Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

2,4,6,8-tetramethyl-1,3,5,7-tetraoxacyclooctane; metaldehyde

EC Number: 203-600-2
CAS Number: 108-62-3

CLH-O-0000001412-86-171/F

Adopted

22 September 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON 2,4,6,8-TETRAMETHYL-1,3,5,7-TETRAOXACYCLOOCTANE; METALDEHYDE

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: 2,4,6,8-tetramethyl-1,3,5,7-tetraoxacyclooctane; metaldehyde
EC number: 203-600-2
CAS number: 108-62-3
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
21.09.2016	United Kingdom	<CONFIDENTIAL>	Company-Manufacturer	1
Comment received				
Corrections: - Page 157: the metaldehyde DT50 in the sand water/sediment total system should read 714 days not 1000 days for the Kane, T. (2009) study - Page 157: the maximum metaldehyde DT50 in soil should read 19.5 days not 19.4 days for the Juozenaite, A. (2009) study - Page 170: The second sentence of the conclusion should read "DT50 values for the dissipation from the total system were 714 to > 1000 days" rather than "> 1000 days for both systems". -Table 43: The second reference to Gauvin, G.V. 2010 should be "Rat…" not "Dog…" and the respective Cat 1 and Cat 2 STOT RE cut-off values are 10 and 100 mg/kg bw/d.				
Dossier Submitter's Response				
Agreed on the proposed corrections.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.09.2016	Switzerland	Lonza Ltd	Company-Manufacturer	2
Comment received				
A complete set of short and long term ecotoxicological tests in fish, Daphnia, alga including an acute study on the Great Ramshorn Snail is available for the aquatic classification of metaldehyde. All studies were performed according to official guidelines				

and under Good Laboratory Practice. From the data the following can be concluded:

• No acute classification is required. The E/LC50 values for fish, daphnids, algae and water snails are > 1 mg/L (LC50 for the water snail Planorbarius corneus was > 200 mg/L).

• No chronic classification is required. The NOEC values for fish, daphnids and algae are > 1 mg/L.

• Metaldehyde is well biodegradable in the receiving compartment soil; however, it is not considered as ready biodegradable/rapid degradable in water systems. It has a low bioaccumulation potential.

Based on the above the manufacturer is in agreement with and supports the proposal of the Rapporteur Austrian Agency for Health and Food Safety (AGES) for metaldehyde that no environmental classification is required.

Dossier Submitter's Response

Agreed. No comment.

RAC's response

The test guideline OECD 204 "Prolonged Toxicity Test: 14-Day Study" has been withdrawn due to test design limitations and it is not considered suitable for generating chronic (long-term) toxicity data. The ECHA guidance Chapter R.7b: Endpoint specific guidance Version 4.0 June 2017 on page 30f states "*Only such studies can be regarded as long-term fish test, in which sensitive life-stages (juveniles, eggs, larvae) are exposed. Thus, tests performed according to OECD 204 (Fish, Prolonged Toxicity Test: 14-Day Study (OECD 1984)) or similar guidelines cannot be considered suitable long-term tests. They are, in effect, prolonged acute studies with fish mortality as the major endpoint examined.*". The study of [redacted] (1990b) must not be regarded as long-term fish test. This is in line with ECHA guidance.

RAC concludes that there is a data gap on chronic (long-term) aquatic toxicity for fish and a second data gap for gastropod molluscs. Metaldehyde is a molluscicide and the gastropod molluscs are, beside fish, the most sensitive species for acute (short-term) aquatic toxicity and other gastropod molluscs may be even more sensitive. The classification should be reconsidered in the future if further data on chronic (long-term) aquatic toxicity for gastropod molluscs becomes available. This might include data from efficacy studies if usable for classification purposes or gastropod molluscs studies following the new OECD Test Guidelines 242 or 243.

The derived endpoint from Egeler et al. (2007) is not justified and instead an EC_{50} at the end of exposure at 48 hr must be used. RAC notes that the raw data for the 4 replicates should be used for the statistical derivation of the 48 hr EC_{50} value however these data are not documented in the study report. An amendment of the original study report could include the raw data and a reassessment of the 48 hr EC_{50}. RAC concludes that until this is available for the 48 hr (immobility at termination of exposure) EC_{50} for Great Ramshorn Snail (*Planorbarius corneus*) for the study Egeler et al. (2007) a value of 78.2 mg/L (nominal) should be used for the purpose of classification.

