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REVIEWS, LECTURES

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THE METHOD OF READ-ACROSS AS A BASIS FOR GROUP STANDARDIZATION OF HARMFUL COMPOUNDS IN THE AIR OF THE WORKING AREA (AS EXEMPLIFIED BY DIALKYLDIMETHYLAMMONIUM CHLORIDES C_8–C_{10} HOMOLOGUES)

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Introduction. The situation of recent years during the SARS-CoV-2 pandemic has aggravated the problem of an insufficient number of approved hygienic standards of active substances included in disinfectants. This, in turn, has become a deterrent to the introduction of such agents into practice. For the proper organization of chemical safety of the workforce new methods of substantiating hygienic standards need to be developed. One of the ways to overcome the outlined higher problem, which will significantly speed up the resolution of the situation, is the introduction of read-across as an express method of substantiating the maximum permissible concentrations for a group (cluster) of compounds.

The purpose of the research is to substantiate the possibilities of developing group regulations for this cluster of compounds in the air of the working area based on data about the physicochemical and toxicological characteristics of dialkyldimethylammonium chloride C_8–C_{10} homologues.

Materials and methods of the research. Data on the physicochemical and toxicological properties of dialkyldimethylammonium chloride C_8–C_{10} homologues were taken from the ECHA home page, National Library of Medicine, U.S. Environmental Protection Agency and are in the public domain. A literature search was conducted in PubMed, Mendeley, Europe PMC databases and specialized journals of Ukraine using the terms «dialkyldimethylammonium halides», «dialkyl(C_{8-10})dimethylammonium chloride», «dioctyldimethylammonium chloride», «didecyldimethylammonium chloride» and the CAS numbers of the specified compounds.

Results. Similar chemical structure of dialkyldimethylammonium chlorides C_8–C_{10} homologues determines their similarity in terms of physicochemical and toxicological properties. All substances are solids in their aggregate state, dissolve well in water, have the ability to penetrate biological membranes and disrupt their integrity. According to parameters of acute oral toxicity, dialkyldimethylammonium chlorides C_8–C_{10} homologues belong to moderately hazardous substances – hazard class 3, do not cause systemic toxicity; the main negative manifestation of their influence is an irritating effect which further provokes signs of general toxicity. The substances do not have carcinogenic, mutagenic effects, they do not affect reproductive function. The most studied representative of the cluster is didecyldimethylammonium chloride (DC_{10}DAC), which is accepted as a standard (analogue) for all dialkyldimethylammonium chlorides C_8–C_{10} homologues. In Ukraine a temporary hygienic standard for didecyldimethylammonium chloride in the air of the working area (approximately safe exposure level, ASEL) has been approved at the level of 0.2 mg/m^3, where the limiting criteria for harmfulness are pronounced irritating effect on the skin and mucous membranes of the eyes and an acute inhalation effect. The calculation standard for quaternary ammonium compounds proposed by G. S. Dotson et al. is 0.1 mg/m^3. Both standards belong to the II class of safety.

Conclusions. The read-across method allows for *accepting didecyldimethylammonium chloride (DC_{10}DAC) as a standard (analogue) for all dialkyldimethylammonium chlorides C_8–C_{10} homologues*. The hygienic regulation of the

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permissible content of *didecyldimethylammonium chloride* obtained on the basis of additional experimental studies as a result of the application of the cluster approach will be legitimate for *dioctyldimethylammonium chloride* (DC_8DAC); octyldecyldimethylammonium chloride ($DC_{8-10}DAC$), didecyldimethylammonium chloride ($DC_{10}DAC$) and their mixtures with different percentage ratios.

