Committee for Risk Assessment

RAC

Annex 1

Background document

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

formic acid ... %

EC Number: 200-579-1
CAS Number: 64-18-6

CLH-O-0000007128-73-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to 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

2 June 2022

CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:
Formic Acid… %

EC Number: **200-579-1**

CAS Number: **64-18-6**

Index Number: **607-001-00-0**

Contact details for dossier submitter:

On behalf of the Belgian Biocides Service

FPS Public Health, Food Chain Safety and Environment
DG 5/ Department of Product Policy and chemical Substances / Management of Chemical Substances
BELGIUM

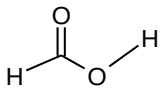
Version number: 2 **Date: 29 July 2021**

CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1. Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	Formic acid
Other names (usual name, trade name, abbreviation)	Carboxylic acid Methanoic acid Ameisensaeure Ameisensäure Aminic acid Formic acid (7CI, 8CI, 9CI) Formira Formisoton Formylic acid Hydrogen carboxylic acid Methanoic acid monomer Myrmicyl Protectol 85 FM
ISO common name (if available and appropriate)	/
EC number (if available and appropriate)	200-579-1
EC name (if available and appropriate)	Formic acid
CAS number (if available)	64-18-6
Other identity code (if available)	/
Molecular formula	CH2O2
Structural formula	
SMILES notation (if available)	O=CO
Molecular weight or molecular weight range	46.03
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not applicable
Degree of purity (%) (if relevant for the entry in Annex VI)	85 – 99 % aquous solution

1.2 Composition of the substance

Table 2. Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self classification and labelling (CLP)**
Formic acid	85 - 99 % aqueous solution	Skin Corr. 1A; H314	Flam. Liq. 3; H226 Metal Corr . H290 Acute Tox. 4 (oral); H302 Acute Tox. 3 (Inhalation - vapour); H331 Skin Corr./Irrit. 1A; H314 Eye Dam./Irrit. 1; H318
Water	1 – 15%	-	-

Table 3. Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
N/A				

Table 4. Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	**Function**	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The additive contributes to the classification and labelling**
N/A					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5.

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	607-001-00-0	Formic acid … %	200-579-1	64-18-6	Skin Corr. 1A	H314	GHS05 Dgr	H314	-	Skin Corr. 1B; H314: 10% ≤ C < 90% Skin Corr. 1A; H314: C ≥ 90% Skin Irrit. 2; H315: 2% ≤ C < 10% Eye Irrit. 2; H319: 2% ≤ C < 10%	Note B*
Dossier submitters proposal					**Add** Metal Corr.	H290	GHS05	H290	-	C ≥ 85%	
					Add Flam. Liq. 3	H226	GHS02	H226	-	C≥99%	
					Add Acute Tox. 4 (oral)	H302		H302	-		
					Add Acute Tox. 3	H331,	GHS06	H331	EUH071		

					(Inhalation - vapour)						
					Add Eye Dam./Irrit. 1	H318			-	C≥10%	
Resulting Annex VI entry if agreed by RAC and COM	607-001-00-0	Formic acid … %	200-579-1	64-18-6	Metal Corr.	H290	GHS05	H290	-	C ≥ 85%	
					Flam. Liq. 3	H226	GHS02	H226	-	C ≥ 99%	Note B
					Acute Tox. 4 (oral)	H302		H302	-		
					Acute Tox. 3 (Inhalation - vapour)	H331,	GHS06	H331	EUH071		
					Skin Corr./Irrit. 1A	H314	GHS05	H314	-	Skin Corr. 1B; H314: 10% ≤ C < 90% Skin Corr. 1A; H314: C ≥ 90% Skin Irrit. 2; H315: 2% ≤ C < 10% Eye Irrit. 2; H319: 2% ≤ C < 10%	
					Eye Dam./Irrit. 1	H318			-	C≥10%	

** Note B: Some substances (acids, bases, etc.) are placed on the market in aqueous solutions at various concentrations and, therefore, these solutions require different classification and labelling since the hazards vary at different concentrations. In Part 3 entries with Note B have a general designation of the following type: 'nitric acid ? %'. In this case the supplier must state the percentage concentration of the solution on the label. Unless otherwise stated, it is assumed that the percentage concentration is calculated on a weight/weight basis.*