In addition RAC has reassessed the study by [redacted] (1990b) as a prolonged acute study and a 21 d EC_{50} (body weight) was derived from this study. RAC concludes that the 21 d EC_{50} (body weight) of 89.1 mg/L (nominal) for *Oncorhynchus mykiss* for the study [redacted] (1990b) should be used for the purpose of classification. RAC notes that this value is just above the highest test concentration of 75 mg/L and notes the remaining uncertainty expressed by the confidence limits.

RAC agrees with the proposal and argumentation of the dossier submitter to not classify metaldehyde as rapidly degradable.

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2016	France		MemberState	3
Comment received				
We agree with the classification proposal regarding HH.				
Dossier Submitter's Response				
Agreed. No comment.				
RAC's response				
Noted.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2016	Germany		MemberState	4
Comment received				
It is supported not to classify metaldhyde for carcinogenicity. However, mechanistic information to support the decision for not taking into account mouse liver adenomas for classification is missing.				
Dossier Submitter's Response				
Agreed. No mechanistic data are available. However, no dose dependent increase was observed for hepatocellular carcinomas and historical control data from two other studies conducted at the same laboratory as the first study in mice (Chun, Wagner; 1993) show that hepatocellular adenomas have been reported in control group mice of the same strain, sex and source (Charles River Laboratories, Portage, MI) in incidences ranging from 6/60 to 13/60. No HCD is available for the second mouse study (Beyrouty; 1998). However, males may have exceeded the tolerable limit in this study since in the 90-day preliminary mouse study (Gill and Wagner, 1990) liver toxicity was observed at all doses ≥ 100 ppm (19 mg/kg bw/day and above). This liver toxicity may have contributed to the incidence of adenomas observed in the long term carcinogenicity studies.				
RAC's response				
Noted. 1000 ppm in the Beyrouty study induces some liver toxicity, but lack of increased mortalities, clinical signs or other signs of severe toxicity do not support that the MTD was exceeded.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2016	Germany		MemberState	5
Comment received				
It is supported not to classify metaldhyde for mutagenicity.				
Dossier Submitter's Response				
Agreed. No comment.				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2016	Germany		MemberState	6
Comment received				
Based on the rat data presented it is supported not to classify metaldhyde for reproductive toxicity. However, considering that in the dog short term toxicity studies atrophy of the testicular germinal epithelium was observed a rational is missing, why this is not taken into account for classification and labelling as reproductive toxicant.				
Dossier Submitter's Response				
No adverse effects on male reproductive organs were found in other species in acute, short, long-term and reproduction studies. Furthermore, reproductive parameters including mating, fertility and gestational indices as well as gestational length were not affected in the two generation study. Therefore, atrophy of the testicular germinal epithelium in dog studies was not considered relevant for a classification proposal for reproductive toxicity but should be covered by STOT RE2.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2016	Germany		MemberState	7
Comment received				
It is supported to classify metaldhyde for acute oral toxicity with H301 (acute tox 3).				
Dossier Submitter's Response				
Agreed. No comment.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2016	Germany		MemberState	8
Comment received				
It is supported not to classify metaldhyde for eye irritation.				
Dossier Submitter's Response				
Agreed. No comment.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2016	Germany		MemberState	9
Comment received				
It is supported not to classify metaldhyde for skin sensitization.				
Dossier Submitter's Response				
Agreed. No comment.				

RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2016	Germany		MemberState	10
Comment received				
It is supported not to classify metaldhyde for STOT-SE. In line with the MSCA we agree that the lethal effects observed at dose levels deserving classification for STOT-SE are already covered by the proposed classification for acute toxicity.				
Dossier Submitter's Response				
Agreed. No comment.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2016	Switzerland	Lonza Ltd	Company-Manufacturer	11
Comment received				
Our weight-of-evidence view is that the effects seen at high dose levels cannot be considered as scientifically sound and thus casts sufficient doubt upon the overall conclusion of classification being required. The salient aspects of the two studies are given in the attached Word document *ECHA note: An attachment was submitted with the comment above. Refer to non-confidential attachment No. 1 (at the bottom of this document).*				
Dossier Submitter's Response				
Histopathological findings in the in the mid dose group (60 mg/kg bw/day) in the 26-week study in dogs: We agree, that is hard to differentiate in the 26-week dog study, if the testes effects were treatment related in the mid dose group because in the control group also atrophy in the testes at a similar level of severity and incidence was observed. However, at the mid dose level of 60 mg/kg bw/day also atrophy of the prostate was observed which was not detected in the control group. This effect also occurred (at a slightly lower incidence) in the highest dose group. Exclusion of effects in the highest dose group in the 52-week study in dogs (Leuschner 2013) due to possible exceedance of the MTD: The MTD (maximal tolerated dose) is defined by an approximately 10% reduction in body weight gain (Guidance on the Application of the CLP Criteria, Version 4.1, June 2015 ECHA). The MTD was not reached up to a dose level of 90 mg/kg bw/day in a valid 26-week study in dogs. Furthermore, in a 4-week dose range finding study dose levels of 10, 30 and 90 mg/kg bw/day were proposed for the 52-week main study by the study director. Nevertheless, the MTD might be exceeded in the 52-week dog study of Leuschner (2003), as the body weight gain appeared to be reduced in the high dose group, however, no statistical significance was noted (see Table 33 of the CLH report). Excessive toxicity, for instance toxicity at doses exceeding the MTD can cause effects such as cell death (necrosis) (Guidance on the Application of the CLP Criteria, Version 4.1,				

June 2015 ECHA). However, atrophy of the testes was also observed at similar dose levels in the 26-week study in dogs, where the MTD was not exceeded. Therefore the testes effects in the 52-week study in dogs (Leuschner 2003) should be considered treatment related.

Mortality in the 52-week study in dogs (Leuschner 2013): No mortality was observed in the control and low dose group in the 52-week study in dogs (Leuschner 2003). Therefore, and also in accordance with the pathology report, mortality seen in the mid and high dose group should be considered treatment related.

RAC's response

The question of whether the MTD has been exceeded should be discussed in relation to carcinogenicity study, but are not an issue to disregard effects seen in repeated dose studies.
The application of guidance values for dogs will be prepared for discussion at the RAC meeting.

Date	Country	Organisation	Type of Organisation	Comment number
21.09.2016	United Kingdom	<CONFIDENTIAL>	Company-Manufacturer	12

Comment received

Repeated dose toxicity
There is information from the ECHA RAC that the RAC prefers to generally start with the guidance values for the 90-day oral rat study, to adapt these 90-day rat guidance values for different durations of exposure to rats and then to use the original or duration-adjusted rat guidance values without further changes for test results with other animal species. Thus for durations of 26- and 52-weeks the 90-day cut-off values for STOT RE 2 are reduced to 50 and 25 mg/kg bw/day (i.e 100 divided by 2 and 4, respectively). If these values were to be applied to the metaldehyde data the effects triggering STOT RE 2 would be above the cut-off values. Thus metaldehyde does not meet the criteria for a STOT RE 2 classification.

Dossier Submitter's Response

Currently in the Guidance on the Application of the CLP Criteria (Version 4.1, June 2015 ECHA) there is no advice on the use of rat-specific guidance values for dog studies.
We do not agree to adjust the 90-day rat guidance value for exposure duration for dog studies, without life time assumptions, because, based on the difference in life span, a 1 year dog study (~8% of life span) is almost comparable with the duration of the rodent 90 day study (10% of life span) (Dose limits for classification with R48 based on dog studies, The Netherlands, 2006, ECBI/64/06).
However, we are aware that RAC accepted lower cut-off values for 13 week and 52 week dog studies (13 week study: 10 mg/kg bw/day for STOT-RE 1 and 100 mg/kg bw/day for STOT-RE 2; 52 week study: 2.5 mg/kg bw/day for STOT-RE 1 and 25 mg/kg bw/day for STOT-RE 2) (cf. RAC opinion on carbetamide 2015). We could agree to extrapolate rats guidance values for allometric scaling, due to differences in the metabolic rate of larger animals having a slower metabolism than small ones resulting in higher internal exposure at the same dose level administered.
We would appreciate if RAC could clearly explain its cut off values for dog studies in its opinion on metaldehyde and if the respective values and the explanation could be included in the ECHA Guidance on the Application of the CLP Criteria.

RAC's response

The application of guidance values for dogs will be prepared for discussion at the RAC meeting.

