Committee for Risk Assessment
RAC

Annex 1
Background document
to the Opinion proposing harmonised classification
and labelling at Community level of

nitric acid

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

CLH-O-0000002560-82-03/A1

The Background Document (BD) 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

31 May 2013

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: Nitric Acid

EC Number: 231-714-2

CAS Number: 7697-37-2

Index Number: 007-004-00-1

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Part A.

Tables

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:	*s. Chapter 1.2*
Impurities:	No impurity is considered relevant for the classification of the substance nitric acid.

1.2   Harmonised classification and labelling proposal

Table 2:   The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	Directive 67/548/EEC (Dangerous Substances Directive; DSD)
Current entry in Annex VI, CLP Regulation	Ox. Liq. 3 - H272 Skin Corr. 1A - H314 Skin Corr. 1A - H314: $C \geq 20\ \%$ Skin Corr. 1B - H314: $5\ \% \leq C < 20\ \%$ Ox. Liq. 3 - H272: $C \geq 65\ \%$	O; R8 C; R35 C; R35: $C \geq 20\ \%$ C; R34: $5\ \% \leq C < 20\ \%$ O; R8: $C \geq 70\ \%$ Footnote: B
Current proposal for consideration by RAC	Acute Tox. 1 – H330 EUH071: Corrosive to the respiratory tract Ox. Liq. 2; H272: $C \geq 99\ \%$	T^{+}; R26
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Ox. Liq. 3; H272: $99\% > C \geq 65\ \%$ Ox. Liq. 2; H272: $C \geq 99\ \%$ Acute Tox. 1 – H330 EUH071: Corrosive to the respiratory tract Skin Corr. 1A - H314 Skin Corr. 1A - H314: $C \geq 20\ \%$ Skin Corr. 1B - H314: $5\ \% \leq C < 20\ \%$	O; R8 T^{+}; R26 C; R35 C; R35: $C \geq 20\ \%$ C; R34: $5\ \% \leq C < 20\ \%$ O; R8: $C \geq 70\ \%$ Footnote: B

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3:   Proposed classification 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 evaluated
2.2.	Flammable gases	none		none	Not evaluated
2.3.	Flammable aerosols	none		none	Not evaluated
2.4.	Oxidising gases	none		none	Not evaluated
2.5.	Gases under pressure	none		none	Not evaluated
2.6.	Flammable liquids	none		none	Not evaluated
2.7.	Flammable solids	none		none	Not evaluated
2.8.	Self-reactive substances and mixtures	none		none	Not evaluated
2.9.	Pyrophoric liquids	none		none	Not evaluated
2.10.	Pyrophoric solids	none		none	Not evaluated
2.11.	Self-heating substances and mixtures	none		none	Not evaluated
2.12.	Substances and mixtures which in contact with water emit flammable gases	none		none	Not evaluated
2.13.	Oxidising liquids	Ox. Liq. 2 - H272	Ox. Liq. 2; $C \geq 99$ % Ox. Liq. 3 - H272: 99 % $> C \geq 65$ %	Ox. Liq. 3 - H272 Ox. Liq. 3 - H272: $C \geq 65$ %	
2.14.	Oxidising solids	none		none	Not evaluated
2.15.	Organic peroxides	none		none	Not evaluated
2.16.	Substance and mixtures corrosive to metals	none		none	Not evaluated
3.1.	Acute toxicity - oral	none		none	Not evaluated
	Acute toxicity - dermal	none		none	Not evaluated
	Acute toxicity - inhalation	Acute Tox. 1 - H330 EUH071		none	

3.2.	Skin corrosion / irritation	Skin Corr. 1A - H314	Skin Corr. 1A - H314: C ≥ 20 % Skin Corr. 1B - H314: 5 % ≤ C < 20 %	Skin Corr. 1A - H314 Skin Corr. 1A - H314: C ≥ 20 % Skin Corr. 1B - H314: 5 % ≤ C < 20 %	
3.3.	Serious eye damage / eye irritation	none		none	Not evaluated
3.4.	Respiratory sensitisation	none		none	Not evaluated
3.4.	Skin sensitisation	none		none	Not evaluated
3.5.	Germ cell mutagenicity	none		none	Not evaluated
3.6.	Carcinogenicity	none		none	Not evaluated
3.7.	Reproductive toxicity	none		none	Not evaluated
3.8.	Specific target organ toxicity –single exposure	none		none	Not evaluated
3.9.	Specific target organ toxicity – repeated exposure	none		none	Not evaluated
3.10.	Aspiration hazard	none		none	Not evaluated
4.1.	Hazardous to the aquatic environment	none		none	Not evaluated
5.1.	Hazardous to the ozone layer	none		none	Not evaluated

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

Labelling: Signal word: Danger

Current hazard statements: H272: May intensify fire; oxidiser.
H314: Causes severe skin burns and eye damage.

Proposed hazard statements: H330: Fatal if inhaled.

Current hazard pictogram: GHS03: Flame over circle
GHS05: Corrosion

Proposed hazard pictogram: GHS06: Skull and crossbones

Proposed additional labelling requirements (CLP supplemental hazard statement):
EUH071: Corrosive to the respiratory tract.

Proposed notes assigned to an entry:

Table 4:   **Proposed classification according to DSD**

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1]	Reason for no classification [2]
Explosiveness	none		none	Not evaluated
Oxidising properties	O; R8	O; R8: C ≥ 70 %	O; R8 O; R8: C ≥ 70 %	
Flammability	none		none	Not evaluated
Other physico-chemical properties	none		none	Not evaluated
Thermal stability	none		none	Not evaluated
Acute toxicity	T^+; R26			
Acute toxicity – irreversible damage after single exposure	none		none	Not evaluated
Repeated dose toxicity	none		none	Not evaluated
Irritation / Corrosion	C; R35	C; R35: C ≥ 20 % 5 % ≤ C; R34 < 20 %	C; R35 C; R35: C ≥ 20 % 5 % ≤ C < 20 %	
Sensitisation	None		none	Not evaluated
Carcinogenicity	None		none	Not evaluated
Mutagenicity – Genetic toxicity	None		none	Not evaluated
Toxicity to reproduction – fertility	none		none	Not evaluated
Toxicity to reproduction – development	none		none	Not evaluated
Toxicity to reproduction – breastfed babies. Effects on or via lactation	none		none	Not evaluated
Environment	none		none	Not evaluated

[1] Including SCLs

[2] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: <u>Indication of danger:</u>   O – Oxidising

                                                              C – Corrosive

<u>Proposed Indication of danger:</u> T^+ - Very toxic

<u>Current R-phrases:</u>
R8 - Contact with combustible material may cause fire.
R35 - Causes severe burns.

<u>Proposed R-phrases:</u>
R26 - Very toxic by inhalation.

2 BACKGROUND TO THE CLH PROPOSAL

Classification and labelling of nitric acid regarding oxidizing properties (O; R8) and its corrosive reactions (C; R35) were agreed by the Technical Committee on Classification and Labelling (TC C&L) (Directive 67/548/EEC). These agreed classifications were adopted by the European Commission for inclusion into Annex I of Directive 67/548/EEC before the introduction of the CLP Regulation. Nitric acid was not listed in any priority list of the Existing Substance Regulation (Regulation 793/93/EC). This CLH proposal aims to amend the classification and labelling of nitric acid for acute inhalation toxicity.

2.1 History of the previous classification and labelling

No previous discussion or decisions on classification and labelling for acute inhalation toxicity.

2.2 Short summary of the scientific justification for the CLH proposal

The acute inhalation toxicity of nitric acid (HNO_3) is described and classification of nitric acid for acute toxicity is proposed only for the inhalation route of exposure.

Nitric acid is acutely toxic by inhalation. There are no apparent species differences in the toxic response to acute inhalation exposure to HNO_3. After a single or relatively brief exposure to nitric acid lethality in animals and humans occurred due to rapid and progressive acute pulmonary oedema. In humans, lethality has been observed after a latency period between 3 and 30 hours. Besides, inhalation of gases and vapours originating from nitric acid can be extremely dangerous because they do not set up a violent respiratory reflex, as observed with chlorine and ammonia, which serves as a warning property. 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). These health hazards are not covered by the existing legal classification of nitric acid in Annex VI for its corrosive reactions as Skin Corr. 1A – H314. In particular, skin corrosion is usually characterised by local effects on the skin, namely, visible necrosis through the epidermis and into the dermis, following the application for up to 4 hours.

HNO_3 meets the criteria for classification and labelling as Acute Tox. 1 – H330 (CLP Regulation).

The evidence for acute inhalation toxicity of nitric acid was obtained from animal testing and from human experience (e.g. data from accident databases and experimental studies).

In numerous human case reports acute lethality was described following accidental exposure to nitric acid fumes, vapours and gases originating from acid solution. Exposure durations were recorded in some case reports, but real exposure concentrations were in most cases not given.

Reliable LC_{50} values for classification of HNO_3 were derived from acute inhalation toxicity studies in the favoured species, the rat. A well-conducted acute inhalation toxicity study in rats, which is suitable for LC_{50} determination of nitric acid, was conducted by Gray et al. (1954). In this comparative study 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. For RFNA and WFNA LC_{50} values of 77.5 ppm/4hr (0.20 mg/L/4hr) and 83.5 ppm/4hr (0.22 mg/L/4hr) were calculated (Gray et al. 1954; NIOSH 1976).

Conclusion: Although the studies by Gray et al. (1954) were conducted decades before standard test guidelines were adopted the studies were considered sufficient reliable to propose classification of nitric acid as acutely toxic by the inhalation route of exposure. 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 is to be classified and labelled as Acute Tox. 1 – H330 according to CLP Regulation (Annex I, Part 3, 3.1 Acute toxicity, Category 1, vapours: ATE ≤ 0.5 mg/L/4hr). This corresponds to T^+ (Very toxic); R26 (Very toxic by inhalation.) following criteria of Directive 67/548/EEC (Dangerous Substances Directive, DSD; Annex VI: LC_{50}, vapours: ≤ 0.5 mg/L/4hr).

The classification of nitric acid as acutely toxic by inhalation involves a hazard of respiratory tract corrosion, since up to now HNO_3 is classified and labelled only for its corrosive reactions as Skin Corr. 1A - H314 (Causes severe skin burns and eye damage.). According to CLP Regulation nitric acid has to be labelled in addition with EUH071 (Corrosive to the respiratory tract.).

Specific concentration limits (SCL) are not applicable for acute toxicity classification. Classification of mixtures is based upon ingredients of the mixture (Additivity formula). For this reason SCLs for acute toxicity will not appear in CLP Annex VI, Table 3.1 or in the classification and labelling inventory.

2.3   Current harmonised classification and labelling

2.3.1   Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Nitric acid is classified and labelled as an oxidizing liquid with Ox. Liq. 3 - H272 (May intensify fire; oxidiser.). For its corrosive reactions nitric acid is classified and labelled as Skin Corr. 1A - H314 (Causes severe skin burns and eye damage.). 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 %.

2.3.2   Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Nitric acid is classified and labelled as an oxidizing liquid with O (Oxidizing); R8 (Contact with combustible material may cause fire.). For its corrosive reactions nitric acid is classified and labelled as C (Corrosive); R35 (Causes severe burns.). The following SCLs are established: for skin corrosion: C; R35: C ≥ 20 %, C; R34: 5 % ≤ C < 20 %, and as an oxidizing liquid: O; R8: C ≥ 70 %.

2.4   Current self-classification and labelling

In the available registration dossiers (e.g. lead master registrant, BASF SE, Germany) nitric acid is classified and labelled for physico-chemical properties and for health hazards as follows:

- *Classification and labelling according to CLP Regulation:*

Classification:

Oxidising liquids: Ox. Liq. 3 - H272: May intensify fire; oxidiser.

Corrosive to metals: Met. Corr. 1 - H290: May be corrosive to metals.

Skin corrosion/irritation: Skin Corr.1A – H314: Causes severe skin burns and eye damage.

The following SCLs are established: for skin corrosion: Skin Corr. 1A; H314: C $\geq$ 20 %, Skin Corr. 1B; H314: 5 % $\leq$ C < 20 %, as an oxidizing liquid: Ox. Liq. 3; H272: C $\geq$ 65 %, and for metal corrosion: Met. Corr. 1; H290: C $\geq$ 20 %.

Labelling: Signal word: Danger

              Hazard pictogram: GHS03: Flame over circle

                                          GHS05: Corrosion

              Hazard statements: H314: Causes severe skin burns and eye damage.

                                            H272: May intensify fire; oxidiser.

                                            H290: May be corrosive to metals.

Precautionary statements:

P234: Keep only in original container.

P210: Keep away from heat/sparks/open flames/... /hot surfaces.... No smoking.

P220: Keep/Store away from clothing/... /combustible materials.

P221: Take any precaution to avoid mixing with combustibles...

P260: Do not breathe dust/fume/gas/mist/vapours/spray.

P264: Wash... thoroughly after handling.

P280: Wear protective gloves/protective clothing/eye protection/face protection.

P301+P330+P331: IF SWALLOWED: rinse mouth. Do NOT induce vomiting.

P305+P351+P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

P303+P361+P353: IF ON SKIN (or hair): Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower.

P363: Wash contaminated clothing before reuse.

P304+P340: IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing.

P310: Immediately call a POISON CENTER or doctor/physician.

P390: Absorb spillage to prevent material damage.

P404: Store in a closed container.

P406: Store in corrosive resistant/... container with a resistant inner liner.

P501: Dispose of contents/container to...

Additional labelling requirements (CLP supplemental hazard statement):

EUH071: Corrosive to the respiratory tract.

Notes: Note B

- *Classification and labelling according to DSD (in Annex I of Directive 67/548/EEC):*

Classification:

O; R8 Oxidising; Contact with combustible material may cause fire.

C; R35 Corrosive; Causes severe burns.

Labelling: Indication of danger: O - Oxidising

C – Corrosive

R-phrases:

R8 - Contact with combustible material may cause fire.

R35 - Causes severe burns.

S-phrases:

S1/2 - Keep locked up and out of reach of children.

S23 - Do not breathe gas/fumes/vapour/spray (appropriate wording to be specified by the manufacturer).

S26 - In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.

S36 - Wear suitable protective clothing.

S45 - In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

The following SCLs are established: for skin corrosion: C; R35: $C \geq 20\ \%$, C; R34: $5\ \% \leq C < 20\ \%$, and as an oxidizing liquid: O; R8: $C \geq 70\ \%$.

