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SCIENTIFIC JUSTIFICATION OF THE GROUP HYGIENE NORM FOR THE CLUSTER OF ALKYLBENZYLDIMETHYLAMMONIUM CHLORIDE COMPOUNDS IN THE AIR OF THE WORKING AREA

Turkina V. A., Kuzminov B. P., Alyokhina T. A.

Danylo Halytsky Lviv National University

Introduction. Poor regulation of active substances in disinfectants in Ukraine holds their legalization on the national market. Cluster approach in the hygienic regulation practice is one of the ways to address this issue.

The aim of the study is to establish group-based hygiene regulations for the benzalkonium chloride (BC) cluster.

Materials and methods of research. The subject of research is BC homologues. The research is based on the analysis of national and international scientific publications and legislative acts regarding BC toxic effects and hygienic regulations.

Results. BC is a mixture of the benzalkonium chloride compounds homologues. The homologues ratio in a mixture plays a key role in assigning CAS numbers to BC. The average lethal doses with oral administration for all BC homologues are below 500 mg/kg. BC skin and oral absorption does not exceed 10 %. BC does not affect reproductive system and does not cause neonatal development abnormalities; it has no carcinogenic and mutagenic properties. Typical adverse effects of BC are related to compound irritant activity. Pursuant to EU regulation 1907/2006, substances with similar physicochemical, toxicological and ecotoxicological properties can be considered as a cluster. The data for reference substance of the cluster make it possible to predict the impact of other substances from this group on human health and environment. In case of BC, alkyl (C12–C16) dimethylbenzylammonium chloride was chosen as the reference substance. In Ukraine, the hygienic regulation sets 0.5 mg/m^3 as occupational exposure limit for this substance. Following the clusters principle, it is advisable to introduce group hygiene regulations for all BC homologues based on alkyl (C12–C16) dimethylbenzylammonium chloride.

Conclusions. The implementation of cluster approach when developing exposure limits for chemical compounds in environmental medium makes it possible to introduce group hygienic regulations of 0.5 mg/m^3 as occupational exposure limit for all BC homologues.

Key words: alkylbenzyldimethylammonium chloride, benzalkonium chloride, hygiene norm, cluster approach, group hygienic regulations

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Introduction

Rapid growth of demand for disinfectants in recent years has aggravated the problem of regulatory and technical regulation of their safety. In Ukraine, there is an insufficient level of regulation of active substances of disinfectants and there is an infringement of the basic principles of hygienic regulation of chemicals, which consists in outstripping the rate of scientific researches on justification of hygienic standards of new compounds in comparison with the rate of introduction of these compounds into economical activity. Namely it actualizes the questions of development of scientific bases and methodical approaches of accelerated regulation of active substances of disinfectants that will allow a rather quick placing on the market and at the same time to prevent the potential negative influence on human health. One of the ways of reduction of terms of development of hygienic regulations of allowable content of substances with specific biological activity, is an introduction a cluster approach of hygienic regulation. It provides for combining into one group (cluster) with a single hygienic standard compounds with similar physico-chemical properties, toxicometric parameters and methods of transformation in the environment.

In our opinion, such an approach can reasonably be applied to alkylbenzyl dimethylammonium chloride (international non-proprietary name benzalkonium chloride (BC). BC is used is large quantities. Thus, in the State register of disinfectants of the Ministry of Health of Ukraine the share of disinfectants with BC content is 16,2–33,9 % [1], according to forecasts of marketing analysts the world market of this compound for 2021–2026 will increase in average by 0,9 % [2]. This may lead to excessive and unjustified economic costs for the development of standards of permissible levels for each of them.

The aim of the study is to analyse the available data on toxic properties of BC and the current state of the problem of its hygienic regulation worldwide and in Ukraine. To justify scientifically the accelerated hygienic regulation of compounds based on the clustering principle by the development of group hygienic regulations for representatives of BC cluster.

Materials and methods of research

The research is based on the analysis of scientific publications in MEDLINE, TOXNET, Mendeley, specialized domestic scientific publications, as well as the current international and domestic normative legal acts and guiding documents concerning the toxicological assessment and hygienic regulation of quaternary ammonium compounds, in particular B.

