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Acute inhalation toxicity of quaternary ammonium compounds

This report contains an addendum d.d. 3 juni 2024 on page 35

RIVM letter report 2023-0312
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Synopsis **New version in addendum**

Acute inhalation toxicity of quaternary ammonium compounds

Harmful or undesirable organisms may cause an area to become unsafe and unhealthy for people, animals or the environment. To control those organisms, companies and households use biocides, including biocides with quaternary ammonium compounds. These are effective against bacteria and are used as disinfectants, especially by professionals.

Biocides are not authorised until their safety and effectiveness have been tested extensively. This is to prevent any unintended harmful effects from their use. In the authorisation procedure for one specific quaternary ammonium biocide, the product was found to be potentially harmful after inhalation by humans in a particular concentration.

There are also other types of quaternary ammonium compounds that are used as biocides. For that reason, RIVM has examined whether the quaternary ammonium compounds that are used as biocides in the Netherlands can be harmful when inhaled. To that end, RIVM drew up an overview of the potential health effects upon inhalation and found that all authorised quaternary ammonium compounds have corrosive properties. This is why RIVM recommends that the packaging of these biocides should include a warning phrase indicating those properties.

The proposed text of the label is as follows: ‘corrosive to the respiratory tract’. According to European rules, this warning is compulsory for corrosive substances that can be inhaled and may not be tested on animals because of their corrosive properties.

The overview was compiled on behalf of the Ministry of Social Affairs and Employment (SZW). At present, most quaternary ammonium compounds do not come with a warning phrase. It is not known how often biocides containing these substances are used. Their concentrations in biocide products are often highly diluted, so the effects will not normally be serious. Still, RIVM recommends that the warning label be added to ensure that users are aware of the potentially harmful effect upon inhalation and handle these products safely.

Keywords: biocides, classification, inhalation toxicity, quaternary ammonium compounds, disinfection

Publiekssamenvatting **New version in addendum**

Acute inhalatietoxiciteit van quaternaire ammoniumverbindingen in biociden

Door schadelijke of ongewenste organismen kan een leefomgeving niet meer veilig en gezond zijn voor mensen, dieren of het milieu. Om deze organismen te bestrijden, gebruiken bedrijven en huishoudens biociden. Voorbeelden zijn biociden met quaternaire ammoniumstoffen. Deze werken tegen bacteriën en worden, vooral door professionals, als ontsmettingsmiddel gebruikt.

Biociden worden pas toegestaan als uitgebreid is beoordeeld of ze veilig zijn en goed werken. Dit voorkomt dat ze onbedoelde schadelijke effecten hebben. Eerder bleek bij de toelatingsprocedure van één bepaalde quaternaire ammoniumbiocide dat deze schadelijk kan zijn als mensen haar in een bepaalde hoeveelheid inademen.

Er zijn nog andere quaternaire ammoniumstoffen die als biocide worden gebruikt. Daarom heeft het RIVM uitgezocht of de quaternaire ammoniumstoffen die in Nederland als biocide worden gebruikt, schadelijk kunnen zijn als ze worden ingeademd. Hiervoor is een overzicht gemaakt van wat daarvan mogelijke gezondheidseffecten zijn. Daaruit blijkt dat alle toegelaten quaternaire ammoniumstoffen bijtende eigenschappen hebben. Het RIVM adviseert daarom hiervoor te waarschuwen op de verpakking van biocideproducten met deze stoffen.

De voorgestelde formulering is ‘bijtend voor de luchtwegen’. Deze waarschuwing is volgens Europese regels verplicht voor bijtende stoffen die kunnen worden ingeademd en die vanwege deze eigenschap niet op dieren mogen worden getest.

Dit overzicht is gemaakt op verzoek van het ministerie van Sociale Zaken en Werkgelegenheid (SZW). De meeste quaternaire ammoniumstoffen hebben nu geen waarschuwingszin. Het is niet bekend hoe vaak biociden met deze stoffen worden gebruikt. Aangezien de concentraties in de biocide-producten vaak sterk verdund zijn, zullen de effecten meestal niet ernstig zijn. Toch adviseert het RIVM om de waarschuwingszin toe te voegen. Daardoor zijn gebruikers op de hoogte van het mogelijke schadelijke effect na inademen en zullen ze veilig met deze producten omgaan.

Kernwoorden: biociden, classificatie, inhalatietoxiciteit, quaternaire ammoniumverbindingen, desinfectie

Contents

Summary

An inventory of the possible effects of inhalation of quaternary ammonium compounds used as biocides was made. The focus of this question was whether these compounds should be classified for acute inhalation toxicity. Information in the public domain, including biocidal active substance assessment reports, harmonised classification and labelling, and public literature were screened for information on the inhalation toxicity of quaternary ammonium compounds.

It was found that for most quaternary ammonium compounds used as biocides, there is a lack of acute inhalation toxicity studies on which classification and labelling can be based. However, from an animal welfare point of view, these studies should also not be conducted considering the corrosive properties of quaternary ammonium compounds. Benzalkonium chloride (CAS 68424-85-1) was the only biocidal active substance present in products authorised in the Netherlands for which information was available on the lethal concentration $(LC)_{50}$ value after acute inhalation exposure. However, the available data was insufficient to draw a firm conclusion as the underlying study report is lacking. For the other quaternary ammonium compounds used as biocides in the Netherlands, no acute inhalation toxicity studies were available. Furthermore, it is not possible to directly extrapolate between these substances, as quantitative differences were observed on the respiratory irritant properties of these substances.

The Classification, Labelling and Packaging (CLP) Regulation (EC) No 1272/2008 states that for corrosive properties of substances, for which acute inhalation tests are not available and which may be inhaled, the supplementary label EUH071 'corrosive to the respiratory tract' needs to be assigned. Considering the corrosive properties of the currently approved quaternary ammonium compounds, it is recommended that at the time of (re)evaluation this supplementary hazard label is applied to these chemicals. This conclusion is in line with the recent decision from the European Chemicals Agency (ECHA) on the classification of mecetronium ethyl sulphate, but this sentence has not yet been applied for other quaternary ammonium compounds.

1 Introduction and approach

Background

A biocidal active substance dossier, which was recently evaluated, revealed public literature showing that quaternary ammonium compounds can cause respiratory effects after inhalation exposure. However, an OECD (Organisation for Economic Co-Operation and development) test guideline compliant study suitable for classification and labelling purposes was not available. RIVM was asked by the Ministry of Social Affairs and Employment (SZW) to further explore the possible inhalation effects of quaternary ammonium compounds used as biocides. The focus of this question was whether these compounds should be classified for acute inhalation toxicity.

