COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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Last data extracted on 10/12/2012

Substance name: Metaldehyde
CAS number: 108-62-3
EC number: 203-600-2
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
07/12/2012	France		MSCA	1
Comment received				
FR agrees with the classification proposal on human health.				
Date	**Country**	**Organisation**	**Type of Organisation**	**Comment number**
05/12/2012			Individual	2
Comment received				
This substance is very dangerous for pets when is used as poison for snail in gardening.				
Date	**Country**	**Organisation**	**Type of Organisation**	**Comment number**
04/12/2012	Switzerland	Lonza Ltd	Company-Manufacturer	3
Comment received				
p.7 and p. 171: Based on the available data the environmental hazard classification should be: DSD: R52/53 CLP: Aquatic Chronic 3, H412				
Date	**Country**	**Organisation**	**Type of Organisation**	**Comment number**
03/12/2012	Spain		MSCA	4
Comment received				
In general terms, the Spanish CA supports Austria proposal to establish a harmonised classification & labelling for metaldehyde.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
06/12/2012	Germany		MSCA	5
Comment received				
We support the proposal to classify Metaldehyde for Acute Toxicity, cat. 3 (H301). The lowest LD50 value was shown to be below 300mg/kg bw in an OECD401 study in the rat but above 50 mg/kg bw. Hence the criteria set in Reg (EC) No 1272/2008 are met.				
Date	**Country**	**Organisation**	**Type of Organisation**	**Comment number**
03/12/2012	Spain		MSCA	6
Comment received				
p. 42 Summary and discussion on acute toxicity				

Acute oral toxicity
The Spanish CA supports the proposed classification of metaldehyde as Xn, R22: Harmful if swallowed according to Directive 67/548/EC (limits 200 < LD50 ≤ 2000 mg/kg bw/day) and as Acute Tox 3 (oral) H301: Toxic if swallowed according to Regulation EC 1272/2008 (limits 50 < ATE ≤ 300 mg/kg bw/day).

This classification is based on to the LD50 value in female and male (LD50 = 283 mg/kg bw, between 210-382 mg/kg bw) obtained in the oral toxicity study in rats (Jones J, Collier T; 1987).

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
06/12/2012	Germany		MSCA	7

Comment received

We support the proposal to classify Metaldehyde for Specific Target Organ Toxicity after repeated exposure. Effects that should be considered include atrophy observed in the testis in 26 and 52 week dog studies and probably also atrophy observed in prostates in the same studies at similar dose levels Decision whether category 1 or 2 is appropriate due to severity of effects should be discussed by ECHA. Occasional mortality for unknown reasons in dogs and neurological effects in rats can be considered supportive for the proposal.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
03/12/2012	Spain		MSCA	8

Comment received

p. 77 to 79 Summary and discussion of repeated dose toxicity findings for classification according to DSD and for classification as STOT RE according to CLP Regulation.

The Spanish CA supports the proposed classification of metaldehyde as Xn; R48/22 (Harmful: danger of serious damage to health by prolonged exposure if swallowed) based on Directive 67/548/EEC and as STOT RE Cat. 2, (H373: May cause damage to organs through prolonged or repeated exposure) according to Regulation EC 1272/2008.
Classification is based on several liver effects observed in the mouse 90 days study (Gil M, Wagner C, 1990), below the cut-off values for R48/22 and for STOT RE cat. 2 H373, according to Directive 67/548/EC and CLP Regulation respectively. Effects on the liver were observed in a dose related manner from the doses of 19/24 mg/kg bw/day in male and female respectably: hepatocellular hypertrophy, inflammation, necrosis and anisokaryosis. This dose is below the cut-off value for the DSD classification criteria (< 50 mg/kg bw/day) and the CLP Regulation criteria (< 100 mg/kg bw/day).

Other effects that can be taken into consideration to support this classification are observed in the followings studies:
- In the study of 28 days in rat (Van Miller J; 1989), most of the surviving animals showed dose-related from the lowest doses (197/233 mg/kg bw/day in male and female respectably): hepatocellular hypertrophy and sporadic foci of hepatocellular degeneration. This dose was the lowest dose used in the study, it is close to the DSD classification criteria (< 150 mg/kg bw/day) and it is below the CLP Regulation classification criteria (< 300 mg/kg bw/day).
- In the study of 1 year in dog (Leuschner J, 2003) at the doses lever of 10 mg/kg bw/day (below the cut off values of 12.5 for DSD classification criteria and 25 mg/kg bw/day for CLP Regulation criteria) and at the doses level of 30 mg/kg bw/day (slightly above the cut off CLP Regulation criteria), atrophy, degeneration of testicular germinal epithelium and suppurative prostatitis were observed. Effects in testes were within historical background data for atrophy and degeneration of the germinative epithelium performed at LPT KG Germany during the years 2003-2006, time period in which the study was conducted. However, at the doses lever of 30 mg/kg bw/d (slightly above the cut off CLP Regulation criteria, two animal (1/4 male and 1/4 female) were found dead. The study clearly shows that these deaths are considered treatment-related.

