Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Acrolein

EC Number: 203-453-4

CAS Number: 107-02-8

ECHA/RAC/CLH-O-0000001792-72-03/A2

Adopted

15 June 2012

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]

Substance name: Acrolein
CAS number: 107-02-8
EC number: 203-453-4

General comments

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
08/09/2011	Germany / Jan Averbeck /MSCA	p. 16 Concerning the labelling proposal (CLP) the corresponding pictograms (GHS02, GHS05, GHS06, GHS09) are missing. Concerning the S-Phrases we like to remark that "(S1/2)" is missing which is standard for toxic or corrosive substances. Furthermore we suggest to add S9 and S16 because of R11. S23 could be omitted as R26 should imply in our opinion avoiding automatically the inhalation of the substance. We propose to add "Note D" p. 10, p.13 The typing error "Flam liq.2 H255" should be corrected in "Flam liq.2 H225".	Thank you, your comments are noted. Note D is already included in Annex VI of CLP. Thank you, we agree with the correction.	noted noted noted
12/09/2011	Spain / Manuel Carbó Martinez	We are in agreement with the acute classification but not with the chronic.	Please refer to our response below discussing the comment.	Noted. See response below
12/09/2011	France / MSCA	According to the Biocidal dossier, classification of acrolein has already been discussed by the EU classification and labelling working group in 1999. This discussion could be added in the CLH report for the relevant endpoints.	We consider that all relevant information pertaining to the current classification and labelling discussion has been included in the CLH report. The minutes of the previous meeting are attached to the RCOM	RAC agrees with the MSCA response

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
			table for convenience.	

Carcinogenicity

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
12/09/2011	France / MSCA	Agree with the non classification.	Thank you, your comment is noted.	Noted

Mutagenicity

Date	Country/ Person/ Organisation/ MSCA	Comment	MSCA Response to comment	RAC response to comment
12/09/2011	France / MSCA	Agree with the non classification. In the conclusion (p 47), it is noted that "It is possible that the positive findings in bacterial test systems are related to the lack of an endogeneous glutathione detoxification pathway. Glutathione has been shown to react readily with reactive electrophiles such as acrolein, protecting sensitive intracellular systems from damage." However according to the Marnett et al study, the addition of glutathione did not decrease mutagenicity in a modified Ames test. Therefore, we consider that this assumption could not be verified and these sentences should be deleted from the conclusion.	Thank you, we agree with the comment.	Noted

Toxicity to reproduction

/Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment

12/09/2011	France / MSCA	In order to not consider the increase in incidence of cleft palate as adverse (p 50), please add in the CLH report supportive historical data for this effect in the mice.	Cleft palate in mice is regarded as not being relevant for human health, as mice tend to have a high and variable spontaneous background incidence. If the rapporteur considers this information to be important, we can of course try and obtain it. It should be noted that the study is quite old and it is therefore possible that the relevant background incidence rate may not be available.	The rapporteurs agree with the MSCA response that this additional information is not necessary

Respiratory sensitisation

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
12/09/2011	France / MSCA	Agree with the non classification.	Thank you, your comment is noted.	noted

Other hazards and endpoints

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
08/09/2011	Germany / Jan Averbeck / MSCA	Acute toxicity: DE supports the proposed classification for acrolein as T+; R28 and Acute Tox 2 – H300, respectively as well as T+; R26 and Acute Tox 1 – H330, respectively as well as T; R24 and Acute Tox 3 – H311, respectively. Please check the calculation of the acute dermal LD50 for acrolein (all animals) on page 23. It seems incorrect that an LD50 (males) of 240 mg/kg bw and an LD50 (females) of 233 mg/kg bw result in an LD50 (combined) of 231.4 mg/kg bw. Corrosivity:	Thank you, your comment is noted. The value is that reported in the study summary based on the data available.	Noted Noted

