Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

mecetronium etilsulfate; N-ethyl-N,N-dimethylhexadecan-1-aminium ethyl sulfate; Mecetronium ethyl sulphate [MES]

EC Number: 221-106-5
CAS Number: 3006-10-8

CLH-O-0000001412-86-235/F

Adopted
14 September 2018

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON MECETRONIUM ETILSULFATE; N-ETHYL-N,N-DIMETHYLHEXADECAN-1-AMINIUM ETHYL SULFATE; MECETRONIUM ETHYL SULPHATE [MES]

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

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Substance name: mecetronium etilsulfate; N-ethyl-N,N-dimethylhexadecan-1-aminium ethyl sulfate; Mecetronium ethyl sulphate [MES]
EC number: 221-106-5
CAS number: 3006-10-8
Dossier submitter: Poland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Germany		MemberState	1
Comment received				
In general the proposed classification is supported. There are data available which suggest that acute toxicity via inhalation needs to be considered (see specific comment on acute toxicity). Additional comment concerning Carcinogenicity (respective field is missing in this webform): In the MES CLH report the "data lacking" for carcinogenicity (page 6) is not clear. Summarized information on "Other existing data" (section 10.9.1, page 46) is presented and could be more detailed, but indicate that quaternary ammonium compounds (QACs) have no carcinogenic potential (Thorup, I. 2000 - Danish Veterinary and Food Administration). A read-across proposal to several other (QACs) is suggested by the DS for some endpoints (e.g. basic toxicokinetics, carcinogenitiicy). Thus, if reference to other homologue compounds is considered acceptable, Table 55 of the MES CLH report at the carcinogenicity hazard class could have been extended with the available information on other QACs.				
Dossier Submitter's Response				
The physico-chemical properties of MES indicate that the substance has no tendency to become airborne. Mecetronium ethyl sulphate [MES] is an ionic substance which is produced as 30% aqueous solution. In addition, the vapour pressure is calculated to be very low, therefore considering the above that the substance does not require the classification. Information included in "Other existing data" (section 10.9.1 of the CLH report) indicates that quaternary ammonium compounds (QACs) and mecetronium ethyl sulphate has no				

carcinogenic potential. Provided information in "Other existing data" (also Thorup, I. 2000 - Danish Veterinary and Food Administration) is not conclusive for classification.
RAC's response
Thank you very much. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2017	Netherlands		MemberState	2
Comm ent received				
We agree with the proposal on classification as follows: Aquatic Acute 1, H400 M=100 Aquatic Chronic 1, H410 M=10 In principle, we can agree with the conclusion on classification for MES however we would like to have clarification on the following points with regards to the aquatic toxicity; Overall issue: Test concentrations in several toxicity tests were either not directly measured or could not be detected. A kinetic study was used to derive the test concentrations. This kinetic study has been mentioned in different aquatic toxicity tests. However, there is no detailed description on this kinetic study. For example, the test concentrations are not known, the duration of this test is also not clearly described. It is suggested that the detailed information on this kinetic study should be supplied.				
Dossier Submitter's Response				
To see details regarding kinetic study please refer to IUCLID format document i.a. MES - Doc III A7.4.1.1.				
RAC's response				
See also comment No 13 from the same MSCA. RAC thanks the MSCA for their comment and to the DS for their response. By the kinetic study, it was confirmed that analytical measurements revealed that the mecetronium ethyl sulfate concentrations are not stable during the test period. The extreme high potential to adsorption may influence the test concentrations. It is known that mecetronium ethyl sulfate is difficult to recover due its high potential for clustering and adsorption, resulting in an irregular distribution in the test vessels. RAC agrees with the commenting MSCA that such informartion are relevant and should be incorporated into the dossier.				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2017	Finland		MemberState	3
Comment received				
The studies in the CLH report were not always reported in detail and no Annex I providing further information was added.				
Dossier Submitter's Response				
All detailed information from reports is included in the IUCLID format document.				
RAC's response				
Thank you very much. Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Germany		MemberState	4

