Committee for Risk Assessment

RAC

Opinion
proposing harmonised classification and labelling at EU level of

nitric acid ... %

EC Number: 231-714-2
CAS Number: 7697-37-2

CLH-O-0000001412-86-210/F

Adopted

8 June 2018

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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 Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: nitric acid ... %

EC Number: 231-714-2

CAS Number: 7697-37-2

The proposal was submitted by Germany and received by RAC on 23 March 2017.

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Germany 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/harmonised-classification-and-labelling-consultation/* on 25 April 2017. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by 9 June 2017.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: Bert-Ove Lund

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on 8 June 2018 by consensus.

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 and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	007-004-001	nitric acid … %	231-714-2	7697-37-2	Ox. Liq. 2 Skin Corr. 1A	H272 H314	GHS03 GHS05 Dgr	H272 H314	EUH071	Ox. Liq. 2; H272: C ≥ 99 % Ox. Liq. 3; H272: 65 % ≤ C < 99 % Skin Corr. 1A; H314: C ≥ 20 % Skin Corr. 1B; H314: 5 % ≤ C < 20 %	B
Dossier submitter's proposal	007-004-001	nitric acid … % [C > 70 %]	231-714-2	7697-37-2	Add Acute Tox. 1	Add H330	Add GHS06	Add H330	Retain EUH071	Retain Ox. Liq. 2; H272: C ≥ 99 % Ox Liq. 3: 70 % ≤ C < 99 %	Retain B
Dossier submitters proposal	TBD	nitric acid … % [C ≤ 70 %]	231-714-2	7697-37-2	Add Acute Tox. 3	Add H331	Add GHS06	Add H331	Retain EUH071	Retain Ox. Liq. 3; H272: C ≥ 65 % Add inhalation: ATE = 2.1 mg/L	Retain B
RAC opinion	007-004-00-1	nitric acid … % [C > 70 %]	231-714-2	7697-37-2	Add Acute Tox. 1	Add H330	Add GHS06	Add H330	Retain EUH071	Retain Ox. Liq. 2; H272: C ≥ 99 % Ox. Liq. 3; H272: 70 % ≤ C < 99 %	Retain B
RAC opinion	TBD	nitric acid … % [C ≤ 70 %]	231-714-2	7697-37-2	Add Acute Tox. 3	Add H331	Add GHS06	Add H331	Retain EUH071	Retain Ox. Liq. 3; H272: C ≥ 65 % Skin Corr. 1A; H314: C ≥ 20 % Skin Corr. 1B; H314: 5 % ≤ C < 20 % Add inhalation: ATE = 2.65 mg/L (vapour)	Retain B
Resulting Annex VI entry if agreed by COM	007-004-00-1	nitric acid … % [C > 70 %]	231-714-2	7697-37-2	Ox. Liq. 2 Acute Tox. 1 Skin Corr. 1A	H272 H330 H314	GHS03 GHS06 GHS05 Dgr	H272 H330 H314	EUH071	Ox. Liq. 2; H272: C ≥ 99 % Ox. Liq. 3; H272: 70 % ≤ C < 99 %	B
Resulting Annex VI entry if agreed by COM	TBD	nitric acid … % [C ≤ 70 %]	231-714-2	7697-37-2	Ox. Liq. 3 Acute Tox. 3 Skin Corr. 1A	H272 H331 H314	GHS03 GHS06 GHS05 Dgr	H272 H331 H314	EUH071	Ox. Liq. 3; H272: C ≥ 65 % inhalation: ATE = 2.65 mg/L (vapour) Skin Corr. 1A; H314: C ≥ 20 % Skin Corr. 1B; H314: 5 % ≤ C < 20 %	B

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

In 2012, Germany submitted a CLH dossier to ECHA with a proposal to revise the current entry for nitric acid by adding Acute Tox. 1; H330 (based on two studies using highly concentrated nitric acid) with the supplemental hazard information EUH071 (Corrosive to the respiratory tract), and to change the then current classification as Ox. Liq. 3; H272 to Ox. Liq. 2; H272 for concentrated nitric acid (C ≥ 99 %).