Table 6. Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	hazard class not applicable	No
Oxidising gases	hazard class not applicable	No
Gases under pressure	hazard class not applicable	No
Flammable liquids	**harmonised classification proposed**	**Yes**
Flammable solids	hazard class not applicable	No
Self-reactive substances	hazard class not applicable	No
Pyrophoric liquids	hazard class not applicable	No
Pyrophoric solids	hazard class not applicable	No
Self-heating substances	hazard class not applicable	No
Substances which in contact with water emit flammable gases	hazard class not applicable	No
Oxidising liquids	hazard class not applicable	No
Oxidising solids	hazard class not applicable	No
Organic peroxides	hazard class not applicable	No
Corrosive to metals	**harmonised classification proposed**	**Yes**
Acute toxicity via oral route	**harmonised classification proposed**	**Yes**
Acute toxicity via dermal route	hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	**harmonised classification proposed**	**Yes**
Skin corrosion/irritation	Existing harmonised classification	No
Serious eye damage/eye irritation	**harmonised classification proposed**	**Yes**
Respiratory sensitisation	hazard class not assessed in this dossier	No
Skin sensitisation	hazard class not assessed in this dossier	No
Germ cell mutagenicity	hazard class not assessed in this dossier	No
Carcinogenicity	hazard class not assessed in this dossier	No
Reproductive toxicity	hazard class not assessed in this dossier	No
Specific target organ toxicity-single exposure	hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	hazard class not assessed in this dossier	No
Aspiration hazard	hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	hazard class not assessed in this dossier	No
Hazardous to the ozone layer	hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

Formic acid (CAS n° 64-18-6) was classified as corrosive to the skin with specific concentration ranges under Dir. 67/548/EEC, and this was transferred into CLP Annex VI, GHS classification.

Formic acid is a biocidal active substance and during its evaluation under the Biocidal Product Regulation (BPR, Regulation (EU) 528/2012) it was concluded that the current harmonized classification was no longer up to date. New hazard classes are now proposed in this CLH report, while the previous ones are retained.

RAC general comment
Formic acid is a colourless, volatile liquid with a pungent odour. The main uses include silaging, feed additive, leather and textile industry and chemical synthesis. Formic acid also occurs in nature (e.g. insect venoms, plants, mammalian body). It is miscible with water and the name of the Annex VI entry, 'formic acid … %', reflects the fact that the substance is placed on the market as aqueous solution. Formic acid has a harmonised classification as Skin Corr. 1A with specific concentration limits. During the assessment of the substance under the Biocidal Products Regulation it was concluded that the harmonised classification should be updated. The current CLH proposal covers selected hazard classes: flammability, corrosion to metals, acute toxicity (oral, inhalation) and eye damage/irritation.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

CLH-report was made in the context of Regulation (EU) No 528/2012. Justification is not required if the substance is an active substance used in BP for which normally all hazard classes should be addressed in the CLH report. The proposal addresses only hazard class(es) or differentiation(s) that are not covered by the current entry and thus considered as new proposal. It is considered justified that action is needed at Community level:

- Flammable liquid: change in existing entry due to changes in the criteria (DSD → CLP)
- Corrosive to metals: this hazard class was not part of DSD and is new in CLP
- Acute toxixity: change in existing entry due to changes in the criteria (DSD → CLP)
- Eye damage: a skin corrosive substance is considered to cause also serious eye damage

  Already existing harmonised classification for Skin Corr.1, H314: causes severe skin burns and eye damage

5 IDENTIFIED USES

Identified Use number	Identified Use name
Industrial uses	
11	Industrial manufacture of polymers, resins
12	Polymer processing
14	Industrial use as processing aid
9	Industrial use in Laboratories
4	Use as an Intermediate
5	Uses in Coatings
6	Use in Cleaning Agents
Uses by professional workers	
7	Use in Cleaning Agents
10	Use in Laboratories
13	Polymer processing
15	Use as processing aid
17	Animal nutrition
19	Use as preserving agent