Notes: Note B

3   JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

The proposal for supplement of classification and labelling of nitric acid for acute inhalation toxicity in accordance with CLP Regulation or Directive 67/548/EEC is based on data (Poisonings reported by physicians according to § 16e of the German Chemicals Act) notified to the Federal Institute for Risk Assessment (BfR) in Berlin, Germany and data (inquiries) of the German poison treatment and information centres. The analysis and the assessment, also under the BfR National Committee "Assessment of Poisonings", revealed cases with - in some instances - serious health damage caused by accidents with specific nitric acid-containing cleaning products in the home. The cases notified to the German poison treatment and information centres show that not only adults but also children were affected. Against this backdrop and based on the scientific findings available up to now, the BfR has published a preliminary assessment of health risk linked to the use of household cleaning products containing nitric acid (see Annex 1: BfR Opinion No. 041/2010, 06 September 2010). It was concluded that the use of nitric acid-containing cleaning products which are sold to consumers,

entails a disproportionately high health risk for consumers. The health risk resulted in casuistic burns and also in acute toxic effects occurring following inhalation of nitric acid and the nitrous gases released from it.

Between 1999 and 2010 the BfR and the German poison treatment and information centres got reports of a total of 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. The safety data sheets indicate nitric acid as the dangerous ingredient with a content of 20-30 %. The products are in some cases sold without any effective child-resistant closure and with incorrect labelling on the German market. Most of the notifications (59.1 %) involved corrosion through the oral intake of nitric acid-containing products. In almost one quarter of the cases (23.7 %), the symptoms were caused by inhalation. In table 5 an overview of cases notified to the BfR and the German poison treatment and information centres between 1999 and 2010 is presented.

Table 5:   **Route of exposure in case reports (1999-2010)**

Exposure	Oral	Inhalation	skin and eye	unknown
Percent (%)	59.1	**23.7**	16.5	0.7

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. In cases of minor health disorders individuals complained of dry cough, sore throat, vomiting and burning of the pharynx.

Especially in contact with metals and by indoor use in small rooms (e.g. bath rooms etc.), nitric acid can lead to severe lung oedema, sometimes delayed with a symptom-free period of 8-24 hours for products with low concentrations of nitric acid. These accidents carry a high risk of the underestimation of the resulting health impairment and can lead to fatal mis- or under-treatment.

Whereas oral intake and dermal contact can be avoided through cautious handling and technical protection, the health risks from inhalation of nitric acid-containing cleaning products are almost unavoidable even in the case of correct use. Moreover, the notifications of intoxications confirm a worrying exposure situation for consumers.

Measures to restrict the placing on the market of nitric acid-containing consumer products are imperative due to the toxic properties of nitric acid outlined and of nitrous gases released it as well as due to the numerous cases of notified health impairments amongst consumers handling nitric acid-containing cleaning agents. Such agents are not suitable for use in the home and their utilisation must be urgently advised against. As consumer products must comply with stricter safety requirements than products for commercial use, nitric acid-containing agents should be regulated for the non-industrial area.

In order to facilitate possible chemical law provisions for risk reduction, classification and labelling of nitric acid (see index No. 007-006-00-1 in Tables 3.1 and 3.2 of Annex VI of the CLP Regulation) should be amended to include the classification and labelling for acute inhalation toxicity. In the existing regulation, only the potential harmful effects on skin and eyes have been considered with respect to classification of health effects. The classification and labelling of nitric acid in terms of toxicity following single exposure through inhalation has not yet been undertaken, although experimental studies on acute inhalation toxicity demonstrating adverse health effects are available.

None of the available registration dossiers includes a proposal to classify nitric acid based on its acute inhalation toxicity.

After supplementation of classification and labelling according to CLP Regulation on acute inhalation toxicity, aqueous mixtures of nitric acid could then become subject of special rules for labelling and packaging in order to protect users from the hazards posed by this substance or mixture. These chemicals if supplied to the general public require packaging rules including provisions of child-resistant fastenings and tactile warning. These provisions are triggered by acute hazard category 1-3 for inhalation exposure. This could then lead to constraints on sale (e.g. in self-service) for consumer products that contain nitric acid at or above a generic cut-off value of 0.1 %.

Although cases of intoxication were only available from Germany, it is assumed that similar household products might be sold in other EU Member States. In order to protect consumers from all Member States against risks from inhalation of nitric acid-containing products action on a community-wide basis is required to harmonise the classification and labelling under CLP Regulation.

Additionally it is proposed that the substance is no more to be classified as Ox. Liq. 3; H272. Instead a classification as Ox. Liq. 3; H272: $C \geq 65$ % and Ox. Liq. 2; H272: $C \geq 99$ % is proposed based on the available test data presented in chapter 3.

Harmonized classification and labelling for Nitric acid as a HPV chemical is considered a Community-wide action under Article 114 and it is recommended that the classification proposal is considered for inclusion on Annex VI of Regulation (EC) No. 1272/2008, table 3.1 and table 3.2.

RAC general comment
The dossier submitter proposes to supplement the current classification of nitric acid by adding acute toxicity (via inhalation) Category 1 as a new classification with the supplemental hazard information statement EUH071 (corrosive to the respiratory tract) and by changing the current classification for concentrated nitric acid ($C \geq 99$ %) from Oxidising liquid Category 3 to Oxidising liquid Category 2.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 6:   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:

OH

NO_2

1.2   Composition of the substance

The confidential information can be found confidential Annex or the technical dossier.

1.3   Physico-chemical properties

Nitric acid is a strong acid with strong oxidizing properties. It 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). Table 7 summarises the physico-chemical properties of nitric acid.

Table 7: **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	BAM 2.2 (2011) BAM 2.2 (2011) BAM 2.2 (2011)	*Data Waiver* *Data Waiver* *Data Waiver*

	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).		
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.

2.3   REACH-Registrations

The REACH-registration data till August 2011 have been taken into account.

3   CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 8:   Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
UN Test O.2 Test for oxidizing liquids	The mean pressure rise time for the 1 : 1 ratio of nitric acid (> 99 %) and cellulose is 320.6 ms and therefore the criteria for Category 2 are met ($R_3 \leq t \leq R_2$).	HNO_3, C > 99 %	BAM 2.23 (2011); BAM Test report, May 06, 2011 (BAM Code 2.23/080411/01)

3.1   Oxid. Liquid 2, H272

3.1.1   Summary and discussion of

3.1.2   Comparison with criteria

3.1.3   Conclusions on classification and labelling

Explosive properties: Testing can be waived based on a consideration of the chemical structure in accordance with REACH Column 2 of Annex VII, section 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.
No classification for explosivity is proposed.

Flammability – flash point (EU Method A.9): The study does not need to be conducted because the substance is inorganic and Nitric acid is non-combustible.
Flammability in contact with water and pyrophoricity (EU Method A.12 and A.13) can be omitted based on a consideration of the structure and experience and use.
No classification for flammability is proposed.

Oxidising properties: In a standard study (BAM 2.23 (2011), BAM Code 2.23/080411/01) nitric acid (C ≥ 99 %) has oxidising properties according to UN Test O.2 as described in the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria, Fifth Revised Edition, 2009.
Proposed classification based on Regulation (EC) No 1272/2008: Ox. Liq. 2; H272 (May intensify fire; oxidiser.)

In the available registration dossiers (e.g. of the lead master registrant, BASF SE, Germany) nitric acid is further classified and labelled for physico-chemical properties as corrosive to metals: Met. Corr. 1 - H290: May be corrosive to metals, with SCLs of C ≥ 20 %.

RAC evaluation of physical hazards
Summary of the Dossier submitter's proposal
<u>Explosive properties:</u>   Testing can be waived based on consideration of the chemical structure in accordance

with REACH Column 2 of Annex VII, section 7.11: the classification procedure need not be applied because there are no chemical groups present in the molecule which are associated with explosive properties. No classification for explosivity is proposed.

Flammability – flash point:
The study (EU Method A.9) does not need to be conducted because the substance is inorganic and nitric acid is non-combustible.

Flammability in contact with water and pyrophoricity
EU Method A.12 and A.13 can be omitted based on a consideration of the chemical structure and experience and use. No classification for flammability is proposed.

Oxidising properties:
In a standard study for determination of oxidising properties of nitric acid performed according to test method O.2 (UN-test O.2; UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria, Fifth Revised Edition, 2009) nitric acid (C ≥ 99 %) produced the results summarised in the table below:

Method	Results	Remarks	Reference
UN-test O.2 Test for oxidising liquids	The mean pressure rise time for a 1 : 1 ratio of nitric acid (> 99 %) and cellulose is **320.6** ms and therefore the criteria for Category 2 are met ($R_3^* \leq t \leq R_2^{**}$).	HNO_3, C > 99 %	BAM 2.23 (2011); BAM Test report, May 06, 2011 (BAM Code 2.23/080411/01)

R_3^* - the mean pressure rise time of a 1:1 mixture, by mass, of 50 % perchloric acid and cellulose; R_3= 45.6 ms
R_2^{**} - the mean pressure rise time of a 1:1 mixture, by mass, of 40 % aqueous sodium chlorate solution and cellulose; R_2 = 1013 ms

The mean pressure rise time for a 1:1 mixture, by mass, of nitric acid (C > 99 %) and cellulose is **320.6** ms, which is longer than that for a 1:1 mixture, by mass, of 50% perchloric acid and cellulose (45.6 ms – upper limit for Category 1), but shorter than the mean pressure rise time for a 1:1 mixture, by mass, of 40 % aqueous sodium chlorate solution and cellulose (1013 ms), which is the upper limit for Category 2.

Nitric acid is currently classified and labelled as an Oxidising liquid in Category 3 (Ox. Liq. 3 - H272; May intensify fire; oxidiser) with an SCL of C ≥ 65 % according to CLP. Based on the results of the above test, the dossier submitter proposed to upgrade the classification to = Ox. Liq. 2 - H272 (May intensify fire; oxidiser) according to CLP criteria. The following SCLs are proposed: Ox. Liq. 3 - H272: 99 % > C ≥ 65 % and Ox. Liq. 2 - H272: C ≥ 99 %.

According to the DSD criteria, nitric acid is currently classified as oxidising (O; R8: Contact with combustible material may cause fire) with an SCL of C ≥ 70 %. Based on the results of tests and taking into consideration the comments received during public consultation that a 1:1 mixture of 65 % aqueous nitric acid with cellulose is given as a reference mixture in the CLP criteria for Category 3 for oxidising liquids, and in the criteria for packing group III in UN-test method O.2, the dossier submitter proposes to classify nitric acid as O; R8 (Contact with combustible material may cause fire) with an SCL of C ≥ 65 %.

Metal corrosion
The dossier submitter noted that in the available registration dossiers (e.g. that of the lead registrant), nitric acid is classified and labelled for physico-chemical properties as

corrosive to metals: Met. Corr. 1 - H290 (May be corrosive to metals), with SCLs of C ≥ 20 %, but the dossier submitter did not include this as a proposed harmonised classification in the CLH report. The reason given for not including this physico-chemical property is the lack of test results which could be compared with the classification criteria.

Comments received during public consultation

Two MSCAs supported the classification of nitric acid as Ox. Liq. 2 - H272, i.e. as proposed by the dossier submitter.

One manufacturer noted the co-existence of two concentration threshold values for oxidising liquids (CLP annex VI, Part 3, table 3.1 vs. table 3.2) and suggested that the threshold concentration for the classification as oxidising liquid be harmonised to 65 % HNO_3. The dossier submitter agreed with this suggestion for a consistent threshold for classification as oxidizing liquid under both CLP and DSD.

One REACH consortium and one trade association proposed the following classification and SCLs:
C ≥ 70 %: Ox. Liq. 2 - H272;
65 % ≤ C < 70 %: Ox. Liq. 3- H272

RAC Assessment and comparison with the classification criteria

Oxidising properties:
The mean pressure rise time (t) of a 1:1 mixture, by mass, of nitric acid (C > 99 %) and cellulose is **320.6** ms, which is longer than that of a 1:1 mixture, by mass, of 50 % perchloric acid and cellulose (45.6 ms (R_3) – the lower limit for Category 1), but shorter than 1013 ms, the mean pressure rise time (R_2) of a 1:1 mixture, by mass, of 40 % aqueous sodium chlorate solution and cellulose (the lower limit for Category 2 and upper limit of Category 3).

Thus, the mean pressure rise time observed in the UN-test O.2 for a mixture of nitric acid (C > 99 %) and cellulose is within a range of values for Category 2 (i.e. between 45.6 ms and 1013 ms).

When comparing with the DSD criteria, based on results of the UN-test O.2 and taking into account that a 1:1 mixture of 65 % aqueous nitric acid with cellulose is given as a reference mixture in CLP criteria for Category 3 for oxidising liquids and in criteria for packing group III in UN-test O.2, nitric acid should be classified as oxidising materials with O; R8 (Contact with combustible material may cause fire) with an SCL of C ≥ 65 %.

In conclusion, the RAC agrees with the proposal of the dossier submitter that nitric acid C ≥ 99 % should be classified in Category 2 for oxidising liquids (Ox. Liq. 2 - H272: May intensify fire; oxidiser) and nitric acid 99 % > C ≥ 65 % in Category 3 for oxidising liquids (Ox. Liq. 3 - H272) according to CLP, and as O; R8 (Contact with combustible material may cause fire) with an SCL of C ≥ 65 % according to DSD.

Metal corrosion
The dossier submitter did not include a proposal for classification in this hazard class in the CLH report and no results of the metal corrosion test listed in the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria were found in either the CLH report or in the registration dossiers. Therefore, RAC could not conclude on a classification.

4 HUMAN HEALTH HAZARD ASSESSMENT

Extensive descriptions on hazards of nitric acid are available in various reports (ACGIH 1991; Durant et al. 1991; Greim 2006; NIOSH 1976; OECD SIDS 2008; OEHHA 2008; US EPA 2008; WHO 1997). The following synopsis for nitric acid was given:

Nitric acid

Nitric acid is an oxidising mineral acid, which has a highly corrosive effect on the skin, eyes and mucosa in case of direct contact. It is a strong oxidizing agent, and poses a considerable risk for fire when in contact with organic materials. Extensive yellow colouring of the affected skin and mucosa (xanthoprotein reaction) is a characteristic feature of this acid. Already after short-term exposure to the eye, undiluted nitric acid causes corneal ulcers and necrosis with permanent impairment of vision ultimately leading to blindness. Oxidation can lead to clouding of the eye lens.

Following ingestion, ulceration of mucosal membranes and adjacent tissues at the site of contact is observed. HNO_3 can produce symptoms ranging from nausea, (bloody) vomiting, haemorrhagic gastritis, strong retrosternal burning finally leading to corrosion (first to third degree), formation of necrosis, shock, glottis oedema with respiratory insufficiency, perforation, methaemoglobinaemia, haemolysis and metabolic acidosis. The vapour and mists of nitric acid may in addition cause erosion of teeth.