Approach

To gather information on the (acute) inhalation toxicity of quaternary compounds a stepwise approach was taken.

1. In the first step an overview was made of the quaternary ammonium compounds that are approved in the European Union (EU) as biocidal active substance, or that are currently under evaluation. This was done by searching the ECHA biocides database[1]. Subsequently, the Dutch Board for the Authorisation of Plant protection products and Biocides (Ctgb) Authorised products database[2] was checked to see if products with these active substances had an approval at national level.
2. For each substance retrieved in step 1 it was determined if a harmonised classification and labelling was already available under Regulation (EC) No 1272/2008. To this end the Classification and Labelling (C&L) inventory database from ECHA[3] was searched using the Chemical Abstracts Service (CAS) number as identifier. More details on this harmonised classification and labelling decision were retrieved from the harmonised classification and labelling (CLH) opinion reports where available.
3. As a third step the assessment reports from biocidal active substance dossiers were checked for the available information on inhalation toxicity for each substance.
4. In the fourth step it was checked if information on the inhalation toxicity of the quaternary ammonium compounds from step 1 was available in the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registration dossiers[4] of these substances.
5. Finally, a public literature search was conducted to gather more information on the inhalation toxicity of quaternary ammonium compounds. This search was not limited to the active substances which are approved or undergoing evaluation, as the retrieved data was used to get an overall picture of the potential

[1] https://echa.europa.eu/information-on-chemicals/biocidal-active-substances
[2] https://pesticidesdatabase.ctgb.nl/en/authorisations
[3] https://echa.europa.eu/information-on-chemicals/cl-inventory-database
[4] https://echa.europa.eu/information-on-chemicals/registered-substances

respiratory effects of quaternary ammonium compounds as a group. The full list of search terms used are included in Annex 1. The retrieved hits were first checked for their relevance based on a quick screening of the title. Only *in vivo* studies or human data focusing on adverse effects after inhalation exposure were considered relevant. This eliminated the majority of the publications as they consisted of *in vitro* exposure or were related to the effectiveness against SARS-CoV-2. Publications that were considered relevant or were of unclear relevance were further checked based on their abstract.

The retrieved information from step 2 to 5 were compared against the classification and labelling criteria under Regulation (EC) No. 1272/2008 to determine the need for classification for acute inhalation toxicity.

The scope of the study was to investigate the need for classification for acute inhalation toxicity. Nevertheless, RIVM was also asked to include repeated dose inhalation toxicity studies where available. This was only the case for the literature search (step 5).

2 Overview of quaternary ammonium compounds either approved or under evaluation at EU level

Table 1 provides an overview of the quaternary ammonium compounds listed in the ECHA biocidal active substance database, which are currently approved in the EU, or for which an evaluation is ongoing. In addition, the table provides information whether the active substance is authorised in the Netherlands for biocidal use.

Table 1 Quaternary ammonium compounds approved for biocidal use or under evaluation at European Union level. The third column shows whether the active substance is authorised in the Netherlands for biocidal use.

Name active substance	**CAS number**	**Dutch authorisation Yes (Y)/No (N)**
Approved active substances		
Alkyl (C12-16) dimethylbenzyl ammonium chloride (ADBAC/BKC (C12-16))/benzalkonium chloride	68424-85-1	Y
Coco alkyltrimethylammonium chloride (ATMAC/TMAC)	61789-18-2	Y
DDACarbonate	894406-76-9	Y
Didecyldimethylammonium chloride (DDAC)	7173-51-5	Y
Poly(oxy-1,2-ethanediyl), α-[2-(13ied-cylmethylammonio)ethyl]- .omega.- hydroxy-, propanoate (salt) (Bardap 26)	94667-33-1	Y
Name active substance	**CAS number**	**Dutch authorisation Yes (Y)/No (N)**
Active substances under evaluation		
Alkyl (C12-18) dimethylbenzyl ammonium chloride (ADBAC (C12-18))	68391-01-5	Y
Alkyl (C12-14) dimethyl(ethylbenzyl) ammonium chloride (ADEBAC (C12-14))	85409-23-0	Y
Alkyl (C12-14) dimethylbenzylammonium chloride (ADBAC (C12-14))	85409-22-9	N
Didecyldimethylammonium chloride (DDAC (C8-10))	68424-95-3	N
Dimethyloctadecyl[2-(trimethoxysilyl)propyl]ammonium chloride	27668-52-6	N
Dimethyltetradecyl[3-trimethoxysilyl)propyl]ammonium chloride	41591-87-1	N
Mecetronium ethyl sulphate (MES)/ Dimethylethylhexadecylammonium-ethylsulfate	3006-10-8	N
N-didecyl-N-dipolyethoxy ammonium borate/dodecylpolyethyl ammonium borate (polymeric betaine)	214710-34-6	N
Polymer of N-Methylmethanamine (EINECS 204-697-4 with (chloromethyl) oxirane	25988-97-0	N

Name active substance	CAS number	Dutch authorisation Yes (Y)/No (N)
Active substances under evaluation		
(EINECS 203-439-8)/Polymeric quaternary ammonium chloride (PQ Polymer)		
Quaternary ammonium compounds, benzyl-C12-18-alkyldimethyl, salts with 1,2-benzisothiazol-3(2H)-one 1,1-dioxide (1:1)	68989-01-5	N

3 Information on acute inhalation toxicity of quaternary ammonium compounds

3.1 Harmonised classification and labelling

The ECHA C&L inventory database[5] was checked to see if the quaternary ammonium compounds listed in Table 1 have a harmonised classification and labelling under Regulation (EC) No 1272/2008. Of these substances only two have a harmonised classification (Table 2). Neither of the substances are classified for acute inhalation toxicity, although mecetronium ethyl sulphate (MES) does have the supplementary hazard statement EUH071 'corrosive to the respiratory tract'.

Table 2 Overview of available harmonised classification and labelling

Name active substance	CAS number	Classification under Regulation (EC) No 1272/2008	Entry into Annex VI*
Approved active substances at EU level			
Didecyldimethylammonium chloride (DDAC)	7173-51-5	Acute Tox 4 H302 Skin Corr. 1B H314	CLP00
Name active substance	**CAS number**	**Classification under Regulation (EC) No 1272/2008**	**Entry into Annex VI***
Active substances under evaluation at EU level			
Mecetronium ethyl sulphate (MES)/ Dimethylethylhexadecylammonium-ethylsulfate	3006-10-8	Skin Corr. 1 H314 Eye Dam. 1 H318 Aquatic Acute 1 H400 Aquatic Chronic 1 H410 Supplementary: EUH071	ATP15

* This indicates when an entry in Annex VI of the Classification, Labelling and Packaging (CLP) Regulation has been inserted and/or updated with an Adaptation to Technical Progress (ATP) to the CLP Regulation.