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
		DE supports the proposed classification for acrolein as C; R34 and Skin Corr. 1B – H314, respectively	Thank you, your comment is noted.	Noted
08/09/2011	Germany / REACH Contact / Evonik Industries AG for and on behalf of Evonik Degussa	Classification and labelling for environmental hazards: Acrolein is a highly reactive cell toxicant that reacts with several molecules containing sulfhydryl groups, exerting direct cytotoxic effects or interrupting cell signalling pathways. Due to this high reactivity Acrolein is acutely toxic to aquatic organisms. The high reactivity of Acrolein prevents its persistence in the environment, and its transportation over long distances (WHO, 2002; U.S.EPA, 2003). Dissipation of Acrolein from aquatic ecosystems includes abiotic and biotic degradation (and metabolisation), volatilization, absorption and dilution. It is unlikely that Acrolein bioaccumulate or bioconcentrate significantly in aquatic organisms (WHO, 1991). Acrolein was not detected in the tissues of fish (Lepomis macrochirus and Ictalurus punctatus) and shellfish (Elliptio complanata and Orconectes virilis) exposed separately to [14C]-Acrolein in water (0.02 and 0.1 mg/L for fish and shellfish, respectively), over a 1-week period, and sampled 1 day after a second exposure. The presence of metabolites indicated that these species were able to rapidly metabolize Acrolein (Nordone et al., 1998). The estimated BCF of 3.2 suggests a low potential for bioconcentration in aquatic organisms (HSDB, 2010). Also the CLH report for Acrolein comes to the conclusion “Based on the substance’s physico-chemical properties, its estimated bioconcentration factor, and supporting information from assimilation studies, the substance is considered to have has a low potential for bioaccumulation, …”. Further and even more important the acute/chronic toxicity ratio for fish, daphnids and algae is very low. As indicated in the CLH report even the NOECs (which are very close to the EC/LC50 values from acute studies with the same species) from the long-term toxicity studies in fish and aquatic invertebrates are the results of or are accompanied by mortality of adults. This obviously indicates that a repeated acute injury and not a chronic /sublethal effect is the result of prolonged exposure resulting in the respective NOEC. The current data available clearly indicate that Acrolein acts via an acute mode of action and not a chronic mode of action. The OECD Guidance No.27 defines acute and chronic toxicity as follows: “Acute toxicity for purposes of classification refers to the intrinsic property of a substance to be injurious to an organism in a short-term exposure to that substance. Acute toxicity is generally expressed in terms of a concentration which is lethal to 50% of the test organisms (LC50), causes a measurable adverse effect to 50% of the test organisms (e.g. immobilisation of daphnids), or leads to a 50% reduction in test (treated) organism responses from control (untreated) (e.g., growth in algae).”	Following the 2nd Adaption to Technical Progress (2nd ATP) to the CLP Regulation 286/2011 chronic aquatic ecotoxicity data should now be considered when deriving the environmental classification and labelling for substances. For acrolein, there are valid chronic NOECs for fish, Daphnia and marine algae. While all NOECs meet Aquatic Chronic classification criteria, the lowest NOEC (0.0051 mg/l for algae) meets the criteria for Aquatic Chronic 1 (≤ 0.01 mg/l for rapidly degradable substances). The NOEC reflects an ecotoxic response over a prolonged period of time. For algae this relates to growth over multiple generations and can be considered a chronic endpoint.	Noted. RAC confirms dossier submitter's presentation of the criteria for classification of chronic aquatic hazards as introduced by the 2nd ATP to CLP regulation in April 2011. With the new criteria, the pronounced acute toxicity of acrolein is well reflected by the acute M-factor of 100, compared to M = 1 for the chronic hazard.

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
		"Chronic toxicity, for the purposes of classification, refers to the potential of a substance to cause adverse effects to aquatic organisms during exposure which are determined in relation to the life cycle of the organism. Such chronic effects usually include a range of sublethal endpoints and are generally expressed in terms of a No Observed Effect Concentration (NOEC), or an equivalent ECx. Observable endpoints typically include survival, growth and /or reproduction. Chronic exposure duration can vary depending on test endpoint measured and test species used." (Cited from "OECD Series on Testing and assessment Number 27 – Guidance document on the use of the harmonised system for the classification of chemicals which are hazardous for the aquatic environment") These definitions clearly distinguish between chronic and acute toxicity due to their mode of action for the purpose of classification. If a substance is classified due its acute toxicity as Acute 1 (like it is the case for Acrolein) the M-Factor further provides information about the potency of the acute toxicity. This sufficiently describes the acute toxicity for the purpose of classification. As Acrolein injures organisms exclusively via an acute mode of action and not via a chronic /sublethal mode of action it is not justified to classify this substance for chronic toxicity. Classification of Acrolein into chronic toxicity categories would implicate that Acrolein acts via a sublethal /chronic mode of action. This is not supported by the available data. Acrolein acts independent of the life cycle and even after prolonged /chronic exposure adverse effects are only visible in concentrations where acute effects are expected.	On the basis of this, acrolein is considered to meet the criteria for Aquatic Chronic 1 classification.	
12/09/2011	Belgium / Els Boel / MSCA	ENVIRONMENT Based on the results of the aquatic toxicity test on the most sensitive species (96h EC50 Xenopus laevis = 7µg/l, 72hNOEC Skeletonema costatum=5.1µg/l) the fact that the substance is rapidly degradable and that the substance shows low potential to bioaccumulate, it is justified to classify, following the classification criteria of the 2nd ATP, as Aquatic acute 1, H400 and Acute chronic 1, H410. In view of the proposed classification and the toxicity band for acute toxicity between 0.001 and 0.01 mg/l, an M-factor for acute toxicity of 100 could be assigned, and an M-factor for chronic toxicity of 1 (rapidly degradable substance and toxicity band between 0.001 and 0.01mg/l). Based on the classification and labelling criteria in accordance with dir. 67/548/EEC, Acrolein should be classified as N,R50.	The CA report for the Biocides Directive calculated hydrolysis half lives at 9°C reflecting marine use in the risk assessment. While these provide a conservative approach, we have listed the half-lives at 12°C as follows: DT_{50} in days at pH 5.3 = 10. 8, pH 7.2 = 4.2, pH9.3 = 1.7.	Noted. According to the most recent procedures for processing CLH reports by RAC, technical details without impacts for the final conclusion on classification are not necessarily mentioned and/or explicitly corrected in the RAC opinion

