Committee for Risk Assessment

RAC

Annex 1
Background document
to the 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

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to public consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

8 June 2018

CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Names:

Nitric Acid ... % (C > 70% aqueous solution)

and

Nitric Acid ... % (C ≤ 70% aqueous solution)

EC Number: **231-714-2**

CAS Number: **7697-37-2**

Index Number: **007-004-00-1**

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CONTENTS

Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***Nitric acid***
EC number:	***231-714-2***
CAS number:	***7697-37-2***
Annex VI Index number:	***007-004-00-1***
Degree of purity:	*This dossier addresses two types of aqueous nitric acid:* • *nitric acid, C ≤ 70%* • *nitric acid, C > 70%*
Impurities:	No impurity is considered relevant for the classification of the substance nitric acid.

1.2 Harmonised classification and labelling proposal

Due to the chemical properties of aqueous nitric acid at different concentrations it is proposed to split the current entry in Annex VI of CLP for '007-004-001 nitric acid …%' into two entries:

- 007-004-001 nitric acid …% [> 70 % in aqueous solution]
- 007-004-… nitric acid …% [≤ 70 % in aqueous solution]

Table 2a: The current Annex VI entry for nitric acid …% and the proposed harmonised classification for nitric acid …% (C ≤ 70 %)

	CLP Regulation
Current harmonised classification for nitric acid …% (C ≤ 70 %)	Ox. Liq. 2; H272 Ox. Liq. 2; H272: C ≥ 99 % Ox. Liq. 3; H272: C ≥ 65 % Skin Corr. 1A; H314 Skin Corr. 1A; H314: C ≥ 20 % Skin Corr. 1B; H314: 5 % ≤ C < 20 % EUH071 Note B
Current proposal for consideration by RAC for nitric acid …% (C ≤ 70 %)	Acute Tox. 3; H331 ATE: 2.1 mg/L/4hr EUH071
Resulting harmonised classification (future entry in Annex VI, CLP Regulation) for nitric acid …% (C ≤ 70 %)	Ox. Liq. 3; H272: C ≥ 65 % Acute Tox. 3; H331 Skin Corr. 1A; H314: C ≥ 20 % Skin Corr. 1B; H314: 5 % ≤ C < 20 % EUH071 Note B

Table 2b: The current Annex VI entry for nitric acid …% and the proposed harmonised classification for nitric acid …% (C > 70 %)

	CLP Regulation
Current harmonised classification for nitric acid …% (C > 70 %)	Ox. Liq. 2; H272 Ox. Liq. 2; H272: C ≥ 99 % Ox. Liq. 3; H272: 70 % < C < 99 % Skin Corr. 1A; H314 EUH071 Note B
Current proposal for consideration by RAC	Acute Tox. 1; H330
Resulting harmonised classification (future entry in Annex VI, CLP Regulation) for nitric acid …% (C > 70 %)	Ox. Liq. 2; H272 Ox. Liq. 2; H272: C ≥ 99 % Ox. Liq. 3; H272: 70 % < C < 99 % Acute Tox. 1; H330 Skin Corr. 1A; H314 EUH071 Note B

1.3 Proposed harmonised classification and labelling based on CLP Regulation

Table 3: Proposed classification and labelling according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	none		none	Not assessed in this dossier
2.2.	Flammable gases	none		none	Not assessed in this dossier
2.3.	Flammable aerosols	none		none	Not assessed in this dossier
2.4.	Oxidising gases	none		none	Not assessed in this dossier
2.5.	Gases under pressure	none		none	Not assessed in this dossier
2.6.	Flammable liquids	none		none	Not assessed in this dossier
2.7.	Flammable solids	none		none	Not assessed in this dossier
2.8.	Self-reactive substances and mixtures	none		none	Not assessed in this dossier
2.9.	Pyrophoric liquids	none		none	Not assessed in this dossier
2.10.	Pyrophoric solids	none		none	Not assessed in this dossier
2.11.	Self-heating substances and mixtures	none		none	Not assessed in this dossier
2.12.	Substances and mixtures which in contact with water emit flammable gases	none		none	Not assessed in this dossier
2.13.	Oxidising liquids	Ox. Liq. 3 - H272: C ≥ 65 %		Ox. Liq. 3 - H272: C ≥ 65 %	Harmonized classification proposed
2.14.	Oxidising solids	none		none	Not assessed in this dossier
2.15.	Organic peroxides	none		none	Not assessed in this dossier
2.16.	Substance and mixtures corrosive to metals	none		none	Not assessed in this dossier
3.1.	Acute toxicity - oral	none		none	Not assessed in this dossier
	Acute toxicity - dermal	none		none	Not assessed in this dossier

	Acute toxicity - inhalation	Acute Tox. 1; C > 70 % Acute Tox. 3; C ≤ 70 % EUH071		none	Harmonized classification proposed
3.2.	Skin corrosion / irritation	Skin Corr. 1A	Skin Corr. 1A - H314: C ≥ 20 % Skin Corr. 1B - H314: 5 % ≤ C < 20 %	Skin Corr. 1A - H314: C ≥ 20 % Skin Corr. 1B - H314: 5 % ≤ C < 20 %	
3.3.	Serious eye damage / eye irritation	none		none	Not assessed in this dossier
3.4.	Respiratory sensitisation	none		none	Not assessed in this dossier
3.4.	Skin sensitisation	none		none	Not assessed in this dossier
3.5.	Germ cell mutagenicity	none		none	Not assessed in this dossier
3.6.	Carcinogenicity	none		none	Not assessed in this dossier
3.7.	Reproductive toxicity	none		none	Not assessed in this dossier
3.8.	Specific target organ toxicity –single exposure	none		none	Not assessed in this dossier
3.9.	Specific target organ toxicity – repeated exposure	none		none	Not assessed in this dossier
3.10.	Aspiration hazard	none		none	Not assessed in this dossier
4.1.	Hazardous to the aquatic environment	none		none	Not assessed in this dossier
5.1.	Hazardous to the ozone layer	none		none	Not assessed in this dossier

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Table 4: Proposed labelling for nitric acid …% (C > 70 %) based according to the CLP Regulation

	Labelling	Wording
Pictograms	GHS03 GHS05 GHS06	Flame over circle Corrosive Skull and crossbones
Signal Word	Dgr	Danger
Hazard statements	H272 H330 H314	May intensify fire; oxidiser. Fatal if inhaled. Causes severe skin burns and eye damage.
Suppl. Hazard statements	EUH071	Corrosive to the respiratory tract.
Precautionary statements		

Table 5: Proposed labelling for nitric acid …% (C ≤ 70 %) based according to the CLP Regulation

	Labelling	Wording
Pictograms	GHS03 GHS05 GHS06	Flame over circle Corrosive Skull and crossbones
Signal Word	Dgr	Danger
Hazard statements	H272 H331 H314	May intensify fire; oxidiser. Toxic if inhaled. Causes severe skin burns and eye damage
Suppl. Hazard statements	EUH071	Corrosive to the respiratory tract.
Precautionary statements		

Proposed notes assigned to an entry:

Note B:

Some substances (acids, bases, etc.) are placed on the market in aqueous solutions at various concentrations and, therefore, these solutions require different classification and labelling since the hazards vary at different concentrations.