For the Spanish proposal, the Haber's rule has been used to adjust the standard guidance values from studies of 90-day duration to studies of longer or shorter durations and to use these values for different species (in line with the recent RAC opinions).

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
07/12/2012	France		MSCA	9

Comment received

We agree with the conclusion raised based on the fate and behaviour of metaldehyde, i.e. the active substance is not considered as ready biodegradable/rapid degradable.
The 2nd ATP on 1272/2008 regulation allows the use of data on species other than fish, crustacean and alga but "Data on other species (e.g. Lemna spp.) shall also be considered if the test methodology is suitable." We therefore agree to use additional species for classification purposes. However, we do not agree to use the efficacy trial on Pomacea canaliculata to assess the acute and chronic toxicity of metaldehyde (Scholtz, 2004). Indeed, the proposed efficacy trial could not be related to any test guideline contrary to the Planorbarius corneus acute toxicity that is a GLP test with a test design based on OECD 202.
Moreover, the efficacy trial on Pomacea canaliculata has been conducted in a rice paddy in Philippines and with a 10% pelleted formulation. The test being performed with a granular formulation could have an impact on the behaviour of metaldehyde. Indeed that EFSA journal (2010) on the peer review of the pesticide risk assessment of the active substance metaldehyde indicated that :
"The representative product assessed, 'Metarex', is formulated as a granular bait. Satisfactory data on the kinetic release rate of metaldehyde from this specific product was provided and used to appropriately parameterise the FOCUS models and calculate the soil predicted environmental concentrations (PEC, as presented in Appendix A). It is important to note that these PECs in soil, surface water, sediment and groundwater are specific to the release rate characteristics of the formulated 'Metarex' product only. Therefore, the PECs in this conclusion should not be extrapolated to other products, as these will exhibit different release kinetics. Data on release rates from each different formulated product will be required for the calculation of PECs specific for each product."
No analytic measurements were available. No raw data allow to be sure of the mortality reported.

In the draft CLH report, this test has been used to estimate the acute and chronic toxicity. As explained above we consider the acute endpoint as poorly reliable. Moreover, no chronic endpoint could be derived from the efficacy trials as there is no information on chronic effect, i.e. on reproductive parameters.
Thus we consider that there is no adequate chronic toxicity data available on molluscs. Based on the 2nd ATP of Re (EC) 1272/2008, for non ready biodegradable/rapid degradable active substances, the chronic classification should be based on acute toxicity data. We therefore propose to consider the Planorbarius corneus acute toxicity test (Egeler et al., 2007). We would consider this value as more relevant for acute hazard, in particular as the test item was maintained constant in the test vessels (measured concentrations were in the range of 80-98% of nominal), and as the test followed suitable method (OECD 202). However, the current EC50 was calculated based on observations made 24 hours after the 48-hour exposure period. Thus, it might be interesting to recalculate the EC50 based on the data at 48 hours when individuals were still exposed to metaldehyde. This will be more in line with the OECD guideline 202, on which the test was based. At 48 hours, 85 and 100% immobility has been reported at 91 and 200 mg/L, respectively. We do not have the percentage of mobility observed at 9, 19 and 41 mg/L. We can therefore not precise our proposal for hazard classification according to Regulation EC 1272/2008. If 48-hours EC50 on Planorbarius corneus is found to be between 10 and 100 mg/L, then a category chronic 3 could be proposed according to Regulation EC 1272/2008 and a R52 according to Directive 67/548/EEC.
Regarding the acute aquatic toxicity, the table under 5.4.5 (page 169) indicates that the Planorbarius corneus acute toxicity test (Egeler et al., 2007) is not GLP, this is incorrect (see summary of the test under 5.4.4 page 166 and Draft Assessment Report on metaldehyde for inclusion of metaldehyde in Annex I of 91/414 directive of January 2006).

Date	Country	Organisation	Type of Organisation	Comment number
07/12/2012	United Kingdom	Metaldehyde Task	Industry or trade association	10

		Force		

Comment received

Consultation on the proposed Harmonised Classification of Metaldehyde Comment on behalf of the Metaldehyde Task Force (MTF) 7 December 2012

ECHA Consultation on the classification of Metaldehyde

Current proposal by Austria for the aquatic environment

In the document "CLH report. Proposal for Harmonised Classification and Labelling" dated 30 January 2012, submitted by the Austrian Agency for Health and Food Safety (AES), the following harmonised classification has been proposed for aquatic toxicity:
According to the CLP Regulation:

Hazardous to the aquatic environment – Aquatic Chronic 2, H411: Toxic to aquatic life with long lasting effects
According to the DSD criteria:

R51/53 Very toxic to aquatic organisms, may cause long term effects in the environment
It is noted that the classification R51/53 in the CLH report has been incorrectly recorded as referring to "Very toxic to aquatic organisms" instead of "Toxic to aquatic organisms".