Nitric acid is a strong toxicant by acute inhalation. The toxic effects resulting from inhalation of nitric acid itself cannot be assessed in isolation but must be considered in conjunction with its conversion products, the nitrous gases. These are either spontaneously formed by slowly releasing nitrogen dioxide (NO_2) and oxygen or in contact with metals with no passivation (above all copper and silver) or alkaline solutions. Nitrous gases may play a significant role in the toxicity of nitric acid (Daunderer 1988).

Nitric acid can decompose to nitrogen dioxide (NO_2), nitric oxide (NO), nitrous oxide (N_2O), and nitrous anhydride (N_2O_3). Nitric oxide, nitrous oxide, and nitrous anhydride may be formed under certain circumstances but they are significantly less toxic than nitrogen dioxide. Nitrous anhydride (N_2O_3) is not further considered because it decomposes at 3.5 °C and would not be present under normal ambient conditions. The most important decomposition product of nitric acid is nitrogen dioxide. NO_2 is highly toxic, and inhalation of nitrogen dioxide may result in fatality. The acute toxic effects from nitric acid fumes are caused by a mixture of nitric acid vapour and oxides of nitrogen, mainly NO_2 and NO. Therefore, acute toxic inhalation effects of nitric acid in humans cannot be isolated from those of its reaction products, since contact with air immediately liberates oxides of nitrogen. Small changes in HNO_3 concentration, or in the concentration or composition of reactant or the temperature, can have dramatic effects upon the reactions that take place. Despite the toxicity of nitric acid and its decomposition/reaction products, the dangers of traumatic injury or death following an explosion must always be kept in mind when using nitric acid. Toxicity data for nitrogen oxides are reviewed for information as they provide relevant data for assessment of acute inhalation toxicity.

Nitrogen oxides

For nitrogen oxides extensive descriptions on hazards are available (ACGIH 1986; Budavari et al. 1989; Daunderer 1988; Greim 2003, 2009; OEHHA 2008a; WHO 1997).

The nitrogen oxides, NO and NO_2 are potent oxidants which cause local tissue inflammation and damage of the distal airways. Inhalation of high concentrations of NO and NO_2 leads to rapid

progressive and life threatening pulmonary oedema due to direct injury of the alveo-capillary membrane resulting in increased microvascular permeability (Hajela et al. 1990; Durant et al. 1991).

Nitric oxide

Nitric oxide (NO; CAS No 10102-43-9) is a small, hydrophobic molecule that can easily pass through membranes. It is a colourless gas which rapidly combines with oxygen to form NO_2. Hence, some NO_2 is invariably present whenever nitric oxide is found in the air. NO is a multi-faceted molecule with dichotomous regulatory roles in many areas of biology. Its biological effects are a consequence of its numerous potential interactions with other molecules such as reactive oxygen species (ROS), metal ions, and proteins. The complex processes steered by NO include, e.g. inflammation, stress, apoptosis and necrosis. Effects of NO are modulated by both direct and indirect interactions that can be dose-dependent and cell-type specific. NO regulates biological functions via post-translational modification of proteins, e.g. in the nervous, immune and cardiovascular systems. NO participates in the regulation of the daily activities of cells as well as in cytotoxic events. It possesses a controversial effect on cell viability by acting both as a protection against apoptogenic stimuli or by inducing apoptosis when produced at elevated concentrations. The mechanisms of NO in regulating these biological functions can be either through cyclic guanylate cyclase (cGMP)-dependent or cGMP-independent pathways (Kim et al. 2001; Schindler and Bogdan 2001; Blaise et al. 2005). High NO concentrations lead to the formation of toxic reaction products like dinitrogen trioxide or peroxynitrite that induce cell death, if not by apoptosis, then by necrosis (Kim et al. 2001).

At concentrations below 50 ppm, however, this reaction is slow, and substantial concentrations of nitric oxide may be present with negligible quantities of nitrogen dioxide. Nitric oxide causes cyanosis in animals, apparently by formation of methaemoglobin. The effect of concomitant exposure to NO_2 will become manifest before methaemoglobin-forming properties of NO will be effective (Procter et al. 1988; Kim et al. 2001).

Nitrogen dioxide

Nitrogen dioxide (NO_2; CAS No 10102-44-0) is a red to brown gas and a liquid below 21.1 °C (boiling point) with a characteristic pungent odour. It is non-combustible, but supports combustion. It is a by-product of nitrate decomposition, formed by the reaction of nitric acid with metals or other reducing agents, or by various processes in which air is heated to high temperature with the formation of nitric oxide (ACGIH 1986).

The effects of NO_2 are diverse, thus, only the most important modes of action are regarded here. NO_2 is an oxidizing free radical which can initiate a variety of destructive pathways in living systems, and several diseases are suspected to be connected with the uncharged free radical formed both exo- and endogenously. The •NO_2 radical, an oxidising agent of medium potency, reacts with a number of biomolecules (e.g. DNA and nucleosides, proteins, lipids), initiates radical reactions and produces reactive oxygen species (Kirsch et al. 2002).

In the gas phase and in non-aqueous solvents, •NO_2 exists in equilibrium with its dimer, the colourless dinitrogen tetroxide (N_2O_4) (Huie 1994). In experiments with volunteers the perception threshold for NO_2 smell in the air was between 0.1 and 0.4 ppmV/m³ and the threshold for symptoms of irritation are between 20 and 30 ppm/m³ (Henschler et al. 1960). However, perception of the odour is reduced if the concentration is increased gradually. In health people between 80 and 90 %, and at maximum respiration rates more than 90 % are absorbed via the respiratory tract (WHO 1997).

The potential of NO_2 to induce acute lung toxicity has been recognized for a considerable period of time. Exposure to high NO_2 concentration results in widespread epithelial destruction; low concentrations produce a distinct lesion principally localized near to the broncho-alveolar junction.

Within the lung, cellular perturbations resulting from gaseous toxicants are indisputably related to absorption of the inhaled toxicant. The inhomogeneous distribution of epithelial injury suggests that different interactions between NO_2 and the lung surfaces may contribute to the extent of regional responses. NO_2 uptake is governed by reaction between inhaled NO_2 and constituents of the pulmonary surface lining layer. The predominant reaction pathway involves hydrogen abstraction producing HNO_2 and an organic radical. Experimental approaches have shown that inhaled gases must initially contact the surface layer, rather than the apical membranes of the air space epithelial cells, so that NO_2 absorption may be dependent on surface conditions. Conditions at the gas/liquid interface modulate the rate of transfer into the aqueous phase. The organic reaction products may directly interact with the air space epithelium and/or alveolar macrophages. In addition, primary reaction products may also interact with other products or with reduced substrates to form secondary products. These interactions may either quench the toxic species or produce products which participate in the toxic cascade (WHO 1997; Postlethwait and Bidani 1994).

Acute exposure to NO_2 may induce pulmonary oedema, pneumonitis, bronchitis, and bronchiolitis obliterans. The rapid lethal effect of NO_2 is caused by pulmonary oedema. Once inhaled, NO_2 reaches the lower respiratory tract, affecting mainly the bronchioles and the adjacent alveolar spaces, where it can produce pulmonary oedema within hours. Many deaths from pulmonary oedema have been induced by acute inhalation of high concentrations of NO_2. Short exposures to 100-500 ppm (190-900 mg/m³) NO_2 may lead to sudden death. More typical is the formation of insidious, delayed pulmonary oedema within hours. Finally, delayed inflammatory changes may lead to death hours or days after exposure (Plog 1988).

Furthermore, exposure to NO_2 induces changes in number and function of neuroendocrine pulmonary cells (APUD cells) in experimental animals. These cells are involved in pulmonary blood pressure regulation by excreting vasoactive substances (Witschi 1988). Through reactions of the NO_2 radicals with components of the alveolar fluid and the epithelial cells, tissue damage is caused in the terminal respiratory tract. Pneumocytes (type I) and cilia-bearing epithelial cells are damaged and replaced by less sensitive cells such as type II pneumocytes and Clara cells. Signs of inflammation and reduced viral immune resistance are also observed (WHO 1997).

4.1   TOXICOKINETICS (absorption, metabolism, distribution and elimination)

Not evaluated in this report.

4.2   ACUTE TOXICITY

The acute inhalation toxicity of nitric acid has been described and assessed. Classification of nitric acid for acute toxicity is discussed and proposed only for the inhalation route of exposure. Table 8 summarises the relevant acute inhalation toxicity studies in rats.

Table 9:   **Summary table of relevant acute toxicity studies**

Method	Results	Remarks	Reference

Acute inhalation toxicity study
10 male albino rats / conc.
Inhalation, as vapour
RFNA, red fuming nitric acid (containing 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

Acute inhalation toxicity study 5 male albino rats / conc. Inhalation; as vapour **WFNA**, white fuming nitric acid (containing 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

4.2.1   Non-human information

4.2.1.1 Acute toxicity: oral

Not evaluated for this report.

4.2.1.2 Acute toxicity: inhalation

The majority of the data on toxicology originates from outdated and/or inadequate studies which were conducted before international guidelines were developed. Their validity is limited, but they are reviewed in the absence of other toxicological information on nitric acid.

There have been only a few toxicological studies of nitric acid, which exists in ambient air generally as a highly water-soluble vapour, suitable for deduction of reliable LC_{50} values. Since inhalation

exposure to nitric acid involves exposure to nitric acid as well as to nitrogen oxides, in particular NO_2, results from acute animal experiments with nitrogen dioxide are also presented.

Nitric acid (HNO_3)

Rat

In a comparative study, lethal effects of nitric acid, in particular of RFNA (containing 8-17 % NO_2), and WFNA (containing 0.1-0.4 % NO_2), and of nitrogen dioxide (purity of 98 %), by inhalation were investigated in male albino rats. The animals were exposed to RFNA or NO_2 in groups of 10 animals, and to WFNA in groups of 5 animals for periods from two minutes to four hours with a post-exposure observation period of three days. The rats inhaled all of the acid fumes but only the NO_2 concentrations were measured and reported for RFNA and WFNA (Gray et al. 1954).

Thirty-minute LC_{50} values for NO_2 and RFNA were reported as 174 ppm (449 mg/m^3) and 138 ppm as NO_2 (356 mg/m^3), respectively, while that for WFNA was 244 ppm as NO_2 (630 mg/m^3). In all cases, deaths were due to pulmonary oedema. Skin burns were observed on hairless parts of rats exposed to WFNA only. The dose-response curves for NO_2 and RFNA for a 30-minute exposure were parallel indicating a possible similar mode of action for the two gases. For exposures at lower concentrations for 240 minutes the curves differed slightly. The approximate LC_{50} value indicates that WFNA is much less toxic (i.e., higher LC_{50}) than either RFNA or NO_2.

However, these LC_{50} values are only based on the concentration of NO_2 during exposure; therefore it can be concluded that the total concentration of nitric acid and products generated from it was considerably higher than the reported measured values of NO_2. Based upon molecular weights and the percentage of NO_2 in RFNA and WFNA, NIOSH (1976) calculated the total concentration of gases and vapours emitted by nitric acid for the 30 minute LC_{50} values presented in Gray et al. (1954). The LC_{50} for NO_2 gas (174 ppm) was below the LC_{50} for both red and white fuming nitric acid, i.e. approximately 310 ppm and 334 ppm. The LC_{50} values obtained for RFNA, WFNA and pure NO_2 in male albino rats are shown in table 9.

Table 10: LC_{50} values for male albino rats exposed to RFNA, WFNA, and NO_2 (Gray et al. 1954)

Chemical agent	Number of rats	Exposure time in minutes	LC_{50} (ppm)	
			for NO_2 only (concentration range)	**total concentration HNO_3 and NO_2**
RFNA	90	30	138 (123 -155)	310*
RFNA	80	240	67 (64 -70)	
WFNA	160	30	244 (range not given)	334*
NO_2 pure	100	30	174 (154 – 197)	
NO_2 pure	70	240	88 (79 – 99)	

*   Total concentration calculated by NIOSH (1976) and based upon molecular weights and the percentage of nitrogen dioxide in RFNA and WFNA; adapted from Gray et al. (1954)

The thirty-minute LC_{50} values for RFNA and WFNA (total concentration of HNO_3 and NO_2) were reported as approximately 310 ppm and 334 ppm. For direct comparison with the classification criteria conversion of the 30-minute exposure values into a 4 hour testing exposure period was carried out in two steps. The 1 hour exposure value was observed by dividing by 2. Because the test atmosphere for RFNA and WFNA was characterised as a vapour the values for a 1 hour exposure were thereafter divided by a factor of 2 for gases and vapours (according CLP Regulation), which amounts to 77.5 ppm/4hr for RFNA and 83.5 ppm for WFNA.

Conclusion: Reliable LC_{50} values for classification of nitric acid are derived from this acute inhalation toxicity study. The acute inhalation LC_{50} value (4 hour exposure) for RFNA was 77.5 ppm for male rats. For WFNA the acute inhalation LC_{50} value for a 4 hour exposure was 83.5 ppm for male rats (Gray et al. 1954; NIOSH 1976).

In another acute inhalation toxicity study groups of 5 Crl:CD®BR rats/sex were exposed nose-only for 1 hour to 260-3100 ppm of nitric acid (70.76 % aqueous solution) followed by a 14-day observation period (Du Pont 1987). The test atmospheres were generated by aerosolizing the aqueous nitric acid solution with various types of nebulisation equipment and the airborne test material was dispersed with a baffle. Generation of the test atmospheres was different between the five lowest exposure concentrations and the next three highest exposure concentrations. In the five lower concentrations the aerosol content ranged from 15 - 73 % as measured by using a gravimetric filter sample. Except for the 2500 and 2700 ppm concentrations, all exposures contained ≥ 70 % respirable particles with a mass median aerodynamic diameter (MMAD) of ≤ 4.0 μm. Unfortunately the aerosol content of the three highest concentrations was not measured but estimated by the authors to be approximately 100 %. The 2500 and 2700 ppm concentrations contained only 59 and 61 % respirable particles and had a MMAD of 6.5 and 6.6 μm. Nitrogen dioxide was not measured in the exposure atmospheres. Chamber temperature ranged between 25 - 28 °C, relative humidity ranged from 34 - 43 %, and chamber oxygen content was 21 %. During the two lowest concentrations tested, little or no aerosol mist was visible in the chamber. At higher concentrations, a moderate to heavy fog was observed. Aerosol content and particle size data for each generated exposure concentration of nitric acid are summarized in table 10.