The RAC opinion on Carbetamide may not be a good example to discuss lower cut-off values for dogs as the effects seen in a 4-week dog study below the guidance values were not seen in studies of longer durations (below the guidance values). The cut-off values taken were identical to those for the rat.

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2016	Germany		MemberState	13
Comment received				
It is supported to classify metaldehyde for specific target organ toxicity after repeated exposure (STOT RE 2, H373 / Testis).				
Dossier Submitter's Response				
Agreed. No comment.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2016	United Kingdom		MemberState	14
Comment received				
Ecotoxicity: We feel the ecotoxicity endpoints from the Egeler et al 2007 study should be based on immobility at 48 hours and not 24 hours after the study terminated. This is consistent with other ecotoxicity endpoints for hazard classification. Given the test species is the only snail data and metaldehyde is a molluscicide, this is important for classification. We feel this should include consideration of any EC50 value as a surrogate for chronic classification. Given ecotoxicity data is only available for one snail species and other gastropod molluscs may be more sensitive, the classification should be reconsidered in the future if further data becomes available. This might include data from efficacy studies if usable or snail studies following new OECD Test Guidelines 242 or 243. The OECD TG 204 has been withdrawn due to test design limitations and it is not considered suitable to fulfill a chronic endpoint. ECHA, 2016 state that only studies in which sensitive life-stages (juveniles, eggs, larvae) are exposed are regarded as long-term fish tests. Therefore the OECD TG 204 (Fish, Prolonged Toxicity Test: 14-Day Study (OECD, 1984) is not considered a suitable long-term test as it is in effect a prolonged acute study with fish mortality as the major endpoint. On this basis we feel the surrogate approach should be employed for the chronic toxicity to fish endpoint. We note that considering the lowest 96-h LC50 of 75 mg/l for a non-rapidly degradable substance would result in Aquatic Chronic 3. References: • Egeler, P., Goth, M., Knoch, E. (2007) Metaldehyde- A study on the toxicity to the Great Ramshorn Snail (Planorbarius corneus) over 48 hours] • ECHA (2016) Guidance on Information Requirements and Chemical Safety				

Assessment. Chapter R.7b: Endpoint specific guidance, version 3.0. February 2016.

Dossier Submitter's Response

Comment on the immobilisation endpoint derived from the study by Egeler et al.:
Taking into the account the effects during the exposure period (48 h) the EC_{50} might be considered to be between 19 and 41 mg/L. At 19 mg/L 50% immobilisation (after agitation of the vessels) was observed, at the next highest concentrations at 41 mg/L 100% immobilisation was observed. However at this concentrations all snails showed mobility after agitation of the vessel. Only at the two highest concentrations (91-200 mg/L) immobility between 85 and 100% was shown.

Tab. 6: Summary of observations concerning the behaviour of the snails during the exposure period.

Nominal concentration [mg/L]	Time [h]	Number of snails introduced	Number of mobile snails	Number of snails mobile after agitation of the vessels	Number of immobile snails after agitation of the vessels	Number of snails with leaking body fluid
Control	24	20	20	0	0	0
9	24	20	20	0	0	0
19	24	20	19	1	0	0
41	24	20	7	13	0	0
91	24	20	1	0	19	0
200	24	20	2	0	18[a]	0
Control	48	20	20	0	0	0
9	48	20	20	0	0	0
19	48	20	10	10	0	0
41	48	20	0	20	0	0
91	48	20	0	3	17	0
200	48	20	0	0	20[a]	0

[a]: Snails lying on the lateral side, foot retracted into shell.

After transfer to non-spiked medium, all animals up to the highest test concentrations recovered and were mobile at the end of the 24 h post-exposure period.

Tab. 5: Summary of observations concerning the mobility of the snails during post-exposure.

Nominal concentration [mg/L]	**Control**	**9**	**19**	**41**	**91**	**200**
0 h (start of exposure)						
Total Introduced:	20	20	20	20	20	20
n:	4	4	4	4	4	4
3 h of post-exposure						
Total Immobile:	0	0	0	2	0	10
n:	4	4	4	4	4	4
6 h of post-exposure						
Total Immobile:	0	0	0	0	0	7
n:	4	4	4	4	4	4
24 h of post-exposure						
Total Immobile:	0	0	0	0	0	0
n:	4	4	4	4	4	4

n = number of replicates

In conclusion, we agree with the comment of UK that the 48 h EC_{50} might be between 19 and 41 mg/L instead of the proposed endpoint of EC_{50} > 200 mg/L (taking into account recovery). However, it should be considered that the change of the endpoint does not change the acute classification of the active substance metaldehyde as the new endpoint is clearly > 1 mg/L.