6 DATA SOURCES

See references under chapter 14 of this report

7 PHYSICOCHEMICAL PROPERTIES

Table 7. Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Liquid	Study no. 07L00084, Dolich, T. (2007)	Organoleptic
Melting/freezing point	4 °C at 1013 hPa	Study no. 07L00084, Dolich, T. (2007)	Measured
Boiling point	100.23 °C at 1013 hPa	Study no. 07L00084, Dolich, T. (2007)	Determination through extrapolation
Relative density	D_4^{20} = 1.2195	Study no. 07L00084, Dolich, T. (2007)	Measured
Vapour pressure	At 20 °C: 42.71 hPa At 25 °C: 54.96 hPa At 50 °C: 170.7 hPa	Study no. 07L00084, Dolich, T. (2007)	Measured
Surface tension	At 20 °C: 71.5 mN/m	Study no. 07L00084, Dolich, T. (2007)	Measured
Water solubility	Completely miscible Corresponding to 1220 g/L (= D_4^{20})	Study no. 02L00109, Drögemüller, A. (2002)	Measured
Partition coefficient n-octanol/water	At pH 5: Log K_{OW} = -1.9 At pH 7: Log K_{OW} = -2.1 At pH 9: Log K_{OW} = -2.3 At 23 ± 1 °C	Study no. 02L00109, Drögemüller, A. (2002)	Measured
Flash point	49.5 °C	Study no. SIK-Nr.07/1018, Bitterlich, S. (2007)	Measured
Flammability	Flammable liquid category 3	/	/
Explosive properties	Not explosive	Gödde, M. (2006)	Expert judgement
Self-ignition temperature	528 °C (corrected according to EN 14522)	Study no. SIK-Nr.07/1018, Bitterlich, S. (2007)	Measured
Oxidising properties	Not oxidising	Gödde, M. (2006)	Expert judgement
Granulometry	N/A	N/A	N/A
Stability in organic solvents and identity of relevant degradation products	Organic solvents not used in the biocidal products	Waived	Waived
Dissociation constant	At 20 °C: pKa = 3.70	Study no. 07L00084, Dolich, T. (2007)	Measured
Viscosity	Dynamic viscosity At 20 °C: 1.80 mPa.s At 40 °C: 1.22 mPa.s	Study no. 07L00084, Dolich, T. (2007)	Measured

Property	Value	Reference	Comment (e.g. measured or estimated)
	Kinematic viscosity At 20 °C: 1.47 mm^2/s At 40 °C: 1.02 mm^2/s		

8 EVALUATION OF PHYSICAL HAZARDS

8.1 Explosives

Hazard class not assessed in this dossier.

8.2 Flammable gases (including chemically unstable gases)

Hazard class is not applicable for this substance.

8.3 Oxidising gases

Hazard class is not applicable for this substance.

8.4 Gases under pressure

Hazard class is not applicable for this substance.

8.5 Flammable liquids

Table 8. Summary table of studies on flammable liquids

Method	Results	Remarks	Reference
EC method A.9	49.5 °C	Closed cup; corrected for atmospheric pressure and rounded to units of 0.5 °C	Study no. SIK-Nr.07/1018, Bitterlich, S. (2007)

Also see § 1.5 of the Confidential Annex I to this CLH report.

8.5.1 Short summary and overall relevance of the provided information on flammable liquids

The flashpoint was experimentally determined according to the closed cup method of German Industrial Standard DIN EN ISO 17376 which is similar to 92/69/EC Annex A.9. The test substance was formic acid with a high purity of 99.48%. The flashpoint is 49.5 °C. The study was performed under GLP.

8.5.2 Comparison with the CLP criteria

Experimental determination as recommended. Result allows to follow decision logic.

Formic acid meets the classification criteria as flammable liquid category 3, as its flash point is ≥ 23 °C and ≤ 60 °C.

8.5.3 Conclusion on classification and labelling for flammable liquids

Formic acid should be classified as Flam. Liq., Cat3, H226.

8.6 Flammable solids

Hazard class is not applicable for this substance.