At RAC-24 this proposal was agreed and it was submitted to the Commission for inclusion in the CLP Regulation, via the 7th adaptation to technical progress (ATP, Regulation 2015/1221 of 24 July 2015). However, the classification and labelling of nitric acid as Acute Tox. 1 was delayed by the Commission after Industry commented that nitric acid is an azeotrope (a constant boiling mixture) at a concentration of just above 68 %, and that there is a non-linear relationship between the nitric acid concentration and acute toxicity. Industry further concluded that the classification of nitric acid mixtures (containing < 70 %) using the additivity formula is not justified.

In view of the above issues, industry subsequently performed an acute inhalation toxicity study in accordance with OECD test guideline (TG) 403 and in compliance with GLP. The objective was to provide quantitative animal data on the hazard potential of nitric acid via acute inhalation, at the azeotropic point (approximately 70 %). In July 2015, the final study report on the acute inhalation toxicity study in Wistar rats (4-hour vapour exposure, nose-only) with nitric acid ≤ 70 % was submitted by industry, and this formed the basis for the current CLH dossier submitted by Germany.

The proposal was to split the current entry in Annex VI of CLP into two separate entries:

- nitric acid … % [C > 70 %]
- nitric acid … % [C ≤ 70 %]

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

The proposal by the dossier submitter (DS) was to confirm the classification of nitric acid > 70 % with Acute Tox. 1; H330, and to add Acute Tox. 3; H331 for concentrations ≤ 70 %, based on the study presented below.

In the new acute inhalation toxicity study in Wistar rats with nitric acid 70 % (BASF SE, 2015) only one concentration, 2.65 mg/L (analytical concentration referring to pure nitric acid) was tested. The test atmosphere of nitric acid was characterised as vapour, containing only 0.8 % aerosol (mist) fraction. According to the DS, the study protocol did not fully meet the essential requirements of the OECD TG 403, as specified for the main study (traditional protocol) which demands sufficient concentration levels to obtain a concentration-response relationship ranging

from non-lethal to lethal outcomes in order to derive a median lethal concentration (LC_{50}). According to the guideline the main study should be performed with at least three concentration levels using five rats/sex/concentration.

One of the five male rats died at the tested concentration on day 9 of the post-exposure observation period. A large number of severe clinical signs were observed in the male that died and also in the surviving male and female rats during the recovery period. The DS reported that there were overt signs of severe clinical effects and concluded that these data provide clear evidence that nitric acid 70 % is acutely toxic by inhalation.

The acute inhalation toxicity study in Wistar rats (4-hour exposure, nose-only) with nitric acid 70 % (vapour) determined an LC_{50} value of > 2.65 mg/L/4h (analytical concentration referring to pure nitric acid). Although no accurate LC_{50} value for nitric acid 70 % was derived, the results of single 4-hour exposure to 2.65 mg/L in conjunction with the observations of severe clinical signs enabled classification and labelling of the test substance according to CLP. The DS proposed that nitric acid ≤ 70 % should be classified as Acute Tox. 3 by inhalation exposure and labelled with the pictogram GHS06, the signal word 'Danger' and the hazard statement H331 (Toxic if inhaled) according to CLP. For a substance tested as a vapour and classified as Acute Tox. 3; H331, the acute toxicity estimates (ATE) range between 2 and 10 mg/L/4h (2.0 < ATE ≤ 10 mg/L/4h) with a converted acute toxicity point estimate of 3 mg/L (CLP, Annex I, Table 3.1.2). However, the DS proposed to correct the default ATE of 3 mg/L to 2.1 mg/L since the solution used to generate the vapour contained 70 % and not 100 % nitric acid.

The DS concluded that according to CLP, nitric acid with concentrations > 70 % should be classified as Acute Tox. 1 for inhalation and labelled with the pictogram GHS06, the signal word 'Danger' and hazard statement H330 (Fatal if inhaled). Nitric acid with concentrations ≤ 70 % should be classified as Acute Tox. 3 for inhalation and labelled with the pictogram GHS06, the signal word 'Danger' and hazard statement H331 (Toxic if inhaled).