Comment regarding the use of the acute fish endpoint for the chronic classification:
AT agrees on the comment by UK considering the prolonged toxicity test with fish. No effects on eggs, juveniles or reproduction were tested in the 21 d test. Taking into account the data requirements for plant protection products an early life stage or fish full life cycle test was not required at the time of application.
Considering the ECHA Guidance (2016) it might be justified to base the chronic risk assessment on the lowest LC_{50} for fish and to withdraw the NOEC value of the 21 d prolonged fish test. In this case a chronic classification of aquatic chronic cat. 3 would be justified (LC_{50} > 10 < 100 mg/L).
Taking into account the available chronic data on aquatic invertebrates (NOEC = 90 mg/L) and algae (NOEC = 25 mg/L) a chronic classification would not be triggered.
In conclusion, AT is of the opinion that this might be a point of discussion as this issue was commented by UK only. Other Member States agreed on the classification proposed by AT. However, taking into account the available data (fish most sensitive species, beside of aquatic snails) the proposed classification of aquatic chronic cat. 3 might be justified.

RAC's response

RAC agrees with the commenting member state and with the response of the dossier submitter that the derived endpoint from Egeler et al. (2007) is not justified and instead a EC_{50} at the end of exposure at 48 hr must be used.

RAC agrees with the commenting member state and with the response of the dossier submitter that the study of [redacted] (1990b) must not be regarded as long-term fish test. This is in line with ECHA guidance.

Metaldehyde is a molluscicide and the gastropod molluscs are, beside fish, the most sensitive species for acute (short-term) aquatic toxicity and other gastropod molluscs may be even more sensitive. RAC agrees with the commenting member state that the classification should be reconsidered in the future if further data on chronic (long-term) aquatic toxicity for gastropod molluscs becomes available. This might include data from efficacy studies if usable for classification purpose or gastropod molluscs studies following the new OECD Test Guidelines 242 or 243.

Date	Country	Organisation	Type of Organisation	Comment number
23.09.2016	Belgium		MemberState	15

Comment received

All LC(E)50s and NOECs for the 3 trophic levels are >1 mg/l. The substance is not rapidly degradable. Thus we agree with the Austrian CA that classification for the environment is not warranted.

Some editorial or/and minor comments :
It is not always clear from the tables if reference is made to a chapter in the CLH report or the DAR or the annexed additional reports to the CLH report f.i. in Table 8 "summary of physicochemical properties" : conclusion/comments : for details see B 8.4 :which is not a chapter from the annexes to the CLH report (additional reports) but a chapter from the DAR.
Furthermore the references are confusing : f.i. hydrolysis (table 8) : Carpenter M, 1989 while in chapter 7.3.1 : Carpenter, M. 1989a Hydrolysis of Metaldehyde as a function of pH at 25°C.
In table 8 it is mentioned that Hydrolysis and phototransformation were not performed GLP, while in the description of those studies it is said that they are GLP.

There is an error in the data given in the summary on environmental distribution (p175).

These are not the same as in the description of the adsorption/desorption and volatilisation studies.
Dossier Submitter's Response
Environmental classification: Agreed. No comment, please refer to comment by UK (No. 14). Some editorial or/and minor comments: Agreed on the proposed editorial/minor corrections.
RAC's response
Noted by RAC.

Date	Country	Organisation	Type of Organisation	Comment number
14.09.2016	Germany		MemberState	16
Comment received				
We support the decision for no need of environmental classification and labelling.				
Dossier Submitter's Response				
Agreed. No comment, please refer to comment by UK (No. 14).				
RAC's response				
Noted by RAC.				

Date	Country	Organisation	Type of Organisation	Comment number
22.09.2016	France		MemberState	17
Comment received				
We agree with the classification proposal regarding environmental hazard.				
Dossier Submitter's Response				
Agreed. No comment, please refer to comment by UK (No. 14).				
RAC's response				
Noted by RAC.				

NON-CONFIDENTIAL ATTACHMENTS

1. Comment STOT RE Metaldehyde 2nd CHL proposal Lonza 22.09.2016. [Please refer to comment(s) No. 11]