Comment received

The information provided in the tables and in the summary of the CLH report is too limited and tabulated studies results (only at IUCLID) would help to directly identify the cytotoxic effects of the in vitro studies (page 37).
- Nevertheless, in the Mammalian cell gene mutation assays, it is not clear regarding the experimental design/ concentrations tested/with or without metabolic activation why the results seem contradictory between the studies.
- When testing other quaternary ammonium compounds (QACs), e.g. benzalkonium chloride, also positive and equivocal results were seen in the B. subtilis rec assays. In an E. coli DNA polymerase assay benzalkonium chloride induced repairable DNA damage (Yam 1984, BIBRA 1989, Anon. 1989 - apud Thorup, I. 2000 - Danish Veterinary and Food Administration).
- In the available in vivo study with MES, no clastogenic effects in males were observed, but in females there is a dose-response increase in the incidence of micronuclei, although not statistically significant.
- A quantitative structural alert (QSA2) was observed in a ToxTree evaluation based on the ethyl sulfate structure of the active substance MES.
Therefore, the MES mutagenicity potential is not conclusive and without any specific additional information on a gene mutation assay (e.g. Comet assay), the data for this endpoint is inconclusive and classification is not possible.

Dossier Submitter's Response

Neither the reason of discrepancies between 1st and 2nd Mammalian cell gene mutation assays (BODE Chemie 1994 and 1994a) has been clarified nor 3rd independent study has been conducted.

Thank you for all providing information about other quaternary ammonium compounds (QACs) test data.
All information for this endpoint is inconclusive and does not confirmate the classification of MES at germ cell mutagenicity.

RAC's response

Thank you very much. RAC agrees that the database is not totally conclusive for establishing a classification for germ cell mutagenicity.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2017	Germany	BODE Chemie GmbH	Company-Downstream user	5

Comment received

Comment on the classification of MES as acute dermal toxicity category 3 (refer to CLH Re-port 10.2).
The evaluating CA suggested that Mecetronium ethyl sulphate (MES) should be classified for acute dermal toxicity in category 3 (Acute Tox. 3, H311 – Toxic in contact with skin).
The applicant is of the opinion to reject a classification for acute dermal toxicity in category 3 as inappropriate and applies for classification for acute dermal toxicity not exceeding category 4 (Acute Tox. 4, H312 – Harmful in contact with skin).
Justification to apply classification for acute dermal toxicity in category 4:
The classification proposal (Acute Tox. 3, H311 – Toxic in contact with skin) is based on

an acute dermal toxicity test that was performed as a limit test with 2000 mg/kg test substance according to OECD Guideline 402. The test substance was MES as manufactured for the use in biocidal products and contained 30% MES resulting in an LC50 of > 600 mg/kg bw for the pure active substance. However, at this point it seems scientifically not justified to use the derived value of > 600 mg/kg bw for classification. Thus, the applicant would like to argue against a classification for acute dermal toxicity in category 3 based on a limit test performed with a diluted compound, which poses here a major problem.
Acute dermal toxicity can be estimated from the available tests:
• In the limit test for acute dermal toxicity only long-lasting irritant effects were observed. The exposure did not reveal any systemic effects.
• In the ADME study MES was applied dermally for 24 h. From this study a dermal absorption of less than 3 % was determined and systemic exposure is considered as very low.
• Moreover, in oral studies with single and repeated exposure the predominant effects of MES were local effects at the site of first contact indicating a low systemic toxicity of MES. The toxicity of the test substance is due to local effects on the mucous membranes in the gastro-intestinal tract even in repeated-dose toxicity studies.
Additional animal studies should not be performed:
• MES has corrosive properties. An additional animal study for acute dermal toxicity to prove that the LC50 after dermal application is considerably higher than 600 mg/kg and meets at least the cut-off value for Acute Tox. 4 or even for non-classification is considered unacceptable due to animal protection reasons.
• The local effects after dermal application of MES are covered by the classification as skin corrosive, subcategory 1C. An additional acute dermal toxicity study would not provide any additional scientific information.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Comment MES acute dermal toxicity_non-confidential-17.07.10.docx
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Comment MES acute dermal toxicity_confidential-17.07.10.docx

Dossier Submitter's Response

Thank you for your explanations. The tests of acute dermal toxicity were not conducted with pure substance but only with solutions of the MES substance. In absence of additional experimental data with pure active substance the classification applied dose was extrapolated to the corresponding dose levels. In our opinion, for safety reasons the classification of MES as Acute Tox. 3; H311 is fully justified.

RAC's response

Thank you very much. Noted.