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

'Nitric acid … %' is legally classified and labelled (Index No. 007-004-00-1) for its corrosive reactions to skin, eyes and mucosa with Category 1A, H314 and regarding oxidizing properties as oxidizing liquid Category 3, H272 according to CLP. The following SCLs are established:

for skin corrosion:	Skin Corr. 1A; H314: C ≥ 20 %,
	Skin Corr. 1B; H314: 5 % ≤ C < 20 %,
and as an oxidizing liquid:	Ox. Liq. 3; H272: C ≥ 65 %.

In 2012 the German CA[1] submitted a proposal to ECHA to supplement the current classification of nitric acid by adding new classification as Acute Tox. 1, H330 with the supplemental hazard information EUH071 (Corrosive to the respiratory tract) and a change of the current classification as oxidizing liquid Category 3 to oxidising liquid Category 2, H272 for concentrated nitric acid (C ≥ 99 %)[2].

RAC-24 agreed with the proposal of the German CA to classify nitric acid as Acute Tox. 1; H330 (Fatal if inhaled) with the supplemental hazard information EUH071 (Corrosive to the respiratory tract). For the oxidising properties RAC-24 agreed to classify nitric acid with a concentration of C ≥ 99 % in Category 2 for oxidising liquids (Oxid. Liq. 2, H272: May intensify fire; oxidiser) and nitric acid at concentrations of 99 % > C ≥ 65 % in Category 3 for oxidising liquids (Oxid. Liq. 3, H272) (ECHA/NA/13/22-2013).

Follow-up to the 13th Meeting of Competent Authorities for REACH and CLP (CARACAL, 26-28 November 2013) the adopted final RAC-24 opinion proposing the new classification of nitric acid in Annex VI of CLP has been published for its potential inclusion in the 7th Adaptation to Technical Progress (ATP).

Reason for testing nitric acid at a concentration of about 70 %

The animal studies used as the basis for the classification proposal for nitric acid in 2012 used highly concentrated nitric acid, red fuming nitric acid (RFNA, containing 8-17 % NO_2), and white fuming nitric acid (WFNA, containing 0.1-0.4 % NO_2).

In February 2014, members of industry commented that the toxic effects of nitric acid at lower concentrations in more diluted aqueous solutions and of pure, highly concentrated acid may be very different with their consequences for different classification. They provided information to the German CA on a non-linear relationship between the nitric acid content in the gas phase and liquid phase and that uncertainty exist whether the linear dependency according to the additivity formula of CLP is applicable for a correct classification of nitric acid (mixtures) at and below a concentration of about 70 %. While concentrated fuming nitric acid is characterised by the release of NO_x (nitrous fumes) the data submitted by industry suggested that diluted nitric acid up to concentrations of about 70 % has a comparably low vapour pressure and does not release nitrous fumes by itself (only in contact with metals). Because of the azeotropic properties of nitric acid the industry argued that nitric

[1] http://www.bfr.bund.de/de/presseinformation/2012/09/totenkopfsymbol_fuer_salpetersaeure-128959.html
[2] http://echa.europa.eu/documents/10162/7617c929-1645-48a4-8945-a47b9c137261

acid in a concentration below the azeotropic point at approximately 70 % would be less acutely toxic by inhalation than derived by the additivity formula of CLP.

Due to these circumstances the German CA requested a postponement of the inclusion of the entry for acute inhalation toxicity for nitric acid into Annex VI to CLP with the 7th ATP at the 14th Meeting of CARACAL (2-3 April 2014).

As the result of a dialogue with industry representatives in April 2014, industry volunteered to perform a guideline conforming acute inhalation toxicity study to provide quantitative animal data on the acute inhalation hazard potential of nitric acid, at the azeotropic point (approximately 70 %). The outcome should clarify whether for this nitric acid concentration a different classification for acute inhalation toxicity might be justified than for the pure nitric acid.

In July 2015, the final report on the acute inhalation toxicity study in Wistar rats (4-hour vapour exposure, nose-only) with nitric acid 70 % was submitted by industry.

In this CLH dossier, the test results from this study are assessed for a classification and labelling of nitric acid solutions at and below 70 % for acute inhalation toxicity.

2.2 Short summary of the scientific justification for the CLH proposal

This CLH proposal should be seen as a supplement to the adopted RAC-24 opinion for harmonised classification and labelling of nitric acid for acute inhalation toxicity of 31 May 2013.

In the acute inhalation toxicity study in Wistar rats with nitric acid 70 % 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 fraction. One of the five male rats died at the tested concentration on study day 9 during the post exposure observation period. A large number of severe clinical signs were observed in the male which died and also in the surviving male and female rats during the recovery period. There are overt signs of severe pain and enduring signs of distress and suffering. 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 % as vapour determined the 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 pain and distress enabled classification and labelling of the test substance. Nitric acid 70 % has to be classified as acute hazard Category 3 for inhalation exposure and labelled with the pictogram GHS06, the signal word ‘Danger’ and hazard statement H331 (Toxic if inhaled.) according to CLP (Annex I, Part 3, 3.1 Acute toxicity, Category 3, vapours: 2.0 < ATE ≤ 10 mg/L/4hr).

It is concluded that the classification for acute inhalation toxicity should distinguish between pure fuming nitric acid, with concentrations > 70 %, and nitric acid at and below 70 %.

According to CLP, nitric acid with concentrations > 70 % should be classified in acute hazard Category 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 in acute hazard Category 3 for inhalation and labelled with the pictogram GHS06, the signal word ‘Danger’ and hazard statement H331 (Toxic if inhaled).

The classification of nitric acid as acutely toxic by inhalation is thought to be based on its corrosive properties to the respiratory tract. Nitric acid is classified and labelled for its corrosive effects as Skin

Corr. 1A - H314 (Causes severe skin burns and eye damage). According to CLP, Note 1 in Table 3.1.3, the supplemental labelling with EUH071 (Corrosive to the respiratory tract) is proposed as data indicate that the mechanism of toxicity is corrosivity.