EU review of metaldehyde

Metaldehyde was recently reviewed under 91/414/EEC and included in Annex I to that Directive, as detailed in Commission Implementing Directive 2011/54/EU of 20 April 2011 with entry into force on 1 June 2011 (as published in the *Official Journal of the European Union*) and transposed into Annex I of Regulation (EC) No. 1107/2009 by Commission Implementing Regulation (EU) No. 540/2011 of 25 May 2011.
As part of the review it was concluded that the classification and proposed labelling with regard to ecotoxicological data is as follows:
R52/53. Harmful to aquatic organisms. May cause long-term adverse effects in the aquatic environment
This is as detailed in the list of endpoints appearing in "Conclusion on Pesticide Peer Review. Conclusion on the peer review of the pesticide risk assessment of the active substance metaldehyde" published in the EFSA Journal 2010;8(10):1856 and is based on the most sensitive aquatic species as follows:
Oncorhynchus mykiss – 96 hr LC50 75 mg/L
Daphnia magna – 48 hr LC50 >90 mg/L
Planorbarius corneus – 48 hr LC50 >200 mg/L
Desmodesmus subspicatus – 72 hr LC50 >200 mg/L
The worse case LC50 of 75 mg/L, found in *O. mykiss,* and the substance not being readily biodegradable form the basis of the proposed classification R52/53.

Comment on the current proposal for aquatic classification

In the current CLH report submitted by Austria, an additional study has been considered as part of the evaluation of the aquatic toxicity. The efficacy study by Scholtz (2004), summarised on page 167 of the report, investigates the toxicity of metaldehyde to the Golden snail *Pomacea canaliculata*. The LC50 has been recalculated by AES to give an LC50 > 3.33 mg/L.
Because metaldehyde is a molluscicide, the potential toxicity to non-target molluscs was raised during the EU review of metaldehyde. A study with *Planorbius corneus* was conducted (by the notifier Lonza) to address this and the EC50 of >200 mg/L was taken to the Annex I list of endpoints as discussed above. The study was fully GLP, and followed the most appropriate regulatory guideline. Subsequently, another aquatic snail, *Gyraulus chinensis* has been tested and the 96-hour LC50 was >100 mg/L. Again the study was fully GLP and followed the most appropriate regulatory guideline.
It is noted that the study by Scholtz is an efficacy study looking at a pest species (*P. canaliculata*). It is not conducted for the purpose of establishing an LC50. The study was not GLP compliant, was non-guideline, has no raw data and there does not appear to be a control. On this basis the data do not appear to be relevant or robust and the lack of controls would make the reliability of recalculated endpoints questionable. Based on the information available for this report it is considered that the data are 'not reliable' (Klimisch score 3) and therefore should not be included in the assessment. The use of this data to set the ecotoxicological endpoint is considered unjustifiable both on scientific

grounds and also on the point of using efficacy data in this way.
On this basis, it is proposed that the study by Scholtz should not be considered for the purposes of classification. Two rigorously conducted studies (one conducted for the EU review and another subsequently) have demonstrated that the LC50 is >200 mg/L and >100 mg/L, respectively.
It is considered that the worst-case aquatic endpoint should be as agreed during the EU review of metaldehyde, *O. mykiss* – 96 hr LC50 75 mg/L. On this basis the classification for aquatic toxicity should be as follows:

DSD - R52/53. Harmful to aquatic organisms. May cause long-term adverse effects in the aquatic environment
CLP - Aquatic Chronic 3: H412 Harmful to aquatic life with long lasting effects

Date	Country	Organisation	Type of Organisation	Comment number
07/12/2012	Belgium		MSCA	11

Comment received

Based on the results of the aquatic toxicity tests (field study on Pomacea canaliculata -most sensitive species-with 48hEC50 = 3.330 mg/l and 14dNOEC<0.5mg/l) and the fact that the substance is not rapidly degradable (2.8% degradation within 28d), it is justified to classify, following the classification criteria of the 2nd ATP, as Aquatic Chronic 2, H411.

Based on the classification and labelling criteria in accordance with dir. 67/548/EEC, metaldehyde should be classified as N, R51/53.

In conclusion : we support the proposed classification for the environment by the Austrian MSCA.