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Germany		MemberState	6

Comment received

The data on acute toxicity via oral and dermal application summarized in the CLH report support the proposed classification as Acute Tox. 4 H302 and Acute Tox. 3 H311, respectively. It should be noted, however, that all four limit tests used for classification purpose (each one with dose level of 2000 mg/kg KG) are performed with commercially available solutions containing 4% and 30% of the active substance. For comparison with the classification criteria, applied doses are linearly extrapolated to the corresponding dose levels of the pure substance (i.e., 100% mecetroniumetilsulfat). Since mortality

observed at limit dose was below the LD50 response (resp. no deaths recorded), the proposed classification can be considered as rather conservative. This concerns specifically the classification as Acute Tox 3 H311, where no animals died in two limit tests with acute dermal application of the 4% and 30% solutions. Nevertheless, in absence of additional experimental data with the pure substance classification as Acute Toxicity category 4- H302 and Acute Toxicity category 3- H311 are supported. Additionally, as the calculation of the oral LD50 for the MES 30% solution was performed in this study (page 22), the same calculation should apply for all the other studies with the same tested concentration (i.e. repeated dose studies).

For the inhalation exposure, as the read across proposal to several other quaternary ammonium compounds (QACs) is suggested by the DS, the CLH report could include details on studies presented at the review by The Institute of Food Safety and Toxicology, Danish Veterinary and Food Administration (Thorup, I. 2000). In this publication:
- Wistar rats were exposed to an alkyl dimethyl ethyl benzyl ammonium compound at a concentration of 5.4 mg/L (maximum attainable) for one hour. This concentration leads to 100% death (Levenson 1965- quoted from Cutler & Drobeck 1970);
- A whole-body inhalation study on cetylpyridinium chloride with five rats per sex were exposed to air containing 0, 0.05, 0.07, 0.13 and 0.29 mg cetylpyridinium chloride dust/l for four hours (equal to 50, 70, 130 and 290 mg dust/m3). The particle size was less than 5 µm. The LC50 was 0.09 mg/l (90 mg/m3) 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). No deaths were seen among controls and all the deaths occurred within 4 days of exposure. Nasal discharge and chromodacryorrhoea (red discoloration around the nares) was found in all exposed groups and during the first week transient laboured breathing/ respiratory difficulty (most pronounced at the higher exposure levels) was seen. The remaining animals were killed after 14 days. Besides lesions in the eyes, no gross lesions attributed to the treatment were seen in these animals. Histopathological examination of lungs and other major organs were not carried out (Lin 1991). The author has calculated that the total cetylpyrimidinium chloride exposure at the LC50 level (0.09 mg/l) was about 4-8 mg/kg bw, and based upon this it was inferred that cetylpyrimidinium chloride could be more toxic by inhalation exposure than by oral or dermal exposure.
- A group of 196 farmers (with or without respiratory symptoms) were evaluated for the relationship between exposure to QACs (unspecified, exposure levels not given) and respiratory disorders by testing for lung function and bronchial responsiveness to histamine. After histamine provocation statistically significant associations were found between the prevalence of mild bronchial responsiveness (including asthma-like symptoms) and the use of QACs as disinfectant. The association seems even stronger in people without respiratory symptoms (Vogelzang et al. 1997).
Therefore, if reference to other homologue compounds is considered acceptable, hazard to aerosol inhalation would be of concern and classification would be required for toxicity via inhalation exposure to mecetronium ethyl sulphate.

Dossier Submitter's Response

Regarding acute dermal toxicity see response to comment no 5.

In repeated dose toxicity study the same calculation of the oral LD50 for theMES 30% solution was unnecessary. In repeated dose toxicity studies other concentrations of MES were used. Calculated doses were described in mg/kg bw/day.

Thank for information on acute inhalation toxicity studies on several other quaternary ammonium compounds (QACs). If the studies report were available it would be considering the possibility of using read across methods.

It should be noted, due to physicochemical properties of MES the generation of an aerosol of MES is rather difficult.
RAC's response
Thank you very much. RAC notes that there was not sufficient data to include read-across assessment in the RAC opinion. The other comments have been noted too.