The harmonised classification for didecyldimethylammonium chloride (DDAC, CAS 7173-51-5) was determined prior to Regulation (EC) No 1272/2008 as indicated by CLP00 in Annex VI. For this substance, it is unclear if an acute inhalation toxicity study was available, as we were unable to retrieve the information used to determine the classification.

[5] https://echa.europa.eu/information-on-chemicals/cl-inventory-database

For MES a recent Committee for Risk Assessment (RAC) opinion[6] is available. No acute toxicity study via the inhalation route was available in the CLH report. One Member State proposed read across to other quaternary ammonium compounds. The RAC opinion reports that the following information was available (the original references were not available to RAC, but according to the RAC opinion the information was published in an open review by The Institute of Food Safety and Toxicology, Danish Veterinary and Food Administration):

- Wistar rats were exposed to an alkyl dimethyl ethyl benzyl ammonium compound (CAS number not specified) at a concentration of 5.4 mg/L (the maximum attainable concentration) for one hour. All animals died at this concentration.
- A whole-body inhalation study with cetylpyridinium chloride (CPC, CAS 123-03-5) in which groups of five rats per sex were exposed to air containing 0, 0.05, 0.07, 0.13 and 0.29 mg CPC dust/L for four hours (equal to 50, 70, 130 and 290 mg dust/m^3). The particle size was less than 5 µm. The LC_{50} was 0.09 mg/L (90 mg/m^3) with upper and lower 95% confidence limits at 0.13 and 0.07 mg/L respectively. Deaths occurred in all treated groups (2/10, 1/10, 8/10 and 10/10, respectively). No deaths were seen among controls and all the deaths occurred within 4 days after exposure. Histopathological examination of the lungs and other major organs was not carried out. The author calculated that the total CPC exposure at the LC_{50} level (0.09 mg/L) was about 4-8 mg/kg body weight. Based on this calculation it was inferred that CPC could be more toxic by inhalation exposure than by oral or dermal exposure.
- In a group of 196 farmers (with or without respiratory symptoms), the relationship between exposure to quaternary ammonium compounds (unspecified, exposure levels not given) and respiratory disorders by testing for lung function and bronchial responsiveness to histamine was studied. After histamine provocation, statistically significant associations were found between the prevalence of mild bronchial responsiveness (including asthma-like symptoms) and the use of quaternary ammonium compounds as disinfectant. The association seemed even stronger in people without respiratory symptoms.

The RAC concluded that there was not enough information available to justify the application of read-across from other quaternary ammonium compounds. Therefore, RAC proposed no classification of MES for acute toxicity via inhalation.

According to Regulation (EC) No 1272/2008 Annex II Section 1.2.6, in cases where no acute inhalation study is available for a corrosive substance, and such substance may be inhaled, the substance shall be supplementary labelled with EUH071 ‘corrosive to the respiratory tract’. On this basis RAC concluded that labelling with EUH071 was required.

[6] https://echa.europa.eu/documents/10162/19c8b515-1ef5-cefe-f7f4-4bf7178338da

3.2 Available information on inhalation toxicity in biocidal active substance dossiers

The information on inhalation toxicity in the available biocidal active substance dossiers on quaternary ammonium compounds are summarised in Table 3. For the substances still under evaluation no public assessment report was available, and therefore, only the approved active substances are included in the table below.

For the currently approved quaternary ammonium compounds no substance specific acute inhalation toxicity studies were available in the assessment reports. These studies were waived with the argumentation that the active substances are non-volatile and for animal welfare reasons as all approved quaternary ammonium compounds were found to be corrosive based on animal data (Skin corr. 1B, H314) in accordance with the requirements for biocides. The assessment report of benzalkonium chloride ADBAC/BKC (CAS 68424-85-1) did refer to two acute inhalation studies from public literature in which irritation in the respiratory tract was observed. Available public literature on the respiratory effects of quaternary compound, including the two studies referred to in the ADBAC/BKC dossier, are reported in section 3.4 of this report.

Table 3 Overview of information on inhalation toxicity from biocidal active substance dossiers

Name approved active substance	Information on inhalation toxicity	Reference
Alkyl (C12-16) dimethylbenzyl ammonium chloride (ADBAC/BKC (C12-16))/ benzalkonium chloride CAS: 68424-85-1	Inhalation toxicity study was considered unnecessary, since the active substance is not volatile (vapour pressure < 1 x 10^{-5} Pa at 20°C) and considering animal welfare reasons for this corrosive chemical. Two acute inhalation studies from public literature were reported (*author names blacked out*) which showed that strong irritant activity was observed after inhalation exposure followed by necrosis of the respiratory cells and lung inflammation. A LOAEC of 19 mg/m3 was derived on the basis of these studies. No classification was proposed for acute inhalation toxicity.	Assessment report ADBAC/BKC (December 2021)
Coco alkyltrimethyl-ammonium chloride (ATMAC/TMAC) CAS: 61789-18-2	Inhalation of ATMAC was not considered a potential route of exposure based on use patterns and vapour pressure (1.8 x 10^{-6} Pa, 20°C). In addition, it was stated that the active substance is classified as irritant/corrosive, therefore, there is no need to perform inhalation studies. It was concluded that irritation of the respiratory tract is expected. No classification was proposed for acute inhalation toxicity.	Assessment report ATMAC/TMAC (April 2016)
DDACarbonate CAS: 894406-76-9	No studies are available to assess the acute inhalation toxicity of DDACarbonate. Nevertheless, it was indicated that given the corrosive properties of DDACarbonate, it is predicted that this substance will also be acutely toxic via the inhalation route.	Assessment report DDACarbonate (July 2012)
Didecyldimethylammonium chloride (DDAC) CAS: 7173-51-5	See ADBAC/BKC, same arguments were used to waive study.	Assessment report DDAC (June 2015)
Poly(oxy-1,2-ethanediyl), α-[2-(18ied- cylmethyl-ammonio)ethyl]-.omega.- hydroxy-, propanoate (salt) (Bardap 26) CAS: 94667-33-1	See ADBAC/BKC, same arguments were used to waive study.	Assessment report Bardap (April, 2021)

3.3 Available information on inhalation toxicity in REACH registration dossiers

The ECHA website[7] was checked to see if the quaternary ammonium compounds listed in Table 1 have registered substances factsheet available under REACH. These registered substances factsheets were evaluated for the availability of information on inhalation toxicity. For nearly all compounds the (acute) inhalation toxicity study was waived. Only two dossiers made reference to a specific acute toxicity study via inhalation, namely ADBAC/BKC (CAS 68424-85-1) and ADBAC (85409-22-9). The same study was used in both the dossiers and has not been previously reported in biocidal assessment reports. Since the study report itself is not publicly available, the validity of the study and its conclusions could not be independently assessed by RIVM.

