Committee for Risk Assessment

RAC

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/F

Adopted

15 June 2012

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of the Regulation (EC) No 1272/2008 (CLP Regulation), the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling of

Substance Name: **Acrolein**

EC Number: **203-453-4**

CAS Number: **107-02-8**

The proposal was submitted by **the United Kingdom** and received by RAC on **18 November 2010.**

The proposed harmonised classification

	Regulation (EC) No 1272/2008 (CLP Regulation)	**Directive 67/548/EEC**
Current entry in Annex VI to CLP Regulation	Flam. Liq. 2 (H225) Acute Tox. 2* (H330) Acute Tox. 3* (H311) Acute Tox. 3* (H301) Skin Corr. 1B (H314) Aquatic Acute 1 (H400)	F; R11 T^+; R26 T; R24/25 C; R34 N; R50
Proposal by dossier submitter for consideration by RAC	Acute Tox. 1 (H330) Acute Tox. 2 (H300) Acute Tox. 3 (H311) Skin Corr. 1B (H314), SCL = 1% Aquatic Chronic 1 (H410) Acute M-factor = 100 Chronic M-factor = 1	T^+; R26/28 T; R24 N; R50, Cn ≥ 0.25%
Resulting harmonised classification (future entry in Annex VI to CLP Regulation) based on the proposal by the dossier submitter	Flam. Liq. 2 (H225) Acute Tox. 1 (H330) Acute Tox. 2 (H300) Acute Tox. 3 (H311) Skin Corr. 1B (H314), SCL=1% Aquatic Acute 1 (H400) Aquatic Chronic 1 (H410) Acute M-factor = 100 Chronic M-factor = 1	F; R11 T+; R26/28 T; R24 N; R50, Cn ≥ 0.25%

PROCESS FOR ADOPTION OF THE OPINION

The United Kingdom has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/web/guest/harmonised-classification-and-labelling-previous-consultations*** on **29 July 2011**. Parties concerned and MSCAs were invited to submit comments and contributions by **12 September 2011.**

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Helmut Greim**
Co-rapporteurs, appointed by RAC: **Annick Pichard, Hans-Christian Stolzenberg**

The opinion of RAC takes into account the comments of MSCAs and parties concerned provided in accordance with Article 37 (4) of the CLP Regulation.

The opinion of RAC on the proposed harmonised classification and labelling has been reached on **15 June 2012** in accordance with Article 37 (4) of the CLP Regulation, giving parties concerned the opportunity to comment. Comments received are compiled in Annex 2.

The opinion of RAC was adopted by **consensus*.***

OPINION OF RAC

RAC adopted the opinion that **Acrolein** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
605-008-00-3	Acrolein; prop-2-enal; acrylaldehyde	203-453-4	107-02-8	Flam. Liq. 2 Acute Tox. 1 Acute Tox. 2 Acute Tox. 3 Skin Corr. 1 Aquatic Acute 1 Aquatic Chronic 1	H225 H330 H300 H311 H314 H400 H410	GHS02 GHS06 GHS05 GHS09 Dgr	H225 H330 H300 H311 H314 H410	EUH071	Skin Corr. 1; H314: C ≥ 0.1 % M = 100 (Acute) M = 1 (Chronic)	D[1]

Classification and labelling in accordance with the criteria of Directive 67/548/EEC

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
605-008-00-3	Acrolein; prop-2-enal; acrylaldehyde	203-453-4	107-02-8	F; R11 T+; R26/28 T; R24 C; R34 N; R50	F; T+; C; N R: 11-26/28-24-34-50 S: 23-26-28-36/37/39-45-61	C; R34: C ≥ 0.1% N; R50: C ≥ 0.25%	D[1]

[1] Note D is defined in Annex VI, 1.1.3.1 of Regulation (EC) No 1272/2008

SCIENTIFIC GROUNDS FOR THE OPINION

This opinion on harmonised classification and labelling relates to all hazard classes and proposes to amend the classification for acute toxicity (by oral and inhalation route) and skin corrosion. The specified endpoint evaluations by RAC relate specifically to the proposal of the Dossier Submitter.

