Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Chloralose (INN); (R)-1,2-O-(2,2,2-trichloroethylidene)-α-D-gluco- furanose; glucochloralose; anhydroglucochloral

EC number: 240-016-7
CAS number: 15879-93-3

CLH-O-0000004852-71-03/F

Adopted

12 September 2014

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ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CHLORALOSE (INN); (R)-1,2-O-(2,2,2-TRICHLOROETHYLIDENE)-A-D-GLUCOFURANOSE; GLUCOCHLORALOSE; ANHYDROGLUCOCHLORAL

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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Substance name: chloralose (INN); (R)-1,2-O-(2,2,2-trichloroethylidene)-a-D-glucofuranose; glucochloralose; anhydroglucochloral
CAS number: 15879-93-3
EC number: 240-016-7
Dossier submitter: Portugal

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
26.03.2014	Germany		MemberState	1
Comment received				
The German CA supports the proposed classification and labelling as Aquatic Acute 1 and Aquatic Chronic 1 as well as the M-factors. Furthermore the German CA supports the proposed classification for Acute Tox. 4; H302 and Acute Tox. 4 *; H332.				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
The support is noted. However, for the oral route RAC concluded on Acute Tox. 3 – H301, based on the lowest LD_{50} of 212 mg/kg bw in female rats (see response to comment 3). As to acute inhalation toxicity: RAC decided that a recommendation for keeping Acute Tox. 4* – H332 or not cannot be made from a scientific point of view (see response to comment 4).				

Date	Country	Organisation	Type of Organisation	Comment number
28.03.2014	Sweden		MemberState	2
Comment received				
The Swedish CA do not support the proposed classification of chloralose as Acute Tox 4; H302. The Swedish CA support the proposed classification of chloralose as Acute Tox 4; H332. The Swedish CA support the proposed classification of chloralose as STOT SE 3; H336. The Swedish CA support the Portuguese CA's proposed environmental classification of chloralose as Aquatic Acute 1 and Aquatic Chronic 1 with Acute and Chronic M-factors of 10.				
Dossier Submitter's Response				
Thank you for your comments and support on classification of chloralose as Acute Tox 4; H332, as STOT SE 3; H336, as Aquatic Acute 1 and as Aquatic Chronic 1 with Acute and Chronic M-factors of 10. For the proposed classification of chloralose as Acute Tox 4; H302, please find our response below.				
RAC's response				
The (non-)support is noted. As to acute oral toxicity: RAC concluded on Acute Tox. 3 – H301, based on the lowest LD_{50} of 212 mg/kg bw in female rats (see response to comment 3). As to acute inhalation toxicity: RAC decided that a recommendation for keeping Acute Tox. 4* – H332 or not cannot be made from a scientific point of view (see response to				

comment 4).

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
28.03.2014	France		MemberState	3
Comment received				
Acute toxicity by oral route: Considering the high sex variability observed in the acute toxicity study by oral route, a classification Acute Tox 3 – H301 should be considered based on the LD_{50} of 212 mg/kg bw in females instead of the proposed Acute Tox 4 – H302 based on the combined male/female LD_{50} of 341 mg/kg bw.				
Dossier Submitter's Response				
Thank you for your comment. The study was conducted in compliance with EC Method B.1. Acute Toxicity (Oral). There were no deviations from this method. The method of determination of LD_{50} was Probit-Analysis (i.e. Finney's method, published by E Weber and combined with Bliss's method). The 70% to 95% confidence interval limits were calculated statistically according to Fieller's method. Although the sex variability, we used the combined male/female LD_{50} for rats estimated of 341 mg/kg bw due to the fact that this value has the higher significance limit of 95% compare to the LD_{50} of 212 mg/Kg bw for female with significance limit of 70%.				
RAC's response				
In line with the guidance, indicating that in general classification is to be based on the lowest LD_{50} value available, RAC concluded on Acute Tox. 3 – H301, based on the lowest LD_{50} of 212 mg/kg bw in female rats.				