As nitric acid is corrosive to the respiratory tract, the additional labelling with EUH071 was proposed to be retained for both concentrations.

Comments received during public consultation

Comments were received from two Member States Competent Authorities (MSCAs) and five industry organisations.

One MSCA agreed with the classification proposal for nitric acid ≤ 70 % (Acute Tox. 3) but proposed to use an ATE of 3 mg/L/4h rather than the recalculated ATE of 2.1 mg/L/4h.

One MSCA questioned whether the new acute inhalation study was really performed according to OECD TG 403, both considering the use of only one (not explained) dose level and with respect to the interpretation of the data, as moribound animals suffering severe pain and distress (as exemplified by four animals losing their nose tip) were neither humanely killed nor considered dead as requested by the OECD test guideline. This MSCA did not express a view in relation to the classification.

According to the sponsor of the study, it was aimed at minimising aerosol while maximising vapour. The concentration tested should therefore be considered as a type of limit concentration. As such, the sponsor considered the study to be in conformity with OECD TG 403.

There was one industry comment in support of the proposed classification, one supporting a specific entry for concentrations ≤ 70 %, and one stating that the Acute Tox. 1 for highly

concentrated nitric acid is based on the toxicity of NO_2 released from fuming nitric acid rather than on nitric acid as such.

There were also industry comments opposing the recalculated ATE of 2.1 mg/L/4h, and rather proposing to use 2.65 mg/L/4h (as used in the recent study) or 3 mg/L/4h (default converted ATE for category 3).

Industry comments also highlighted that the non-linearity of the vapour pressure for nitric acid results in that the CLP additivity formula for acute toxicity by inhalation is not relevant for nitric acid. Based on the non-linearity, one comment suggested to introduce additional concentration thresholds for classification and that no classification is needed at concentrations < 53-55 % (vapour pressure < 0.4 mmHg).

One comment was received as to the negative impact on the dairy industry of any classification of nitric acid.

Assessment and comparison with the classification criteria

Based on two acute inhalation studies in rats, giving LC_{50} values of 0.2 mg/L/4h, RAC confirms that the relevant classification for concentrated nitric acid (> 70 %) is Acute Tox. 1 (LC_{50} < 0.5 mg/L); H330 (Fatal if inhaled).

RAC notes that the new rat acute inhalation toxicity study (BASF SE, 2015) is stated to follow OECD TG 403, but as also pointed out by the DS, used only a single exposure level (2.65 mg/L/4h). For the purpose of classification and labelling of nitric acid at ≤ 70 %, the single concentration tested allowed RAC to determine the acute toxicity category. In addition, this exposure level was the highest vapour concentration that could be generated from a 70 % solution of nitric acid without simultaneous generation of aerosols. The 4h nose-only inhalation exposure to nitric acid resulted in one dead male (day 9) and a large number of severe clinical signs in the remaining nine rats. The CLH dossier describes depressed respiration during exposure, intermittent and or abdominal respiration after exposure, gasping, respiration sounds, nose discharge, red encrusted nose, swelling nose, red encrusted eye, redden conjunctiva, loss of nose tip in 3/5 males and 1/5 females, and summarize this as "*obvious signs of severe pain and enduring distress and suffering, providing clear evidence of acute inhalation toxicity*". The DS concluded that the LC_{50} was > 2.65 mg/L/4h, the only concentration tested.

RAC also notes that the OECD TG 403 makes it clear that "*moribound animals or animals obviously in pain or showing signs of severe and enduring distress should be killed and are considered in the interpretation of the test result in the same way as animals that died on the test*" (OECD TG 403, §8). The same requirements are given by the OECD Guidance document on acute inhalation toxicity testing (OECD, 2009; Guidance document No. 39). The OECD Guidance document on the recognition, assessment, and use of clinical signs as humane endpoints for experimental animals used in safety evaluation (OECD, 2000; Guidance document, No. 19) defines when animals should be humanely killed due to pain, distress, and suffering. As to suffering, the document concludes that "*if something is known to cause suffering in humans, it should be assumed to cause suffering in animals*." RAC is of the opinion that the loss of nose tip due to corrosion could therefore be expected to lead to extreme suffering. Clarification was therefore sought from the study director of the performing laboratory as regards to what the finding described as "loss of nose tip" meant.