HUMAN HEALTH HAZARD ASSESSMENT

Acute Toxicity

Summary of Dossier Submitter's proposal

By comparing the LD_{50} and LC_{50} values with the criteria in CLP (Regulation 1272/2008) and DSD (Directive 67/548/EC), the data indicate that classification is justified for all three routes of exposure.
The relevant CLP criteria are the following: $\leq$0.5 mg/l for acute inhalation toxicity 1 (vapours), 5 – 50 mg/kg for acute oral toxicity category 2 and 200 – 1000 mg/kg for acute dermal toxicity category 3.
The relevant DSD criteria are the following: $\leq$0.5 mg/l for R26 (vapours), ≤ 25 mg/kg for R28 and > 50 – ≤ 400 mg/kg for R24. The toxicity category of both oral and inhalation toxicity require an amendment; the dermal toxicity category remains unchanged in the current acrolein Annex VI entry of the CLP Regulation.

Comments received during public consultation

Germany supported 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.

RAC assessment and comparison with classification criteria

Acute Toxicity: Inhalation

Acrolein is extremely volatile and thus will exist solely as a gas in the ambient atmosphere. Since acrolein is a gas, the CLP criteria for gases are applied.
In rats the LC_{50} is 57.9 mg/m3 (25 ppm) and 18.5 mg/m3 (8 ppm) for 1 and 4 hrs exposures, respectively. Since these values are below the limit value for gases for Category 1 of 100 ppm, the proposal for Acute inhalation toxicity category 1 for gases (H330) is justified.
Since the mechanism of toxicity is corrosivity, acrolein is also labelled as EUH071: 'corrosive to the respiratory tract', in accordance with section 3.1.2.3.3 and Note 1 of Table 3.1.3 in Annex I of CLP.

Acute Toxicity: Oral

In rats and mice the oral LC_{50}'s are 10.3 and 11.8 mg/kg (M/F rats), 13.9 and 17.7 (M/F mice). Since these values are higher than 5 mg/kg bwt (Category 1) and below 50 mg/kg, the limit value for category 2, the proposal for Acute oral toxicity category 2 (H300) is justified.

Acute Toxicity: Dermal

In rabbits the dermal LC_{50}'s are 240 and 233 mg/kg in males and females, respectively. Since these values are above 200 mg/kg bwt (Category 2) and below 1000 mg/kg bwt, the limit value for category 3, the proposal for Acute dermal toxicity category 3 (H311) is justified.

Respiratory Tract Irritation

Summary of the Dossier Submitter's proposal

No classification is proposed.

Comments received during public consultation

France does not agree with the summary for 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 as R37 is not necessary.

RAC assessment and comparison with classification criteria

No classification is proposed. However, since the mechanism of toxicity is corrosivity, acrolein is also labelled as EUH071: 'corrosive to the respiratory tract', in accordance with section 3.1.2.3.3 and Note 1 of Table 3.1.3 in Annex I to CLP.

Skin Corrosion

Summary of the Dossier Submitter's proposal

Acrolein caused severe adverse skin reactions in a non-standard study in human volunteers, indicative of skin corrosion. Acrolein also caused severe skin reactions in a standard study in rats[1], which became progressively more severe over the 14-day observation period. Severe skin reactions were also observed in rabbits after single (see Annex 1, table 11 and section 4.2.1.3) and repeated dermal application (see Annex 1, section 4.7).

Comments received during public consultation

Germany supports the proposed classification for acrolein as C; R34 and Skin Corr. 1B (H314), respectively. France argues that 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.