Key words: dialkyldimethylammonium chloride C_8–C_{10} homologues, dialkyl(C_8–C_{10})dimethylammonium chloride, dioctyldimethylammonium chloride, didecyldimethylammonium chloride, read-across, hygienic standard, cluster approach, group hygienic regulation

Introduction

Dialkyldimethylammonium halides are a common type of quaternary ammonium compounds (QAC), which are the active ingredient in insecticidal, algicidal, bactericidal and fungicidal agents. Compounds with the length of C_8–C_{10} carbon chains are the most active in relation to the microbial association of microorganisms among dialkyl QAC and, therefore, the most popular among them are dioctyldimethylammonium chloride (DC_8DAC); octyldecyldimethylammonium chloride ($DC_{8-10}DAC$), didecyldimethylammonium chloride ($DC_{10}DAC$) and a mixture with different percentages of discrete chemicals with two alkyl chains with 8 or 10 carbon atoms [1].

The pandemic situation of recent years has led to a significant increase in the use of disinfectants, in particular based on dialkyldimethylammonium halides [2]. At the same time there no legally established hygienic regulations regarding maximum permissible concentrations (MPC) for these compounds in the air of the working area in Ukraine, which is a restraining factor for their legitimate use in the composition of disinfectants. The implementation of read-across as an express method of justifying hygiene regulations for a group (cluster) of compounds will allow to significantly speed up the resolution of the situation that has arisen.

Read-across allows, based on the information about the chemical structure, to identify well-studied substances (analogues) from the point of view of toxicology, which are further used to predict the toxicity of similar new chemicals and to group chemicals in order to assess their toxicity as a whole (cluster). This makes it possible to further justify the normatively accepted safety criteria of substances for which no toxicological tests were conducted, provided there are grounds for including them in a certain cluster. Confirming that a chemical belongs to a cluster or is similar to another chemical (called analogue validity) is one of the key aspects of performing read-across. The method begins with the analysis of the similarity of the structure, physicochemical properties, toxicokinetics and toxicodynamics of the target and resulting compounds. It is believed that the comparability of these parameters determines similar dangers for a human [3].

The guidelines of the Organization for Economic Co-operation and Development (OECD) on the grouping of chemical compounds into clusters were published in 2007 [4], a few months later the European Chemicals Agency (ECHA) published the document «R6 QSARs and Grouping of Chemicals», which is almost identical to the OECD guidelines [5]. Prerequisites for the application of the read-across approach are defined by the European Chemicals Agency in the document «Read-across Assessment System» (RAAF) [6].

In Ukraine this approach is not implemented at the legislative level and is practically not used. Although there are examples of implementation of the principle of group hygienic regulation of inorganic compounds in the air of the working area [7]. In a preceding publication, we extensively rationalized the airborne

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standard for a benzalkonium chloride compound cluster through the utilization of a read-across approach [8]. Employing a similar methodology to establish the hygienic regulation standards for admissible concentrations of dialkyldimethylammonium chloride homologs (C_8–C_{10}) as a group (cluster) would also be deemed feasible and judicious in our assessment.

The purpose of the research – the objective of this research is to comprehensively analyze the existing data pertaining to the physicochemical and toxicological attributes of dialkyldimethylammonium chloride (C_8–C_{10}) homologues for further justification of the possibility of developing group regulations for this cluster of compounds in the air of the working area.

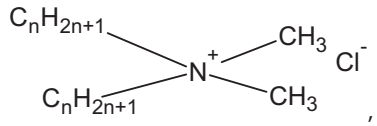
Materials and methods of the research

Data on the physicochemical and toxicological properties of dialkyldimethylammonium chloride C_8–C_{10} homologues were taken from the ECHA home page, National Library of Medicine, U.S. Environmental Protection Agency and are in the public domain.

A literature search was conducted in PubMed, Mendeley, Europe PMC databases and specialized journals of Ukraine using the terms «dialkyldimethylammonium halides», «dialkyl(C_{8-10}) dimethylammonium chloride», «dioctyldimethylammonium chloride», «didecyldimethylammonium chloride» and the CAS numbers of the specified compounds.