The registered substance factsheet provided some details on the conduct of the study which are described in Annex 2 of this report. While the study appears to be conducted in accordance with international test guideline procedures, the main limitation is that a mixture of C12-C16 ADBAC and C12-C16 DMAC was tested. Therefore, it is not possible to draw a conclusion for one individual quaternary ammonium compound on the basis of this study.

3.4 Information on inhalation toxicity of quaternary ammonium compounds from public literature

A literature search was conducted to find further information on the inhalation toxicity of quaternary ammonium compounds (see Annex 1). Twelve relevant publications were found which are summarised below.

3.4.1 *Cetylpyridinium chloride (CAS 123-03-5)*

Cetylpyridinium chloride (CPC) is a quaternary ammonium salt which is currently not authorised nor included in the review programme for active substance evaluation for biocides at EU level. However, since it is one of the few quaternary ammonium compounds for which an acute inhalation toxicity study is available, it was included in this report. More details on these studies can be found in Annex 2 of this report.

In the first acute inhalation study in rats (Lin et al., 1991), mortality and respiratory effects were observed leading to a combined LC_{50} value (males and females) of 0.09 mg/L. It is noted that the RAC opinion of MES also referred to this study (see section 3.1).

In the second study (Kim et al., 2020), rats were exposed via inhalation to an acute 4 hour exposure or a subacute exposure during a 28 days period. Respiratory irritation was observed in this study, but no mortality. This is not surprising as the concentrations applied in this study (0 to 0.103 µg/L) were much lower than those used in the study by Lin et al. (1991).

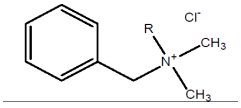
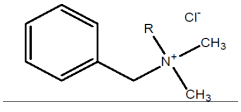
3.4.2 *Benzalkonium chloride (ADBAC/BKC (C12-16), CAS 68424-85-1)*

It should be noted that different structures of benzalkonium chloride with different CAS numbers are available. They are highly structurally

[7] https://echa.europa.eu/information-on-chemicals/registered-substances

similar. The differences between these compounds relates to the ratio of different alkyl chain lengths in the mixture. Therefore, results from public literature with another benzalkonium chloride (CAS 8001-54-5) or where the exact CAS number is unknown are also reported here, considering the structural similarity to the approved benzalkonium chloride (CAS 68424-85-1). A comparison between these two different compounds is provided in the overview below (source: United States Environmental Protection Agency (US EPA) evaluation[8] benzalkonium chloride).

Table 4 Comparison of the chemical structure of two benzalkonium chloride compounds

CAS #	Structure	Chain length
68424-85-1		R = C12 (40%) C14 (50%) C16 (10%)
8001-54-5		R = C12 (50%) C14 (30%) C16 (17%) C18 (3%)

The publication by Luz et al. (2020), on the human health hazard assessment of benzalkonium chloride, refers to the US EPA risk assessment of ADBAC[8] which includes the evaluation of an acute inhalation toxicity study. Very little information is provided about this study. According to the evaluation by the US EPA, the study was conducted in accordance with the EPA health effects guideline for acute inhalation toxicity (OPPTS 870.1300) resulting in an LC_{50} above 0.054 mg/L and below 0.51 mg/L. No other information is provided and since the study report is not available RIVM is not able verify the acceptability of the study.

Three other inhalation studies with benzalkonium chloride are available in the public domain (see Annex 2 for more details on the studies).

In the study by Swiercz et al. (2008) acute inhalation exposure to benzalkonium chloride (CAS 8001-54-5) resulted in mortality in 2 out of 5 animals at 52.84 mg/m^3 (highest achievable dose). The study authors argued that the LC_{50} would be close to the highest dose level of 52.84 mg/m^3 with 40% mortality based on the steep dose response with no mortality at the low dose of 37.64 mg/m^3. In the second stage of this study animals were exposed to 30 mg/m^3 for a single and 3 days exposure period resulting in respiratory irritation and inflammation, but no mortality.

Similar signs of respiratory irritation were observed in a 14-day inhalation study in rats with benzalkonium chloride (CAS number not specified) at 4 and 20 mg/m^3 (Choi et al., 2020) and in a 14-day inhalation study in rats with benzalkonium chloride (CAS number not specified) at 4.1 mg/m^3 (Kwon et al., 2019).

[8] https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_G-2_3-Aug-06.pdf

3.4.3 *Didecyldimethylammonium chloride (DDAC, CAS 7173-51-5)*

For DDAC, two public literature studies are available on its adverse effects after inhalation (see Annex 2 for more details). In the first study (Kim et al., 2017), respiratory irritation was observed in rats after 13 weeks of exposure at a concentration of 0.36 mg/m^3 and higher with a NOAEL of 0.11 mg/m^3. In a similar study (Lim and Chung, 2014), rats were exposed to DDAC for two weeks leading to respiratory effects at a concentration of 0.58 mg/m^3 and higher with a NOAEL of 0.15 mg/m^3. Mortality was not observed in these two studies and therefore they do not provide information that can be used in the context of classification for acute inhalation toxicity.

3.4.4 *Multiple quaternary ammonium compounds*

Two studies were available that evaluated multiple quaternary ammonium compounds at the same time. More details on the studies are included in Annex 2 of this report.

In the first study by Larsen et al. (2011), the acute respiratory effects of four compounds, namely benzylkonium chloride (BAC, CAS 8001-54-5), hexadecyl trimethyl ammonium bromide (HTA, CAS 112-02-7), CPC (CAS 123-03-5), and dimethyl dioctadecyl ammonium bromide (DDA, CAS 3700-67-2) were tested in mice. All of the four compounds showed an effect on the measured respiratory endpoints with varying degrees of adversity. BAC was found to be the most potent of the four compounds tested followed by CPC, HTA and DDA.

In a human volunteer study, quaternary ammonium compound concentrations in blood were measured in 43 individuals (Hrubec et al., 2020). Quaternary ammonium compounds were detected in 80% of the participants, and were associated with markers for inflammation.