Table 11: Aerosol content and particle size of nitric acid exposure (Du Pont 1987)

Nitric acid concentration	Percent[a] aerosol	Particle size:[b]	
		percent respirable	MMAD
260 ppm	15 %	n.m.	n.m.
470 ppm	n.m.	n.m.	n.m.
1300 ppm	73 %	70 %	4.0 μm
1500 ppm	13 %	72 %	3.2 μm
1600 ppm	32 %	71 %	3.3 μm
2500 ppm	n.m.	59 %	6.5 μm
2700 ppm	n.m.	61 %	6.6 μm
3100 ppm	n.m.	74 %	2.0 μm

[a]   Percent of test material present as an aerosol as determined by gravimetric analysis of filter samples and liquid chromatographic analysis of impinger samples; assumed to be approximately 100 % for the 3 highest exposure concentrations.

b   Percent by weight of particles with aerodynamic diameter less than 10 μm.

n.m.   not measured

During or immediately following exposure, the test material caused yellow-stained faces of rats of all groups. Clinical signs included clear nasal discharge at some concentrations, partially closed eyes at ≥ 1300 ppm, reduced or no response to sound at ≥ 1500 ppm, and lung noise and gasping at ≥ 1600 ppm. At 3100 ppm, rats were lethargic after exposure. Two males exposed to 1600 ppm and one male exposed to 2700 ppm died during exposure.

A large number of clinical signs were observed in both male and female rats during the recovery period. The incidence of clinical signs was generally increased dose-dependently. Some signs persisted throughout the recovery period, and some signs appeared and became more severe over time indicating a general deterioration. Common clinical signs included impaired breathing (lung noise, laboured breathing or gasping), dry red nasal, ocular or oral discharges, heads stained yellow by the test material, and sores or burns of the extremities (faces, heads, eyes, noses, ears, feet). Other clinical signs generally seen only at higher concentrations included lethargy, hunched posture, partially closed eyes, wet or stained perineum, and hair loss. In addition, body weight changes were observed in both male and female rats. Males and females exposed to 260 or 470 ppm and females exposed to 1500 ppm had slight to moderate weight loss over the first 1 to 2 days of recovery, followed by normal weight gain. Continuing weight loss for up to 12 days of recovery period was observed in males at ≥ 1500 ppm and in males and females at ≥ 1600 ppm, resulting in average total weight losses of 15 - 29 % of the initial body weight.

The majority of male rat deaths occurred during exposure and up to 2 days post-exposure, except one male exposed to 1500 ppm dying 7 days after exposure and 2 males exposed to 3100 ppm dying 5 to 8 days after exposure. The female rats that died following exposure to 2500 or 2700 ppm died 7 to 9 days after exposure, while females exposed to 3100 ppm died 2 to 9 days after exposure. Exposure concentration and mortality data for male and female rats are summarised in table 11.

Table 12:   Lethality in rats exposed nose-only to nitric acid for 1 hour (Du Pont 1987)

Nitric acid concentration (ppm)[a]		Mortality	
mean	range	Males	Females
260	200 - 320	0/5	0/5
470	0 - 560	0/5	0/5
1300	200 - 1300	1/5	0/5
1500	1200 - 1800	1/5	0/5
1600	1300 - 1800	2/5	0/5
2500	1300 - 3200	2/5	1/5
2700	1800 - 3500	2/5	1/5
3100	2200 - 3800	5/5	5/5

a   Concentration is based on the amount of nitric acid, excluding the amount of water.

Results of autopsy generally supported the clinical signs observed during daily weighing, and were indicative of the corrosive behaviour of the test material. Observed lesions ranged from alopecia to severe ulceration of the skin of the nose and face and occasionally of the pinna of the ear. Ulcerative

lesions in face and nose were only seen in rats that survived the 14-day recovery period; no lesions were noted at any location within the nasal passage. No indications of systemic toxicity were observed.

Conclusion: Under the conditions of this inhalation study the 1-hour LC_{50} value for nitric acid (approx. 71 % aqueous solution) for male and female rats combined was 2500 ppm. The adjustment of this 1-hour value to a 4-hour value for direct comparison with the classification criteria is not trivial, since the test atmosphere was not well-defined at this concentration. The aerosol content was not measured but estimated by the authors to be approximately 100 %. However, based on a synopsis of all these data it was assumed that test atmosphere presented itself as a mixture of liquid, gaseous and vapour phase. Thus, it was not possible to perform an exact conversion of the one hour exposure value into a 4 hour testing exposure. Overall it was concluded that this LC_{50} value is not suitable for classification since the test atmosphere for nitric acid at 2500 ppm was not well-defined and because at this concentration rats were exposed to an atmosphere containing only 59 % respirable particles with a MMAD of 6.5 μm, which exceeded the guidance value of 1 - 4 μm for an aerosol.

Rabbit and cat

Only outdated inhalation studies in rabbits and cats are available. The typical symptoms of poisoning with fumes produced by heating concentrated nitric acid were reported (Diem 1907 cited in Henschler 1992). Animals were individually exposed to various concentrations of nitric acid fumes for different durations. A rabbit exposed to 191.2 ppm HNO_3 for 100 minutes showed few visible signs of dyspnoea but appeared 'apathetic'. Autopsy one week later revealed inflammation of the larynx and trachea, hyperaemia, and hypostasis in the lower lung lobes. Two rabbits exposed to lower concentrations (15.3 and 68.8 ppm) had no remarkable signs of toxicity. Cats (one animal per concentration) were exposed to 9 different concentrations of nitric acid ranging from 15.3 to 336.5 ppm for varying durations of time. The highest value for severe injury was ascertained to be 164.4 ppm for 90 minutes. At this exposure concentration the animal exhibited salivation, nasal secretion, lacrimation, progressive dyspnoea, gulping and retching, and clonic convulsions in trunk and extremities. The cat was prostrate and panting at end of exposure. However, the cat appeared to have completely recovered one day later. Higher concentrations (191.2 to 336.5 ppm) resulted in death or severe pulmonary injury requiring 8 days to recover. Extensive lung oedema was observed in animals that died. Cats exposed to concentrations below 164.4 ppm showed little or no grossly observable effects from exposure; autopsy revealed little to no pulmonary oedema in these cats.

Conclusion: Summary of observations in rabbits and cats exposed to various concentrations and durations of nitric acid fumes is given in table 12. However, it was concluded that these values in rabbits and cats are not suitable for classification.

Table 13: Acute toxicity of fumes from heated, concentrated nitric acid inhaled by animals (Diem 1907 cited in Henschler 1992)

Species (1 animal exposed)	Concen- tration (ppm)	Duration (min)	Observations
Rabbit Rabbit	15.3 68.8	180 150	One animal after 100 min.: spastic muscle twitching in breast and abdomen; both animals: apart from a few minutes restlessness, apathy, no salivation, no nasal secretion, respiration normal; no visible damage
Rabbit	191.2	100	Apathetic, hardly any dyspnoea; after exposure: no visible damage; autopsy after 7 days: catarrhal irritation in larynx and trachea, hyperaemia; hypostasis in lower lung lobes
Cat	15.3	180	Salivation; muscle twitching in breast and abdomen; no visible damage
Cat	68.8	150	Salivation; muscle twitching in breast and abdomen, nasal secretion; slight dyspnoea; eyes tightly closed; after exposure: animal rather dazed but no visible damage
Cat	76.5	335 Interrupted by a 3 hr break	Salivation; muscle twitching in breast and abdomen, nasal secretion; slight dyspnoea; eyes tightly closed; during the exposure free interval no food consumption; animal ate again on the next day; no visible damage
Cat	130.0	315 Interrupted by 2 breaks	Symptoms as at 76.5 ppm, but more severe; in addition shrieking, lacrimation, animal looked very battered; autopsy: no corrosion, catarrhal inflammation in trachea and larynx, hyperaemia and foamy fluid in the lungs; no emphysema or oedema
Cat	164.4	90	Salivation, nasal secretion, lacrimation; progressive dyspnoea; gulping and retching; clonic spasms in trunk and extremities; at the end of exposure: animal was prostrate and panting, but one day later completely recovered
Cat	191.2	60	Symptoms as at 164.5 ppm were seen in this animal, in addition severe clonic spasms, foam at the mouth, death; autopsy: acute catarrhal inflammation in larynx and trachea; severe lung emphysema and oedema, hyperaemia, hypostasis
Cat	191.2	150	Animal very excited; all the above-mentioned symptoms more severe; animal very battered; completely recovered after 8 days
Cat	260	120	Symptoms as at 191.2 ppm; in addition pupils wide open; death; autopsy: acute catarrhal inflammation in larynx and trachea; severe lung emphysema and oedema, hyperaemia,

			hypostasis
Cat	270.2	35	Symptoms as at 260 ppm; in addition clonic and tonic spasms; foam at the mouth, death; autopsy: acute catarrhal inflammation in larynx and trachea; severe lung emphysema and oedema, hyperaemia, hypostasis
Cat	336.5	200	Symptoms as at 270.2 ppm; in addition cornea completely clear, animal survived for several hours; autopsy: acute catarrhal inflammation in larynx and trachea; severe lung emphysema and oedema, hyperaemia, hypostasis; blood count normal

Lehmann and Hasegawa (1913) conducted a series of experiments using cats exposed to gases of nitric acid which were produced as follows: nitrogen oxide gas was produced by reaction of copper with nitric acid; the gas produced was collected over water and mixed with fresh air. Concentrations of total oxidation products, expressed as nitrous acid concentration, were determined analytically by either oxidation using hydrogen peroxide or by reduction using potassium iodide. The exposure concentrations were measured at three time-points (at the beginning, during and at the end of exposure). The generated atmospheres were likely a mixture of nitrogen oxides, however, the exposure concentrations were expressed as total nitric acid content. For LC_{50} estimation one animal for each test concentration was used. In general, with increasing concentration and/or duration of exposure deaths from severe pulmonary oedema occurred. For concentrations below ~388 ppm (1000 mg/m^3), examination of the data as exposure concentration (C) multiplied by exposure time (t) revealed that Ct products greater than ~900 ppm hr resulted in death while a Ct up to 760 ppm hr resulted in only a slight increase in respiration for several hours after exposure. Further, exposure to 287 ppm (740 mg/m^3) for 1.83 hours (Ct = 526 ppm hr) caused no effects whereas exposure to either 341 ppm (880 mg/m^3) for 3.83 hours (Ct = 1309 ppm hr) or 217 ppm (560 mg/m^3) for 4.25 hours (Ct = 922 ppm hr) resulted in death. In contrast for concentrations of 388 ppm (1000 mg/m^3) or higher, severe clinical signs or death occurred at a Ct product as low as 277 ppm hr. The response probably depended on whether either the concentration of the acid, or the duration of exposure, was great enough to induce corrosive effects leading to oedema.

Conclusion: In the cat, the following LC_{50} values were derived: LC_{50} = 341 ppm (880 mg/m^3) for 3.83 hours and LC_{50} = 217 ppm (560 mg/m^3) for 4.25 hours. However, the data are not considered suitable for classification, because only one cat was used at each concentration and time combination.

Nitrogen dioxide (NO$_2$)

Studies in rats, mice, rabbits, guinea pigs, dogs, and monkeys are available.

Nitrogen dioxide poisoning has first been described over 100 years ago. NO$_2$ may be liberated from nitric acid.

The most comprehensive acute lethality study for NO$_2$ in Long-Evans rats, Swiss-Webster mice, rabbits, guinea pigs, and dogs was performed by Hine et al. (1970). Groups of animals were exposed by inhalation (whole body exposure) to NO$_2$ gas. Several exposure durations, ranging from 5 minutes to 24 hours, were examined for test concentrations of NO$_2$ ranging from 5 to 250 ppm. The mice were young males, weighing 20 ± 3 g; the rats were 200 ± 50 g males; the rabbits were of both sexes, weighing 2.5 ± 0.5 kg; the guinea pigs were of both sexes, weighing 3.0 ± 1.0 kg; the dogs were of

both sexes, weighing 10 ± 4.0 kg. At low levels of exposure up to 20 ppm, signs of irritation were minimal, and no effects on behaviour were noted. At 40 ppm and above, signs of toxicity included eye irritation, lacrimation, and increased respiration followed by laboured breathing. In all five species, 50 ppm was considered as a critical concentration, below which mortality rarely occurred for exposure durations up to 8 hours. Deaths generally occurred within 2 to 8 hours after the time of gassing, and the majority of deaths occurred within 24 hours. The acute lethal effect of NO_2 was due to acute pulmonary oedema. Delayed deaths occurred in about 20 % of the animals and were secondary to acute bronchiolitis and bronchopneumonia.

Fractional mortalities were obtained between 60 and 480 minutes for most species at 75 ppm, and between 30 and 120 minutes at 100 ppm. Acute deaths were characterized by marked bronchiolitis, desquamated bronchial epithelium, infiltration by polymorphonuclear cells, and oedema fluid in the alveoli. In animals which developed pulmonary oedema there was profuse, occasionally haemorrhagic fluid discharge from the nares. Gross pathology revealed mottled, fluid-filled lungs. Microscopy revealed hyperaemia, oedema fluid, swelling, and even necrosis of some of the epithelial cells of the bronchi and terminal bronchioles, but little evidence of damage to the alveoli themselves, which were distended. Animals sacrificed within 1 to 4 hours after exposure has started did not appear ill, but the lungs showed patchy hyperaemic consolidation with adjoining normal or emphysematous areas. Transudation was present in the perivascular spaces, indicating the early development of pulmonary oedema. In table 13 summary of mortality ratio for five species exposed for 4 hours to nitrogen dioxide examined in this study is presented.

Table 14: Summary of acute toxicity of NO_2 for five species exposed for 4 hours (Hine et al. 1970)

Concentration	Mortality ratio[a]				
	Rat	**Mouse**	**Guinea pig**	**Rabbit**	**Dog**
75 ppm	7/12	5/6	2/4	2/8	1/3
85 ppm	5/10	n.e.	n.e.	n.e.	n.e.
100 ppm	29/29	10/10	n.e.	3/4	2/2

[a]   Number dead/total number in each group

n.e.   not examined

Animals surviving the acute effects and dying after 96 hours showed decreased activity, a ruffled, mussy appearance, unkempt fur, decreased food and water intake, and a mucopurulent discharge around the nares. In addition, animals dying after 8 days had marked weight loss. Gross pathologic changes during the period of death from pneumonitis and bronchopneumonia consisted of a congested lung, interspersed with areas of deep staining, and on gross section of purulent exudates from the cut surface. Some areas of the lung were relatively clear. In others there were adhesions of the lung to the surface of the thoracic cavity. Microscopy revealed marked bronchiolitis, the lumen of the bronchial tree being filled with purulent material and desquamated bronchial epithelium. Many alveoli contained moderate amounts of fibrin and polymorphonuclear cells. Some alveoli had oedema fluid and mononuclear cells. Occasionally there was evidence of atelectasis. Interstitial fibrosis occurred in about one-third of the surviving animals at 30 days, which persisted up to 6 months in some animals. Some guinea pigs exhibited sudden exaggerated gasping for air, then convulsed and died. Pulmonary oedema was not present in these animals but the vocal cords were slightly oedematous, which suggested asphyxiation due to laryngeal spasm.