Results of the research and their discussion

Chemical characterization of the BC cluster. By it's chemical nature BC is a mixture of homologues of benzalkonium chloride compounds having a benzene aromatic ring and a side chain with an even number of carbon atoms from C8 to C18 (Figure). Hence, structurally BC contains a polar hydrophilic group and a lipophilic non-polar hydrocarbon radical.

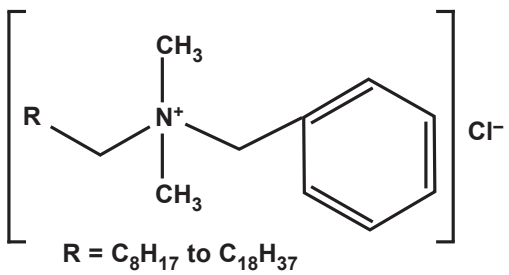

Figure. General structural formula of benzalkonium chloride

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The ratio of homologues in the mixture itself is the key to assigning CAS numbers to BC. Table 1 shows the representatives of the BC cluster.

The compounds shown in Table 1 in Annex VI of Regulation (EC) No. 1272/2008 of the European Parliament and of the Council of 16 December 2008 [4] are grouped under the general term «Quaternary ammonium compounds, C8–C18 alkylbenzyl dimethyl chlorides». The US Environmental Protection Agency has also grouped C8–C18 BC compounds [3].

It is important to note that homologues with the C12 and C14 alkyl chain lengths have high biocidal activity and, therefore, quantitatively dominate in products [5, 6].

In terms of aggregate state, all representatives of BC cluster are white crystalline powders, whose solubility in polar solvents (water) decreases, and in nonpolar ones increases with increasing molecular weight and chain length [7].

Mechanism of bioactivity of BC. For all representatives of BC, the first step of the mechanism of action is the interaction with the cell membrane. The hydrophobic carbon chains of a compound sink into the membrane bilayer, leading to a change and/or disruption of the configuration of membrane proteins responsible for catabolism and cellular transport. The cationic nature of BC provokes the displacement of divalent cations and may lead to a decrease in membrane fluidity and voiding and, consequently, to lysis and cell death. At high enough concentrations of BC, this process can occur both with the membrane of the microbial cell (pathogen) and potentially at the point of contact with the mammalian epithelial cell [8].

Biotransformation of BC compounds. Biotransformation of BC occurs in liver microsomes. NAPDH-dependent oxidative metabolism of the compound was experimentally established, but oxidation is limited to alkyl side chains [9].

Table 1

Compounds of the benzalkonium chloride cluster [3]

No.	Number CAS	Name, ratio of homologues
1	53516-76-0	Alkyl (5 % C12, 60 % C14, 30 % C16, 5 % C18) dimethylbenzylammonium chloride
2	68391-01-5	Alkyl (67 % C12, 25 % C14, 7 % C16, 1 % C18) dimethylbenzylammonium chloride
3	68424-85-1	Alkyl (40 % C12, 50 % C14, 10 % C16) dimethylbenzylammonium chloride
4	8001-54-5	Alkyl (50 % C12, 30 % C14, 17 % C16, 3 % C18) dimethylbenzylammonium chloride
5	63449-41-2	Alkyl (67 % C12, 25 % C14, 7 % C16, 1 % C8, C10, C18) dimethylbenzylammonium chloride
6	61789-71-7	Alkyl (trace amounts C8; 2,5 % C10, 61 % C12, 23 % C14, 11 % C16, 2,5 % C18) dimethylbenzylammonium chloride
7	85409-22-9	Alkyl (70 % C12, 30 % C14) dimethylbenzylammonium chloride
8	139-07-1	Alkyl (100 % C12) dimethylbenzylammonium chloride
9	139-08-2	Alkyl (C 12 (1 %) C14 (98 %) C16 (1 %) dimethylbenzylammonium chloride

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Due to the ionic nature and physicochemical properties of BC, a low absorption potential of the compound is assumed. In a study [3] it was found that cutaneous resorption of the compound does not exceed 10 % when applied in doses with no irritant effect.