Results of research and their discussion

The structure of dialkyldimethylammonium chloride C_8–C_{10} homologues is characterized by the presence of a positively charged nitrogen covalently bonded to two alkyl and two methyl substituents and an anionic counterion (chloride) (Figure).



where n = 8 ÷10

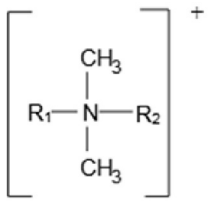
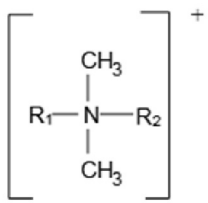
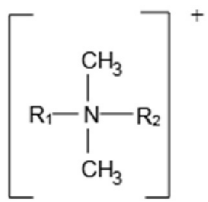
Figure. General structural formula of the dimethyldialkylammonium chloride cluster

Quaternary nitrogen constitutes the hydrophilic part and determines the ability of the compound to interact with polar environments and is responsible for solubility in water. The alkyl chain forms a hydrophobic part capable of penetrating non-polar agglomerates [9].

Similar chemical structure of dialkyldimethylammonium chloride C_8–C_{10} homologues determines their similarity in terms of physical and chemical properties (Table). All the mentioned compounds are solids by their aggregate state, have low vapour pressure and are non-volatile, they are well soluble in water under normal conditions and are photostable. It is important to note that the feature of the industrial synthesis of compounds of the dialkyldimethylammonium chloride C_8–C_{10} cluster determines that the active ingredients of the technical level are a composition of homologues [10]. It is also noted that during the production of these compounds, a «technical product» is first obtained, which is a 50 % or 80 % solution. In order to carry out specific scientific research, recrystallization and drying of commercial forms of these substances are performed [11]. The latter complicates the comparative analysis of the physicochemical properties of the compounds, as information for commercial products is often provided in various databases without indicating their purity.

Table

Physicochemical characteristics of dialkyldimethylammonium chloride homologues

Indicator	Name and CAS number			
	Dioctyldimethylammonium chloride (CAS 5538-94-3) [18]	**Octyldecyldimethylammonium chloride (CAS 32426-11-2) [20]**	**Didecyldimethylammonium chloride (CAS 7173-51-5) [22]**	**N,N-dialkyl(C_8–C_{10})-N,N-dimethyl ammonium chloride (CAS 68424-95-3) [25]**
Molecular weight	305.97 [18]	334.0 [20]	362.08 [22]	521.8 [25]
Molecular formula	$C_{18}H_{40}ClN$ [18]	$C_{20}H_{44}ClN$ [20]	$C_{22}H_{48}$ ClN [22]	Multicomponent substance
Structural formula	 $R_1 = C_8$ $R_2 = C_8$ [18]	 $R_1 = C_8$ $R_2 = C_{10}$ [20]	 $R_1 = C_{10}$ $R_2 = C_{10}$ [22]	Mixture of discrete chemical compounds with two alkyl chains of 8 to 10 carbon atoms. [25]
Steam pressure	0.001 Pa at 20 °C [18]	No data available	0.006 Pa at 25 °C [22]	< 0.00005 Pa at 25 °C [25]
LogKow	1.57 [19]	2.03 [21]	3.26 [23]	No data available
Solubility	In water: 250 mg/l at 25 °C [19]	No data available	In water: 390 mg/l at 25 °C [22]	No data available
Critical concentration for micelle formation	$2.83 \cdot 10^{-2}$ M [14]	No data available	1.50 ± 0.08 mM for 80 % water-ethanol solution [24]	No data available

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The most active representative of the cluster, didecyldimethylammonium chloride ($DC_{10}DAC$), in the vast majority of scientific literature is accepted as a standard (analogue) for all dialkyldimethylammonium chloride C_8-C_{10} homologues [12]. The activity of chemicals in a group containing a limited number of homologues is determined experimentally or theoretically using descriptors (identifiers) taking into account the correlation between activity and the value of the identifier. That is, if the value of descriptors (identifiers) is known, the activity of compounds can be reasonably predicted [13]. From this point of view, it is worth analysing the most significant descriptors of $DC_{10}DAC$ homologues.