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
		In conclusion : we agree with the proposed environmental classification by the UK MSCA. Some editorial or/and minor comments: 5.1.1 Hydrolysis study, p.53 In the CLH report it is mentioned that, in the frame of assessment under the biocides directive, the study results were adjusted for the temperature to 9°C. Is this an adjustment for the marine environment or fresh water? The TGD on risk assessment gives the advice to establish a pH of 7 and a temperature of 12°C (285 K) for fresh water, sediment and soil and a pH of about 8 and an average temperature of 9°C (282 K)for marine water. 5.2.2 Volatilisation Although it does not change the conclusion, can you please mention the values used to estimate the Henry's law constant? Using a vapour pressure of 31920 Pa at 25°, MW of 56,0633 and a water solubility of 237628 mg/l at 25°C results in a Henry's law constant of 7.5 Pa.m3/mol. 5.1.2.2 Screening test, p 54, 3th last sentence 23-hydroxypropionic acid is mentioned instead of 3-hydroxypropionic acid 5.3.2 Summary and discussion of aquatic bioaccumulation The word "have" is used in succession.	The Henry's Law Constant (HLC) information quoted in the CLH report is based on the HLC information agreed in the ESR assessment for which we do not have the original basis. It would appear the quoted EU TGD value of 6.1 $Pa.m^3/mol$ is based on a water solubility around 289 g/l at 25^oC (from quoted water solubility of 206 to 270 g/l at 20^oC) and a vapour pressure around 31920 Pa at 25^oC. We note the HLC of 7.5 $Pa.m^3/mol$ as quoted in the CA Report. We have noted the typographical errors.	or in the RAC boxes inserted to the background document. The documentation of such issues in this RCOM as Annex 2 to the RAC opinion is considered sufficient by ECHA and RAC.
12/09/2011	Sweden / Ing-Marie Olsson / MSCA	SE comments on the environmental classification: We believe that more information is required in order to allow a conclusion on whether the substance is or is not readily biodegradable. Since the substance seems to be toxic to microorganisms the data set of valid results is not very extensive and consists of: (i) a positive inherent biodegradation study and (ii) a simulation test in aerobic freshwater. The available anaerobic studies in freshwater and soil are not considered relevant since their conditions do not reflect the aquatic environment that is generally regarded as the aerobic compartment where the aquatic organisms, such as those employed for aquatic hazard classification, live (see II.2.3.7 in the Guidance Document). Since neither the inherent biodegradation study is relevant for the assessment, the results from the simulation test in aerobic freshwater are the basis for decision on whether the substance is rapidly degradable. In the aerobic simulation study the UK CA adjusted (to 9° C) half life of the substance was 121.2 h. From	Acrolein was discussed by the TCNES C&L Working Group and harmonised as N; R50. The group agreed the substance was rapidly degradable. This was consistent with the conclusions of the ESR assessment. There are no new data available. The results of the aerobic study are discussed in	Noted. RAC considers evidence sufficient as provided in the CLH report, taking into account the additional reference to previous assessments by other regulatory bodies and corresponding documentation.