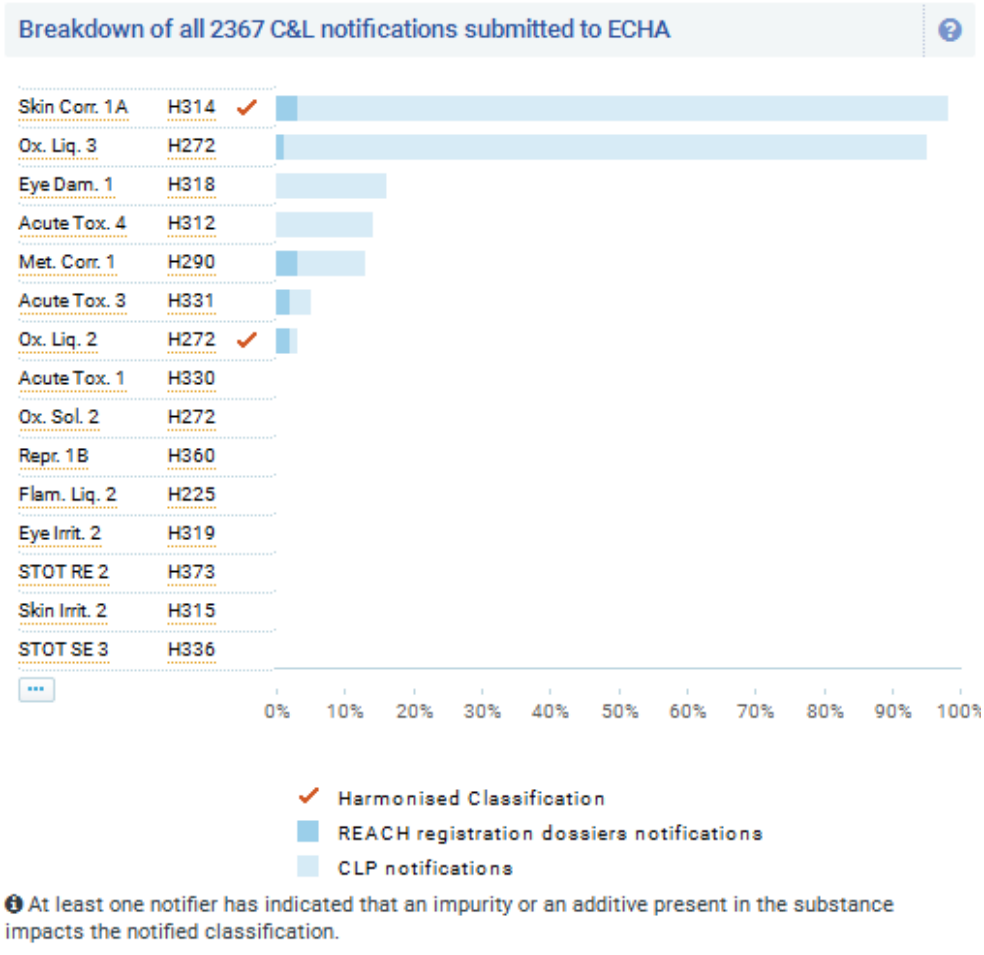
2.3 Current harmonised classification and labelling

Table 6: Current harmonised classification and labelling of nitric acid …% (CLP, Table 3.1)

Index No	Classification		Labelling			Specific Conc. Limits, M-factors	Note
	Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
007-004-00-1	Ox. Liq. 2 Acute Tox. 1 Skin Corr. 1A	H272 H330 H314	GHS03 GHS06 GHS05 Dgr	H272 H314 H330	EUH071	Skin Corr. 1A; H314: C ≥ 20 % Skin Corr. 1B; H314: 5 % ≤ C < 20 % Ox. Liq. 2; H272: C ≥ 99 % Ox. Liq. 3; H272: 99 % > C ≥ 5 %	B

2.4 Current self-classification and labelling

Table 7: Entry in the C&L Inventory (March 2017)



RAC general comment
In 2012, the German Member States Competent Authority (MSCA) 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 into the CLP Regulation, via the 7th adaptation to technical progress (ATP, Regulation 2015/1221 of 24 July 2015). However, the classification and labelling 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 decided to perform an acute inhalation toxicity study in accordance with OECD test guideline (TG) 403 and in compliance with GLP. The main objective was to provide quantitative animal data on the acute inhalation hazard potential of nitric acid, 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 this CLH dossier from 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 %]

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

The initial concern for the supplement of classification and labelling of nitric acid for acute inhalation toxicity in accordance with CLP was related to poisonings which occurred via inhalation during normal use of specific nitric-acid containing cleaning products in households. Of the 134 cases of severe health effects related to the use of these cleaning agents by consumers, which were reported by the German poison centres during 1999–2010, roughly 30 cases were caused by inhaling fumes or vapours during the use of such mixtures containing nitric acid (BfR Opinion 041/2010).

The fumes, vapours and gases originating from nitric acid may have a detrimental health effect after a single exposure or short-term inhalation. Therefore, the reported use of nitric acid in cleaning agents entails a disproportionate health risk for the general population, in particular when these agents are used indoors.

The current classification of nitric acid by adding classification for acute inhalation toxicity is needed in order to ensure precautions for safe handling, use and disposal, e.g. international trade of nitric acid. Also the classification and labelling is a prerequisite for appropriate risk management on legislative and company level and may trigger substitution in some markets.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 8: Substance identity

EC number:	231-714-2
EC name:	nitric acid
CAS number (EC inventory):	7697-37-2
CAS number:	7697-37-2
CAS name:	nitric acid
IUPAC name:	nitric acid
CLP Annex VI Index number:	007-004-00-1
Molecular formula:	HNO_3
Molecular weight range:	63.01 g/mol

Structural formula:

1.2 Composition of the substance

The proposal for classification of ‘nitric acid …%’ aims at a different classification regarding acute inhalation toxicity: Nitric acid …% [C > 70 %] and Nitric acid …% [C ≤ 70 %]

Table 9: Constituents (non-confidential information)

Constituents of Nitric acid …% (C > 70%)	**Typical concentration**	**Concentration range**	**Remarks**
Nitric acid	> 70 % w/w	Up to 99 %	The Annex VI dossier was divided into two parts to cover aqueous solutions of nitric acid: C>70% C≤70% Following the definition of a substance according to article 3 number 1 of the REACH regulation water is no constituent of the substance nitric acid. However, due to reasons of transparency water was added here.
water	< 30 % w/w		

Table 10: Constituents (non-confidential information)

Constituents of Nitric acid …% (C ≤ 70%)	**Typical concentration**	**Concentration range**	**Remarks**
Nitric acid	≤ 70 % w/w	5 to 70 %	The Annex VI dossier was divided into two parts to cover aqueous solutions of nitric acid: C>70% C≤70% Following the definition of a substance according to article 3 number 1 of the REACH regulation water is no constituent of the substance nitric acid. However, due to reasons of transparency water was added here.
water	≥ 30 % w/w		

Table 11: Impurities (non-confidential information)

Impurity	**Typical concentration**	**Concentration range**	**Remarks**
Unknown impurities	≤ 0.25 % w/w		NH_4^+, NO_2^-, SO_4^{2-}, Cl^-, Fe^{2+}, SiO_2

Table 12: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
none				

1.3 Physico-chemical properties

Nitric acid is a strong acid with strong oxidizing properties. Nitric acid (HNO_3) is produced in a variety of acid strengths containing nitric acid from approximately 50 to 99 %, with variable amounts of dissolved nitrogen dioxide (NO_2). Commercial formulations of the compound contain approximately 56-68 % HNO_3. The pure acid is a rarity (NIOSH 1976). With water, nitric acid forms an azeotropic mixture which contains 69.2 % HNO_3 and is designated concentrated nitric acid; dilute nitric acid is available with 12 % HNO_3 (Henschler 1992).