8.7 Self-reactive substances

Hazard class is not applicable for this substance.

8.8 Pyrophoric liquids

Hazard class is not applicable for this substance.

8.9 Pyrophoric solids

Hazard class is not applicable for this substance.

8.10 Self-heating substances

Hazard class is not applicable for this substance.

8.11 Substances which in contact with water emit flammable gases

Hazard class is not applicable for this substance.

8.12 Oxidising liquids

Hazard class is not applicable for this substance.

8.13 Oxidising solids

Hazard class is not applicable for this substance.

8.14 Organic peroxides

Hazard class is not applicable for this substance.

8.15 Corrosive to metals

Table 9. Summary table of studies on the hazard class corrosive to metals

Method	Results	Remarks	Reference
UN Test C.1 (37.4)	Corrosive to metal	85% solution in water is corrosive to steel Not corrosive to aluminium	Study no 16011907G979 Henke, W. (2016) Study no. 16092902G979 Krebs, F. (2017)

Also see § 1.15 of the Confidential Annex I to this CLH report.

8.15.1 Short summary and overall relevance of the provided information on the hazard class corrosive to metals

Studies performed on the active substance at 85% concentration show a clear corrosion to steel, and are enough to lead to classification for corrosive to metals. The studies performed on the substance at 99.4% concentration show signs of corrosion, but to a level that should normally not lead to classification. However, given the need to classification at 85%, the signs of corrosion at 99.4%, and the need to avoid steel containers at this concentration, it is likely that the weaker corrosion at higher concentration is only due to the lack of water, which leads to a weaker dissociation of the proton from the acid molecule, thus impairing the corrosiveness. The decreased corrosion sign is thus an artefact and both concentration have to be classified as corrosive to metal.

Not compatible material:

- carbon steel

Formic acid is stored and sold in containers made from different types of plastics (BASF , 2005/2006/2007):

- polyethylene (Lupolen, Hostalen, Lucalen)
- copolymer of ethylene and butylacrylate (Lucofin)
- polypropylene (Moplen)
- ethylene propylene diene monomer rubber (EPDM)
- ethylene tetrafluoroethene (ETFE)

8.15.2 Comparison with the CLP criteria

According to CLP guidance , the conclusion corrosive to metals can be reached when the corrosion rate on either steel or aluminium surfaces exceeding 6,25 mm per year at a test temperature of 55 oC when tested on both materials.

This value is exceeded for the formulation at 85%, but not fully reached for the concentration at 99.4%.

8.15.3 Conclusion on classification and labelling for corrosive to metals

Formic acid is to be classified as the available information are conclusive and sufficient for classification.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

Flammable liquids

The dossier submitter (DS) presented a study with 99.4% formic acid reporting a flash point of 49.5 °C (Bitterlich, 2007). The criterion for classification is a flash point of ≤ 60 °C. The DS proposed classification as Flam. Liq. 3 with a specific concentration limit of ≥ 99%.

Corrosive to metals

85% formic acid was positive and 99.4% formic acid was negative in 7-day corrosion tests

according to the UN method C.1. Initially (in the CLH report) the DS proposed classification as Met. Corr. with a specific concentration limit of ≥ 85%.

Comments received during consultation

Comments on flammable liquids were received from two member-state competent authorities (MSCAs). One of them stated that the usual flash point of formic acid is 69-71 °C. The other MSCA questioned the proposed specific concentration limit of ≥ 99% and provided a set of flash point data for various concentrations of formic acid that had been used as a basis for the current concentration limit of > 85% in the UN Recommendations on the Transport of Dangerous Goods, Model Regulations.

Comments on corrosivity to metals were received from 1 MSCA and 1 manufacturer. The industry commenter requested no classification for formic acid at ≥ 99% due to the negative result at 99.4%; they proposed the classification to apply only at 85% ≤ C < 99%. The DS disagreed, explaining that although 99.4% formic acid does not meet the criteria, the corrosion hazard may appear after a relatively small addition of water.

The commenting MCSA pointed out that corrosivity of solutions containing less than 85% formic acid was not investigated and therefore a concentration limit cannot be established without further testing. The DS agreed and did not anymore support the originally proposed specific concentration limit of 85%.