The most significant characteristic from the point of view of predicting the biological activity of surfactants is the critical concentration for micelle formation (CCM) – the concentration range above which most of any surfactant, due to its amphiphilic nature (diphilicity), appears in solution in micellar form [14]. It has been proven that any amphiphiles show the highest antimicrobial effect, regardless of the strain of the microorganism, as well as toxic effects in the range of CCM [15]. This is explained by the fact that molecules due to the optimal cationic-hydrophobic balance at such a concentration are able to dissolve the components of the hydrophobic membrane [16].

In research of Mozrzymas, Anna [13] showed that the structure and nature of the head group influence the value of CCM of cationic surfactants. Since all representatives of the analysed cluster have the same main group, this indicator in the homologous series does not have a significant difference.

Analysis of the irritant activity of 19 cationic surfactants using the neural network method showed a relationship between the intensity of the irritant action and the concentration, logP (log [octanol/water partition coefficient]) and log CCM [17]. Molecules with intermediate logP values (from 0 to 5) easily cross membranes. In the dialkyldimethylammonium chloride C_8-C_{10} family, as the length of the alkyl chain of the molecule increases, the value of logKow increases, but its value does not exceed the limits characteristic of the substances with a high resorption potential (Table). Therefore, all compounds of the cluster have the ability to penetrate biological membranes and disrupt their integrity.

Metabolism and mechanism of action

The metabolism of $DC_{10}DAC$, as a standard (analogue) for all homologues of dialkyldimethylammonium chloride C_8-C_{10}, is summarized by A. Luz et al. [12]. The dose and duration of exposure with a single oral administration of the compound does not affect its toxicokinetics. It is poorly absorbed when taken orally, and 89–99 % of the administered dose is excreted in faeces unchanged or as metabolites within 3 days after entering. Four oxidative metabolites of $DC_{10}DAC$ were identified, with oxidation limited to the side chains of the parent compound. $DC_{10}DAC$ or its metabolic products were found in the urine.

At the same time Terry C. Hrubec et al. [24] believes that the removal of a significant amount of QAC with faeces does not indicate their low adsorption. In particular, approximately 40 % of faecally excreted $DC_{10}DAC$ were oxidized metabolites, which may actually reflect substantial intestinal absorption followed by hepatic conversion and biliary excretion back into the faeces [26].

Percutaneous absorption of $DC_{10}DAC$ does not exceed 10 % when exposed in non-corrosive doses [22].

The toxic dynamics of compounds of the dialkyldimethylammonium chloride C_8-C_{10} cluster is

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associated in the scientific literature with their cytotoxic activity. Damage to the cellular structure by these compounds is well studied in the researches of the mechanism of their biocidal activity. At low concentrations QAC monomers attach to the cell surface due to electrostatic interaction and can affect the curvature of the lipid bilayer, surface charge, etc. This provokes a change in the function of membrane proteins without gross destruction of the membrane. At higher concentrations the Ca^{2+} cation, which stabilizes the bacterial membrane, is replaced by the positive charge of cationic QAC, closer to the CCM, which allows the hydrophobic alkyl chain to be embedded in the phospholipid layer. This causes the loss of membrane fluidity and its segmentation into clusters, which then fall from the phospholipid bilayer into the aqueous medium, which leads to cell death. The interaction of QAC with intracellular proteins and nucleic acids was also reported [9, 16].

It is believed that according to this mechanism, QAC acts on the epithelial cells of the eye, skin, lungs or stomach of mammals. Membrane integrity changes under the influence of concentrations of $DC_{10}DAC$ approximately 3 mg/cm^3 and higher [27].