In the anhydrous, highly concentrated state, nitric acid is a colourless or yellowish liquid which fumes in humid air. The yellow colour is due to the release of NO_2 on exposure to light. Concentrated nitric acid containing dissolved NO_2 is termed fuming nitric acid (Budavari et al. 1989). The nitric acid fumes consist of acid molecules and their breakdown products: nitrogen oxides (nitrogen dioxide, NO_2 and nitric oxide, NO), oxygen and water. The material evaporating from this acid is therefore always a mixture of degradation products whose composition is determined by various factors such as temperature, humidity, and other materials the fumes comes into contact to (Henschler 1992).

According to military specifications the terms “white fuming” and “red fuming” are applied to differentiate two concentrations of fuming nitric acid. White fuming nitric acid (WFNA) contains about 97.5 % nitric acid by weight while red fuming nitric acid (RFNA) contains 82.4 - 85.4 %. The percentages of dissolved NO_2 content in WFNA and RFNA are about 0.5 and 14 %, respectively. In practice, HNO_3 is usually found in conjunction with NO_2 (ACGIH 1991). The following table summarises the physico-chemical properties of nitric acid.

Table 13: Summary of physico - chemical properties

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
State of the substance at 20°C and 101,3 kPa	liquid	RÖMPP Online, 2003	
Melting/freezing point	- 42 °C	Lewis RJ, 1989	
Boiling point	83 °C at 1013.25 hPa	CRC Handbook, 61st edition	
Relative density	1.5 g/cm³ at 25 °C	Lewis RJ, 1989	
Vapour pressure	64 hPa at 20 °C	Stern et al., 1960	
Surface tension	-	-	
Water solubility	miscible	BASF AG, 1993	
Partition coefficient n-octanol/water	-	-	
Flash point	Testing can be waived, the substance is inorganic and Nitric acid is non-combustible.	BAM 2.2 (2011)	*Data Waiver*
Flammability	Flammability upon ignition (solids, gases): Testing can be waived, substance is a liquid. Flammability in contact with water: Testing can be waived in accordance with REACH Column 2 of Annex VII, 7.10: The classification procedure needs not to be applied because the substance does not contain metals or metalloids. Pyrophoric properties: Testing can be waived in accordance with REACH Column 2 of Annex VII, 7.10: The classification procedure needs not to be applied because the substance is known to be stable into contact with air at room temperature for prolonged periods of time (days).	BAM 2.2 (2011) BAM 2.2 (2011) BAM 2.2 (2011)	*Data Waiver* *Data Waiver* *Data Waiver*

Explosive properties	Testing can be waived in accordance with REACH Column 2 of Annex VII, 7.11: The classification procedure needs not to be applied because there are no chemical groups present in the molecule which are associated with explosive properties.	BAM 2.2 (2011)	*Data Waiver*
Self-ignition temperature	Testing can be waived, substance is a liquid.	BAM 2.2 (2011)	*Data Waiver*
Auto-ignition temperature-liquids and gases	Testing can be waived, the substance is inorganic and Nitric acid is non-combustible.	BAM 2.2 (2011)	*Data Waiver*
Oxidising properties	HNO_3, C ≥ 99 %: Oxidizing Liquid, Category 2	BAM 2.23 (2011)	UN Test O.2
Granulometry	-	-	
Stability in organic solvents and identity of relevant degradation products			
Dissociation constant	-	-	

2 MANUFACTURE AND USES

2.1 Manufacture

Not evaluated for this report.

2.2 Identified uses

Not evaluated for this report.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Hazard classes not assessed in this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Not evaluated in this report.

4.2 Acute toxicity

Table 14: Summary table of relevant acute inhalation toxicity studies

Method	Results	Remarks	Reference
Inhalation Acute inhalation toxicity study LC_{50} test **Rat:** 10 male albino rats / conc. Inhalation, as **vapour** **RFNA**, red fuming nitric acid (containing 82.4-85.4 % nitric acid and about 8-17 % NO_2) Exposure: 2 min – 4 hr Observation period: 3 days	**LC_{50} values (male):** (NO_2 only) = 138 ppm/30 min (range: 123-155 ppm) (NO_2 + HNO_3) = 310 ppm/30 min **(NO_2 + HNO_3) = 77.5 ppm/4 hr** **(= 0.20 mg/L/4hr)**	LC_{50} test Reliability 2 as the testing protocol was not standardized and validated internationally.	Gray et al. 1954; NIOSH 1976
Inhalation Acute inhalation toxicity study LC_{50} test **Rat:** 5 male albino rats / conc. Inhalation; as **vapour** **WFNA**, white fuming nitric acid (containing about 97.5 % nitric acid and about 0.1-0.4 % NO_2) Exposure: 2 min – 4 hr Observation period: 3 days	**LC_{50} values (male):** (NO_2 only) = 244 ppm/30 min (NO_2 + HNO_3) = 334 ppm/30 min **(NO_2 + HNO_3) = 83.5 ppm/4 hr** **(= 0.22 mg/L/4hr)**	LC_{50} test Reliability 2 as the testing protocol was not standardized and validated internationally.	Gray et al. 1954; NIOSH 1976
Inhalation Acute inhalation toxicity study Protocol similar to OECD TG 403/EU B.2 **Rat:** Wistar (RccHan:WIST) 5/sex Inhalation; as **vapour**, 0.8 % liquid aerosols of the total concentration **Nitric acid 70.8 %** Particle size, MMAD: 1.66 - 2.33 µm Exposure: 4 hr (nose only) Observation period: 14 days	**LC_{50} value (male/female):** **> 2.65 mg/L/4hr** (referring to pure nitric acid) Mortality: Males: 1/5 on study day 9 Females: 0/5 Clinical signs: 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 their nose tip:** 3/5 males 1/5 females **obvious signs of severe pain and enduring distress, and suffering providing clear evidence of acute inhalation toxicity**	OECD TG 403 / EU B.2 Reliability 2 as Only one concentration tested; no accurate LC_{50}	BASF SE 2015, unpublished study report, confidential

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Hazard class not assessed in this dossier.

4.2.1.2 Acute toxicity: inhalation

The first CLH dossier on nitric acid was submitted by Germany to ECHA in 2012. It contained a proposal together with the justification and background information documented in a CLH report to supplement the current classification of nitric acid by adding a new classification as acutely toxic by inhalation. RAC-24 agreed with the proposal of the German CA to classify nitric acid as Acute Tox. 1; H330 (Fatal if inhaled) with the supplemental hazard information EUH071 (Corrosive to the respiratory tract) (ECHA/NA/13/22-2013).

Follow-up to the 13th Meeting of Competent Authorities for REACH and CLP (CARACAL, 26-28 November 2013) the adopted final RAC-24 opinion proposing the new classification of nitric acid in Annex VI of CLP has been published for its potential inclusion in the 7th Adaptation to Technical Progress (ATP). However, industry provided information to the German CA on a non-linear relationship between the nitric acid content in the gas phase and liquid phase and that uncertainties exist whether the linear dependency according to the additivity formula of CLP is applicable for a correct classification of nitric acid (mixtures) at a concentration of about 70 %. While concentrated fuming nitric acid is characterised by the release of NO_x (nitrous fumes) the data submitted by industry suggested that diluted nitric acid up to concentrations of about 70 % has a comparably low vapour pressure and does not release nitrous fumes by itself (only in contact with metals). Because of the azeotropic properties of nitric acid the industry argued that nitric acid in a concentration below the azeotropic point at approximately 70 % would be less acutely toxic by inhalation than derived by the additivity formula of CLP.