Date	Country	Organisation	Type of Organisation	Comment number
28.03.2014	Sweden		MemberState	4
Comment received				
Acute oral toxicity: The Swedish CA does not agree to the proposed classification of chloralose as Acute Tox Cat 4; H302 In the acute oral toxicity study in the rat it could be noted that female rats were more sensitive than male rats. The LD_{50} value for female rats was determined at 212 mg/kg, whereas the LD_{50} value for male rats was 611 mg/kg and the LD_{50} value for male and female rats combined was 341 mg/kg. The Swedish CA proposes that the classification of chloralose should be based on the most sensitive sex (female) and consequently a classification Acute Tox Cat 3; H301 (range for classification in this category according to CLP Annex I, Table 3.1.2 is $50 < ATE \leq 300$) is warranted. Acute inhalation toxicity: The Swedish CA agrees to the proposed classification of chloralose as Acute Tox Cat 4; H332. The LC_{50} rat (4-hour nose only, particle) in the acute inhalation toxicity study in the rat was estimated at >1.99 mg/L (the highest concentration at which the actual exposure was considered certain). At the concentration of 1.99 mg/L one female animal died. At the concentration of 4.55 mg/L (highest concentration) another female animal died. However, since the actual exposure of the rats at the highest concentration of 4.55 mg/L was unclear				

(the exposure concentration varied by more than 15% of the mean value; only 40.9% of particles were less than 4 µm, the relative humidity was low) the study does not allow a conclusion regarding the LD_{50} value. Therefore it is appropriate to maintain the current minimum classification of chloralose as Acute Tox 4; H332.
Dossier Submitter's Response
Thank you for your comments. Acute oral toxicity: Although the sex variability, we used the combined male/female LD_{50} for rats estimated of 341 mg/kg bw due to the fact that this value has the higher significance limit of 95% compare to the LD_{50} of 212 mg/Kg bw for female with significance limit of 70%. Acute inhalation toxicity: Thank you for the support.
RAC's response
The (non-)support is noted. As to acute oral toxicity: RAC agrees that Acute Tox. 3 – H301, based on the lowest LD50 of 212 mg/kg bw in female rats, is indeed more appropriate (see response to comment 3). As to acute inhalation toxicity: RAC considers the results of the available study inconclusive for classification purposes. There is no information on whether this study was the basis for originally classifying chloralose as Xn; R20 under DSD, or whether it was based on other data. In the absence of adequate information it is not possible for RAC to determine whether this classification, which was translated into Acute Tox. 4* – H332 under CLP, is justified or not. Hence, a recommendation for keeping Acute Tox. 4* – H332 or not cannot be made from a scientific point of view.

Date	Country	Organisation	Type of Organisation	Comment number
26.03.2014	Germany		MemberState	5
Comment received				
An oral LD_{50}=341 mg/kg bw supports the removal of the "*" in the current classification of Chloralose (i.e., Acute Tox. Cat. 4 for 300<ATE≤2000 is justified).				
Dossier Submitter's Response				
Thank you for the support and comment.				
RAC's response				
The support is noted. However, RAC concluded on Acute Tox. 3 – H301, based on the lowest LD_{50} of 212 mg/kg bw in female rats (see response to comment 3).				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
28.03.2014	Sweden		MemberState	6
Comment received				
The Swedish CA agrees to the proposed classification of chloralose for STOT SE 3; H336. Narcotic effects were observed in humans and in animal studies.				
Dossier Submitter's Response				
Thank you for the support and comment.				
RAC's response				
The support is noted.				

Date	Country	Organisation	Type of Organisation	Comment number
26.03.2014	Germany		MemberState	7

Comment received
The criteria for classification in STOT SE3 cover transient respiratory tract irritation and narcotic effects. Chloralose has been used (in the past) as sedative, hypnotic, anaesthetic agent and management of alcohol withdrawal in humans. In addition, animal data also show transient effects of CNS depression. Since reversibility of effects is a significant discriminator for Cat. 3, and the observed narcotic effects were transient, a classification as STOT SE3 is justified and is therefore supported.
Dossier Submitter's Response
Thank you for the support and comment.
RAC's response
The support is noted.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
28.03.2014	Belgium		MemberState	8