Conclusion: In this study a 4-hour LC_{50} value of 75 ppm/4hr was derived for NO_2 from all five species examined: rat, mouse, guinea pig, rabbit, and dog (Hine et al. 1970).

In another lethality study, rats were exposed once for 5- to 60-, and rabbits for 15-minute periods to various concentrations of NO_2 gas (Carson et al. 1962). Young male rats (weighing 100 to 120 g) were exposed in groups of 10 by inhalation (whole body exposure), and the survivors were weighed and observed for 21 days after exposure. Rabbits (weighing 2.2 to 2.7 kg) were exposed in groups of five, and were observed daily for 7 days after exposure and were sacrificed 21, 42, and 90 days after exposure for pathologic studies. Gross pathology was performed for both species; only lungs from rabbits were examined microscopically.

The toxic effects of NO_2 seen in rats and rabbits were severe respiratory distress, irritation of the eyes, effects in the lungs, and death. The time of death varied from 30 minutes to three days after end of exposure. Gross pathology in rats revealed darkened areas over the surface of the lungs and in some instances purulent nodules involving the entire lungs in some of the surviving rats. Rabbits occasionally showed darkened areas about the surface of the lungs, but no purulent nodules were noted.

Conclusion: The pulmonary damage is considered to be the most serious effect of NO_2 gas. The 5-, 15-, 30-, and 60-minute LC_{50} values for rats and the 15-minute LC_{50} value for rabbits exposed to NO_2 with their statistics are given in table 14.

Table 15: Overview of LC_{50} values for rats and rabbits exposed to NO_2 from 5 up to 60 minutes (Carson et al. 1962)

Species	Exposure time (min)	LC_{50} (ppm)		
		Confidence limits	Slope	Standard error of the slope
rat	5	416		
		376 - 461	9.5	± 4.2
	15	201		
		191 – 212	15.3	± 4.1
	30	162		
		152 – 169	20.7	± 5.9
	60	115		
		113 – 117	43.3	± 12.8
rabbit	15	315		
		290 – 342	13.1	± 5.9

Steadman et al. (1966) examined acute inhalation effects of nitrogen dioxide gas in several animal species. Fifteen Sprague-Dawley rats weighing 200-300 g, 15 guinea pigs weighing 313-637 g, three New Zealand albino rabbits weighing 2.3-3.7 kg, three squirrel monkeys weighing 504-890 g, and two beagle dogs weighing 8.3-11.8 kg were exposed by inhalation (whole body exposure) to 123 mg/m³ NO_2 gas for 8 hours. No direct control animals were used. All animals were checked routinely for signs of toxicity. At the termination of each study, selected animals were sacrificed and autopsied, and tissues were taken for microscopic evaluation. Signs of eye and nose irritation were noted in all animals during the first hour of exposure, accompanied by anorexia and lethargy. Dogs

appeared to be the species least affected. After 5 hours of exposure, the eyes of the rabbits were nearly closed, and there was little activity in any of the animals. The dogs were lethargic and showed signs of dyspnoea and some frothing around the mouth. Several rats and guinea pigs had died during this period, but verification of the exact time of death was not possible until the end of exposure when the animals could be removed and examined. Monkeys were the most susceptible to the lethal effects of NO_2, with 3 out of 3 dying at each exposure level within the first 6.5 hours. At the end of the 8-hour exposure period, 6 rats and 10 guinea pigs were found dead. One dog was prostrate, with much laboured breathing and excessive frothing but did not appear moribund. Little change was noted in the rabbits, except that the eyes showed signs of corneal opacity, although still reactive to light. Weight loss was noted both in dead animals, and in survivors at the end of exposure.

All survivors were observed for 20 days. One rabbit died 15 hours after termination of the exposure. Examination of the eyes of surviving rabbits after 16 hours revealed opacity of the cornea and a good pupillary reflex to light, but the sudden exposure to light appeared to be painful to the animal. No recovery from corneal opacity was noted 48 hours after termination of exposure or during the 20-day observation period. The pattern of deaths in the five species exposed to 123 mg/m³ NO_2 for 8 hours is shown in table 15.

Table 16: Mortality ratio in animals exposed to 123 mg/m³ nitrogen dioxide once for 8 hours (Steadman et al. 1966)

Species	Mortality ratio[a]	Hour of deaths		
		0-8	9-24	25-72
Rat	6/15	6	0	0
Guinea pig	13/15	10	1	2
Rabbit	1/3	0	1	0
Dog	2/2	0	1	1
Monkey	3/3	3	0	0

[a]   Number dead/total number in each group

All deaths occurred within the first 72 hours. No additional deaths or toxic signs in the survivors were noted during the remainder of the 20-day observation period. The gross pathological findings in the lungs of surviving animals indicated haemorrhagic pulmonary oedema. Microscopy of lung sections revealed no significantly different findings from control.

Conclusion: The 8-hour LC_{50} value of 123 mg/m³ NO_2 was observed in guinea pigs, dogs and monkeys.

The pulmonary inflammatory response to NO_2 in adult male Fischer 344 rats (specified pathogen-free, virus-free, Harlan Sprague Dawley, Indianapolis, Ind.; weighing 240-260 g) exposed for brief exposure periods was examined by Stavert and Lehnert (1990). Groups of animals were exposed to 10, 25, 50, or 100 ppm NO_2 gas once for durations of 5, 15, or 30 minutes. The exposure tubes have been designed to provide continual passage of an exposure atmosphere over the facial region of a rat. Rats exposed to anhydrous filtered air for a period of 30 minutes served as controls. Twenty-four hours after exposure, animals were sacrificed for lung gravimetric analyses and histopathology. Histopathology focused on changes in the periterminal bronchiolar-alveolar duct-alveolar region of the lung. Results obtained following a particular NO_2 exposure regimen were directly compared with data obtained with sham air-treated control animals. Exposure atmosphere concentrations were continuously monitored with the dual-channel IR-UV spectrophotometer calibrated with primary gas standards.

Lung gravimetric analyses revealed that acute exposure of rats to 10 ppm NO_2 for a duration of 30 minutes or to 25-50 ppm NO_2 for periods of up to 15 minutes produced no significant increase in lung wet weight or right cranial lobe dry weight. A significant increase in these parameters was found, however, following exposure of the animals to 50 ppm NO_2 for 30 minutes and after exposure to 100 ppm NO_2 for periods of 5-15 minutes. Such increases generally paralleled increasing NO_2 exposure concentrations and prolongation of exposure times. Histopathology revealed detectable lung changes in animals which had inhaled 25 ppm NO_2, for 30 minutes and following exposure to 50 ppm for only 5 minutes. Generally, the severity of NO_2-induced lung injury, expressed as the accumulation of fibrin, polymorphonuclear leukocytes, alveolar macrophages, extravasation of erythrocytes, and type II pneumocyte hyperplasia 24 hours post exposure, became more pronounced with increasing NO_2 exposure concentrations and times.

Conclusion: No evidence of lung injury was observed in Fisher 344 rats following exposure to 10 ppm NO_2 for 30 minutes or to 25 ppm NO_2 for 5 and 15 minutes.

4.2.1.3 Acute toxicity: dermal

Not evaluated for this report.

4.2.1.4 Acute toxicity: other routes

Not evaluated for this report.

4.2.2   Human information

Data from accidents and experimental studies are referred.

Nitric acid: Accidental exposures

Assessment of health risks from the use of household cleaning agents containing nitric acid was conducted by the Federal Institute for Risk Assessment (BfR) in Berlin, Germany (BfR Opinion No. 041/2010, 06 September 2010) based on BfR data (poisonings reported by physicians according to § 16e of the German Chemicals Act) and data (inquiries) of the German poison treatment and information centres. The analysis and the assessment, also under the BfR National Committee "Assessment of Poisonings", revealed cases with - in some instances - serious health damage caused by accidents with specific nitric acid-containing cleaning products in the home. The cases notified to the German poising treatment and information centres show that not only adults but also children were affected. The health risk resulted in caustic burns and also in acute toxic effects occurring following inhalation of nitric acid and the nitrous gases released from it.

Between 1999 and 2010 the BfR and the German poison treatment and information centres got reports of a total of 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. The safety data sheets indicate nitric acid as the dangerous ingredient with a content of 20 - 30 %. The products are in some cases sold without any effective child-resistant closure and with incorrect labelling on the German market. Most of notifications (59.1 %) involved corrosion through the oral intake of nitric acid-containing products. 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 were observed in such persons. In cases of minor health disorders individuals have complained of dry cough, sore throat, vomiting and burning of the pharynx.

Especially in contact with metals and indoors use in small rooms (e.g. bath rooms etc.), nitric acid can lead to severe lung oedema, sometimes delayed with a symptom-free period of 8-24 hours for products with low concentrations of nitric acid. These accidents carry a high risk of the underestimation of the resulting health impairment and can lead to fatal mis- or under-treatment.

A case of nitric acid-induced lung oedema of delayed type was reported by Hahn et al. (2007). A 69-year old female had stored a bottle of nitric acid in her bathroom. When the bottle broke, its content spread over the floor and came into contact with a metal shelf. The reaction between metal and nitric acid resulted in formation of nitrogen oxides, which were inhaled by the patient while she was wiping up the liquid. The patient was sitting in her living room with severe dyspnoea. Later, artificial respiration was necessary and she was transferred into hospital.

Findings made by the emergency physician included cyanosis, a rattling respiration and an oxygen saturation level of 78 %. In addition, hypertension up to 220 mmHg was found. Initial treatment included administration of glycerol trinitrate and furosemide. On the next morning, i.e. 18 hours after the accident had happened, the patient required artificial respiration due to lung oedema of delayed type. In the further course, placing of a central venous catheter into her right jugular vein was followed by pneumothorax requiring intercostal drainage. Due to her severe pulmonary problems, the patient was transferred to a specialized hospital because of drained pneumothorax and a deranged general condition. The respiratory situation rapidly improved by administration of high doses of corticosteroids. In the further course, the patient developed peak blood pressure values of more than 300 mmHg followed by rapid falls in blood pressure. This was followed by signs of hemiparesis on the left side of her body. After nine days the patient got a total atelectasis of the left lung due to a mucous plug. After a total of 12 days of intensive therapy with different complications, the patient could be transferred to her regional hospital and was discharged two weeks later. From the therapeutic aspect, the early oxygen supply is the most important measure. A central role has also been attributed to the early administration of corticosteroids.

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. Sawdust used to absorb the spill rapidly oxidized and burst into flame. Of the 20 individuals exposed to the fumes, dyspnoea was present in 100 %, cough in 93 %, pain in the sides, stomach, lungs, throat, loins, and head was present in 87 %, dizziness and nausea in 73 %, and vomiting in 53 %. Relapse of these symptoms occurred in 33 % of the cases generally 3 weeks after exposure for an average duration of 15.5 days. Four individuals died, two on the second day following exposure and two several weeks later from relapse. Autopsy revealed haemorrhagic oedema of the lungs and coagulation necrosis of the mucous membrane of the complete respiratory tract. Exposure concentrations were not measured but the authors concluded that the "severity of the initial exposure" was the most important factor in determining recovery or death.

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). For a short time following exposure the guard complained of nausea, dizziness, and restlessness. Shortly after that the guard

became acutely ill and suffered from chest pain and dyspnoea. During the day, he developed swelling of the lower extremities and cyanosis, finally lapsed in to coma and died approximately 26 hours after the exposure. Autopsy revealed pulmonary oedema as the immediate cause of death. There was also marked evidence of acute tracheobronchitis and bronchopneumonia, slight acute hepatitis and cerebral oedema.

A case of nitric acid fume pneumonia is reported by Treiger and Przypyszny (1947). A white male, aged 58, engaged by a plating firm was affected by accident. He had made a mistake and dipped the wrong metal into the vat of nitric acid causing an escape of nitric acid fumes. He wore no mask and stayed in the room for 5 to 10 minutes. After one hour he experienced a headache and fatigue. Ten hours after the accidental inhalation of the fumes the man fell acutely ill with moderate cyanosis and severe respiratory distress. In the hospital bronchopneumonia was diagnosed followed by fatal termination on the eighteenth day. Autopsy one and one-half hours after death revealed enlarged lungs which have filled the entire chest cavity. The surface of the lung was mottled black, while at the periphery, over-aerated lung could be seen. On palpation, numerous nodules 2 to 10 millimetres in size could be felt throughout both lungs. Cut section revealed a greyish purple surface with protruding firm nodules, greyish white in colour, scattered throughout. At microscopy the alveoli could barely be distinguished in areas and were filled with exudate composed of polymorphonuclear cells, lymphocytes, macrophages, eosinophils, and infiltrating fibroblasts. Fatal termination resulted from pulmonary fibrosis after control of pulmonary oedema, cardiac failure, and bronchopneumonia was attained.

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. All stages of an extensive bronchiolitis and alveolitis obliterans, of haemorrhagic and desquamate pneumonia, and haemorrhagic oedema were found. The remarkably long asymptomatic interval was assumed to be due to the relatively slight damage to the respiratory epithelium by the nitrogenous fumes; whereby organizational processes have occurred until relatively late. Subjective freedom from distress leads to an underestimation of the danger accompanying inhalation of nitrogenous fumes.

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. Escape from the building took 10 - 15 minutes. No respiratory problems were apparent upon immediately occurring medical examination, however, increasing respiratory difficulties developed 4 - 6 hours later. On admission to the hospital, all patients were cyanotic with frothy fluid escaping from the nose and mouth. All patients died within 21 hours after the accident. At necropsy bronchiolar epithelial necrosis, marked capillary engorgement and slight interstitial oedema of alveoli were observed. Notably, protein-rich oedema fluid filled all alveolar spaces, most markedly in peribronchiolar and, especially, alveolar duct areas where thin hyaline membranes were also evident. Electron microscopy of the formalin-fixed lungs revealed necrotic neutrophils within alveolar capillaries, often spatially related to necrotic endothelial cells. Immunohistochemistry showed small and large serum proteins, including immunoglobulin M, in the oedema fluid and hyaline membranes. The concentrations of nitric acid or its oxides were not determined at the area where the accident happened.

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. The first symptoms of respiratory distress occurred 30 minutes later; approximately 1 hour later he entered a hospital emergency room with dyspnoea, expiratory stridor, peripheral cyanosis, and general paleness. Chest X-ray showed pulmonary oedema. Two hours after admission intubation and mechanical ventilation was necessary because of fulminant respiratory insufficiency. As all sources of mechanical ventilation failed, extracorporeal membrane oxygenation had to be established 7 hours after admission. With the additional use of surfactant and low dose inhalation therapy with nitric oxide (NO), the patient could be stabilised for 3 days and lung function improved temporarily. However, on the fourth day the patient died from refractory respiratory failure. Necropsy revealed massive pulmonary oedema without signs of inflammation. Thus, nitric acid inhalation induced pulmonary oedema appears to be a most severe situation in which even most modern therapeutic interventions fail.