At the same time it is noted in the scientific literature that the effect of cationic QAC on prokaryotic and eukaryotic cells cannot be equated. The cell wall of bacteria is characterized by the presence of a peptidoglycan layer in contrast to the presence of cholesterol and unbranched phospholipid chains in the membrane of eukaryotic cells. Bacterial membrane integrity is maintained by hydrophobic and electrostatic interactions, while mammalian cells take advantage of membrane phase separation and hydrophobic interactions. The eukaryotic cell membrane is also less positively charged due to a relatively low percentage of negatively charged lipids [9]. In our view, these differences may influence the threshold levels of exposure, but not its overall mechanism. Furthermore, double-chain QAC was found inside the mitochondria of eukaryotic cells. Cationic QAC is the only group among surfactants for which cytotoxicity was detected at concentrations that do not cause cell lysis. Mitochondrial dysfunction was noted even at sublethal concentrations. In vitro experiments have demonstrated that pre-apoptotic signalling occurs at low doses of QAC, whereas high levels rapidly deplete ATP and cause necrotic cell death. When the concentration in the cell approaches the CCM, the surface-active effect of QAC prevails and leads to cell lysis. Cell death by apoptosis can lead to inflammation, but most likely to a lesser extent than by necrosis. Cell damage at low levels of exposure leads to inflammation that is reversible and ceases below a certain dose. This mechanism is inherent in both the effect on the respiratory epithelium and the epithelial cells of the gastrointestinal tract [27].

Toxicological effects and nature of biological action

Dialkyldimethylammonium chloride C_8-C_{10} homologues have similar hazard profiles: they do not cause systemic toxicity and mainly cause local effects.

According to the parameters of acute oral toxicity, $DC_{10}DAC$ and DC_8DAC belong to moderately hazardous substances – hazard class 3 (LD_{50} is 329 mg/kg and 238 mg/kg, respectively). A macroscopic examination of the internal organs revealed irritation of the intestinal mucosa, haemorrhages in the glandular part of the stomach, and a change in the colour of the contents of the stomach and intestines [18, 22].

The main negative effect of dialkyldimethylammonium chloride C_8-C_{10} homologues when

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inhaled is a dose-dependent inflammatory reaction of tissues [28]. Loss of airway cell membrane integrity in vivo upon administration of $DC_{10}DAC$ promotes increased vascular permeability and protein leakage, leading to the induction of oxidative damage. Proinflammatory signalling caused by cell death leads to increased numbers of polymorphonuclear cells and macrophages in bronchoalveolar lavage fluid [27].

In case of percutaneous contact the negative effect of $DC_{10}DAC$ is realized through local tissue damage in the form of swelling, redness, erythema and necrosis, which subsequently determines the occurrence and development of general toxic effects in the animal body. The average lethal dose when applied to the skin for rats exceeds 2000 mg/kg [49, 22].

Under the conditions of subchronic and chronic toxicological experiments a clear pattern of toxic manifestations under the influence of $DC_{10}DAC$ is observed. Initially, local reactions occur, which are later replaced by signs of general toxicity [12, 27].

It was found that the minimum dose of $DC_{10}DAC$, which causes signs of systemic toxicity when applied to the skin, is 6 times higher than the local toxicity dose [10]. Therefore, skin irritation is a threshold effect regardless of exposure time.

The results of the Draize test indicate a pronounced irritating effect of 0.1–0.5 % $DC_{10}DAC$ solution on mucous membranes [22].

In general, representatives of amphiphilic detergents are recognized as potential immunotoxicants [29]. The literature provides data on hypersensitivity reactions after occupational exposure to $DC_{10}DAC$ both by percutaneous and inhalation contact [30]. The Association of Occupational and Environmental Clinics (AOEC) lists this compound among asthmogens and respiratory sensitizers [31].

An excellent analytical work by Peyneau Marine et al. [30] presented retrospective data for QAC in terms of manifestations of their allergenicity, summarized existing hypotheses in the scientific literature regarding the mechanisms of such manifestations. It is noted that it is difficult to distinguish between irritating and sensitizing properties, because clinically they are very similar. Usually sensitizers are agents with a high molecular weight (> 10 kDa) and only allergens are able to activate adaptive immunity (especially CD8+ T cells). On the contrary, irritants cause damage to keratinocytes, followed by rapid tissue renewal. According to this theory, QACs, which are low molecular weight agents, should act as haptens, i. e., bind to proteins to induce the sensitization step. However, direct peptide reactivity assay (DPRA) showed that $DC_{10}DAC$ did not bind to any peptides. The authors present the results of research by Anderson et al., in which they studied the sensitization potential of $DC_{10}DAC$ (at concentrations of 0.0625–1 %) by the method of local lymph node assay (LLNA). A dose-dependent increase in lymphocyte proliferation and a significant increase in the number of activated CD44+ CD4+ and CD8+ T-cells and CD86+ B-cells and dendritic cells were revealed. Thus, $DC_{10}DAC$ was classified as a skin sensitizer. Regarding the asthmagenicity of QAC the authors note that they induce asthma on first contact, which is contrary to the sensitization required for IgE-dependent asthma. Furthermore, a number of studies have shown that QAC is not a specific inducer of IgE.