Due to these circumstances the German CA requested a postponement of the inclusion of the entry for acute inhalation toxicity for nitric acid into Annex VI to CLP with the 7th ATP at the 14th Meeting of CARACAL (2-3 April 2014). Subsequently, industry volunteered to perform a guideline conform acute inhalation toxicity study to provide quantitative animal data on the acute inhalation hazard potential of nitric acid, at the azeotropic point (approximately 70 %).

The purpose of the now presented acute inhalation toxicity study was to see if the test atmosphere of nitric acid 70 % is a vapour or liquid aerosol, and to provide animal data to assess the acute inhalation hazard potential at this test concentration. The outcome should clarify whether a different classification for acute inhalation toxicity of nitric acid ≤ 70 % is justified.

The acute inhalation toxicity of nitric acid 70 % was determined in Wistar (RccHan:WIST) rats (5/sex; males 8 wk, females 10 wk) according to OECD TG 403 (07 Sep 2009, “Acute Inhalation Toxicity”, as well as EU B.2 Acute Toxicity (Inhalation), and EPA (U. S. EPA Health Effects Test Guidelines OPPTS 870.1300, August 1998, “Acute Inhalation Toxicity”) guidelines. No control groups were used. Male and female rats were single exposed (nose only) for 4 hours to only one concentration, 2.65 mg/L (analytical concentration referring to pure nitric acid) of nitric acid as a vapour followed by a 14-day observation period (BASF SE 2015, unpublished study report).

Prior to the main study, various modifications of vapour generation procedures were tested, especially vaporizer, air bubbling through test substance column, and nebulization with or without aerosol blocker. Atmospheres of nitric acid were generated by aerosolizing the test item containing 70 % nitric acid. The atmosphere generation via bubbling air through a test substance column or via a

vaporizer was found inappropriate. The nebulization of the test substance in an aerosol mixing stage was used for the acute inhalation toxicity study with nitric acid 70 %. The test atmosphere was generated by continuously pumping amounts of the test substance to a two-component atomizer. Using compressed air, the aerosol was produced first with the atomizer inside the aerosol-mixing vessel. Due to the high surface area of the aerosol droplets, the test substance evaporated immediately within the glass vessel and was passed into the exposure system.

The nominal concentration was calculated from the amounts of test substance dosed and the supply airflows.[3] The actual concentration of the test substance in inhalation atmosphere was determined on the basis of nitrate ion. For each sample the concentration was calculated in mg/L from the analytically determined mass values of the test substance in the samples and the respective volume sampled from the inhalation atmosphere. Mean and standard deviation was calculated for the concentration from the results of the individual measurements. Nitrite ion concentration in different samples was below the detection limit of the analysis method (0.5 mg/L solvent). The mean atmospheric concentration of the test substance was 2.65 mg/L (Standard deviation 0.19). The test atmosphere of nitric acid 70 % was characterised as vapour containing in average 0.8 % aerosol fraction.

Particle size measurement using an aerodynamic particle sizer showed respirable particles with mass median aerodynamic diameters (MMAD) between 1.66 and 2.33 µm (GSD 2.35 to 3.09). The particle count concentration ranged from 1300 to 2030 particles per cm^3.

After a single nose-only inhalation exposure to 2.65 mg/L nitric acid 70 % for 4 hours one of the five males died on study day 9 during the post exposure observation period. No lethality was observed in females.

During or immediately following exposure to 2.65 mg/L nitric acid 70 % and during the recovery period all animals showed a series of clinical signs of toxicity. Some signs persisted throughout the recovery period. There were visually 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 of eyes. At the end of the exposure period, three males and one female lost their nose tip. It is to be expected that this tissue damage has led to severe pain and severe distress lasting for the duration of the damage, the ensuing inflammatory process and persists after the local tissue damage has healed. Such persistent pain and distress lead to suffering of animals. There were also some unspecific toxic effects, especially piloerection and yellow-stained fur.

The male animal that died showed several clinical signs of toxicity as mentioned above, was dehydrated and in a poor general condition. Its body weight decreased significantly since the end of exposure.

The mean body weights of the surviving male and female animals were decreased during the first post exposure observation days and increased thereafter.

Necropsy of the male that died prematurely revealed yellow discoloration of the nose region, encrusted, red and swelling nose, and dilation of the intestines with gaseous content. Histology was performed on the respiratory tract and small intestine. In the respiratory tract focal desquamation of squamous epithelium at level I of the nasal cavity was observed. This finding was accompanied by a

[3] According to the study director the nominal concentration (mass of test article disseminated into the exposure system during the generation period divided by the total airflow through the inhalation chamber during the same time period) of the test substance is given with 51 % referring to 70 % nitric acid and 73 % referring to pure nitric acid.

minimal luminal inflammatory exudate of the same region. Moreover, at level I of larynx epithelial alteration, focal, minimal (base of epiglottis) and at level III of larynx, minimally increased number of mucus cells, moderate focal flatten epithelium were noted. There were no adverse changes in nasal cavity levels II to IV, trachea, lung, pharynx, larynx level II. No findings were seen in the small intestine.

The necropsy of the animals sacrificed at the termination of the post exposure observation revealed yellow discoloration of the fur in the nose region of all 4 of the 5 males and all of the 5 females. Two of the 5 females showed skin lesion in the nose region. A loss of nose tips was seen in 3 of 5 males and one of 5 females. Histology was not performed.

Conclusion: Nitric acid 70 % is acutely toxic by inhalation. The presented acute inhalation toxicity study in rats was accepted with restrictions, because only one test concentration was used for testing and no accurate LC_{50} value for nitric acid 70 % was derived in this study. Under the conditions of this acute inhalation toxicity study in Wistar rats (4-hour exposure, vapour, nose-only) the LC_{50} value of > 2.65 mg/L/4hr (analytical concentration referring to pure nitric acid) was determined for nitric acid 70 %. The results of single 4-hour exposure to 2.65 mg/L in conjunction with the observations in exposed male and female rats showing severe and enduring signs of pain and distress are enabling for classification and labelling of nitric acid 70 % regarding acute inhalation toxicity. Based on all available data it is assumed that nitric acid 70 % fulfils the criteria for classification as acutely toxic and can be allocated to a hazard category on acute inhalation toxicity.

4.2.1.3 Acute toxicity: dermal

Hazard class not assessed in this dossier.

4.2.1.4 Acute toxicity: other routes

Hazard class not assessed in this dossier.

4.2.2 Human information

In the following summarised data of case studies of humans accidently exposed to nitric acid is given. Detailed description of all available human data are presented and discussed in the first CLH report for classification of nitric acid as acutely toxic by inhalation submitted by Germany in 2012. It is attached in Annex I. For more details, see there.