Additional key elements

Additional information on flammable liquids and corrosivity to metals (Germany, 2004)

One of the commenting MSCAs submitted publicly available documentation (Germany, 2004) used as a basis for the flammability classification in UN Model Regulations entry no. 1779. The data underlying the specific concentration limit of 85% for flammability is presented in the following table.

Flash point of formic acid: data from Germany (2004)	
Concentration (%)	Flash point (°C)
100	48
95	51
90	57
85	65
80	82

An excerpt from the Model Regulations entries for formic acid (as of 2021) is shown below.

UN No.	Name and description	Class	Subsidiary hazard
1779	FORMIC ACID with more than 85% acid by mass	8 (corrosive substances)	3 (flammable liquids)
3412	FORMIC ACID with not less than 10% but not more than 85% acid	8 (corrosive	

	by mass	substances)	
3412	FORMIC ACID with not less than 5% but less than 10% acid by mass	8 (corrosive substances)	

In the Model Regulations the classification as 'corrosive' covers corrosivity to skin and metals. The concentration limit of 5% is driven by corrosivity to metals (the current concentration limit for corrosivity to skin for the substance is 10%, see the current CLP Annex VI entry and Germany, 2004). Germany (2004) presents the following information on corrosivity to metals:

4.10 Corrosivity (2.8) to:

4.10.1	mild steel ...	**C>5%**	**more than 6.25 mm/year at 55 °C**
4.10.2	aluminium ...	**C>5%**	**more than 6.25 mm/year at 55 °C**

However, due to lack of further details it is not clear whether the data represent results of specific tests or whether these are estimates based on other (possibly non-experimental) information.

Assessment and comparison with the classification criteria

Flammable liquids

Liquid substances are classified in Category 3 if their flash point is ≥ 23 °C and ≤ 60 °C. With a flash point of 48 °C pure formic acid (100%; Germany, 2004) meets the CLP criteria for Flam. Liq. 3.

The flash point of aqueous solutions of formic acid increases with decreasing concentration. The threshold for classification (flash point 60 °C) lies between 85% and 90% (Germany, 2004). This information served as a basis for the concentration limit for flammability of formic acid of > 85% in the UN Model Regulations (entries 1779 and 3412).

RAC proposes a classification as **Flam. Liq. 3; H226** with a concentration limit of **> 85%** in line with the UN Recommendations on the Transport of Dangerous Goods, Model Regulations.

Corrosive to metals

The results of the two available C.1 tests are summarised below. The criteria for a positive result in a 7-day test are mass loss of ≥ 13.5% or localised corrosion with an intrusion depth of ≥ 120 µm. Both criteria were fulfilled for steel in the test with 85% formic acid (Henke, 2016). The criteria were not met by 99.4% formic acid (Krebs, 2017) presumably due to the low content of water leading to suppressed dissociation.

UN C.1 tests (exposure duration 7 days)					
Reference	Concentration	Steel		Aluminium	
		mass loss	intrusion depth	mass loss	intrusion depth
Henke (2016)	85%	28.2%	>120 µm	4.8%	none
Krebs (2017)	99.4%	2.0%	none	0.0%	none

RAC considers that classification is clearly warranted. Nevertheless, as pointed out in the third-party consultation, the available data do not allow setting of a lower specific concentration limit. The corrosivity classification in Model Regulations has a limit of ≥ 5% (see the "Additional key elements" section above and Germany, 2004) but the data behind this value are not available to RAC.

Singh and Gupta (1996) investigated corrosion rate of mild steel in formic acid at different concentrations (5% to 80%), temperatures (25 to 45 °C) and immersion periods (6 to 72 h). They found that the corrosion rates were highest at formic acid concentrations around 20%, and that the corrosion rates at 5% were higher than at 80%. Although this investigative study did not follow the UN C.1 protocol, the results indicate that the specific concentration limit of 5% from the UN Model Regulations should not be adopted under CLP without further verification.

As to the upper limit of 99% proposed by industry, RAC agrees with the DS that such a limit would not be appropriate as the corrosion hazard will appear on dilution.