3.4.5 *Mode of action*

Two public literature studies evaluated the potential mode of action of the respiratory effects of quaternary ammonium compounds (Park et al., 2022; Osimitz and Droege, 2022; see Annex 2 for more details). These studies showed that respiratory exposure to quaternary ammonium compounds results in disruption of the epithelial cell membrane in lungs as well as disruption of mitochondrial function leading to cell death and inflammatory responses. No metabolism or distribution is involved in the mode of action.

4 Comparison of available information with classification and labelling criteria

Two public literature studies, described in chapter 3, investigated the acute inhalation toxicity of quaternary ammonium compounds at a concentration high enough to induce mortality.

A study with CPC (CAS 123-03-5), a quaternary ammonium compound not approved for biocidal use in the EU, showed an LC_{50} value of 0.09 mg/L. This LC_{50} value would lead to a classification with category 1 acute inhalation toxicity (H330).

For benzalkonium chloride, the LC_{50} was above the highest achievable concentration with a mortality of 40% at 0.05284 mg/L. In addition, the US EPA evaluation of BAC referred to an acute inhalation toxicity study resulting in an LC_{50} of above 0.054 mg/L and below 0.51 mg/L. However, without access to the study itself it is difficult to conclude on the acceptability of the study for classification purposes. The study report should be available before a definitive conclusion can be drawn.

In addition to classification for acute inhalation toxicity, Regulation (EC) No 1272/2008 Annex II section 1.2.6 states the following:

'For substances in addition to classification for skin corrosivity, if no acute inhalation test data are available and which may be inhaled, the substance shall be supplementary be labelled with EUH071'

It is clear from the information in the biocidal active substance dossiers that all of the approved quaternary ammonium compounds have corrosive properties. Therefore, a general recommendation can be drawn for these chemicals to include the classification EUH071 'corrosive to the respiratory tract' in cases where these substances can be inhaled. This classification could be considered at the time of the re-evaluation. This is line with the most recent RAC decision for mecetronium ethyl sulphate. Similarly for new quaternary ammonium compounds, EUH071 could be assigned when the data show that the substance is corrosive and an acute inhalation toxicity study is not available.

5 Discussion and conclusions

For most quaternary ammonium compounds there is a lack of acute inhalation toxicity studies on which classification and labelling can be based. All of the approved quaternary ammonium compounds were concluded to be corrosive. For animal welfare reasons, acute inhalation toxicity studies should not be conducted for corrosive compounds as is indicated in OECD test guideline 403 for acute inhalation toxicity. However, when data are available these can be considered for classification and labelling purposes.

Benzalkonium chloride was the only biocidal active substance approved in the EU for which information was available on the LC_{50} value after acute inhalation exposure. However, the available data was insufficient to draw a firm conclusion since the study report was not available.

For the other quaternary ammonium compounds used as biocides no acute inhalation toxicity studies are available nor would this be required under the Biocidal Product Regulation due to the corrosive properties of these compounds. Therefore, no conclusion can be drawn on the need for classification and labelling based on for acute inhalation toxicity studies for these substances. It is difficult to extrapolate the effects observed in the study by Lin et al. (1991) for cetylpyridinium chloride and by Swiercz et al. (2008) for benzalkonium chloride to other quaternary ammonium compounds as quantitative differences in the respiratory irritation potential of these compounds have been observed (Larsen et al., 2011).

Based on the available data the following recommendations are made:

- For the approved quaternary ammonium compounds which were concluded to be corrosive and for which acute inhalation toxicity data is lacking: assign labelling with EUH071 ‘corrosive to the respiratory tract’ at the time of re-evaluation in cases where these substance can be inhaled.
- For new quaternary ammonium compounds assign with the labelling with EUH071 ‘corrosive to the respiratory tract’ if they are found to be corrosive and acute inhalation toxicity data is lacking and they can be inhaled.
- For benzalkonium chloride specifically it is recommended to try to retrieve the acute inhalation toxicity study reported in the evaluation by the US EPA at the time of the re-evaluation at active substance level or when a CLH report will be prepared for opinion forming by RAC.

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Swiercz 2008, Pulmonary irritation after inhalation exposure to benzalkonium chloride in rats. International Journal of occupational medicine and environmental health 2013, 26(4): 647-656

Publicly available biocidal assessment reports

ABDAC/BKC: https://echa.europa.eu/documents/10162/bb845cfc-5dab-4270-6349-ec8d562eb01c
ATMAC/TMAC: https://echa.europa.eu/documents/10162/b1406a51-874a-ea4c-83b5-df2c1b898632
Bardap: https://echa.europa.eu/documents/10162/e15a7307-e2af-cae9-a6bf-10cf97971391
DDACarbonate: https://echa.europa.eu/documents/10162/fd4543c7-2d6c-f995-e208-cdaf0b37e941
DDAC: https://echa.europa.eu/documents/10162/81fb9122-9b96-d284-cbdd-f3e28ba67632

Annex 1 Literature search

Search data base: Scopus
Data of search: 25-01-2023

Search terms:

Search terms	Number of hits
(Quaternary ammonium compounds OR QAC) AND (inhalation OR respiratory)	339
Benzalkonium chloride AND (inhalation OR respiratory)	264
Cetylpyridinium chloride AND (inhalation OR respiratory)	65
DDAC AND (inhalation OR respiratory)	12
ADBAC AND (inhalation OR respiratory)	4
ADEBAC AND (inhalation OR respiratory)	1
PQ Polymer AND (inhalation OR respiratory)	1
ATMAC AND (inhalation OR respiratory)	0
DDACarbonate AND (inhalation OR respiratory)	0
Bardap AND (inhalation OR respiratory)	0
mecetronium ethyl sulphate AND (inhalation OR respiratory)	0
polymeric betaine AND (inhalation OR respiratory)	0

Annex 2 Detailed information on the toxicity studies

A2.1 REACH registration dossier ADBAC/BKC and ADBAC

Groups of five Sprague-Dawley rats per sex were exposed to 0, 0.17, 0.24 and 0.34 mg/L of a mixture containing C12-C16 ADBAC (40% active) and di C12-16 DMAC (37.5% active). The whole body exposure lasted for 4 hours after which animals were observed for a period of 21 days. The geometric standard deviation (GSD) was above the acceptable range for the high dose group (3.5 vs 3.0).
Mortality was observed at the low dose (1 male), mid dose (3 males and 1 females) and high dose (5 males and 4 females) group. Clinical signs were considered to be consistent with inhalation of an irritant aerosol including partial closing of the eyes and exaggerated respiratory movement. Histopathological evaluation showed focal alveolar necrosis, diffuse congestion and eosinophilic material in alveoli in the high dose group. To a lesser degree these effects were also observed in the low and mid dose group. Under the study conditions, the 4 hours LC_{50} of the test substance was calculated to be 0.25 mg/L or 250 mg/m^3 (95% CI: 0.22-0.28 mg/L or 220-280 mg/m^3).