On oral ingestion, 87–99 % of the administered dose was excreted in the faeces, 5–8 % in the urine and less than 1 % was found in the tissues. Radioactive analysis using the ^{14}C tag showed that 58–72 % of the detected radioactivity in faeces was the parent compound; four major metabolites formed after oxidation of the decyl side chains were also identified, which are thought to be formed with intestinal flora. In intravenous administration, 20.6–30.6 % of the administered dose of BC was found in urine, while 44.4–55.1 % in faeces, 30.2–32.7 % in muscle tissue and 3.1–3.2 % in other organs (gastrointestinal tract, heart, kidneys and liver) [3].

Toxicometric characteristics and toxic characteristics of BC. The mean lethal dose at oral intake for all BC homologues is below 500 mg/kg (Table 2). No specific target organ was found, and the main effects were related to irritant effects. Clinical signs of poisoning or death of animals were recorded when BC was administered at a dose that irritated the intestinal mucosa.

In studies of oral subchronic toxicity of BC in rats and beagles, the established NOAEL ranges from 3.7 to 188 mg/kg. Toxic effects frequently reported are decreased food intake and clinical signs associated with irritation and intestinal mucosal damage in the face of weight loss [15].

According to our experiments, the average lethal concentration for alkyl (C12–C16) dimethylbenzylammonium chloride is 510 mg/m^3, the threshold of single inhalation action is 25 mg/m^3, the zone of acute action is 20.4 mg/m^3 [16].

In a study of subchronic inhalation exposure to BC in rats, irritation of the nasal cavity and upper lungs was observed. In addition, the parasympathetic nerve reacted to irritation, resulting in nasal secretions, wheezing and deep breathing, weight loss due to decreased feed intake. These changes caused a shift in blood biochemical homeostasis and haematological parameters, which gradually returned to reference values during the recovery period. According to the results of the experiment, the NOAEL value is below 0.8 mg/m^3 [17]. BC at 30 mg/m^3 (exposure once and for 3 days, 6 h/day) induced a strong inflammatory and irritant response in the lungs, in particular, it stimulated IL-6 and IgE synthesis and decreased CC16 concentration, statistically significant increase of lactate dehydrogenase activity and blood-brain protein intake into bronchoalveolar lavage [18, 19].

The compound under conditions of inhalation experiment showed non-selective irritant effect and hepatotoxic effect at threshold concentrations. Chronic poisoning in white rats at concentrations of 5–10 mg/m^3 was accompanied by an increase in plasma alanine aminotransferase and aspartate aminotransferase levels in experimental animals in comparison with those in control group animals, a statistically probable increase in serum cholesterol level was observed.

S. Kim et al. showed under *in vitro* conditions the ability of BC to induce necrosis, apoptosis, ER-stress and EMT in lung epithelial cells in a time and concentration dependent manner [20]. It should be noted that, because BC is not volatile, inhalation exposure is only possible under aerosol conditions with a particle size not exceeding 100 μm.

As there is a strong irritant effect for BC compounds [3], setting an LD_{50} *per cut* is not considered feasible. However, according to the literature,