In a review by Durant et al. (1991) toxic effects of nitric acid and its decomposition products were summarised. In humans single exposure to 100 ppm nitric acid by inhalation is immediately dangerous to life or health. Inhalation of nitric acid induced mucous membrane irritation and pneumonitis after exposures to 2 - 25 ppm nitric acid for 8 hours. Pulmonary oedema occurred after exposure to ≥ 200 ppm, which may be fatal. Acute inhalation of nitric acid fumes may cause severe respiratory irritation with coughing, choking, and possibly yellowish burns of the mucous membranes. Other initial symptoms may include dizziness, headache, nausea, and weakness. Pulmonary oedema may occur immediately in the most severe exposure settings, but more likely after a latent period of one to 24 hours, sometimes up to 72 hours after inhalation. The symptoms may include tightness in the chest, dyspnoea, dizziness, frothy sputum, and cyanosis. Physical findings may include hypotension, weak rapid pulse, moist rales, and haemoconcentration. In non-fatal cases, complete recovery may occur within a few days or weeks or convalescence may be prolonged with frequent relapses and continued dyspnoea and other signs and symptoms of pulmonary insufficiency. In cases of severe exposure, death due to anoxia may occur within a few hours after onset of the symptoms of pulmonary oedema or following a relapse.

Inhalation of gases and vapours originating from nitric acid can be extremely dangerous because they do not set up a violent respiratory reflex, as occurs with chlorine and ammonia, which serves as a warning property. Thus, inhalation of nitric acid fumes at potentially fatal concentrations may go undetected by the affected person (Hardy and Hamilton 1974 cited in Durant et al. 1991). Symptoms following the inhalation of nitrous fumes (vaporized nitric acid, nitrogen dioxide, and other nitrogen oxides that might be present) include cough, headache, and the sensation of "fullness" in the head and chest. These symptoms are reported to be the same, regardless of the level or intensity of exposure.

Delayed symptoms of over-exposure can appear as dyspnoea (shortness of breath), which is caused by acute pulmonary congestion and progresses more or less rapidly to oedema (abnormal accumulation of fluid in cells, tissues, or cavities of the body, in this case, the lungs). Depending upon how deeply the victim inhaled (the dose), death can follow within 36 hours. Very high acute exposure levels of nitrous fumes in a serious accident may lead to death immediately. More commonly, industrial accidents have led to delayed symptoms, with the exposed person developing oedema of the lungs within 48 hours. A third group of accident victims consists of persons who apparently recover from the immediate effects, but who subsequently suffer from chronic "chest disease" of varying severity. This depends on a number of factors, including the dose received, intercurrent infections, and smoking habits.

Autopsy findings include damage to the small bronchioles, intense congestion in the gastrointestinal tract, sometimes with haemorrhage, congestion of the meninges (membranes enveloping the brain and spinal cord), and sometimes, spotty haemorrhage of the cerebrum. Venous blood is thick, tarry, and coagulates rapidly, while methaemoglobin is also present in some cases. Erythrocyte destruction and lesions of the liver and kidney have also been observed following nitrous fume poisoning. The pathologic sequelae of accidental (acute) exposure to high concentrations of nitrous fumes are a function of the dose. No anatomic findings beyond congestion are seen in cases of rapid fatality, whereas lobular pneumonia with emphysema occurs if the patient survives for some days. If survival is longer, fibrotic processes are evident.

Other acute inhalation effects from nitric acid and lethal exposure scenarios in humans have been summarised by ACGIH (1991), NIOSH (1976) and Hardy and Hamilton (1974 cited in Durant et al. 1991). Exposure concentrations were not given in the primary reports. After exposure to nitric acid fumes irritation of the respiratory tract is caused initially. Symptoms of respiratory tract irritation following acute nitric acid exposure include coughing, gagging, chest pain, and dyspnoea. Cyanosis and acute pulmonary oedema have been reported following high acute exposure. Severe injury and deaths resulting from exposure of humans to vapours and gases originating from nitric acid solutions have been divided into three categories: (1) immediate fatalities from very high concentrations, (2) delayed effects occurring within 48 hours, and (3) mild immediate effects followed by a short recovery period, but culminating in pneumonia. In some cases, recovery occurred within two weeks, but in others, it took place after a prolonged period. After this time, a relapse may occur with death caused by bronchopneumonia and/or pulmonary fibrosis.

Nitric acid: Experimental studies

An experimental self-exposure was reported by Lehmann and Hasegawa (1913). Nitrogen oxide gas was produced by reaction of copper with nitric acid; the gas produced was collected over water and mixed with fresh air. Concentrations of total oxidation products, expressed as nitrous acid concentration, were determined analytically by either oxidation with hydrogen peroxide or by reduction using potassium iodide. Although the generated atmospheres were likely a mixture of nitrogen oxides, the exposure concentrations were expressed as total nitric acid content and are listed here in ppm as reported by NIOSH (1976). One of these researchers exposed himself to 62 ppm (160 mg/m^3) for 1 hour and reported irritation of the larynx, thirst, and an objectionable odour. He was then exposed to 74-101 ppm (190-260 mg/m^3) for 1 hour followed by 23-43 ppm (60-110 mg/m^3) for another hour and experienced immediate severe irritation with cough and an increase in pulse and respiratory rates after 40 minutes. He was able to tolerate exposures up to 158 ppm (408 mg/m^3) but for only 10 minutes due to coughing, severe burning in the nose and throat, lacrimation and heavy mucous secretion from the nose, a feeling of suffocation, headache, dizziness, and vomiting. Based on their results of human exposures and by comparing this to other work, the authors estimated that the concentration causing no significant adverse effects would be below 50 ppm (130 mg/m^3).

In contrast to the above report, another researcher exposed himself and another individual to nitric acid fumes at a concentration of 11.6-12.4 ppm (30-32 mg/m^3) for 1 hour (Diem 1907 cited in Henschler 1992). Initial symptoms included sneezing because of irritation of the nasal mucosa, marked secretion from the nose and salivary glands, moderate burning of the eyes and lacrimation, and burning and itching of facial skin. Deep inhalation resulted in a feeling of pressure in the chest, slight stabbing pains in the trachea and larynx, and coughing, so the researchers kept their breathing

shallow. After 20 minutes, all symptoms except nasal secretion abated somewhat and a slight frontal headache developed. Some of these symptoms persisted for about 1 hour post exposure. Tiredness, especially in the legs, and feeling of dry skin of the hands were late or delayed symptoms of the exposure. The authors concluded that exposure longer than 1 hour to this concentration of nitric acid cannot be tolerated without risk of adverse effects on health. From this experiment it was concluded that vapours from heated nitric acid in concentrations of 11.6-12.4 ppm (30-32 mg/m^3) could not be inhaled for longer than 1 hour without causing health effects in humans.

In a second experiment, exposure to 85 ppm (219 mg/m^3) nitric acid could only be tolerated for 2 to 3 minutes by the author. Symptoms were comparable to the previous exposure of 11.6-12.4 ppm (30-32 mg/m^3), but at a much greater intensity. All symptoms persisted after the end of exposure. In these experiments, the exposure concentrations were produced by warming the acid and samples of the chamber air were measured for concentration by simple titration with the indicator Congo red. The differences in the methods used by Lehmann and Hasegawa (1913) and Diem (1907 cited in Henschler 1992) for the production of nitric acid fumes as well as the detection methods probably account for the differences in reported effect levels.

In a study by Sackner and Ford (1981) five healthy volunteers were exposed to nitric acid fumes at a concentration of 1.6 ppm (4.2 mg/m^3) in air for 10 minutes. This did not affect pulmonary function over a 1 hour follow up period. Exposure to nitric acid fumes of 1.6 ppm (4.2 mg/m^3) for 10 minutes did not produce acute bronchoconstriction in healthy adults. Further details were not reported.

Nitrogen dioxide (NO$_2$)

Sackner et al. (1981) examined pulmonary function in asthmatic adults which were exposed to NO$_2$. In this study nitrogen dioxide was administered to 6 asthmatic adults for four hours by face mask at 0.1, 0.3, 0.5 and 1.0 ppm in air, along with clean compressed air as a randomized double-blind trial. One day prior to the exposure, one day after exposure, and 1 to 2 weeks later, spirometry, body plethysmography, single breath nitrogen washout, single breath diffusing capacity and respiratory mechanics by random noise oscillations were measured. In addition, ear oximetry was continuously monitored, and heart rate and blood pressure were measured every 30 minutes. The respiratory pattern i.e. frequency, tidal volume, minute ventilation, fractional inspiratory time and mean inspiratory flow were remarkably similar in a given subject for each of the exposures and showed no significant variation with exposure conditions. There was no change in arterial oxygen saturation; heart rate and blood pressure were stable, in addition, no changes were observed in lung volumes, distribution of ventilation, diffusing capacity and mechanics of breathing, either immediately or after a delay for up to 1 or 2 weeks nor were there any subjective complaints associated with the exposure.

Data on the respiratory functional responses of animals and humans to inhaled nitrogen dioxide and the induced pulmonary effects were reviewed and compared by Mauderly (1984). Responses of humans, sheep, and guinea pigs to 4-hour exposures to NO$_2$ were compared. Although different parameters were measured (breathing pattern in guinea pigs and airflow limitation in humans and sheep), the comparison demonstrated that acute exposure to NO$_2$ affected respiration e.g. the breathing patterns of all three species. Inhalation of high concentrations of NO$_2$ (10 to 100 ppm) also apparently caused similar responses in lungs of humans and animals. The clinical syndrome in nonfatal human cases lasted several hours to days and consisted of breathing pattern changes, productive cough, and leukocytosis. The most prominent functional changes were increased

ANNEL 1 – BACKGROUND DOCUMENT TO RAC OPINION ON NITRIC ACID

respiratory frequency and reduced CO diffusing capacity, resulting from alveolar epithelial damage, oedema, and haemorrhage. Overall, the comparison illustrated that although accurate quantitative data for life-threatening exposures to NO_2 in humans were lacking, the clinical syndrome and the pulmonary effects observed in accidental human exposure cases were similar to that seen in experimental animals exposed to high levels of nitrogen dioxide.

Four cases of poisoning from nitrous fumes were reported by Jones et al. (1973). Three patients suffered from pulmonary oedema, and one of these progressed to the phase of bronchiolitis obliterans; the fourth patient was seriously affected with the clinical features of bronchiolitis obliterans. Based on these case descriptions the various clinical presentations and the biphasic character of the pulmonary response to these gases were demonstrated: (1) the first phase is one of acute pulmonary oedema, the onset of which may be delayed up to 36 hours from the time of exposure. Breathlessness is often severe while central cyanosis, sinus tachycardia, and respiratory sounds are commonly present. Death may occur in the first phase but some patients, even without treatment, will survive. In these patients symptoms may partially remit for a period of several days only to recur; (2) the second phase, two to six weeks after exposure, is characterized by rigors, pyrexia, and recurrence of cough, sever breathlessness, and cyanosis. Chest radiographs show miliary mottling throughout the lungs, while histology of the lung obtained at biopsy or necropsy suggests that these opacities are due to an obliterating bronchiolitis. Pulmonary function studies in both phases show a predominantly restrictive pattern of ventilatory abnormality with a tendency to hypoxaemia, hypocapnia, and reduced transfer factor.

In an Austrian chemical factory producing artificial fertilizers "spontaneous decomposition" occurred in 1966, setting free large amounts of nitrous fumes. Clinical findings and results of pulmonary functions tests were reported from 34 workers accidentally affected by inhalation of nitrous fumes (Muhar and Raber 1974). Death occurred in 7 men within few hours. In 17 workers pulmonary oedema was apparent. 13 of the injured men underwent control in 1967. In 1973, seven years after the accident, 24 of the 27 survivors were examined. 18 were chemistry workers, and 6 construction workers engaged in assembly jobs in the factory at the time of the accident. The most important results were the following: 7 years after the accident the dynamic compliance (C dyn) was substantially decreased in the 10 persons who suffered from pulmonary oedema. This finding was interpreted as an elasticity-loss of the lung. However, compared to the examination in 1967 (one year after the accident), amelioration was observed. The mean value of C dyn was 103 mL/cm H_2O in 1967, and 124 mL/cm H_2O in 1973 (normal value > 200). The difference was statistically significant. Bronchial resistance was 1.9 cm H_2O/L/sec in 1967, and 4.6 cm H_2O/L/sec in 1973 (normal value < 3.0). Comparison of resistance values between 1967 and 1973 was made on 8 chemical workers and 5 construction workers. The mean values for the chemical workers were 2.1 and 6.0 cm H_2O/L/sec; of the construction workers 1.7 and 2.6 cm H_2O/L/sec. In 1967 none of the 16 chemical workers had a resistance higher than 3.0; in 1973 this value was exceeded in 7 cases. The resistance values of the construction workers were also below 3.0 in 1967; in 1973 only one of them showed a resistance higher than 5.0. No statistically significant age difference between the two worker groups was proven. As a possible cause for the varied development in bronchial resistance by these workers a difference in the working conditions was assumed. The chemistry workers were subject to long-term exposure of nitrous fumes even under optimum working conditions.

Clinical and therapeutic aspects of nitrous gas poisoning were discussed by Schibli (1975). The author noted that intoxication with lung-aggressive gases was quite common at that time: an average of 20 cases of acute poisoning by inhalation of lung-aggressive gases was reported to the Accident Insurance Company (SUVAU) in Switzerland per year. Acute toxicity with nitrous gases usually occurred in the metal industry when metals or organic substances came into contact with nitrous acid (HNO_2) or nitric acid (HNO_3). A common source of intoxication was the development of nitrous gases from atmospheric nitrogen at very high temperatures, e.g., during welding operations in small rooms. In addition, there were incidents in the explosives industry with inhalation of smoke during use of nitro-explosives and incomplete combustion of nitrocellulose. When coming in contact with mucous membranes of the respiratory tract, acidic action commenced, leading to highly severe lesions of the alveoli and pulmonary capillaries as well as the bronchial and tracheal mucosa. Acute toxicity by inhalation of nitrous gas proceeded in a biphasic fashion. In the first stage, immediately after inhalation of nitrous gas, coughing, throat irritation, giddiness, headache and possibly vomiting occurred. Oedema of the glottis was observed at very high concentrations. Initial symptoms disappeared after 15 to 30 minutes. No symptoms occurred during a subsequent interval of 8-10 (rarely 24) hours. Stage two followed the asymptomatic interval. Pulmonary oedema of varying severity developed within a short period of time, accompanied by the corresponding symptoms. In the initial phases, densification of the hila and fine, spotty, shadows very visible after X-ray of the lungs. In many cases pulmonary oedema was protracted with relapses over 2 to 3 days.