The additional information received from the study director is summarised below:

"Exposure to the test substance caused superficial, small-area tissue damage at the very tip of the noses of the 4 animals, which is indicative of the known corrosivity of the test item. The consequence of this tissue damage was formation of a scurf of 2 to 3 mm in diameter within one

day after exposure, which fell off at the end of the observation period, disclosing young healthy skin underneath. The wording "loss of the nose tip" was chosen to describe this shedding of a piece of dead skin, i.e., the scurf, and is considered a normal step in successful wound healing. We realize, however, that the wording 'loss of the nose tip' is misleading and will amend the study report to clarify the effect."

"The clinical signs indicate that these rats were affected by the local effects of the test item: Piloerection was observed during the first few days after exposure, but not exceeding day 4. During the observation period, intermittent respiration, respiratory sounds and abdominal respiration were observed, which is not unexpected after exposure to an acid. Furthermore, the animals showed encrusted red nose, red nose discharge, and, in some cases, swelling of the nose, which are considered attendant symptoms of the tissue damage that resulted in falling off of the scurf. However, these signs improved or disappeared completely during the post-observation period, until all surviving animals were in normal general condition by the end of the post-observation period."

"In accordance with the study plan, the animals were checked for clinical signs and moribundity by highly qualified scientific personnel in full compliance with the OECD GD 19. In the present study, however, the signs and conditions marking impending death, moribund condition, or severe pain and distress as criteria for humane killing were not met. The clear result of the evaluation of the clinical signs was that no surviving animal was in a moribund state during the study."

In the view of RAC, it seems likely that most animals suffered from the exposure, but according to the additional information of the study director, suffering was concluded not to be sufficiently severe to warrant pre-term humane killing of the animals.

Based on one death (out of 10) together with respiratory problems, encrusted red nose, red nose discharge, and tissue damage at the very tip of the noses, the exposure level of 2.65 mg/L/4h supports an LC_{50} value in the order of $2.0 < LC_{50} \leq 10.0$ mg/L, warranting classification in Category 3. RAC also takes note of the human case reports, indicating health impairment after accidental inhalation of 20-30 % nitric acid and one death after inhalation of 34 % nitric acid, both of unknown exposure duration.

Regarding the ATE, RAC agrees with the comments submitted during the public consultation that a recalculation of the default ATE based on having a 70 % solution generating the vapour is not relevant. Indeed, the classification is based on the measured concentration in the inhalation study and not related to the initial concentration of nitric acid in the solution. Therefore, although the default ATE for Category 3 is 3 mg/L, RAC supports the concentration measured in the study as the ATE, i.e. 2.65 mg/L.

The non-linearity of the vapour pressure for nitric acid was addressed during the public consultation, and it was suggested that the classification should be more tightly connected to the vapour pressure. However, RAC agrees with the DS that strictly correlating classification with the vapour pressure and the resulting inhalation exposure potential is not relevant. The reported human cases of lethal inhalation toxicity of mixtures containing ≥ 34 % nitric acid are suggestive of effects worse than those that can be predicted based on the volatility of nitric acid. Also, the CLP Regulation is aimed at providing information on the intrinsic hazardous properties of chemicals and mixtures. Thus, the proposal of the DS to assume linearity below and above the azeotropic point (70 %), and to classify nitric acid with two different entries in Annex VI of CLP, is supported by RAC.

Because of clear corrosive effects in the respiratory tract, retaining the additional labelling with EUH071 in both entries (all concentrations) is supported by RAC.

RAC thus confirms the DS proposal for classifying:

- nitric acid > 70 % as Acute Tox. 1; H330, with the additional labelling EUH071 and;
- nitric acid ≤ 70 %, as Acute Tox. 3 (H331) with an ATE = 2.65 mg/L (inhalation of vapours) and the additional labelling with EUH071.

ANNEXES:

Annex 1 The Background Document (BD) gives the 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'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).