance diquat. EFSA Journal. 2015;13(11):4308. doi:10.2903/j.efsa.2015.4308.
3. Dopustymi dozy, kontsentratsii, kilkosti ta rivni vmistu pesticidiv u silskogospodarskii syrovyni, kharchovykh produktakh, povitri robochoi zony, atmosfernomu povitri, vodi vodoimyshch, grunti: Derzhavni sanitarni pravyla ta normy DSanPiN 8.8.1.2.3.4-000-2001 [Permissible doses, concentrations, amounts and levels of pesticides in agricultural raw materials, foodstuffs, working zone air, atmospheric air, water bodies of water, soil: State sanitary rules and norms of DSanPiN 8.8.1.2.3.4-000-2001]. Resolution of the Chief State Sanitary Doctor of Ukraine of September 20, 2001 No. 137. 2001. 244 p. (in Ukrainian).
4. Rafalsky V.V. Perelik pestytsidiv i agrokhimikativ, dozvolenikh do vykorystannia v Ukraini [List of pesticides and agrochemicals authorized for use in Ukraine]. In: Rafalsky V.V., Vashchenko V.M., Tchaikovsky V.V. et al. Catalog Ministry of Ecology and Natural Resources of Ukraine. Kiev: Univest Media; 2018, 1040 p. (in Ukrainian).
5. Shvartau V.V. Gerbitsydy. Osnovy reguliatsii fitotoksychnosti ta fizyko-himichni i biologichni vlastivosti [Herbicides. Fundamentals of phytotoxicity regulation and physicochemical and biological properties: in 2 volumes]. Shvartau V.V., eds. Kiev: Logos; 2009, 1040 p. (in Ukrainian).
6. Morderer Ye.Yu. Gerbitsydy. Mekhanizmy dii ta praktyka zastosuvannia. [Herbicides. Mechanisms of action and practice of application: in vol. 1]. Morderer Ye.Yu., Merezhinskii, Yu.G., eds. Kiev: Logos; 2009. 379 p. (in Ukrainian).
7. Balan G., Prodanchuk N., Bubalo V. et al. Sostoyanie i perstpektivy antidotnoj terapii ostryh otravlenij pesticidami. [The state and prospects of antidote therapy for acute pesticide poisoning.]. Suchasni problem toksykolohiyi, kharchovoyi ta khimichnoyi bezpeky.2015; 1-2(69-70):67–76. (in Ukrainian).
8. Vanholder R., Colardyn F., Renck De J. et al. Diquat intoxication. Report of two cases and review of the literature. Am. J. Med. 1981;(70):1267–1271.
9. Clark D., Hurst E. The toxicity of diquat. Br. J. ind. Med. 1970;(27):51–55.
10. Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Diquat (addendum). 2013:177–214.
11. Diquat Dibromide. FAO Specifications and Evaluations for Agricultural Pesticides. Food and Agriculture Organization of the United Nations. 2008, 26 p. Available from: http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Specs/Diquat08.pdf. Accessed: October 10, 2019.
12. Scott R., Corrigan M. The in vitro percutaneous absorption of diquat: a species comparison. Toxic. In Vitro. 1990;4(2):137–41. doi: 10.1016/0887-2333(90)90035-r.

13. Hickox W.H., Denton J.E., Fan A.M. et al. Diguat in Drinking Water. California Public Health Goal (PHG) 2000, 25 p. Available from: https://pdfs.semanticscholar.org/7321/221eb69f007ca2e78fd82ffac12facc3f42b.pdf. Accessed: October 10, 2019.
14. Feldmann R., Maibach H. Percutaneous penetration of some pesticides and herbicides in man. Toxicol. Appl. Pharmacol. 1974;28(1):126–32. doi: 10.1016/0041-008x(74)90137-9.
15. Kirsenko V., Yastrub T., Kovalenko V. et al. Otsenka professionalnogo riska dikvata s uchetom novyh toksicologicheskych dannyh [Professional risk assessment to exposure of diquat taking into account new toxicological data]. Ukrainskyi zhurnal z problem medytsyny pratsi. 2006;(2):23–30. https://doi.org/10.33573/ujoh2006.02.023. (in Russian).
16. EFSA (European Food Safety Authority). Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products. EFSA Journal. 2014;12(10):3874, 55 p. doi:10.2903/j.efsa.2014.3874.
17. Commission Implementing Regulation (EU) 2018/1532 of 12 October 2018 concerning the non-renewal of approval of the active substance diquat, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market, and amending Commission Implementing Regulation (EU). No 540/2011. Official Journal of the European Union. 2018;(L 257):10–12. Available from: https://op.europa.eu/en/publication-detail/-/publication/46e9fcd2-d054-11e8-9424-01aa75ed71a1/language-en/format-PDF/source-114547122. Accessed: October 10, 2019.

The research was funded by the «Quantitative determination of dermal absorption in optimization of models of risk assessment of adverse effects of pesticides on workers», № state registration 0120U100753.

ORCID and contributionship:
Tatyana O. Yastrub: 0000-0002-5084-3773 [A,B,D]
Sergii T. Omelchuk: 0000-0003-3678-4241 [E,F]
Andrii M. Yastrub: 0000-0003-2674-5265 [C]

Conflict of interest:
The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Tatyana O. Yastrub
State institution "Institute of Labor Medicine named after Yu. I. Kundiev NAMS of Ukraine"
75 Saksagansky st., 01033 Kyiv, Ukraine
tel: +380442894274
e-mail: tatyanayastrub@gmail.com

Received: 18.03.2020
Accepted:19.06.2020

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article