The assessment of health risks from the use of household cleaning agents containing 20-30 % nitric acid conducted by the Federal Institute for Risk Assessment (BfR) in Berlin, Germany (BfR Opinion No. 041/2010, 06 September 2010) has presented 134 cases of serious health damage caused by the handling of specific nitric acid-containing cleaning products in the home, specifically of two limestone and rust removers produced in (or imported from) Turkey. In almost one quarter of the cases (23.7 %), the symptoms were caused by inhalation. In individuals exposed to nitric acid by inhalation minor to moderate health impairments were observed at which the outcome could not been estimated. Such persons showed prolonged cough, dyspnoea, obstruction of the respiratory tract, recurrent vomiting, spasticity, congestion of the lungs and reduced oxygen partial pressure.

Severe injury and death of a plant guard were observed following accidental exposure to vapours and gases originating from a 34 % nitric acid solution (Rossano 1945).

Hall and Cooper (1905) described case reports of firemen exposed to nitric acid fumes. Approximately 10 gallons of a 38 % nitric acid solution were spilled and came in contact with zinc.

Autopsy revealed haemorrhagic oedema of the lungs and coagulation necrosis of the mucous membrane of the complete respiratory tract.

Long-term sequelae after accidental inhalation of fumes from nitric acid are reported (Schmid 1974, 1974a). A 25-year-old truck driver died three weeks after inhaling a considerable amount of fumes while cleaning up spilled 60 % nitric acid. At autopsy severe lesions were observed in the lungs.

A case of acute inhalation injury of nitric acid in a 56-year old white male was reported by Bur et al (1997). The man cleaned a copper chandelier with a 60 % nitric acid solution by placing the chemical and chandelier in a bowl.

Three men died of rapidly progressive pulmonary oedema with delayed onset after inhalation of fumes from an accidental nitric acid explosion (Hajela et al. 1990). The men entered the area with the heaviest concentration of fumes and dust following an explosion of a tank containing approximately 1736 L of 68 % nitric acid.

In the following table an overview on cases of accidental exposed humans to nitric acid solutions is given.

Table 15: Overview on cases of accidental exposed humans to nitric acid solutions

Nitric acid solutions	**Accidental exposed humans**	**References**
20-30 %	23.7 % from 134 cases	BfR Opinion No. 041/2010, 06 September 2010
34 %	1 plant guard (lethality)	Rossano (1945)
38 %	8 / 20 firemen (lethality)	Hall and Cooper (1905)
60 %	1 truck driver (lethality)	Schmid (1974, 1974a)
60 %	1 man (lethality)	Bur et al (1997)
68 %	3 men (lethality)	Hajela et al. (1990)

Exposure of volunteers to nitric acid fumes showed an absence of symptoms at the low concentration of 0.0042 mg/L (Sackner and Ford 1981).

4.2.3 Summary and discussion of acute toxicity

The acute inhalation toxicity of nitric acid has been described and classification of nitric acid for acute toxicity is proposed only for the inhalation route of exposure. Overall the results show nitric acid is acutely toxic by inhalation.

RAC-24 has adopted the first CLH proposal submitted by Germany in June 2012 for classification of nitric acid as ‘Acute Toxicity Category 1’ for inhalation with the hazard statement code H330 (Fatal if inhaled), and labelled with the pictogram GHS06, the signal word ‘Danger’, and the supplemental hazard information EUH071 (Corrosive to the respiratory tract) according to CLP (ECHA/NA/13/22-2013). The adopted RAC-24 opinion proposing the new classification of nitric acid in Annex VI of CLP was published for its potential inclusion in the 7th ATP as follow-up to the 13th Meeting of CARACAL (26-28 November 2013).

The collected data on acute inhalation toxicity for nitric acid obtained from animal testing and from experiences in humans (e.g. information from poison centres) together with the justification and

background information documented in the CLH report were analysed and compared with classification criteria for this endpoint.

Severe injuries and death of humans accidently exposed to vapours and gases originating from nitric acid solutions were reported in the literature. Cases of human poisoning were observed at nitric acid concentrations of 20 % and higher. After single or relatively short exposure to nitric acid, lethality has been caused in humans due to acute pulmonary oedema. In humans, severe effects and/or lethality occurred after a typical latency period of 3 up to 30 hours after exposure. Inhalation of gases and vapours originating from nitric acid can be extremely dangerous since there is no violent respiratory reflex, serving as a warning property, as is observed with e.g. chlorine and ammonia. Thus, inhalation of nitric acid fumes at potentially fatal concentrations may initially remain undetected by the affected person (Hardy and Hamilton 1974, cited in Durant et al. 1991).

The acute lethal effects of so-called 'red fuming nitric acid' (RFNA, containing 8-17 % nitrogen dioxide), 'white fuming nitric acid' (WFNA, containing 0.1-0.4 % nitrogen dioxide), and nitrogen dioxide (NO_2) by inhalation was examined in male albino rats. The test atmosphere for RFNA and WFNA was characterised as a vapour. Deaths occurred by acute pulmonary oedema (Gray et al. 1954; NIOSH 1976).

LC_{50}-values of 77.5 ppm/4hr (0.20 mg/L/4hr) for RFNA and 83.5 ppm/4hr (0.22 mg/L/4hr) for WFNA were calculated. The 4-hour values were derived from the 0.5 hour LC_{50}-values for RFNA (310 ppm) and for WFNA (334 ppm) as calculated by NIOSH (1976) based on results of Gray et al. (1954).

The studies were considered sufficiently reliable to propose classification of nitric acid as acutely toxic by the inhalation route of exposure, in particular since the high inhalation toxicity of nitric acid is supported by data in humans showing severe effects and lethality after single inhalation exposure to nitric acid at concentrations of 20 % and higher.

Nitric acid …% [C ≤ 70 %]

Due to the azeotropic properties of nitric acid uncertainties were discussed by industry whether the linear dependency according to the additivity formula of CLP is applicable for a correct classification of nitric acid at and below 70 %. The German CA requested a postponement of the inclusion of the entry for acute inhalation toxicity for nitric acid into Annex VI to CLP with the 7th ATP at the 14th Meeting of CARACAL (2-3 April 2014).

To assess whether the test atmosphere of nitric acid 70 % by testing for acute inhalation toxicity is a vapour or liquid aerosol and to evaluate the acute inhalation hazard potential of concentrated nitric acid, approximately 70 % (at the azeotropic point) acute inhalation toxicity study in Wistar rats (4-hour vapour exposure, nose-only) with nitric acid 70 % was submitted by industry in July 2015. The outcome should clarify whether for this nitric acid concentration a different classification for acute inhalation toxicity might be justified than for the pure nitric acid. The used study protocol of the available acute inhalation toxicity test with nitric acid 70 % in rats does not fully meet the essential requirements of the OECD testing guideline 403/EU B.2, 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. In the presented test, acute inhalation toxicity with nitric acid 70 % only one concentration, 2.65 mg/L (analytical concentration referring

to pure nitric acid) of nitric acid as a vapour was tested in 5 male and 5 female rats. Thus no accurate LC_{50} value for nitric acid 70 % was derived.

Whether the test atmosphere consisted mainly of aerosol or vapour is highly relevant for classification and labelling. The test atmosphere of nitric acid 70 % was characterised as vapour containing only 0.8 % aerosol fraction containing respirable particles with a MMAD between 1.66 and 2.33 µm.