In conclusion, RAC agrees with the revised DS's proposal of **Met. Corr. 1; H290**. The available data do not allow setting a specific concentration limit.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

Not evaluated

Only new hazards are addressed in this CLH report which are proposed to be added to the existing entry in CLP Annex VI. The evaluation of these hazards (acute oral and inhalation toxicity, serious eye damage) are directly related to the corrosivity of formic acid, i.e. the tissue at the point of contact is affected and toxicokinetics play no role. Therefore, toxicokinetic information was omitted for the sake of clarity.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

Also see § 3.1 of the Annex I (confidential) to this CLH report.

Table 10. Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels, duration of exposure**	**Value LD_{50}**	**Reference**
OECD TG 401 Deviations: no GLP: no (not compulsory at the time the study was conducted) Key study Reliability 1	Rat Wistar m+f 5/sex/group	Formic acid Purity 99%	501, 631, 794, 1000 mg/kg bw Single dose **gavage**	730 mg/kg bw (m +f) Males: 863 mg/kg bw Females: 618 mg/kg bw	REACH Registration dossier (Anonymous 1, 1985)
Acute oral toxicity study No GLP No guideline followed	Mouse (strain and sex unspecified)	Formic acid (Purity unknown)	Doses and vehicle not reported **Oral (no more info)**	1100 mg/kg bw	REACH Registration dossier (Anonymous 2, 1969)

Table 11. Summary table of human data on acute oral toxicity

Human case reports on accidental and suicidal *oral* exposure to formic acid are available.

Species Sex, No/group	**Route of exposure**	**Test substance**	**Observations**	**Result**	**Reference**
1 male, 27-year-old Case report	Oral	Formic acid 60%	Suicidal ingestion, 45-90 ml (decalcifying agent). Clinical signs: vomiting, abdominal pain	Corrosion of the gastro-intestinal tract, metabolic acidosis,	Westphal F, *et al.* (2001) Fatal intoxication with a

			Blood: pH 6.86, pCO_2 70.4 mmHg, HCO_3 10.6 mmol/l, base deficit -22 mmol/l, initial serum formate level 370.3 µg/ml, haemolysis Autopsy: ulceration of oesophagus, complete necrosis of gastric mucosa, oedema e necrotic areas in deeper tissue layers of stomach, no perforation, coagulated blood in stomach, necrosis of mucosa duodenum. Post-mortem formate concentrations: 855.4 µg/ml (heart blood) 2712 µg/ml (gastric contents) 1128 µg/ml (hemorrhagic fluid abdominal cavity) 3051 µg/ml (bile) 2664 µg/ml (contents small intestine) 442.7 µg/g (liver) 542.3 µg/g (kidney) Within 30 hours after ingestion: corrosion of the gastro-intestinal tract, metabolic acidosis, haemolysis, massive bleeding, hepatic and renal failure, death.	haemolysis, massive bleeding, hepatic and renal failure, death	decalcifying agent containing formic acid. Int. J. Legal Med. 114, 181-185. BPD ID A6.12.2_01
1 female, 39-year-old Case report	Oral	Formic acid 50%	Suicidal ingestion, 200 ml (descaling product). Clinical signs: severe retrosternal and epigastric pain, dyspnea, cyanotic appearance, vomiting blood (2 h after ingestion) Blood: pH 6.87, pCO_2 46.1 mm Hg, HCO_3 8.6 mmol/l, base deficit of -26.4 mmol/l, haemolysis (20 min after admission to hospital) Initial serum formate level 348 µg/ml (7.6 mmol/l), elimination $T_{1/2}$ 2.5 hours Urine: red Gastroscopy: severe lesions oesophagus and stomach, superficial burns duodenum Complications: severe gastrointestinal bleeding, pneumonia, acute tubular necrosis, adult respiratory distress syndrome, peritonitis, sepsis Death: 6 weeks after ingestion	Local: corrosion and massive bleeding, loss of blood pressure Systemic: Severe metabolic acidosis and haemolysis, renal failure Death	Verstraete AG *et al.* (1989). Formic acid poisoning: Case report and in vitro study of the hemolytic activity. Am J Emerg Med 7, 286-290. BPD ID A6.12.2_02 Summary : BPR: Ann II 8.12.2.02
30 males 23 females 16 to 46 year-old Case report	Oral	Formic acid conc. not known	Suicidal ingestion, ≥ 10 ml, (rubber workers) Major complications: Gastro-intestinal: facial burns, ulcerations of oral and pharyngeal mucosa, abdominal pain, contractures and keloid formation of affected skin, oesophagus stricture (16/53 cases) requiring reparative surgery Respiratory system: inhalation pneumonitis (45 of 53 patients) with cough dyspnea, cyanosis, could proceed to respiratory infection and failure	Local: corrosion and massive bleeding, loss of blood pressure Systemic: Severe metabolic acidosis and haemolysis, renal failure Death	Rajan N *et al.* (1985). Formic acid poisoning with suicidal intent: a report of 53 cases. Postgrad. Med. J. 61, 35-36. BPD ID A6.12.2_03 Summary : BPR: Ann II 8.12.2.03