Comment received
Based on the results of the acute aquatic toxicity test on the most sensitive species (*Daphnia magna*, 48hEC_{50}=0.027mg/l) it is justified to classify Chloralose, following the classification criteria of regulation 1272/2008, as Aquatic acute 1, H400. In view of the proposed classification and toxicity band for acute toxicity between 0.01mg/l and 0.1 mg/l, an M-factor for acute toxicity of 10 could be assigned. There are no chronic toxicity data available for all three trophic levels which implies that both the available NOEC (for one trophic level) and LC_{50} for the other trophic levels should be checked against the CLP criteria and the most stringent outcome should be taken to classify the substance. A NOEC is available for algae with *Pseudokirchnierella subcapitate* (formerly *Selenastrum capricornutum*) as most sensitive species with 72hNOErC= 0.02mg/l, the substance is considered as not rapidly degradable by which it should be classified as Aquatic chronic 1, H410 and $M_{chronic}$=1(0.01mg/l <NOEC <0.1mg/l). Based on the lowest LC_{50} of the other trophic levels (*Daphnia magna*, 48hEC_{50}=0.027mg/l), and the fact that the substance is not rapidly degradable, a classification with Aquatic chronic 1, H410 and M-factor of 10 (0.01mg/l <EC_{50} <0.1mg/l) should be applied. The most stringent chronic classification is based on the LC_{50} : Aquatic chronic 1, H410 with $M_{chronic}$=10 In conclusion : we agree with the proposed environmental classification by the Portuguese CA. Some minor comment: Aquatic toxicity results of the key studies are based on measurement of the concentration at the beginning and the end of the test in the range finding study (100mg/l) and were found >80% of nominal concentration. Despite the recent realization dates of the environmental studies and the test guidelines used, no concentrations were measured during the test itself. Based on the solubility, non volatility and non rapid degradability it can be assumed that also >80% of the nominal concentration was maintained. However in a second study with *Pseudokirchnierella subcapitata* (2005) the concentration dropped to 77% of nominal (0.01mg/l) after 72h. Is there an explanation given in the study report why

the concentration dropped <80%?
Dossier Submitter's Response
Thank you for the support and comment. No explanation was given in the study report since the validity criterion was based on the % of the measured initial concentration. The results from the range finding study for the second study with *Pseudokirchnierella subcapitata* (2005) show that, after 72h, concentrations were >80% of the measured initial concentration, and therefore fulfilled that validity criteria. However, comparing the 72h-measured concentration i.e. 0.0077 mg/L presented in study report, with nominal concentration (0.01 mg/L) a result of 77% was obtained.
RAC's response
The support and comment are noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.03.2014	France		MemberState	9
Comment received				
Environmental hazards FR supports the classification proposed by Portugal: - Aquatic acute 1 – H400 with M-factor 10 - Aquatic chronic 1 – H410 with M-factor 10				
Dossier Submitter's Response				
Thank you for the support.				
RAC's response				
The support is noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.03.2014	Sweden		MemberState	10
Comment received				
Minor comments: Page 9, section 2.1 History of the previous classification and labelling: It would have been helpful to the reader if it was clarified that the directive Dir. 98/8/EC is the Biocidal Product Directive. Page 27, section 5.1 Degradation, Table 21 Summary of relevant information on degradation: Interpretation of the results would have been facilitated if it was clarified under Results in the table what % at the different days is standing for. Page 30, section 5.3.2 Summary and discussion of aquatic bioaccumulation: It would have been valuable with a reasoning of log K_{ow}, since it is an important parameter for classification purpose when it comes to bioaccumulation potential. Page 35, section 5.5 Comparison with criteria for environmental hazard: It would have been valuable with information about the substance potential to bioaccumulate by reasoning of log K_{ow}.				
Dossier Submitter's Response				
Thank you for the comments.				

Page 9, section 2.1 History of the previous classification and labelling: We can agree that this information could be clarified. Page 27, section 5.1 Degradation, Table 21 Summary of relevant information on degradation: In fact, the % identified in table 21 are cumulative % and this clarification could be helpful. Page 30, section 5.3.2 Summary and discussion of aquatic bioaccumulation and Page 35, section 5.5 Comparison with criteria for environmental hazard: Although the reference to log K_{ow} is an important parameter for the bioaccumulation potential, the measured log K_{ow} was not considered to be valid. Therefore, the conclusion on this particular property was inconclusive since no further data was deemed necessary for this purpose. Nevertheless, the CLH proposal was not affect by this.
RAC's response
Noted.