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Table 2

Toxicometric parameters of benzalkonium chloride compounds

Number CAS	Name	Toxicometric parameters	Source of information
53516-76-0	Alkyl (5 % C12, 60 % C14, 30 % C16, 5 % C18) dimethylbenzylammonium chloride	LD_{50} *per os* = 580 mg/kg NOEL = 516 mg/kg	[10]
68391-01-5	Alkyl (67 % C12, 25 % C14, 7 % C16, 1 % C18) dimethylbenzylammonium chloride	LD_{50} *per os* = 304,5 mg/kg LD_{50} *per cut* = 2300 mg/kg	[11]
68424-85-1	Alkyl (40 % C12, 50 % C14, 10 % C16) dimethylbenzylammonium chloride	LD_{50} *intraperitoneal* 200 mg/kg (mice) LD_{50} *per os* = 919 mg/kg (mice) LD_{50} *intraperitoneal* = 100 mg/kg (rats) LD_{50} *per os* = 426 mg/kg (rats) LD_{50} *per cut* = 2848 mg/kg	[11]
8001-54-5	Alkyl (50 % C12, 30 % C14, 17 % C16, 3 % C18) dimethylbenzylammonium chloride	LD_{50} *per os* = 240 mg/kg (rats) LD_{50} *subcutaneous* = 64 mg/kg (mice) LD_{50} *intraperitoneal* = 14,5 mg/kg (rats) LD_{50} *intravenous* = 13,9 mg/kg (rats) LD_{50} *subcutaneous* = 400 mg/kg (rats) LD_{50} *per cut* = 930 mg/kg	[11] [12]
63449-41-2	Alkyl (67 % C12, 25 % C14, 7 % C16, 1 % C8, C10, C18) dimethylbenzylammonium chloride	LD_{50} *intravenous* = 16 mg/kg (mice) LD_{50} *per os* =150 mg/kg (mice) LD_{50} *per cut* = 1420 mg/kg (rats)	[11]
61789-71-7	Alkyl (trace amounts C8, 2,5 % C10, 61 % C12, 23 % C14, 11 % C16, 2,5 % C18,) dimethylbenzylammonium chloride	Acute toxicity: not classified for acute toxicity as no data are available	
85409-22-9	Alkyl (70 % C12, 30 % C14) dimethylbenzylammonium chloride	LD_{50} *per os* = 795/585–1081/ mg/kg LD_{50} *per cut* = 3412.5 mg/kg	[13]
139-07-1	Alkyl (100 % C12) dimethylbenzylammonium chloride	LD_{50} *intraperitoneal* = 100 mg/kg (rats) LD_{50} *per os* = 400 mg/kg (rats)	[11]
139-08-2	Alkyl (1 % C12, 98 % C14, 1 % C16) dimethylbenzylammonium chloride	LD_{50} *intravenous* = 18 mg/kg (mice) LD_{50} *per os* = 426 mg/kg (rats) LD_{50} *intraperitoneal* = 100 mg/kg (rats) LD_{50} *per os* = 919 mg/kg (mice) LD_{50} *intraperitoneal* = 200 mg/kg (mice)	[14]

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certain LD_{50} *per cut* values range from 800 to 1400 mg/kg (Table 2). Aqueous solutions of BC at concentrations of 0.5 % or higher cause contact dermatitis, and with prolonged exposure or a compromised skin barrier, cause sensitization and induce allergic contact dermatitis [21].

In *in vivo* and *in vitro* experiments, BC has shown damaging effects on cornea and cultured cells. The intensity of ocular damage was found to depend on the composition of the homologues in the mixture and varies in the series C12-BC < BC mixture < C14-BC [5].

A number of Good Laboratory Practice (GLP) compliance studies have been conducted on the effects of BC on reproductive function and perinatal development in mammals. The results showed that BC does not cause gonadotoxic and embryotoxic effects and does not affect fertility [3].

A 2006 EPA report noted that BC compounds have no carcinogenic, mutagenic and genotoxic potential [3].

Substantial data on the toxic properties of BC were obtained during the registration phase of the compound. These studies were funded by registrants and conducted by independent research organisations under contract in accordance with GLP rules and procedures. A. Luz et al. [22] have published the results of many toxicological studies of quaternary ammonium compounds (QACs), including BCs, referring to evaluation by regulatory authorities. Each of these studies evaluates different endpoints for human health and the environment and is reviewed in detail by agencies independent of the various agencies (e. g. US, EU, Japan and California). The findings of A. Luz et al. results are generally consistent with the toxicological profile of BC given in this section.

Consequently, it is considered that, based on EPA regulations (40 CFR 158.2230) [23], the compilation of a database regarding the toxic properties of BC has been completed. Available studies indicate that cutaneous and oral absorption of BC does not exceed 10 %. BC has no systemic toxicity, does not affect the reproductive system and does not cause impairment of neonatal development, and has no carcinogenic and mutagenic effects. The most commonly reported adverse effects of BC are due to the irritant activity of the compound. The sensitizing potential of BC remains problematic, as epidemiological studies have been published linking exposure to consumer products containing BC to allergic skin reactions and/or asthma [22].

Epidemiological data on the adverse effects of BC. There are reports in the literature of cases of asthma associated with the use of BC-containing products [24–26].