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2017	Finland		MemberState	7
Comment received				
FI CA does not support the proposed classification Acute Tox. 3; H311 for mecetronium ethyl sulphate. Our view is that classification for Acute Tox. cannot be based on a study, in which none of the animals died and where only local skin effects were observed.				
Dossier Submitter's Response				
Regarding acute dermal toxicity see the response to comment no 5. please.				
RAC's response				
Thank you very much. Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Germany		MemberState	8
Comment received				
Classification as Skin Corr. 1C is supported. The CLH-report should be clearer with respect to which of the observed effects lead to the proposed classification (i.e., irreversibility, scars, fissures etc.). Also, observations from the acute toxicity test with dermal application of the substance appear to support this conclusion. The role of the (very limited) human data for the classification of the substance is not clear and should be addressed.				
Dossier Submitter's Response				
As mentioned in the CLH report (10.4.3) after exposure on mecetroniumetilsulfat 4% little or no signs of reversibility; observations might indicate irreversible tissue damage. Due to irreversibility of skin damage within 14 days of the study the classification as Skin Corr. 1C is most justified.				
RAC's response				
Thank you very much. Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2017	Finland		MemberState	9
Comment received				
According to the CLP criteria a substance is corrosive to skin when it produces destruction of skin tissue, namely, visible necrosis through the epidermis and into the dermis. The CLH report contains no information on observed necrosis. Local irritation effects were reported in both dermal irritation/corrosion study and dermal acute toxicity studies. FI CA considers that the criteria for Skin Corr. 1C is not met.				
Dossier Submitter's Response				
According to CLP criteria skin corrosion means the production of irreversible damage to the skin following the application of a test substance for up to 4 hours. As mentioned in the CLH report (10.4.3) the classification of undiluted MES substance as skin corrosive				

was based on the irreversibility of dermal changes after exposure on mecetroniumetilsulfat 4%. See also the response on comment no 8.
RAC's response
Thank you very much. Noted.

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2017	Germany		MemberState	10
Comment received				
The proposed classification is supported.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you very much. Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2017	Finland		MemberState	11
Comment received				
FI CA is concerned about the validity of the skin sensitisation test. It is stated in the CLH report that "mecetronium ethyl sulphate applied as 5% preparation (1,5% active component)" did not cause skin sensitisation. However, it is unclear whether this dose was used for the intradermal induction, topical induction or topical challenge. In addition, no explanation was provided for how the doses were selected based on the results of the pilot study and whether the doses chosen were high enough as described in OECD TG 406. Furthermore, no information related to the use of positive controls was included. Positive controls would have been important, because the result was considered negative.				
Dossier Submitter's Response				
No animals sensitised to Mecetroniumetilsulfat 30% in conducted tests. According to MES - DocIIIA6.1.5 document following concentrations used for induction: Intradermal: 0.5% in water or in FCA/water (concentration of the active component: 0.15%); 0.1 ml/ injection site. Topical: 10% in water (3% active component); 4 x 5 cm filter paper loaded with test solution, occlusive, removal after 48 h. Concentration caused very slight erythema and no edema in preliminary experiments. More details are available in IUCLID format document MES - DocIIIA6.1.5.				
RAC's response				
Thank you very much. Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2017	France		MemberState	12
Comment received				
We agree on the classification proposal, based on the results from the biodegradability tests and the proposed time weight average endpoints from the ecotoxicity tests. Nevertheless, there is no enough information regarding the so-called "kinetic study" on				

which the calculations of the time weight average concentrations are based. Could you please provide more information on the "kinetic study"? Are these calculations supported by the monitoring analysis when there are available?

Moreover, on page 91, it is indicated that the test substance was monitored in the second acute study on Daphnia magna, however no result on this monitoring was provided. Do these analyses support the calculation of the time weighted average concentrations?

Dossier Submitter's Response

To see details regarding kinetic study please refer to IUCLID format document i.a. MES - Doc III A7.4.1.1.

Direct comparison between monitoring and kinetic study is possible only for invertebrates chronic toxicity test, where both studies were performed with similar media/test design (start concentration, duration). Summary of these data is presented below.

During the kinetic study performed in line with OECD 211 the measured test item concentrations of the freshly prepared test solutions were 0.67, 2.19, and 6.80 µg a.i. per litre, corresponding with 115 - 270 % of nominal loading. In 24 h aged test solutions, test item concentrations decreased considerably to 28 – 54 % of nominal loading. The calculated time weighted averages (TWA) based on the two-compartment models fitted to the measured concentrations were 0.22, 0.53, and 2.44 µg a.i. Results from calculations are shown in Table below.