Controlled acute exposure studies were performed to determine whether exposure to a realistic concentration of nitrogen dioxide could increase the bronchial sensitivity of asthmatic patients to bronchoconstrictor agents (Orehek et al. 1976). 20 asthmatics volunteered for this study. All were outpatients, suffering from slight to mild asthma. The bronchial sensitivity to carbachol before and after NO_2 exposure in order to establish whether NO_2 could make the airways "hyperreactive" was measured. In 13 of 20 subjects exposed to 0.1 ppm (0.19 mg/m³) NO_2 for one hour a moderate bronchial obstruction and a marked increase in bronchial sensitivity to a bronchoconstrictor agent was reported.

Extensive summary of the effects of nitrogen oxides on human volunteers exposed under controlled exposure conditions has been provided by Greim (2003). Table 16 summarises key health effects observed from controlled human exposure studies with NO_2 exposure durations of short, one-off exposure (maximum 4 hours).

Table 17: Key effects of exposure to nitrogen dioxide on human health (Greim 2003)

Observed effects	NO₂ exposure
Indications of inflammatory reactions	> 0.6 mL/m³
Elevated bronchial reactivity	> 1.5 mL/m³
Changes in pulmonary function (elevated respiratory system resistance)	> 2.0 mL/m³
Bronchitis, bronchopneumonia	25-75 mL/m³
Bronchiolitis and focal pneumonitis	50-100 mL/m³
Lethal bronchiolitis fibrosa obliterans	150-200 mL/m³

Lethal pulmonary oedema and asphyxia (methaemoglobinaemia)	> 300 mL/m³

4.2.3 Summary and discussion of acute toxicity

The acute inhalation toxicity of HNO_3 has been described and classification of nitric acid for acute toxicity is proposed only for the inhalation route of exposure.

Nitric acid is acutely toxic by inhalation. There are no apparent species differences in the toxic response to acute inhalation exposure to HNO_3. After a single exposure or relatively brief exposure to nitric acid lethality in animals and humans occurred due to rapid and progressive acute pulmonary oedema. In humans lethality has been observed after a latency period of 3 to 30 hours. Besides, inhalation of gases and vapours originating from nitric acid can be extremely dangerous because they do not set up a violent respiratory reflex, as observed with chlorine and ammonia, which serves as a warning property. 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). These health hazards are not covered by the existing legal classification of nitric acid in Annex VI of CLP Regulation for its corrosive reactions as Skin Corr. 1A – H314. In particular, skin corrosion is usually characterised by local effects on the skin, namely, visible necrosis through the epidermis and into the dermis, following the application for up to 4 hours.

The evidence for acute inhalation toxicity of nitric acid was obtained from animal testing and from human experience (e.g. data from accident database and experimental studies).

In numerous human case reports acute lethality was described following accidental exposure to nitric acid fumes, vapours or gases originating from acid solution. Exposure durations were recorded in some case reports, but real exposure concentrations were in most cases not given.

In humans, severe pulmonary sequelae due to inhalation of vapours and gases originating from nitric acid solutions can be divided into three categories: (1) immediate fatalities from very high concentrations, (2) delayed effects occurring within 48 hours, and (3) mild immediate effects followed by a short recovery period, but culminating in pneumonia. In some cases, recovery occurred within two weeks, but in others, it took place only after a prolonged period. After this time, a relapse may occur with death caused by bronchopneumonia and/or pulmonary fibrosis (ACGIH 1991; NIOSH 1976; Hardy and Hamilton 1974 cited in Durant et al. 1991).

Mechanism of inhalation toxicity

Exposure to nitric acid fumes involves exposure to nitric acid as well as nitrogen oxides. Toxicity to the respiratory tract is mediated by generation of nitrogen oxides, mainly NO_2 and NO. Inhalation effects from "nitric acid fumes" exposure are induced by a mixture of nitric acid vapour and oxides of nitrogen (Durant et al. 1991; Budavari et al. 1989; NIOSH 1976). When nitric acid is exposed to air or comes in contact with organic matter, it decomposes to yield a mixture of oxides of nitrogen: nitrogen dioxide (NO_2), nitric oxide (NO), nitrous oxide (N_2O), and nitrous anhydride (N_2O_3). The most important decomposition products of nitric acid are NO_2 and NO. Nitric acid is also readily decomposed by light or heat to yield yellow to red-brown fuming nitric acid, which contains about 90 % HNO_3. In practice, nitric acid is usually found in conjunction with NO_2. In contact with steam the emitted fumes of NO_2 form equimolar amounts of nitrous and nitric acid. NO quantitatively reacts with oxygen in air to form NO_2 which in turn reacts with water to form nitric acid (ACGIH 1991;

NIOSH 1976). Thus, the toxic action of nitric acid can not be considered without taking into account the effects of NO_2.

The course of acute inhalation toxicity to such mixtures of nitric acid and nitrogen oxides is consistent between humans and animals. The nitric acid-induced acute inhalation toxicity is characterized by a variable degree of effects in the respiratory tract, which may or may not be manifested immediately. The severity of effects depends upon the airborne concentration of nitric acid or oxides of nitrogen as well as the duration of exposure. In human exposure to nitric acid vapour may cause severe breathing difficulties (which may delay in onset), bronchial catarrh, pneumonia, and bronchiolar and alveolar epithelial necrosis. Based on the high lipid solubility of nitrous gases released from nitric acid cell damage in the alveolar capillary membranes and further toxic processes are subsequently caused, lethality may be produced due to acute fatal pulmonary oedema after a typical latency period of 3 to 30 hours (ACGIH 1991; NIOSH 1976; Hardy and Hamilton 1974 cited in Durant et al. 1991).

Nitric acid vapour is highly water-soluble and reactive. Based on these properties, nitric acid would be expected to undergo significant removal within the upper respiratory tract. The nitric acid-induced effects already noted suggest penetration of inhaled acid through the upper respiratory tract and into the lungs. Some examinations indicated that HNO_3 induces alterations in both the conducting and respiratory airways. In order to explain these toxicological results, Schlesinger et al. (1994) hypothesized that inhaled acid reached the lower respiratory tract not as a vapour, but following conversion into particulate form. This may have occurred by two potential mechanisms. One was formation of pure nitric acid droplets within the humid airways. The humidity within the airways is very high, and because of its solubility, some of the inhaled HNO_3 vapour within such an environment will likely combine with water condensed into small droplets, which can serve as vectors for acid delivery to the deep lung. The second mechanism involves reactions of endogenous respiratory-tract ammonia with inhaled gaseous HNO_3, producing particulate ammonium nitrate (Larson 1989). Once formed, these particles may then also serve as absorption surfaces, and additional vectors, for HNO_3.

In a model system, Chen and Schlesinger (1996) have shown that particulates can act as vectors for adsorbed/absorbed nitric acid transport to the lower respiratory tract. Reaction with endogenous ammonia and water may also produce particulates which can act as vectors.

The assumption that nitric acid and NO_2 interact to cause enhanced toxicity is also supported, in part, by the inhalation experiments of Goldstein et al. (1977) in Rhesus monkeys. Approximately 50-60 % of the inhaled NO_2 was retained by the animals and distributed throughout the lungs. Radioactivity was retained in the lungs during the 21-minute post exposure period with extrapulmonary distribution (per cent not quantified) via the bloodstream. The authors speculate that the reaction of inhaled NO_2 with water vapour in the lungs and with liquid water in the mucus results in the formation of nitric acid and accounts for the long retention time in the lung.

Data analysis for determination of LC_{50} value for nitric acid

Multiple LC_{50} values for HNO_3 and NO_2 from several animal species were determined in acute inhalation toxicity studies of various exposure duration and different study quality and reliability. In table 17 a survey of LC_{50} values for HNO_3 and NO_2 in several animal species is presented.

Table 18:   Survey of LC_{50} values for HNO_3 and NO_2 in several animal species

Animal Species	Inhaled material Physical state	LC_{50} value	Reference
rat	**HNO_3** vapour	**77.5 ppm/4hr** **(= 0.20 mg/L/4hr)**	Gray et al. (1954); NIOSH (1976)
rat	**HNO_3** vapour	**83.5 ppm/4hr** **(= 0.22 mg/L/4hr)**	Gray et al. (1954); NIOSH (1976)
rat	**HNO_3** mixture of liquid, gaseous and vapour phase	2500 ppm/1hr	Du Pont (1987)
rat	**NO_2** gas	88 ppm/4hr	Gray et al. (1954)
rat	**NO_2** gas	115 ppm/1hr	Carson et al. (1962)
rabbit	**NO_2** gas	315 ppm/15 min	Carson et al. (1962)
rat mouse, rabbit, guinea pig dog	**NO_2** gas	75 ppm/4hr	Hine et al. (1970)
rat, rabbit, guinea pig, dog, monkey	**NO_2** gas	123 mg/m³/8hr	Steadman et al. (1966)
cat	**HNO_3** fumes (by heating concentrated HNO_3)	191.2 ppm/1hr	Diem (1907 cited in Henschler 1992)
cat	**HNO_3** gas	341 ppm (= 880 mg/m³/3.83 hr) 217 ppm (= 560 mg/m³/4.25 hr)	Lehmann and Hasegawa (1913)

In conclusion reliable LC_{50} values for classification of HNO_3 for acute inhalation toxicity were derived in the favoured species, the rat. Acute inhalation toxicity studies in rats, which are suitable for LC_{50} determination of nitric acid, were conducted by Gray et al. (1954). Although the studies by Gray et al. (1954) were conducted decades before standard test guidelines were adopted the studies were considered sufficient reliable to propose classification of nitric acid as acutely toxic by the inhalation route of exposure.

In a comparative study 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 were examined in male albino rats. The test atmosphere for RFNA and WFNA was characterised as a vapour. Deaths occurred due to pulmonary oedema. For RFNA and WFNA LC_{50} values of 77.5 ppm/4hr (0.20 mg/L/4hr) and of 83.5 ppm/4hr (0.22 mg/L/4hr) were deduced (Gray et al. 1954; NIOSH 1976).

4.2.4   Comparison with criteria

Nitric acid is acutely toxic by inhalation. After a single exposure or relatively brief exposure to nitric acid lethality was caused in humans and animals due to acute pulmonary oedema. In humans severe effects and/or lethality occurred after a typical latency period of 3 up to 30 hours. Besides, inhalation of gases and vapours originating from nitric acid can be extremely dangerous because they do not set up a violent respiratory reflex, as occurs with chlorine and ammonia, which serves as a warning property. Thus, inhalation of nitric acid fumes at potentially fatal concentrations may go undetected by the affected person (Hardy and Hamilton 1974 cited in Durant et al. 1991). These health hazards are not covered by the existing legal classification of nitric acid in Annex VI for its corrosive reactions as Skin Corr. 1A – H314. In particular, skin corrosion is usually characterised by local effects on the skin, namely, visible necrosis through the epidermis and into the dermis, following the application for up to 4 hours.

It is concluded that the data presented in the report provide clear evidence of acute inhalation toxicity of nitric acid.

The evidence for acute inhalation toxicity of nitric acid was obtained from animal testing and human data. A number of studies of different types and reliability have been found in several animal species to investigate acute inhalation toxicity. In humans relevant information with respect to severe effects and lethality after single exposure or exposure of less than 24 hours to nitric acid were available from accident databases and experimental studies.

Reliable LC_{50} values for classification of HNO_3 in the hazard class - acute inhalation toxicity - were identified in acute inhalation toxicity studies in the favoured species, the rat. According to the existing studies on acute inhalation toxicity in experimental animals, which provide conclusive evidence that nitric acid induced acute toxic effects by inhalation, HNO_3 does require classification for this endpoint. The most relevant animal studies determining LC_{50} values were received from Gray et al. (1954). Although the studies by Gray et al. (1954) were conducted decades before standard test guidelines were adopted the studies were considered sufficient reliable to propose classification of nitric acid as acutely toxic by the inhalation route of exposure. These studies were utilized as key studies in acute toxicity evaluation of nitric acid due to their high adequacy, reliability and relevance for this endpoint.

In numerous human case reports acute lethality was described following accidental exposures to nitric acid fumes, vapours and gases originating from acid solution. Exposure durations were recorded in some case reports, but real exposure concentrations were in most cases not given.

- **Rationale for classification of nitric acid in the hazard class - Acute inhalation toxicity:**

The CLP criteria for classification in Acute toxicity hazard category 1, inhalation, Danger, H330, Fatal if inhaled, vapours (Annex I, Part 3, 3.1) is as follows: ATE ≤ 0.5 mg/L/4hr.

HNO_3 meets the criteria for classification and labelling as Acute Tox. 1 – H330 (CLP Regulation).

In a comparative study toxicity by inhalation of 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) was examined in male albino rats. The test atmosphere for RFNA and WFNA was characterised as a vapour. Deaths occurred due to pulmonary oedema (Gray et al. 1954; NIOSH 1976).

For RFNA the thirty-minute LC_{50} value of approximately 310 ppm and for WFNA of approximately 334 ppm was observed. However, the classification criteria for acute inhalation toxicity relate to a 4-hour experimental exposure period. Therefore, for direct comparison with the criteria for classification adjustment of the 30-minutes exposures to a 4 hour testing exposure was carried out by dividing by 2 for a 1 hour exposure and thereafter by dividing by a factor of 2 for gases and vapours (according to the CLP Regulation), which amounts to a LC_{50} value of 77.5 ppm/4hr for RFNA and 83.5 ppm/4hr for WFNA.

The conversion of the volumetric gas unit "ppm" into the mass per volume metric, such as "mg/L" was performed for RFNA and WFNA by using the algorithms recommended in OECD GD No. 39 on acute inhalation toxicity testing (2009). The following LC_{50} values were deduced:

$LC_{50, rat}$ RFNA: 310 ppm/30 min = 77.5 ppm/4 hr = 0.20 mg/L/4hr (Gray et al. 1954; NIOSH 1976)

$LC_{50, rat}$ WFNA: 334 ppm/30 min = 83.5 ppm/4hr = 0.22 mg/L/4hr (Gray et al. 1954; NIOSH 1976).