A2.2 Public literature information on cetylpyridinium chloride (CAS 123-03-5)

In an acute inhalation study, groups of five rats per sex were exposed to aerosols containing, 0, 0.05, 0.07, 0.13 and 0.29 mg cetylpyridinium chloride (CPC)/L (Lin et al. 1991). Exposure lasted for 4 hours and animals were observed for toxicity and ocular effects for 14 days after treatment. Mortality occurred in all males at 0.13 and 0.29 mg/L and 1 female at 0.07 mg/L, 3 females at 0.13 mg/L and all females at 0.29 mg/L. Laboured breathing and respiratory difficulty, nasal discharge and chromodacryorrhea (secretion of red tears) were observed in all groups with more pronounced effects at increasing doses. These effects were reversible in surviving animals. The combined LC_{50} value(males and females) was 0.09 mg/L.

In another study, the inhalation toxicity of CPC was assessed using both *in vitro* and *in vivo* methods (Kim et al., 2020). In the *in vivo* study, rats were either exposed via intratracheal instillation or via aerosol inhalation.
In the intratracheal installation part of study, groups of five male rats were exposed to a single dose of 0, 0.0001, 0.04 or 16 µg/kg bodyweight of CPC. No deaths were observed nor clinical signs of toxicity. Levels of total protein (TP) in bronchoalveolar lavage (BAL) fluid, which is an indicator of lung function damage, were increased in the high-exposure group (sacrificed 1 day after exposure).
In the inhalation part of the study, groups of five rats were exposed either acute (4h) or subacute for 6 hours/day, 5 days a week during a 28 days period. Half the rats were sacrificed 1 day after exposure. The other half were sacrificed 7 days after exposure for the acute study and 14 days after exposure for the repeated dose study. The concentrations achieved were 0, 0.63, 7.44 and 103 µg/m^3 in the acute study and 0, 0.15, 6.42 and 114 µg/m^3 for the repeated dose study.

Repeated exposure resulted in a decreased body weight in the high-exposure group and decreases in the relative weights of the lungs and kidneys of the high recovery group, but no changes were evident in the histological and serum chemical analyses in either group. The bronchoalveolar lavage fluid (BALF) analysis showed a significant increase in proinflammatory cytokines interleukin (IL)-6, IL-1β, and tumour necrosis factor (TNF)-α levels. These effects mainly occurred in the low and mid dose groups in the acute study and in all dose groups in the repeated dose study.

A2.3 Public literature on benzalkonium chloride

Swiercz et al. (2008) assessed the inhalation irritation properties of benzalkonium chloride (CAS 8001-54-5) in groups of five female Wistar rats per concentration. The study consisted of two stages. In the first stage the LC_{50} value for BAC was determined after nose-only exposure to 37.64 mg/m^3 or 52.84 mg/m^3 (highest concentration achievable) Benzalkonium chloride for 4 hours. After exposure the animals were observed for 14 days. In the second stage of the study the respiratory effects were investigated in a second group of animals after a single 6 hours and a repeated dose (3 days, 6 hours per day) exposure during which the concentration was <50% of the LC_{50} value. Bronchoalveolar lavage (BAL) fluid was collected from the exposed and control animals at two time-points: immediately after termination of exposure and 18 hours afterwards. BAL fluid concentrations were measured for parameters considered indicative of irritation including total protein, Clara cell protein (CC16), matrix metalloproteinase-9 (MMP-9), hyaluronic acid (HA), immunoglobulin E (IgE) and cytokines (TNF-α, IL-6 and MIP-2), lactate dehydrogenase (LDH) and Glutathione-S-transferase (GST).
In the first part of the study all rats in the low dose group survived. At the high dose level 2 out of 5 rats died within 24 hours of exposure. No clear LC_{50} can be derived on the basis of this study. The study authors argued that the LC_{50} would be close to the highest dose level of 52.84 mg/m^3 with 40% mortality based on the steep dose response with no mortality at 37.64 mg/m^3. Therefore, a concentration of 30 mg/m^3 was applied in the second part of the study. After single and repeated exposure, lung weight, total protein, HA and LDH activity in BALF of exposed rats were higher than in controls while CC16 levels were decreased. In addition, a significantly higher BALF concentration of IL-6 and IgE was noted in animals exposed to single and repeated doses compared to controls. No effect was observed on MMP-9, TNF-α, and MIP-2 levels. Based on these findings, the study authors concluded that BAC showed strong inflammatory and irritation activity on the lungs.

Similar signs of respiratory irritation were observed in a 14-day inhalation study in rats with benzalkonium chloride (CAS # not specified) at 0, 0.8, 4 and 20 mg/m^3 (Choi et al., 2020). The no observed adverse effect level (NOAEL) was found to be less than 0.8 mg/m^3.

In another 14-day inhalation study in rats with benzalkonium chloride (CAS number not specified), respiratory irritation and pulmonary cell damage was observed at 4.1 mg/m^3 (Kwon et al., 2019).

A.2.4 Didecyldimethylammonium chloride

Kim et al. (2017) investigated the effects of DDAC on groups of 10 Sprague-Dawley rats per sex after 13 weeks of whole body inhalation exposure. The animals were exposed to 0, 0.11, 0.36 or 1.41 mg/m^3. Body weight was reduced by 35% in the high dose group and by 15% in the mid dose group compared to the control group. Lung weight was increased in the mid and high dose groups and inflammatory cell infiltration and interstitial pneumonia were observed in the lungs. However, severe histopathological symptoms, including proteinosis and/or fibrosis, were not found. Based on the results the study authors considered that the NOAEL for the 13-week exposure duration was 0.11 mg/m^3.

In a similar study, male Sprague-Dawley rats were exposure to DDAC for two weeks of whole body inhalation exposure (Lim and Chung, 2014). The animals were exposed for 24 hours to 0, 0.15, 0.58 and 3.63 mg/m^3. The number of animals per dose group was not clearly reported. Body weight gain was significantly reduced in the high dose group. Mild effects were observed in the BAL cell differentiation counts and cytotoxicity parameters from BAL fluid. The lung weights of the DDAC-exposed groups were not changed compared to the control group. Histopathological findings showed migration of inflammatory cells, elimination of epithelial cells, and focal thickening of the alveolar wall caused by infiltration and proliferation in most of the lungs of DDAC-exposed rats. Furthermore, inflammatory cell infiltration and interstitial pneumonia were partially observed in the medium and high groups. The study author concluded a NOAEL of 0.15 mg/m^3.