Nominal test item (µg/L)	Measured initial test item (µg/L)	TWA concentration (% of initial)	TWA concentration
24-h assay in purified drinking water			
0.30	0.67	32.6	0.22
0.81	2.19	24.2	0.53
5.93	6.80	35.9	2.44

During monitoring study, three times (once a week) test solutions with the nominal concentrations i.a. 0.30, 0.81, 5.93 µg a.i./L were analysed right after preparing. The same test solutions of the nominal concentrations i.a. 0.81 and 5.93 µg a.i./L were analysed also after 24h aging with algae. The solution with a nominal concentration of 0.30 µg a.i./L was neglected due to the results of the pretests (values < LOQ). The average time weighted means of mean measured initial and recalculated mean measured aged concentration (considering the mean leakage due to algae centrifugation) at test solution renewal were i.a. 0.42, 0.58, 4.31 µg/L, corresponding with 141, 71 and 73 % of the nominal concentrations. Results from calculations are shown in Table below.

Nominal conc.	0.30 µg a.i./L	0.81 µg a.i./L	5.93 µg a.i./L
Mean measured initial conc.	0.59 (±0.18)	1.00 (±0.24)	6.52 (±0.66)
% of nominal	195.1	122.8	109.9
Mean recalculated aged conc.	<LOQ	0.04 (±0.06)	2.68 (±0.58)
% of nominal	-	5.0	45.2
Time weighted mean con.	0.42 (±) 0.07	0.58 (±0.08)	4.31 (±0.56)
% of nominal	140.9	71.0	72.7

Both analytical measurements revealed that the MES concentrations are not stable during the test period. The high adsorptivity of the test substance may influence the test substance concentrations. From other aquatic studies it is known that MES is difficult to recover due its high potential for clustering and adsorption, resulting in an irregular distribution in the test vessels. However, since all effect data are based on mean measured values the study gives reliable results.

To see more details regarding monitoring of MES in the second acute study on Daphnia magna please refer to IUCLID format document MES - Doc III A7.4.1.2_02.

RAC's response

RAC thanks the MSCA for their comment and thanks to the DS for their response.

It seems the response by the DS explains only the OECD 211 Daphnia magna Reproduction Test by Bode Chemie (2008) and the IUCLID format document MES - Doc III 7.4.3.4 but not the mentioned Doc III A7.4.1.1 (BODE Chemie (1992)) OECD 203 Fish Acute toxicity test.

In addition to this several documents were made available to RAC giving further details for the acute and chronic testing. RAC agrees with the commenting MSCA that such informartion are relevant and should be incorporated into the dossier.
Time weighted average values were also used for one acute test on fish (A7.4.1.1), on daphnia (A7.4.1.2_02) and for the test on algae (A7.4.1.3). By the kinetic study, it was confirmed that analytical measurements revealed that the mecetronium ethyl sulfate concentrations are not stable during the test period. The extreme high potential to adsorption of mecetronium ethyl sulfate may influence the test concentrations. From other aquatic studies it is known that mecetronium ethyl sulfate is difficult to recover due its high potential for clustering and adsorption, resulting in an irregular distribution in the test vessels.

Date	Country	Organisation	Type of Organisation	Comment number
27.06.2017	Netherlands		MemberState	13

Comment received

Daphnia magna acute toxicity test:
The concentrations of the first acute Daphnia toxicity test were not measured because the test method was not sensitive enough. The effect concentrations were expressed as nominal. This is different from the acute fish toxicity test, in which the LC50 value was corrected by TWA. Should the effect concentrations be corrected in the first Daphnia acute toxicity test?

Algae study:
The EC50 and NOEC values are available in the table 75 but not described in the text. It is unknown whether the validity criteria were met or not. The TWA was used in this study. It seems that TWA value here used is different from the one in fish toxicity test. It should be clearly stated how and why the different TWA values are used.

Chronic toxicity tests:
Results of NOEC values for daphnia and fish tests are not clearly stated in the text. These should be indicated.

Dossier Submitter's Response

Daphnia magna acute toxicity test:
Since in the first Daphnia magna study the method of analysis proved to be not sensitive enough for the concentration range tested and there was no kinetic study which simulate test conditions according to OECD 202 method, the endpoints from this study had to be based on nominal concentrations. The second Daphnia magna study with more sensitive analysis method was performed and more reliable endpoints were received. Therefore, the effect on Daphnia magna exposed to MES is assessed and there is no need to correct endpoints from first acute Daphnia toxicity test.
Algae study:
The validity criterium of cell concentration in control cultures was met. However, there were no valid data available to consider if concentration of test substance was equal or higher that 80% of initial concentration during test. In order to overcome the shortcomings regarding test substance monitoring the "Kinetic Study" was initiated and used in calculation of MES concentration.
To see more details please refer to IUCLID format documents MES – Doc III A7.4.1.3.
Chronic toxicity tests:
NOEC values for daphnia and fish tests are presented in Table 81 of CLH report.