At the same time, LaKind et al. [27], based on an analysis of data from various sources, noted that the current state of the science does not allow a proper assessment of the potential association between the effects of QAC and occupational asthma. In his opinion, methodological problems that remain unresolved include:

1) lack of quantitative impact data to determine the threshold of asthmogenicity;
2) insufficient information on whether QAC are sensitizers or act through dose-dependent irritation or some other mechanism;
3) the risk of asthma cannot be quantified.

Another important aspect of uncertainty is the lack of information on which specific QAC was used. There is a lack of data to distinguish the effects of QAC from those of other chemical and biological factors in the workplace. Addressing these research questions will require additional research. Current gaps in knowledge do not allow a judgement on the ability of QAC to cause pneumotoxic effects.

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Regulatory policy on BC and the concept of clustering in the regulation of chemical compounds. According to the Resolution of the Cabinet of Ministers of Ukraine «On Approval of Procedure for State Registration (Re-registration) of Disinfectants» [28], the safety of disinfectants is implemented by compliance with the established hygienic standards for the active substances in their composition. For BC (CAS RN 68424-85-1) in Ukraine there is a hygienic regulation (MAC) in workplace air at the level of 0,5 mg/m^3 [29]. For other representatives of BC cluster there are no approved norms of permissible content in workplace air as of 2022.

In EU the regulatory policy for BCs is the prerogative of the European Commission according to the Regulation on Biocidal Products [30]. The basic principles for the regulation of compounds with a specific biological activity are laid down in the Biocidal Products Regulation Guidelines of the European Chemicals Agency (ECHA). Under European legislation biocidal products must be authorised before they can be placed on the market in EU. It is required that all active ingredients in these products have to be approved for use. Similarly to the Ukrainian legislation the first step of approval is hazard identification to determine toxic effects based on the analysis of all available information on acute and chronic toxicological properties, including data from *in vivo*, *in vitro*, *in silico* experiments and epidemiological observations [31]. Substances and products are separately registered and entered in separate registers published on the ECHA website.

Product registration can be done through a national procedure with the possibility of expanding the list of countries through a mutual recognition procedure or through a centralised procedure at EU level.

It is important to note that the EU Regulation 528/2012 prescribes a provision for the revision of registered active ingredients every seven years. This means that the active substance regulations for disinfectants are relatively constant and a review is foreseen if necessary.

In the US, the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) regulate BC. They regularly update regulations for use based on current scientific evidence, occasionally restricting the use of compounds found to be hazardous. However, final decisions may be delayed by requests from the industrial sector commercialising such products. This is precisely the situation with BC. No final decision on BC regulations has yet been taken and letters of deferral of legislative approval have been granted at the request of manufacturers. Decisions to postpone any action to regulate BC have been made on the basis of insufficient data in the literature [32]. However, many researchers have studied the safety aspects of the compound for many years, which include data on toxicity to humans and the environment, which we have reflected in the sections above.

In March 2020 the US EPA published List N: Disinfectants for use against SARS-CoV-2 [33]. As of 20 August 2020. List N numbered 482 EPA-eligible disinfectants, 81 % of which contain a single active ingredient and the remainder are a mixture of two or more components. It is important to note that among single active ingredient formulations, 48 % are QAC. In 2019, the EPA asked the US National Toxicology Program (NTP) to investigate the link between respiratory disease and worker exposure to antimicrobial active ingredients [34], as most active ingredients in disinfectants, including BC, do not have occupational exposure limits (OEL).

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G. S. Dotson et al. [35] proposes overcoming the problem of the lack of an OEL by introducing a group-based standard, in particular for QAC. Based on the toxicological screening of QAC using estimated DNELs (derived safe levels of human exposure to the chemical) derived from the following criteria: total toxicity (1), irritant activity (2) and reproductive system effects (3), the OEL values for QAC were 0.1 mg/m^3, 0.7 mg/m^3 and 0.5 mg/m^3 respectively. The authors justified this approach by the presence of a common functional group responsible for chemical class toxicity, structural and physico-chemical similarity in all QACs.

The lowest OEL value of 0.1 mg/m^3 was taken as the basis for the TWA value (time-weighted average concentration) when taking into account 8-hour working days. For short-term or acute exposure regulations, the authors refer to the recommendations of the Association of Governmental Industrial Hygienists (ACGIH): «Short-term increases in worker exposure levels may not exceed three times the TLV-TWA value of no more than 15 minutes at a time, no more than four times at 1-hour intervals during the working day and in no case shall they exceed five times the TLV-TWA value measured as the 15-minute TWA». In other words, the value of the maximum single concentration will range from 0.3–0.5 mg/m^3 for QAC.