A2.5 Public literature information with multiple quaternary ammonium compounds

Larsen et al. (2011) evaluated the acute airway effects of four quaternary ammonium compounds after inhalation exposure in BALB/cJ mice. The tested substances were a benzylkonium chloride (BAC, CAS 8001-54-5), hexadecyl trimethyl ammonium bromide (HTA, CAS 112-02-7)), CPC (CAS 123-03-5), and dimethyl dioctadecyl ammonium bromide (DDA, CAS 3700-67-2). Groups of seven to eight female mice were exposed head only to concentrations of 0 (saline), 0.049, 0.19, 1.8 or 19 mg/m^3 for 30 minutes. During a recovery period of 45 minutes respiratory parameters were measured including respiratory rate, time from end of inspiration until the beginning of expiration (time of break, TB), time from end of expiration until beginning of the next inspiration (TP), tidal volume (VT) and mid-expiratory flow rate (VD). Sixteen hours after exposure bronchoalveolar lavage (BAL) fluid LDH was measured which is a marker of epithelial cell damage.
Exposure to all four compounds resulted in reduced tidal volume which was the strongest effect. The decrease in VT was almost fully reversible at lower concentrations, whereas the VT effects were only slightly reversible at the highest exposure level during the 45-min.recovery period. A 15% reduction in VT was observed at 0.12, 1.3, 2.9 and 19 mg/m^3 for BAC, CPC, HTA and DDA respectively. A concentration dependent increase in respiratory rate was observed for BAC, CPC and HTA in all exposure groups, but not DDA. TP elongation was only observed at the highest concentration of BAC. TB elongation or an effect

on VD was not seen for any of the tested substances. Exposure to BAC and CPC gave rise to a concentration-dependent increase in the number of inflammatory cells in BAL fluid 16 hr after. The study authors concluded that the pulmonary effects seen after inhalation of BAC also apply to other members of the quaternary ammonium compound family, although BAC was the most potent of the quaternary ammonium compounds studied.

In a human volunteer study, quaternary ammonium compound concentrations in blood were measured in 43 individuals (Hrubec et al., 2020). Furthermore, it was evaluated if these concentrations were associated with markers of inflammation, mitochondrial function and cholesterol synthesis. Quaternary ammonium compounds were detected in 80% of the participants, and were associated with decreased mitochondrial function and a dose dependent increase in inflammatory cytokines. Cholesterol synthesis pathway intermediaries were generally increased, indicating disruption in cholesterol homeostasis. The primary source of exposure was not investigated in the study, as no personal identifying information was collected. The study authors mentioned a few limitations of the study including the small sample size and lack of information on other influential variables that could impact the investigated endpoints. They also mentioned that it is not known if the exposure to quaternary ammonium compound measured in the study correlates with diseases in the human population.

A2.6 Public literature information on the potential mode of action information of the respiratory effects

Benzalkonium chloride (CAS number not specified) was exposed weekly via pharyngeal aspiration to groups of 16 male and female ICR mice) for 14- and 28 days at 50 µl of 0.001, 0.005 and 0.01% concentration. This resulted in chronic inflammatory lesions with formation of lamellar body-like structures. These lamellar body-like structures were considered as a predictive marker for fibrotic lesions based on previous in vitro studies. Whole blood cells counts were decreased in high dose males, whereas the proportions of neutrophils and monocytes were altered in high dose females. Enzyme-linked immunosorbent assay (ELISA) analysis showed changes in immunologic messenger molecules in all exposed groups compared to controls.
In vitro studies showed that cytotoxicity increased rapidly with increasing concentrations. Lysosomal volume, nitric oxide (NO) production, and lipid peroxidation increased in treated cells, whereas intracellular reactive oxygen species (ROS) level decreased accompanying structural and functional damage of mitochondria. Benzalkonium chloride also affected the expression level of proteins indicating an immune response, DNA damage, and amino acid biosynthesis-related molecules. Lamellar body- and autophagosome-like structures were notably observed in cells exposed to benzalkonium chloride, and necrotic and apoptotic cell death were identified accompanying cell accumulation in the G2/M phase. The study authors suggested that repeated respiratory exposure of benzalkonium chloride causes pulmonary inflammation and lung tissue damage and that dead and damaged cells may contribute to the inflammatory responses. The

formation process of lamellar body-like structures was proposed as a key toxicity mechanism (Park et al., 2022).

An adverse outcome pathway has been proposed for the effects on the respiratory tract of quaternary ammonium compounds (Osimitz and Droege, 2022) which supports the mode of action proposed in the paper by Park et al. (2022) summarised above. When inhaled, these compounds are incorporated into the epithelial cell membrane at the point of contact. At high enough exposures, the epithelial membrane is disrupted, reducing its fluidity and releasing cellular contents. Further, quaternary ammonium compounds might disrupt mitochondrial functions leading to decreased ATP production. This might lead to cell death, either attributed to direct lysis, necrosis or apoptosis. Pro-inflammatory mediators are recruited to the tissue, including inducing inflammation, oedema, and excess mucus production. The primary tissue-level adverse outcome is epithelial degeneration and dysplasia. The study authors also concluded that no apparent metabolism or distribution is involved in the mode of action.

Addendum

Letter report 2023-0312
Acute inhalation toxicity of quaternary ammonium compounds

Bilthoven: 14-05-2024
Subject: Addendum to letter report 2023-0312

Synopsis

Acute inhalation toxicity of quaternary ammonium compounds

Harmful or undesirable organisms may cause an area to become unsafe and unhealthy for people, animals or the environment. To control those organisms, companies and households use biocides, including biocides with quaternary ammonium compounds. These are effective against bacteria and are used as disinfectants, especially by professionals.

Biocides are not authorised until their safety and effectiveness have been tested extensively. This is to prevent any unintended harmful effects from their use. In the authorisation procedure for one specific quaternary ammonium biocide, the product was found to be potentially harmful after inhalation by humans in a particular concentration.

There are also other types of quaternary ammonium compounds that are used as biocides. For that reason, RIVM has examined whether the quaternary ammonium compounds that are used as biocides in the Netherlands can be harmful when inhaled. To that end, RIVM drew up an overview of the potential health effects upon inhalation and found that all authorised quaternary ammonium compounds have corrosive properties.