RAC's response

See also comment No 2 from the same MSCA.
RAC thanks the MSCA for their comment and to the DS for their response.
Concerning the first acute study on Daphnia RAC please see our response to comment by United Kingdom.
Concerning the algae study RAC notes the response by the DS.

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2017	United Kingdom		MemberState	14

Comment received

We feel further data is required to interpret some of the fate testing. We are unclear if the adaptations using silica gel and humic acid are relevant for assessing biodegradation for the purpose of classification. For example, for BODE Chemie, 2011a, b and c and BODE Chemie, 2013a and b details of IC concentrations over time and mass balance would be useful. This is important to understand the test validity in relation to IC concentrations and that degradation reflects solely the test item. The amounts silica gel employed are also unclear and important to determining how environmentally relevant these modifications are for classification purposes.

The CLH presents ecotoxicity endpoints based on time weighted averages which have been calculated based on a 'kinetic study'. Further details of this study and the methods of determining each TWA endpoint are required to consider the validity of the approach for the varied test systems relevant for acute and chronic classification.

It would also be useful to present details of the first Daphnia magna study (Confidential, 2000) to understand measured exposure concentrations and whether it is appropriate to base the endpoint on nominal concentrations.

Dossier Submitter's Response

Due to the quaternary ammonium compound MES has a high adsorption potential and its inhibition to bacteria adding silica gel balances the effects of toxicity with non-availability to the microorganisms.
Silica gel and humic acid used in the performed studies with quaternary ammonium compounds (QAC's) let to reduce the toxicity of these substances towards microorganisms and to avoid inhibition of the microbial activity. In the IUCLID format document MES – Doc III A7.1.1.2.1 weight of evidence approach and summary of publicly available information regarding using silica gel and humic acid in the biodegradability test systems in QAC's studies are provided.

To see details regarding kinetic study please refer to IUCLID format document i.a. MES - Doc III A7.4.1.1.
To see details regarding the first Daphnia magna study please refer to IUCLID format document MES - Doc III A 7.4.1.2.
Since in the first Daphnia magna study the method of analysis proved to be not sensitive enough for the concentration range tested and there was no kinetic study which simulate test conditions according to OECD 202 method, the endpoints from this study had to be based on nominal concentrations. The second Daphnia magna study with more sensitive analysis method was performed and more reliable endpoints were received. Therefore, the effect on Daphnia magna exposed to MES is assessed and there is no need to correct endpoints from first acute Daphnia toxicity test.

RAC's response

RAC thanks the MSCA for their comment and to the DS for their response.
The question if these modifications are environmentally relevant for the purpose of classification was not answered and is also not addressed in the weight of evidence by the dossier submitter (A7.1.1.2.1). RAC agrees with the commenting MSCA that to understand the test validity in relation to IC concentrations and to ensure that the measured degradation reflects solely the test item details of IC, concentrations over time and mass balance are needed. Some details were made available to RAC through the documents Doc III A7.1.1.2.1 and A7.1.1.2.1/01 to A7.1.1.2.1/07. RAC agrees with the commenting MSCA that such information is relevant and should be incorporated into the dossier.

RAC has assessed the available information on the test on ready biodegradability and performed a weight of evidence approach. Please refer to the final opinion document by RAC. Concerning the comment on the kinetic study please refer to answers on comments by France and Netherlands. Concerning the first acute study on Daphnia RAC agrees with the commenting MSCA that for this study a correction based on meassuered data or based on TWA concentrations would lead to a lower test result and consequently would be relevant for classification, however by the response of the DS it seems not possible.

PUBLIC ATTACHMENTS

1. Comment MES acute dermal toxicity_non-confidential-17.07.10.docx [Please refer to comment No. 5]

CONFIDENTIAL ATTACHMENTS

1. Comment MES acute dermal toxicity_confidential-17.07.10.docx [Please refer to comment No. 5]