In conclusion, the study by Gray et al. (1954) is most appropriate basis for classification of nitric acid as acutely toxic by the inhalation route. 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 signal word "Danger" and hazard statement H330 (Fatal if inhaled.) according to CLP Regulation (Annex I, Part 3, 3.1 Acute toxicity, Category 1, vapours: ATE ≤ 0.5 mg/L/4hr). Based on criteria of Directive 67/548/EEC (Dangerous Substances Directive, DSD; Annex VI: LC_{50}, vapours: ≤ 0.5 mg/L/4hr) nitric acid is classified and labelled as T$^+$ (Very toxic); R26 (Very toxic by inhalation.).

The classification of nitric acid as acutely toxic by inhalation involves a hazard of respiratory tract corrosion, since up to now HNO_3 is classified and labelled only for its corrosive reactions as Skin Corr. 1A - H314 (Causes severe skin burns and eye damage.). According to CLP Regulation nitric acid has to be labelled in addition with EUH071 (Corrosive to the respiratory tract.).

4.2.5   Conclusions on classification and labelling

According to CLP Regulation, nitric acid should be classified in acute hazard category 1 for inhalation exposure and labelled with signal word "Danger" and hazard statement H330 (Fatal if inhaled). In addition to classification for acute inhalation toxicity nitric acid has to be supplementary labelled with EUH071 (Corrosive to the respiratory tract.).

According to Annex VI of the EC Council Directive 67/548/EEC, nitric acid has to be classified as very toxic by inhalation (hazard symbol: T[+]; risk phrase: R26, Very toxic by inhalation.).

Specific concentration limits are not applicable for acute toxicity classification. Classification of mixtures is based on ingredients of the mixture (additivity formula). For this reason SCLs for acute toxicity will not appear in CLP Annex VI, Table 3.1 or in the classification and labelling inventory.

RAC evaluation of acute toxicity
Summary of the Dossier submitter's proposal
Acute oral toxicity   No data on the oral acute toxicity of nitric acid was presented by the dossier submitter in the CLH dossier and no classification for oral acute toxicity was proposed.   Acute dermal toxicity   No data on the dermal acute toxicity of nitric acid was presented by the dossier submitter in the CLH dossier and no classification for dermal acute toxicity was proposed.   Acute inhalation toxity   *Acute inhalation toxicity, human study*   In numerous human case reports, acute lethality and other severe acute toxic effects have been described following accidental exposure to fumes, vapours or gases originating from nitric acid solutions. Exposure durations were recorded in some case reports, but actual exposure concentrations were in most cases not given.   After single or relatively short exposures to nitric acid, lethality has been caused in humans due to acute pulmonary oedema. In humans, severe effects and/or lethality occurred after a latency period of 3 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 protective mechanism, 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).   During the public consultation, in response to some comments from industry stakeholders, the dossier submitter provided information that when HNO_3, as an ingredient in cleaning products, comes in contact with other materials (metal) or substances (e.g. alkaline ingredients from other cleaning agents) the release of nitrous gases, especially NO_2, is expected. There are many case reports from the poison information centers in Germany providing evidence of severe health damages after use (and presumably misuse) of descaling products containing 20-30% of HNO_3 (between 1999 and 2010). In 23.7% of all cases the symptoms were caused by inhalation.   *Acute inhalation toxicity, animal studies*   The acute lethal effects of different nitric acids were reported by Gray *et al*. (1954, in NIOSH 1976). 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) were examined by inhalation in male albino rats. The test

atmospheres for RFNA and WFNA were characterised as a vapour. Deaths occurred by acute pulmonary oedema. The terms "white fuming" and "red fuming" are applied to differentiate between 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 dossier submitter calculated LC_{50}-values of 77.5 ppm/4h (0.20 mg/l/4h) for RFNA and 83.5 ppm/4h (0.22 mg/l/4h) for WFNA. 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).

For direct comparison with the classification criteria conversion of the 0.5-hour exposure values into a 4 hour testing exposure period was carried out in two steps. The 1 hour exposure value was derived by dividing by 2. Because the test atmosphere for RFNA and WFNA was characterised as a vapour the values for a 1 hour exposure were thereafter divided by a factor of 2 for gases and vapours (according CLP Regulation), which amounts to 77.5 ppm/4h for RFNA and 83.5 ppm for WFNA.

Nitric acid can decompose to nitrogen dioxide (NO_2), nitric oxide (NO), nitrous oxide (N_2O), and nitrous anhydride (N_2O_3). The most important decomposition product of nitric acid is nitrogen dioxide. Nitrogen dioxide is highly toxic, and inhalation of nitrogen dioxide may result in fatality. The acute toxic effects from nitric acid fumes are caused by a mixture of nitric acid vapour and oxides of nitrogen, mainly NO_2 and NO. Therefore, acute toxic inhalation effects of nitric acid in humans cannot be isolated from those of its reaction products, since contact with air immediately liberates oxides of nitrogen.

The other acute inhalation toxicity studies using rabbits and cats reviewed in the BD supported the high toxicity of nitric acid fumes; however, they did not enable an LC_{50} value to be established.

According to the dossier submitter, HNO_3 meets the CLP criteria for classification and labelling as Acute Tox. 1 – H330 with the supplemental hazard information statement EUH071 (Corrosive to the respiratory tract) as well as the DSD criteria for classification as T^+; R26 (Very toxic by inhalation).

Comments received during public consultation

Nine comments on the classification proposal for acute inhalation toxicity were received during public consultation.

Two comments were received from MSCAs supporting classification of nitric acid as proposed by the dossier submitter, i.e. Acute Tox. 1 - H330 and the additional hazard statement EUH071 (Corrosive to the respiratory tract).

One of these MSCAs agreed that action at community level is justified for the acute inhalation toxicity of nitric acid because it is considered a High Production Volume chemical, and in addition it poses a high health risk to consumers. According to the C&L inventory the majority of notifiers do not self-classify for acute inhalation toxicity or for STOT SE with the respiratory tract as target organ. Therefore, a harmonised classification for acute inhalation toxicity to protect human health is justified. No self-classification of acute oral toxicity is notified in the C&L inventory and according to BfR Opinion No. 041/2010, the lowest fatal dose of oral exposure for humans is 430 mg/kg bw (the minimum lethal dose reported for humans could be used as equivalent ATE, and the resulting classification would be Category 4).

Seven comments were received from industry:
One manufacturer noted that at higher concentrations of nitric acid, the effects of the nitric acid itself and its precursors or decomposition products cannot be clearly

differentiated in studies using fuming acid. Therefore, the effects of nitric acid at lower concentrations in more diluted aqueous solutions and HNO_3 partial pressure should be considered. This manufacturer does not, however, recommend HNO_3 for consumer use.

The dossier submitter clarified in its response, that even using the low partial vapour pressure of 0.336 hpa for the calculation (provided by Fertilizers Europe, France, based on the same parameters as those used in the calculations in BfR Opinion No. 041/2010, except for partial vapour pressure; see RCOM) of the concentration of nitric acid in a bathroom cleaned with a cleaning product containing nitric acid at a concentration of approximately 30%, the resulting nitric acid concentration in the cleaned bathroom is still very high, ca. 8mg/m^3. The dossier submitter also noted that even at a low concentration in the cleaning products (20 -30%), nitric acid poses a risk for acute inhalation poisoning in humans. Out of 134 reported cases with health effects attributed to nitric acid reported to BfR, by the poison treatment and information centres in Germany (BfR Opinion No 041/2010), in almost one quarter (23.7%) the symptoms were caused by the inhalation of ingredients in the cleaning products. Therefore, these data support a view of high inhalation toxicity of nitric acid even at lower concentrations in aqueous solutions. The dossier submitter further noted that contact of aqueous solution of nitric acid (as in the cleaning products) with calcium carbonate deposits, metals or ingredients of other cleaning products may release toxic nitrous gases.

One REACH consortium and two national trade associations emphasized that the nitric acid in the REACH registration dossier submitted by the former does not have any consumer use. In reference to the REACH regulation, it means that the consumer use of nitric acid is not authorised in Europe since 1 December 2010.

According to one trade association, there are two different types of nitric acids with different toxicities, and they can be distinguished by concentration ranges: the 'aqueous nitric acid' (up to 68%) and the 'smoking nitric acid' (higher than 68%). Smoking nitric acid is only obtainable by bubbling NO_x into aqueous HNO_3 (impossible to obtain by distillation as the 68% acid is an azeotropic mixture). Due to this chemical difference, these products have different acute toxicity profiles. In the study of Gray *et al*. (1954), the acute toxicity observed with concentrated nitric acid (higher than 70%) is due to the inhalation of toxic NO_x gases released by concentrated acid. The acute toxicity Category 1 classification for inhalation should therefore only apply to aqueous solutions with nitric acid content greater than 70%, while for nitric acid containing aqueous solutions with concentrations lower than 70%, classification for acute toxicity Category 4 should be applied. They also expressed a view that it is safer to highlight the corrosive risk rather than using the acute toxicity Category 4 classification, because this classification is more restrictive in terms of risk management measures.

The dossier submitter disagreed with the above proposal for the classification of nitric acid based on specific concentrations above or below 70 %, since many cases of nitric acid poisoning were observed following the use of a detergent called 'POR ÇÖZ' (produced in or imported from Turkey) containing only 25 % nitric acid, which was far below the concentration limits of C <70 % proposed by the above trade association.

According to the guidance on the application of CLP criteria, SCLs are not applicable for acute toxicity classifications according to CLP. Classification of mixtures is based on ingredients in the mixture (using the 'additivity formula'). In addition, inhalation of gases and vapours originating from nitric acid do not induce a violent respiratory reflex, which serves as a protective mechanism, as occurs with e.g. chlorine and ammonia. Thus, inhalation of nitric acid fumes at potentially fatal concentrations may go undetected by the affected person. This health hazard is not covered by the existing Annex VI entry where nitric acid has a harmonised classification as Skin Corr. 1A – H314.

The same national trade associations questioned the validity of the Gray *et al*. study

(1954) used for calculating the LC_{50}/4h for nitric acid, and suggested using the study of du Pont de Nemours and Company (1987) for this purpose, which was performed with a 70.7% nitric acid aqueous solution and provided data for calculating a 4 hour LC_{50} of 1562.5 mg/m^3. In line with this suggestion, the aforementioned manufacturer stated that although the aerosol criteria were not fully met in the du Pont study, one could estimate that concentrations around 70% nitric acid and the given 1 hour value of 2500 ppm, would correspond to an aerosol value of about 1,6 mg/l/4h. The mortality observed was attributed to corrosive effects. From aerosol exposure, the inhalation toxicity of 70% nitric acid would lead to classification as acute toxicity Category 4. They further stated that lower concentrations cannot have a higher classification than acute inhalation toxicity Category 4, and that therefore, separate, concentration dependent entries in Annex VI of the CLP are needed.

In its response, the dossier submitter pointed out that in the study performed by du Pont (1987), the 1-hour LC_{50} value for nitric acid (approx. 71 % aqueous solution) for male and female rats combined was derived at 2500 ppm. However, the test atmosphere was not well-defined at this concentration. The aerosol content was not measured, but estimated by the authors to be approximately 100 %. It was assumed that the test atmosphere presented itself as a mixture of liquid, gaseous and vapour phases. Thus, it was not possible to perform an exact conversion of the 1-hour exposure value into a 4-hour value. Although the studies by Gray *et al*. (1954) were conducted decades before standard test guidelines were adopted, these studies were considered sufficiently reliable to propose classification of nitric acid as acutely toxic by the inhalation route. The LC_{50}-values for RFNA and WFNA were deduced by using the algorithms recommended in OECD GD No. 39 on acute inhalation toxicity testing (2009). For RFNA a LC_{50}-value of 0.20 mg/l/4h was derived, and the corresponding value for WFNA was 0.22 mg/l/4h.

Assessment and comparison with the classification criteria
Comparison with the criteria

The studies by Gray *et al*. (1954) were conducted decades before standard test guidelines were adopted. However, 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 exposure or severe effects in animals exposed from 35 minutes to 315 minutes to fumes at concentrations of 15.3 ppm to 336.5 ppm from heated concentrated nitric acid (see furtherreview in BD).

The study by du Pont (1987) in which rats were exposed for 1 hour to an aerosol of 70.76 % aqueous solution of nitric acid at concentrations of 260 – 3100 ppm was not considered appropriate for the determination of LC_{50} of gases and vapours emitted by nitric acid. The nitric acid was airborne as particles and aerosol samples were taken using a gravimetric filter samplebut at the highest concentrations, the nitric acid content was not measured. Thus, the respirable concentrations of nitric acid in this study are uncertain.

The case studies of humans accidently exposed to nitric acid can be taken as supportive evidence of the high acute inhalation toxicity of nitric acid.

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

Nitric solutions	Accidental exposed humans	References
20-30 %	134 cases, 23.7% identified as due to inhalation	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)

Cases of human poisoning were observed at nitric acid concentrations of 20% andabove. No data are available to predict whether mixtures containing 20% nitric acid represent the lowest concentrations resulting in adverse acute effects. 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). There are no data on toxic effects resulting from acute inhalation exposures between this NOAEC and nitric acid at concentrations of 20%.

According to the Guidance on the Application of CLP criteria (version 3.0, November 2012, point 3.1.2.5), SCLs are not applicable for acute toxicity classifications according to CLP. Instead, the relative potency of substances in a mixture, taking into account the 'additivity formula' (section 3.1.3.6.1 of Annex I of CLP regulation) should be used to decide on classification of the aqueous solution of nitric acid with a low concentration of the acid.

Taking into account the data submitted in the CLH dossier and the arguments provided by the dossier submitter, as well as data and arguments provided during public consultation, the RAC is of the opinion that classification with Acute Tox. 1 – H330 (inhalation) with the supplemental hazard information EUH071 (Corrosive to the respiratory tract) and T+; R26 (DSD) is warranted for nitric acid. The classification is based on the lowest derived LC_{50}-value of 77.5 ppm/4h (0.20 mg/l/4hr) for gases and vapours released from liquid RFNA in the rat (Gray *et al*. 1954; NIOSH 1976, and the dossier submitters calculations, see the BD) (Acute Tox. 1 – H330, vapours ATE ≤ 0.5 mg/L/4h; T+; R26: LC_{50}, vapours ≤0.5 mg/L/4h).

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

Not evaluated for this report.

4.4   Irritation

Not evaluated for this report.

4.5   Corrosivity

Not evaluated for this report.

4.6   Sensitisation

Not evaluated for this report.

4.7 Repeated dose toxicity

Not evaluated for this report.

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

Not evaluated for this report.

4.9 Germ cell mutagenicity (Mutagenicity)

Not evaluated for this report.

4.10 Carcinogenicity

Not evaluated for this report.

4.11 Toxicity for reproduction

Not evaluated for this report.

4.12 Other effects

Not evaluated for this report.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated for this dossier.

6 OTHER INFORMATION

Not evaluated for this report.

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8   ANNEXES

BfR Opinion on Nitric
Acid in consumer Proc