RAC assessment and comparison with classification criteria

In the rabbit study acrolein did not induce corrosions. Since there is no information which concentrations have been used the study is invalid for proper evaluation. In the human study a 10% solution induced necrosis in all exposed subjects. Although these data do not formally meet the criteria for corrosion RAC agrees with the conclusion of the Dossier Submitter: "The proposal is to retain the current corrosion classification, based on a weight of evidence assessment. However, we acknowledge that it is difficult to identify the correct corrosion subcategory based on the available information." This is supported by the acute dermal toxicity study in rabbits (Muni 1981a), which showed ulceration, oedema and haemorrhage of the dermis at all dose groups (200, 240, 280 mg/kg). Since the available data do not allow differentiation between the skin corrosion subcategories 1A/1B/1C, RAC concludes that acrolein should be assigned Skin Corr. 1 only (see BD

[1] RAC: according to the BD the species was rabbits: Muni 1982

3.2.2.4 Decision on classification).
Based on a weight of evidence evaluation RAC confirms the C&L proposal for Skin Corr. 1 (H314).

Specific Concentration Limit

In the human volunteer patch tests acrolein has been applied at concentrations of 0.01, 0.1, 1 and 10% in ethanol on groups of 8, 10, 48 and 20 volunteers, respectively (Lacroix *et al*., 1976). No further information, especially on duration of application, is available. At 1%, positive skin reactions were recorded in 6 out of 48 subjects; four of the six with serious oedema and bullae and the remaining two with erythema. No adverse skin reactions were observed at 0.01 (n = 8) or 0.1% (n = 10). RAC concludes that a specific concentration limit of 1% does not protect from skin reactions, whereas 0.1% is a concentration limit which is considered sufficiently protective.

Skin Sensitisation

Summary of the Dossier Submitter's proposal

No classification is proposed.

Comments received during public consultation

None.

RAC assessment and comparison with classification criteria

Upon recommendations by RAC members, RAC has re-evaluated the possible sensitising potential of acrolein, because of its high reactivity. This is supported by Ashby et al[2], who evaluated the genotoxicity and skin sensitising potential of reactive chemicals. It has been concluded that genotoxicity data of an agent can provide indications of the agent's potential to induce skin sensitisation and that genotoxins which are skin sensitising agents have an enhanced potential to initiate skin carcinogenesis.
It is basically correct to assume that highly reactive compounds are potential sensitisers although several might be so reactive that they do not penetrate into the skin to reach the critical cells. In the EU RAR on acrolein (2001) the guinea pig maximisation test of Susten and Breitenstein (1990) has been described as negative. However, the study was poorly reported so no definite conclusion with respect to the sensitisation potential could be made here that labelling with R43 is indicated. These data have also been evaluated by TC C&L in October 1999 (ECBI/61/99 Rev 2), which concluded that classification was not justified on the basis of the available data. Accordingly, SCOEL (SCOEL/SUM/32, September 2007) concluded that there is no clear indication for a sensitizing effect of acrolein in animals or in humans, whereas the critical effect of acrolein in humans is irritation of the eye and of the respiratory tract. The recent review by Bein and Leikauf[3], states that acrolein has not been reported to produce antigenic-type bronchial hyper-reactivity. As an irritant it can augment bronchial hyper-reactivity in laboratory animals and human tissue in vitro. Although there is significant human exposure e.g. from environmental tobacco smoke, the review did not identify reports that indicate sensitisation in humans. For example, more than 30 million non-smokers in the United

[2] Ashby J, Hilton J, Dearman RJ, Callander RD, Kimber I: Mechanistic relationship among mutagenicity, skin sensitisation, and skin carcinogenesis. Env. Health Perspect 101, 62-67, 1993.
[3] Acrolein – a pulmonary hazard. Mol Nutr Res 55, 1342-1360, 2011.

States are exposed to acrolein. In taverns permitting smoking, indoor acrolein concentration (24-60 x 10^{-3} mg/m^3) is equal to 1200 times the ambient RfC. Acrolein levels from 10 cigarettes in a 30 m^3 room can be much higher and have reached 0.23 mg/m^3. Acrolein is also formed endogenously during inflammation – a common characteristic of several respiratory diseases including chronic obstructive pulmonary disease (COPD) and asthma (Bein and Leikauf 2011).
RAC concluded that the available information does not indicate a sensitising potential of acrolein.