Some editorial or/and minor comments:
Table 2 : please mention the resulting harmonised classification

Date	Country	Organisation	Type of Organisation	Comment number
06/12/2012	United Kingdom		MSCA	12

Comment received

The key aquatic study is for the snail Pomacea canaliculata. However this is an efficacy test on a target organism so it is not surprising that mortality is observed. We are unconvinced that classification should be based on this test/species, for the following reasons:

a) The test was a field study and did not follow any standardised test guideline, so the contribution of other factors to the result is unknown.

b) The original study appears to be poorly reported (the raw data are not available, and it was not used in the DAR), so it is not possible to assess its reliability (should it be considered as Klimisch 4?). We think it is wrong to try to extract a result based on assumptions.

c) Further information is needed on the method of exposure. It is unclear whether the pellet exposure/consumption reflects normal aquatic exposure - i.e. via dissolved substance in water. This is important as classification is for the substance, not the marketed formulation.

d) There should be an explanation for why a 14-day mortality result from a field study represents chronic data in a hazard classification context . Could this not be a sub-acute end point? (Contrast this with the OECD 204 test for fish - we do not use prolonged acute data for hazard assessment.) Can the rapporteurs provide justification from other chronic mollusc tests for why this timescale/endpoint is suitable for chronic classification?

e) Hazard classification is effectively a comparative exercise to rank substances in terms of their overall intrinsic hazard, and we do not know whether this snail species is generally more sensitive to substances than other standard test organisms (especially given the lack of toxicity in a second snail species).

In summary, we do not think this result is robust enough to act as the key data point for

environmental hazard classification.

Date	Country	Organisation	Type of Organisation	Comment number
06/12/2012	Germany		MSCA	13

Comment received

p.169 - We do not agree with the selected endpoint for classification and labelling. There is no sufficient explanation given why the results of a efficacy study of a formulation (with only 10% active substance and no information about the other ingredients) with Pomacea canaliculata is used for classification and labelling of Metaldehyde. We would suggest to use this results only as additional information and not use for classification of Metaldehyde solely.
There are already valid acute and chronic data for all 3 aquatic trophic levels and additional molluscs for the active substance available (most sensitive Oncorhynchus mykiss with LC50 (96h) = 75 mg/L) that lead to the classification R52/53 (DSD) and no classification according CLP-VO.

Date	Country	Organisation	Type of Organisation	Comment number
05/12/2012	Sweden		MSCA	14

Comment received

SE supports the environmental classification of Metaldehyde (Cas no:108-62-3) as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard classes and differentiations.
The current proposal for consideration by RAC and harmonized classification is Aquatic Chronic 2,H411.
Metaldehyde is photolytically stable and hydrolytically stable at environmentally relevant pH values. Metaldehyde is not readily biodegradable under test conditions within 28 days. In UK simulation study (two less oxidizing systems) DT50 whole system is > 1000 d, therefore based on these data, the substance is considered not to be ready biodegradable.
Metaldehyde is chronic toxic to aquatic molluscs like the fresh water snail Pomacea canaliculata NOEC(14 d)= <0.5 mg/L Therefore Metaldehyde fulfills the criteria forthe proposed classification as Aquatic Chronic 2, H411.

Date	Country	Organisation	Type of Organisation	Comment number
04/12/2012	Switzerland	Lonza Ltd	Company-Manufacturer	15

Comment received

p. 167-169: A complete set of short and long term ecotoxicological tests in fish, Daphnia, alga and an acute study on the Great Ramshorn Snail is available for the aquatic classification of metaldehyde. However, the efficacy test, which is used as the basis for the proposed environmental classification in the CLH report, is not suitable for deriving a quantitative endpoint for aquatic toxicity for the purpose of classification. Furthermore, the study does not meet the necessary quality criteria and cannot be considered reliable.
1. The aim of the study was to assess the oral efficacy of a 10% slug pellet formulation against Golden Snails. The feeding on pellets is the route of intake not only for soil but also for water snails. Therefore, the mortality correlates with the ingested quantity of pellets and not with the quantity of metaldehyde potentially dissolved in water. Any derivation of an LC50 or NOEC for metaldehyde in water is scientifically not correct.
2. The amount of pellets ingested by a single snail was not monitored. Therefore no information about the lethal dose of metaldehyde for Golden Snails can be derived from the study.
3. No analytical determination of the metaldehyde concentration in the water was performed. Although the exposure via water is not relevant for the outcome of this study the lack of chemical analysis make the test invalid as an aquatic ecotoxicological study. Consequently, the study should have been classified as not reliable.
4. The study protocol did not conform to any recognized testing guideline and was not performed under Good Laboratory Practice. Consequently, the study should have been classified as not reliable.