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
		the description of the test it can also be concluded that the substances undergoes hydrolysis and forms metabolites. In the case the metabolites are formed fast (i.e. DT50 < 16 days) the substance should be regarded as readily biodegradable if the metabolites are not classifiable. According to what is stated in the description it seems that the DT 50 is fast (121.2 h) and thus a classification of the metabolites should be preformed in order to see whether they are classifiable and whether based on this classification the parent compounds may be regarded as readily biodegradable. No such analysis is performed since the DS is of the opinion that process of an ultimate degradation is very fast and thus comparable to the pass level of the ready biodegradation test. The ultimate degradation was measured as carbon dioxide however it is unclear in the text how large was the development of the carbon dioxide in the aerobic study. According to our understanding the value presented regards the anaerobic conditions (not relevant for the classification). Regarding the aerobic freshwater conditions the text states that biodegradation of the hydrolysis products was likely to be the major pathway. Based on the above we believe that more information should be provided to allow a conclusion on readily biodegradation of the substance. However we tend, based on the description of the test, to consider this substance as not readily biodegradable. In the section 5.1.3. it is stated that the substance degrades rapidly both through biodegradation and hydrolysis and that degradation and mineralization were faster under anaerobic conditions. We believe that further information and clarification are needed in order to arrive at this conclusion. If the new assessment would lead to the conclusion that the substance is not readily biodegradable the proposed classifications both according to the DSD and CLP will be different (including the chronic M factor).	section 5.1.2.3 – this states "In the 32 day aerobic study conducted at 25 ºC, biodegradation was observed with the production of carbon dioxide (expressed as bicarbonate ion, representing greater than 90% on days 5 and 32)". For the anaerobic study the text states: "Carbon dioxide was the major degradation product, representing greater than 60% of the initial test dose on days 30, 93 and 178" The fate and ecotoxicity of environmental metabolites are considered in the DAR. The data indicates they are not more toxic than the parent acrolein. Overall we feel there is sufficient and robust evidence that the substance should be considered as readily biodegradable.	
12/09/2011	Spain / Manuel Carbó Martinez	Although the same chronic classification is derived from the surrogate system used the Xenopus LC50 or the Skeletonema NOEC, the issue is that Skeletonema is not the most sensitive specie nor the most sensitive trophic level; this particular case is recorded in the example D on the new CLP guidance, when	The available acute toxicity data are all of the same order of magnitude,	Noted. RAC agrees to apply chronic classification

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
		the chronic data are not adequate to represent the long term hazard, therefore our recommendation is to change the proposal to Acute 1 M factor 100, Chronic 1 M factor 1 based on the surrogate system using the Xenopus LC50, although the same classification is reached the meaning is completely different.	differing by a factor of three between highest and lowest. On that basis, we do not consider there to be any significant difference in sensitivity between any of the species tested. As there are adequate chronic toxicity data available (i.e. valid NOECs for fish, crustacea and algae/plants) a surrogate chronic classification should not apply.	according to CLP criteria based on long-term tests as proposed by dossier submitter. Moreover, the surrogate approach would not be applicable as acrolein is considered both rapidly degradable and not bioaccumulative according to CLP and DSD criteria.
12/09/2011	France / MSCA	Respiratory tract irritation: (p 26) Not agree with the summary of respiratory tract irritation. According to the acute and repeated inhalation studies, local effects were observed (such as epithelial necrosis) and could be related to a respiratory tract irritation. However since acrolein is classified R34, a classification R37 is not necessary. Corrosivity: Since the rabbits were exposed to acrolein for 24 hours, no conclusion on the subcategory for Skin Corr (1A, 1B or 1C) could be made. Please add the specific limit concentration of 1% for skin corrosivity in Table 2 page 7 (Resulting harmonised classification).	Thank you, the comment is noted. The proposal is to retain the current corrosivity classification, , based on a weight of evidence assessment. However, we acknowledge that it is difficult to identify the correct corrosivity sub-category based on the available. information. We agree that the specific concentration limits should have been included in table 2.	Noted

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
		Repeated-dose toxicity studies: According to the Biocidal dossier, the Feron et al study in rats, rabbits and hamsters lasted 90 days instead of 62 days (p 34). Please correct.	We note that the duration of the Feron study was 90-days and not 62 as stated in the CLH report.	
		In the Biocidal dossier, a study performed in Dahl rats was reported (Kutzman et al 1984, 1986). Maybe this study could also be reported in the CLH report.	Dhal rats are a non standard strain, and as there is a lot of information with more standard strains, we decided not to include this study. However, if the rapporteur thinks it would be useful, we can of course include it.	
		ENV_FR_1: Part A, section 1.2, Table 2, concentration limit Could you please harmonize the value of the concentration limit for the environment in the Table 2 (Cn= 25%) with the conclusions presented in the section 5.6 Conclusions on classification and labelling for environmental hazards (Cn = 0.25%)?	The correct concentration limit is: Cn $\geq$ 0.25 % N;R50	Noted. For no classification it should read: Cn < 0.25% (CLH report states slightly incorrect: Cn $\leq$ 0.25%)
		ENV_FR_2: Part B, section 5.2.1 Adsorption/Desorption The value of log K_{ow} presented in section 5.2.1 (log K_{ow}= -1.1) differs from the one presented in the section 1.3 physico-chemical properties (log K_{ow}= 0.04). Where does the value of -1.1 come from? Could you please derive the K_{oc} value with the value presented in the section 1.3?	The log K_{ow} value of -1.1 is presented in the EU ESR assessment (reference 2 in the CLH Report).	Noted.
			Using the TGD default QSAR for nonhydrophobics and the log K_{ow} value 0.04, the calculated K_{oc} value is	Noted.

Date	Country / Person / Organisation / MSCA	Comment	MSCA Response to comment	RAC response to comment
			10.99 l/kg (log Koc 1.041). We note this value does not change the proposal.	