ENVIRONMENTAL HAZARD ASSESSMENT

Aquatic Acute and Aquatic Chronic Toxicity

Summary of the Dossier Submitter's proposal
The Dossier Submitter (DS) proposed to classify acrolein as hazardous to the aquatic environment, Acute category 1 (H400) and Chronic category 1 (H410), with M-factors 100 and 1 respectively, according to Regulation (EC) 1272/2008 (CLP), and R50 (and SCLs corresponding to the acute M-factor of 1), according to Directive 67/548/EEC (DSD).

Acrolein is subject to considerable abiotic and biotic degradation. Hydrolysis shows measured half lives ranging from 14 h (pH 9 at 25°C) to 13.7 d (pH 5, adjusted to 9°C). The reaction with water is reversible, yielding 3-hydroxypropanal (HPA) as major and further hydration products, some of them more complex. The equilibrium of these reversible hydrolytic reactions lies far on the right, ca. 9% acrolein remains at all pHs after more than seven half lives. Acrolein is quite volatile, and in air half-lives of less than one day have been calculated for indirect photo-oxidation by hydroxyl radicals, while photolysis half-lives were 7.7 d (calculated) and 10.9 d (measured).

Although no valid screening tests for ready biodegradability are available, the Dossier Submitter presents evidence from several studies for ready biodegradation. In several studies, the applied concentrations of acrolein are toxic to microorganisms, thus limiting their validity for the purpose of estimating biodegradability. Additional information comes from two simulation studies with ^{14}C radiolabelled acrolein in aerobic and anaerobic freshwater. Under aerobic conditions at 25°C, more than 90% radioactivity was found on days 5 and 32 as bicarbonate ions (representing CO_2). Hydrolysis was found to be the major initial degradation pathway, with competing microbial transformation of acrolein and HPA to acrylic acid and allyl alcohol. The half life of acrolein in the test was 33.7 h, equating to 121.1 h when adjusted to 9ºC. In the anaerobic study at 22ºC no acrolein was detected beyond the first day of the study. CO_2 was the major degradation product with more than 60% of the initial test dose on days 30, 93 and 178. As for the aerobic study, biodegradation of the hydrolysis products was likely to be the major pathway. Based on both studies the Dossier Submitter proposes to confirm acrolein as being rapidly degradable in water.

With a log K_{ow} of -1.1, the highly water soluble and rapidly degradable substance is considered to have a low potential for bioaccumulation. A BCF of 344, calculated from a 28 d fish study with ^{14}C-radiolabelled acrolein, is based on total radioactivity and therefore considered overestimated. In further studies with fish, crayfish, and mussels, tissue analyses showed rapid metabolism and degradation: no acrolein was detected 26 hours after the last application.

With a view on its rapid degradation and high volatility, reliable toxicity tests with acrolein should be conducted under flow-through conditions with analytical verification of the test concentrations. The classification proposal is based on studies throughout fulfilling these technical requirements. Results are available from acute and long-term ecotoxicological tests using organisms from the standard groups of fish, water fleas, and

algae. A further key study is a 96 h flow-through test with tadpoles from the African claw frog.

Acute toxicity of acrolein is quite similar in all three standard groups of test organisms, with lowest EC/LC_{50} values of 14, 23, 11 µg/l for fish, water fleas, and algae, respectively. Although no standard test, the Dossier Submitter considers the 96 h flow-through test with claw frog tadpoles as valid for classification purposes. The LC_{50} of 7 µg/l is both in line with the other acute effect concentrations and, as the lowest figure, decisive for classification.

Consistent with its high reactivity and pronounced acute toxicity, the effect thresholds of acrolein in long-term tests are close to the acute effect concentrations. The lowest valid NOECs for fish, daphnids, algae are 11.4, 16.9, and 5.1 µg/l, respectively.