It should be noted that the proposed guideline is intended for all TWAs, as it was assumed on the basis of limited data that each representative of QAC has the same toxicity. When sufficient data are available for an individual QAC representative to determine differences in severity (effect), a modification of the standard is envisaged. That is, there is a group standard, with the possibility of revision for individual representatives should new scientific evidence emerge regarding their adverse effects on humans.

This approach of cross-reading the adverse effects associated with a chemical through data on other chemicals causing toxicity through the same mode of action via similar structures and physico-chemical properties is presented in the Organisation for Economic Co-operation and Development (OECD) guidelines for grouping chemicals [36] and is well described in Escher et al. [37].

It is important to note that the EC regulation 1907/2006 [38] legislates the principle of grouping or «clustering» based on the European experience of substance registration. According to it, substances whose structural similarity allows for the prediction of similar physico-chemical, toxicological and ecotoxicological properties can be regarded as a cluster. Research data for the reference substance/substances in the cluster make it possible to foresee (predict) the physico-chemical properties, human health and environmental effects of other substances in this group. That is, if a substance little-studied from the standpoint of environmental and human hazard is included in a cluster, whose reference compound has a full toxicological profile and is already listed in the register, there is no need to conduct toxicological studies according to the full scheme. Accordingly, all properties and requirements for the cluster apply to the substance [38].

In summary, the concept of clustering in the justification of a group hygienic standard is widely discussed by scientists around the world, is legislated in the EU and its methodological basis is described in the OECD guidelines.

In case of BC the reference substance in toxicological dossiers of EPA and ECHA is alkyl (C12–C16) dimethylbenzylammonium chloride (CAS RN 68424-85-1), for which the greatest completeness of data on toxic properties is determined. In Ukraine

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for this substance regulations of the permissible content in workplace air by the results of acute and chronic experiments on inhalation intake were approved [16]. Guided by the principle of clusters, we can introduce group hygienic regulations in workplace air for all BC homologues at the level of 0.5 mg/m^3. This approach is supported not only by the above data, but also by the statutory changes in the «Regulations on hygienic regulation and state registration of hazardous factors» the possibility of developing temporary hygienic regulations based on available information, including information received from relevant international organizations, in case of insufficient scientific data [39].

Conclusions

In the light of harmonization of Ukrainian legislation in the field of regulation of chemical compounds with the regulations of the EU and the USA, it is relevant to implement the concept of cluster approach in the development of allowable content of chemical compounds in the environmental objects. It will accelerate the development of hygienic standards of allowable content with a significant reduction in costs, without compromising the reliability of regulations. This concept is presented by the example of benzalkonium chloride, for all its homologues irrespective of CAS number, the group hygienic regulations in workplace air is set at the level of 0.5 mg/m^3. Alkyl (C12–C16) dimethylbenzylammonium chloride (CAS RN 68424-85-1) was selected as a reference substance. A full toxicological characterization with the inhalation experiment data is available and the Regulations for the permitted content in the workplace air were approved in Ukraine.

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ORCID ID of co-authors and their contribution to preparation and writing of article:
Turkina V. A. (ORCID ID 0000-0002-0660-8485) – formulation of the idea, key aims and objectives, analytical review of the literature, drafting of the manuscript, its critical revision with the introduction of valuable intellectual comments, responsibility for all aspects of work, article, the final version of the manuscript;
Kuzminov B. P. (ORCID ID 0000-0002-8693-1046) – development of key goals and objectives, critical revision of draft manuscript with valuable intellectual comments, responsibility for all aspects of the work;
Alyokhina T. A. (ORCID ID 0000-0002-8350-9392) – responsibility for all aspects of the work, integrity of all parts of the article, final manuscript, preparation of the article for print.

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Contact person: Turkina V. A., Research Institute for Epidemiology and Hygiene, Danylo Halytsky Lviv National University, 12, Zelena str., Lviv. Tel.: + 38 0 97 967 12 15. E-mail: ver.apachi85@gmail.com