This is why RIVM recommends that the packaging of biocides containing these compounds with corrosive properties should include a warning phrase. This ensures that users are aware of the potentially harmful effect upon inhalation and handle these products safely. This warning phrase may be superfluous, for instance, when the concentrations of these compounds in the products are highly diluted.

The proposed text of the label is as follows: ‘corrosive to the respiratory tract’. According to European rules, this warning is compulsory for corrosive substances that can be inhaled and may not be tested on animals because of their corrosive properties.

The overview was compiled on behalf of the Ministry of Social Affairs and Employment (SZW). At present, most quaternary ammonium compounds do not come with a warning phrase. It is not known how often biocides containing these substances are used.

Keywords: biocides, classification, inhalation toxicity, quaternary ammonium compounds, disinfection

Publiekssamenvatting

Acute inhalatietoxiciteit van quaternaire ammoniumverbindingen in biociden

Door schadelijke of ongewenste organismen kan een leefomgeving niet meer veilig en gezond zijn voor mensen, dieren of het milieu. Om deze organismen te bestrijden, gebruiken bedrijven en huishoudens biociden. Voorbeelden zijn biociden met quaternaire ammoniumstoffen. Deze werken tegen bacteriën en worden, vooral door professionals, als ontsmettingsmiddel gebruikt.

Biociden worden pas toegestaan als uitgebreid is beoordeeld of ze veilig zijn en goed werken. Dit voorkomt dat ze onbedoelde schadelijke effecten hebben. Eerder bleek bij de toelatingsprocedure van één bepaalde quaternaire ammoniumbiocide dat deze schadelijk kan zijn als mensen haar in een bepaalde hoeveelheid inademen.

Er zijn nog andere quaternaire ammoniumstoffen die als biocide worden gebruikt. Daarom heeft het RIVM uitgezocht of de quaternaire ammoniumstoffen die in Nederland als biocide worden gebruikt, schadelijk kunnen zijn als ze worden ingeademd. Hiervoor is een overzicht gemaakt van wat daarvan mogelijke gezondheidseffecten zijn. Daaruit blijkt dat alle toegelaten quaternaire ammoniumstoffen bijtende eigenschappen hebben.

Het RIVM adviseert daarom hiervoor te waarschuwen op de verpakking van biocideproducten met stoffen die deze bijtende eigenschappen hebben. Daardoor zijn gebruikers op de hoogte van het mogelijke schadelijke effect na inademen en zullen ze veilig met deze producten omgaan. De waarschuwing is niet altijd nodig, bijvoorbeeld bij producten waarin de concentraties van deze stoffen sterk zijn verdund.

De voorgestelde formulering is ‘bijtend voor de luchtwegen’. Deze waarschuwing is volgens Europese regels verplicht voor bijtende stoffen die kunnen worden ingeademd en die vanwege deze eigenschap niet op dieren mogen worden getest.

Dit overzicht is gemaakt op verzoek van het ministerie van Sociale Zaken en Werkgelegenheid (SZW). De meeste quaternaire ammoniumstoffen hebben nu geen waarschuwingszin. Het is niet bekend hoe vaak biociden met deze stoffen worden gebruikt.

Kernwoorden: biociden, classificatie, inhalatietoxiciteit, quaternaire ammoniumverbindingen, desinfectie

The RIVM letter report 2023-0312 titled "*Acute inhalation toxicity of quaternary ammonium compounds"* required more explanatory text to improve understanding.

Therefore, some clarifications are described in this addendum. This concerns the following sections:

1. On page 3, containing the synopsis, explanatory text is needed. Subsequently, to maintain readability, some text has been (re)moved.
   - The third paragraph is split in two and the remaining text in this new fourth paragraph needs to be changed from '*This is why RIVM recommends that the packaging of these biocides should include a warning phrase indicating those properties.*' to '*This is why RIVM recommends that the packaging of biocides containing these compounds with corrosive properties should include a warning phrase. This ensures that users are aware of the potentially harmful effect upon inhalation and handle these products safely. This warning phrase may be superfluous, for instance, when the concentrations of these compounds in the products are highly diluted.*'.
   - The last sentences of the fifth (now sixth) paragraph need to be removed as they have partially been included in the new fourth paragraph. The deletion/ replacement concerns this text: '*Their concentrations in biocide products are often highly diluted, so the effects will not normally be serious. Still, RIVM recommends that the warning label be added to ensure that users are aware of the potentially harmful effect upon inhalation and handle these products safely*.'.
2. Accordingly, on page 5 containing the 'publiekssamenvatting', additional clarifications are needed. Consequently, to maintain readability, some text has been (re)moved.
   - The third paragraph is split into two paragraphs and the text in this new fourth paragraph needs to be changed from '*Het RIVM adviseert daarom hiervoor te waarschuwen op de verpakking van biocideproducten met deze stoffen.*' to '*Het RIVM adviseert daarom hiervoor te waarschuwen op de verpakking van biocideproducten met stoffen die deze bijtende eigenschapen hebben. Daardoor zijn gebruikers op de hoogte van het mogelijke schadelijke effect na inademen en zullen ze veilig met deze producten omgaan. De waarschuwing is niet altijd nodig, bijvoorbeeld bij producten waarin de concentraties van deze stoffen sterk zijn verdund.*'
   - The last sentences of the fifth (now sixth) paragraph need to be removed as they have partially been included in the new fourth paragraph. The deletion/ replacement concerns this text: '*Aangezien de concentraties in de biocide-producten vaak sterk verdund zijn, zullen de effecten meestal niet ernstig zijn. Toch adviseert het RIVM om de waarschuwingszin toe te voegen. Daardoor zijn gebruikers op de hoogte van het mogelijke schadelijke effect na inademen en zullen ze veilig met deze producten omgaan.*'

3. In chapter 5, the following paragraph should be included prior to the recommendations to explain in more detail the labelling requirements for the substance as such and products thereof:

"Overall, it can be concluded that the currently registered quaternary ammonium compounds have corrosive properties (H314). This is a legal basis to not perform acute inhalation studies and subsequently precludes classification and labelling for acute inhalation toxicity. However, this property does require assignment of the label EUH071 'corrosive to the respiratory tract' to the active substance and mixtures thereof. Some products containing quaternary ammonium compounds, may be exempted from labelling in accordance with Regulation (EC) No 1272/2008, for example when they are highly diluted. Assessment of these exemptions is performed by the designated legal authorities at product authorisation stage."

The text was edited by K. Mahieu (RIVM).

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