Overall, the ecotoxicological data constitute a highly consistent basis on which the Dossier Submitter concludes to propose for acrolein a classification as Aquatic Acute 1 (H400) with a corresponding M-factor of 100 (CLP), and N; R50 with an SCL of 0.25% (DSD). For the long-term aquatic hazard it is proposed to classify into Aquatic Chronic 1 (H410) with M = 1 (CLP criteria). The surrogate classification criteria under DSD provide for no chronic classification when the substance is rapidly degradable and has low potential for bioaccumulation.

Comments received during public consultation

Comments on the environmental hazard assessment were submitted by four Member States (MS) and one industry stakeholder (IND). While MS commentators in general did not object to the classification and M-factors as proposed by the Dossier Submitter, apart from several amendment proposals for technical details not changing the conclusions, one MS asked for some more details to confirm the rapid degradability of acrolein, and another MS advocated to use the surrogate approach for chronic classification (however with the same results as the approach using the available long-term test results from fish, daphnids, and algae – the latter is in accordance to CLP guidance, proposed by the Dossier Submitter, and recommended by RAC).

The IND comment referred to the high reactivity, rapid degradability, low bioaccumulation potential and pronounced acute toxicity of acrolein, and questioned on this basis the need for classification of chronic hazards. While this is true according to the DSD criteria, chronic classification criteria according to 2nd ATP of CLP warrant indeed chronic classification, however with a 100-fold lower M-factor, well reflecting the lower chronic hazard in comparison to acute classification.

For further details of comments and responses given by the Dossier Submitter and RAC, cf. Annex 2.

RAC assessment and comparison with classification criteria

RAC supports the proposal by the Dossier Submitter to classify acrolein according to the CLP criteria as **Aquatic Acute 1 (H400)** with **M-factor = 100**, and as **Aquatic Chronic 1 (H410)** with **M-factor = 1**, and according to the DSD criteria as **N; R50** with a specific concentration limit **(SCL) Cn ≥ 0.25%**.

Under CLP, the classification of acute aquatic hazards should be based on the lowest acute LC_{50} of 7 µg/l from a test with tadpoles, which is – as all lowest valid test results from the standard groups of test organisms (i.e. fish, daphnids, algae) – well below the 1 mg/l criterion for classification, and with 0.001 < 0.007 ≤ 0.01 mg/l warrants an M-factor of 100. Although the tadpole test has not been used for risk assessment purposes for reasons explained by the Dossier Submitter in the CLH report, RAC confirms the

Dossier Submitter's proposal to consider this test valid for classification purposes. The results are well in line with all figures from the standard tests and with the expected pronounced acute toxicity of acrolein. Regarding chronic aquatic hazards, the NOEC from the most sensitive algae test is below the 0.01 mg/l threshold effect reference value criterion for rapidly degradable substances, and with $0.001 < 0.0051 \leq 0.01$ mg/l warrants an M-factor of 1. Although somewhat higher, the lowest valid NOECs from the other tested groups (fish, water fleas) are close enough to be highly consistent with the decisive algae test figure. As well consistent with the particular reactivity and acute toxicity of acrolein, all test results from long-term tests are very close to corresponding figures from short-term testing.

Under DSD, the classification for acute aquatic hazards, again based on the 96h-LC_{50} of 7 µg/l from a test with tadpoles being well below the classification criterion of 1 mg/l, should be N; R50 with a SCL corresponding to M = 100, i.e. Cn ≥ 0.25% and no classification with Cn < 0.25%. According to the DSD criteria, classification of chronic aquatic hazards would be based only on non-rapid degradability and/or bioaccumulation potential as surrogates justifying concern for long-term hazards (which could be disburdened by NOECs > 1 mg/l from long-term tests). Acrolein is, however, rapidly degradable and has no potential for bioaccumulation and thus requires no chronic classification R53 under the DSD criteria.

ANNEXES:

Annex 1 Background Document (BD)[4]
Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excl. confidential information).

[4] The Background Document (BD) gives detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the dossier submitter; the evaluation performed by RAC is contained in RAC boxes.