The statement that the main mechanism of negative effects in the case of inhalation intake of QAC is cytotoxicity was confirmed by in vitro experiments. The effect of QAC on muscarinic receptors in peripheral and central nervous receptors, and the subsequent release of histamine in mast cells of

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rodents has a minor contribution to pathological manifestations. Histamine H_1-receptor antagonists cause only a slight decrease in histamine release, which indicates the secondary nature of this path of the pathological process [27].

For homologues of the dialkyldimethylammonium chloride C_8-C_{10} family no carcinogenic or mutagenic effects were found [12], no effects on reproductive function [32].

Justification of the regulation of the permissible content in the air of the working zone of dialkyl(C_8-C_{10})dimethylammonium chloride homologues cluster

Hence, based on the nature of their impact, the dialkyldimethylammonium chloride C_8-C_{10} homologues can be categorized as substances exerting a selective irritating effect.

Regardless of the route of exposure, the compounds disrupt cell membranes, which can lead to cell irritation or lysis. This is consistent with the reversibility of irritation and subsequent effects from low doses of $DC_{10}DAC$ with oral or inhalation exposure. Inflammatory processes are balanced by anti-inflammatory processes and the mechanism of cell recovery [27]. Clinical and histopathological observations showed mucus formation after inhalation of $DC_{10}DAC$, which is characteristic of inhaled stimuli as inducers of mucus secretion [27]. Within the realm of Ukrainian toxicology, the standardization of inhalation irritants adheres to toxicometric parameters governing acute inhalation effects. These parameters encompass the average lethal concentration, the threshold for an irritating effect, and the zone wherein this irritation is manifested. This approach is founded on scientifically proven facts that for the initiation of sensory irritation, the leading part in the toxic dynamics of compounds belongs to the concentration and minimum duration of exposure [33]. After all, short-term and long-term exposure to small doses at the same quantitative values of dose/concentration leads to the same effect. This is consistent with empirical observations and mathematical analysis that airway irritation does not obey Haber's law [34].

According to Order of the Ministry of Health of Ukraine No. 881 dated 06/05/2021, the temporary hygienic standard of didecyldimethylammonium chloride in the air of the working area (ASEL) was approved at the level of 0.2 mg/m^3, aerosol, with a « + » mark. The developers of the standard emphasize that the limiting criteria for harmfulness are pronounced irritating effect on the skin and mucous membranes of the eyes, and an acute inhalation effect [35].

G. S. Dotson et al. [36] proposes the value of the calculated norm of quaternary ammonium compounds in the air of the working area (OEL) at the level of 0.1 mg/m^3. The author notes that exposure levels may exceed the level of 0.3 mg/m^3 for 15 minutes or less with an interval of not less than 1 hour and not more than four times during a working day; furthermore, exposure levels should not exceed 0.5 mg/m^3, in any case, when measuring the 15-minute TWA. All the above standards are within the hazard class 2 according to Order of the Ministry of Health of Ukraine No. 1596 dated 14/07/2020 [37].

Thus, the experimental establishment for $DC_{10}DAC$ of the average lethal concentration, the threshold of irritant effect and the threshold of specific allergenic effect will allow to substantiate the maximum permissible concentration of the compound in the air of the working area. This standard will be sufficiently reliable for all representatives of the dialkyldimethylammonium chloride C_8-C_{10} cluster due to their similar physicochemical properties, comparable toxicological profile and the fact that technical products are mostly a mixture of homologues.

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