One of the five male rats died after a single nose-only inhalation exposure to 2.65 mg/L nitric acid 70 % for 4 hours on study day 9 during the post exposure observation period. A large number of severe clinical signs were observed in the male which died and also in the surviving male and female rats during the recovery period. The observed severe lesions, especially the loss of the nose tip in three males and one female are overt indicators of distress, severe pain, or impending death of the animals. These data showing clear signs of severe pain and enduring distress, and suffering of the animals[4] provide clear evidence that nitric acid 70 % is acutely toxic by inhalation.

Under the conditions of this acute inhalation toxicity study in Wistar rats (4-hour exposure, vapour, nose-only) the LC_{50} value of > 2.65 mg/L/4hr (analytical concentration referring to pure nitric acid) was determined for nitric acid 70 %. 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 pain and distress enable classification and labelling of the test substance. Based on all available data it is assumed that nitric acid 70 % fulfils the criteria for classification as acutely toxic and can be allocated to a hazard category on acute inhalation toxicity.

The evidence on acute inhalation toxicity of nitric acid ≤ 70 % in humans is documented in Section ‘4.2.2 Human information’. From case studies lethality is reported after single exposure or exposure of less than 24 hours to nitric acid. In numerous human case reports, acute lethality was described following accidental exposure to nitric acid fumes, vapours or gases originating from acid solutions. Cases of human poisoning were observed at nitric acid concentrations of 20 % and above.

In the synopsis of data from animal testing, from human case reports, and special physico-chemical properties of nitric acid it is concluded that the classification of nitric acid for acute inhalation toxicity should distinguish between pure fuming nitric acid, with concentrations > 70 %, and nitric acid at and below 70 %. The entry in Annex VI of CLP for ‘007-004-001 nitric acid …%’ should be divided in:

‘007-004-001 nitric acid …% [> 70 % in aqueous solution]’ and

‘007-004-00? nitric acid …% [≤ 70 % in aqueous solution]’.

4.2.4 Comparison with criteria

Acute toxicity means those adverse effects occurring following oral or dermal administration of a single dose of a substance or a mixture, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours. Acute toxicity relates to effects occurring after a single or relative brief exposure to a substance or mixture. Acute toxicity classification is generally assigned on the basis of evident lethality. In contrast, contemporary study protocols, such as the fixed dose procedure, use signs of evident toxicity rather than lethality as indications of acute toxicity. Further as described in OECD

[4] OECD, 2000. Guidance Document on the Recognition, Assessment and Use of Clinical Signs as Humane Endpoints for Experimental Animals used in Safety Evaluation. Environmental Health and Safety Monograph Series on Testing and Assessment No. 19, OECD, Paris. Available at: [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono%282000%297&doclanguage=en]

Guidance Document no. 39 (2009) an evaluation of acute toxicity data should include the relationship, if any, between the animals' exposure to a specific test article chamber concentration and the incidence and severity of all abnormalities, including behavioural and clinical effects, the reversibility of observed effects, gross lesions, body weight changes, effects on mortality, and any other toxic effects. The evidence for acute toxicity of nitric acid is obtained from animal testing and case studies in humans accidently exposed to nitric acid. Substances can be allocated to one of four toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the numeric criteria shown in the Table 3.1.1 of Annex I, Part 3, Table 3.1.1 of the CLP Regulation.

Acute inhalation toxicity:

The following applies for the classification as

'Acute inhalation toxicity - Category 1 (vapour): ATE ≤ 0.5 mg/L/4hr.'

Nitric acid … % [C > 70 %]

The evidence for acute inhalation toxicity of nitric acid, the discussion of available data from experimental animals and case studies of humans accidently exposed to nitric acid and the conclusion for classification of nitric acid as acutely toxic by inhalation is provided in the CLH report submitted by Germany to RAC 2012 (see Annex I).

Based on the lowest derived LC_{50} value of 77.5 ppm/4hr (0.20 mg/L/4hr) for RFNA in the rat (Gray et al. 1954; NIOSH 1976), nitric acid has to be classified as acute hazard category 1 for inhalation exposure and labelled with the pictogram GHS06, signal word "Danger" and hazard statement H330 (Fatal if inhaled.) according to CLP (Annex I, Part 3, 3.1 Acute toxicity, Category 1, vapours: ATE ≤ 0.5 mg/L/4hr).

RAC-24 has adopted this CLH proposal submitted by Germany. The adopted RAC-24 opinion proposing the new classification of nitric acid in Annex VI of CLP was published for its potential inclusion in the 7th ATP as follow-up to the 13th Meeting of CARACAL (26-28 November 2013).

The following applies for the classification as

'Acute inhalation toxicity - Category 3 (vapour): 2.0 < ATE ≤ 10.0 mg/L/4hr.'

Nitric acid … % [C ≤ 70 %]

The data from the acute inhalation toxicity study in Wistar rats (4-hour vapour exposure, nose-only) with nitric acid 70 % have shown that nitric acid 70 % induced mortality in one of the five male rats at the tested concentration of 2.65 mg/L (analytical concentration referring to pure nitric acid) on study day 9 during the post exposure observation period. A large number of severe clinical signs were observed in the male which died and also in the surviving male and female rats during the recovery period. There are clear signs of severe pain and distress, and suffering. Under the conditions of this acute inhalation toxicity study in Wistar rats the LC_{50} value of > 2.65 mg/L/4hr was determined for nitric acid 70 %. No accurate LC_{50} value for nitric acid 70 % was derived. However the results of single 4-hour exposure to 2.65 mg/L in conjunction with the observations of severe pain, enduring distress, and suffering of animals enable classification and labelling of the test substance. It is assumed that the real LC_{50} value for nitric acid 70 % lies within the range of the cut-off values for classification in the acute inhalation toxicity hazard Category 3 (vapours) according to CLP and which is 2.0 < ATE ≤ 10.0 mg/L/4hr.

Based on the review of available experimental data for acute inhalation toxicity for nitric acid it is concluded that nitric acid 70 % meets the criteria for classification and labelling as acutely toxic Category 3 for inhalation exposure according to CLP (Annex I, Part 3, 3.1 Acute toxicity, Category 3, vapours: 2.0 < ATE ≤ 10 mg/L/4hr), in addition nitric acid 70 % should be labelled with the pictogram GHS06, signal word 'Danger' and hazard statement H331 (Toxic if inhaled).

Cases of severe poisoning (including death) were observed in humans exposed accidently to vapours and gases during the use of nitric acid at concentrations of 20 % and higher. According to the Guidance Document on the application of the CLP Criteria, the minimum dose or concentration shown or expected to cause mortality after a single human exposure can be used to derive the human ATE directly, without any adjustments or uncertainty factors. In the reported poisoning cases, however, calculation of a human ATE on the vapour that can be directly compared with the values obtained from the animal study is not possible. Thus, this information was considered not contradictory to the present classification of nitric acid ≤ 70 %. The potentially additional, but not quantifiable release of toxic gases in these cases has been largely attributed to the reactivity of nitric acid with metals and other materials. Overall, there is some uncertainty as to whether these accidents are due to the inherent properties of the substance or rather to its particular use (or a combination of both). Uses (and possibly misuses) of the substance should be (could be) addressed by other regulatory measures outside the scope of CLP.

4.2.5 Conclusions on classification and labelling

According to CLP, nitric acid with concentrations > 70 % should be classified in acute hazard Category 1 for inhalation and labelled with the pictogram GHS06, signal word 'Danger' and hazard statement H330 (Fatal if inhaled).

Nitric acid with concentrations ≤ 70 % should be classified in acute hazard Category 3 for inhalation and labelled with the pictogram GHS06, signal word 'Danger' and hazard statement H331 (Toxic if inhaled).

The classification of nitric acid as acutely toxic by inhalation involves a hazard of respiratory tract corrosion, since up to now nitric acid is classified and labelled only for its corrosive reactions as Skin Corr. 1A - H314 (Causes severe skin burns and eye damage.). According to CLP nitric acid has to be labelled in addition with EUH071 (Corrosive to the respiratory tract).

Acute inhalation toxicity estimate (ATE; inhalation):

According to the Guidance on the application of CLP criteria (version 4.1, June 2015, point 3.1.2.5) specific concentration limits (SCLs) are not applicable for acute classification. The relative potency of substances is implicitly taken into account in the additivity formula (see Section 3.1.3.3.3.). For this reason specific concentration limits for acute toxicity will not appear in CLP Annex VI, Table 3.1 or in the classification and labelling inventory (CLP Article 42).

According to Annex I, Part 3, Point 3.1.3.6.1. ('Classification of mixtures based on ingredients of the mixture (Additivity formula), Data available for all ingredients') classification of mixtures is based on the calculated ATE of a mixture. The ATE for a mixture is determined by calculation from the ATE values for all relevant ingredients to the following additivity formula:

$$\frac{100}{ATE_{mix}} = \sum_{n}\frac{C_i}{ATE_i} \quad (1)$$

where:
C_i = concentration of ingredient i (% w/w or % v/v); i = the individual ingredient from 1 to n
n = the number of ingredients;
ATE_i = Acute Toxicity Estimate of ingredient i.

For the classification of mixtures containing nitric acid …% [C ≤ 70 % in aqueous solution] an ATE value of 2.1 mg/L/4h is proposed for the calculation with the additivity formula according to Annex I, Part 3, and Point 3.1.3.6.1. or 3.1.3.6.2.3 of the CLP.

Justification for the calculated ATE value, inhalation of 2.1 mg/L/4h:

In the available acute inhalation toxicity study according to OECD TG 403/EU B.2 in Wistar rats (4-hour vapour exposure, nose-only), the LC_{50} value of 70 % nitric acid solution could not be determined exactly. The LC_{50} value of 70 % nitric acid solution was considered to be greater than 2.65 mg/L/4h (vapour).

In this case conversion from the experimentally obtained acute toxicity range value (or acute toxicity hazard category) to an acute toxicity point estimate for use in the formulas (CLP Annex I, Part 3, and Point 3.1.3.6.1. or 3.1.3.6.2.3) for the classification of mixtures is applied. According to CLP, Annex I, Table 3.1.2. the converted acute toxicity point estimate for inhalation (vapours) classified in the hazard category 3 is 3 mg/L/4h (see Note 1: 'These values are designed to be used in the calculation of a mixture based on its components and do not represent test results.'). Thus, the converted acute toxicity point estimate for nitric acid ≤ 70 % (vapour) is set as 3 mg/L/4h and was used for the further calculations.

For the purposes of applying the additivity formula according CLP Annex I, Part 3, Point 3.1.3.6.1. or 3.1.3.6.2.3 an ATE value is used as the basis for calculation that is not related to 70 % but to 100 % acid. Therefore the converted acute toxicity point estimate of 3 mg/L/4h that refers to 70 % nitric acid was then converted to the 100 % nitric acid as follows:

$$ATE_{mix} = \frac{100}{C_{y\%}} \cdot ATE_x \quad (3)$$

$$ATE_{mix,\,70\%\,HNO3} = 3\frac{mg}{L}/4h \quad (4)$$

$$ATE_{100\%} \cdot \frac{100}{70} = 3\frac{mg}{L}/4h \quad (5)$$

$$\Rightarrow \underline{ATE_{100\%}} = \frac{70}{100} \cdot 3\frac{mg}{L}/4h = \underline{2.1\frac{mg}{L}/4h} \quad (6)$$

Accordingly, an ATE value of 2.1 mg/L/4h should be used in the additivity formula for the classification of mixtures containing nitric acid …% [C ≤ 70 % in aqueous solution]. This extrapolation to an "$ATE_{100\%}$" is only valid for mixtures containing ≤ 70 % nitric acid as mixtures containing > 70 % nitric acid should always be considered Acute Tox. 1; H330 according to this proposal.

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.

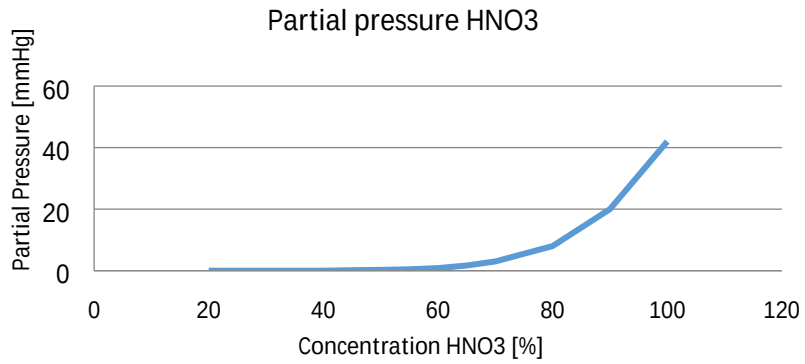
There were also industry comments opposing the recalculated ATE of 2.1 mg/L/4h, and rather proposing to use 2.65 mg/L/4h (as used in the recent study) or 3 mg/L/4h (default converted ATE for category 3).

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.

Additional key elements

The figure below illustrates the partial pressure of nitric acid at different concentrations of nitric acid, and the steep increase at the azeotropic point at 68 %, as presented in comments received during the public consultation.



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 4 h 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.

4.3 Specific target organ toxicity – single exposure (STOT SE)

Hazard class not assessed in this dossier.

4.4 Irritation

Hazard class not assessed in this dossier.

4.5 Corrosivity

Hazard class not assessed in this dossier.

4.6 Sensitisation

Hazard class not assessed in this dossier.

4.7 Repeated dose toxicity

Hazard class not assessed in this dossier.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

Hazard class not assessed in this dossier.

4.9 Germ cell mutagenicity (Mutagenicity)

Hazard class not assessed in this dossier.

4.10 Carcinogenicity

Hazard class not assessed in this dossier.

4.11 Toxicity for reproduction

Hazard class not assessed in this dossier.

4.12 Other effects

Hazard class not assessed in this dossier.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Hazard class not assessed in this dossier.

6 OTHER INFORMATION

Hazard class not assessed in this dossier.

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8 ANNEXES

Annex I – CLH report on nitric acid, submitted by Germany (2012)