			Vascular hypotension: 17/53 cases Haemolysis, haematuria within few hours of ingestion, rapidly followed by renal failure in severe cases, within a day in less severe cases, in total 20/53 cases Death: 15/53 patients		
1 male 2 females 35, 56, 66 year-old Case report	Oral	Formic acid 40-55%	Suicidal ingestion, estimated volumes 'one mouthful' to 50-100 ml (descaling product) *35-year-old woman, 40% formic acid, 3 mouthfuls:* massive bleeding, haemolysis, died on d14 after shock and massive haematemesis. Ulcerations throughout oesophagus and stomach, tubular necrosis, early thrombosis of the portal vein *66-year-old woman, 55% formic acid, 55 to 100 ml:* massive bleeding, haemolysis, extensive erosion of oesophagus, stomach, duodenum, died on d5 *56-year-old man, mouthful of 55% formic acid:* died on d11 due to circulatory failure	Local: corrosion and massive bleeding, loss of blood pressure Systemic: Severe metabolic acidosis and haemolysis, renal failure Death	Naik RB *et al.* (1980). Ingestion of formic acid-containing agents - report of three fatal cases. Postgrad. Med. J. 56, 451-456. BPD ID A6.12.2_04 Summary : BPR: Ann II 8.12.2.04
male/female <12 years to adult 45 cases Case report	Oral	Formic acid 44 to 60%	Accidental and suicidal ingestion Estimated doses: < 10 g (children) to 200 g (adults) Children: accidental ingestion of low doses (≤ 10 g), reversible oropharyngeal burns in 9 children, no deaths Adults: suicidal ingestion (34/36 cases), accidental ingestion (2/36) 5-30 g: reversible oropharyngeal burns (16); abdominal pain, vomiting, dyspnea, dysphagia (5); hematemesis, pneumonitis, esophageal strictures (2) 30-45 g: intravascular coagulation, acute renal failure, hematemeses, liver impairment, oesophagal strictures 45-200 g: corrosive perforations of the abdominal viscera and gastrointestinal hemorrhage, acute renal failure dose up to 45g: 28/29 patients survived dose 45g-200g: 14/16 patients died	Local: corrosion and massive bleeding, loss of blood pressure Systemic: Severe metabolic acidosis and haemolysis, renal failure Death	Jefferys DB, and Wiseman HM (1980). Formic acid poisoning. Postgrad. Med. J. 56, 761-763.BPD ID A6.12.2_05
male/female children 183 cases Case report	Oral	Formic acid 87 to 96%	Accidental ingestion: only small quantities Vomiting (10/183 children) and visible caustic lesions in mouth and throat (28/183 cases):	Reversible burns of oesophagus	von Muehlendahl KE *et al.* (1978). Local injuries by accidental ingestion of corrosive substances by children. Arch Toxicol 39, 299-

					314. BPD ID A6.12.2_06 Summary : BPR: Ann II 8.12.2.06
Males and females Age: 29.7-55, mean age 42.8 years 302 cases Retrospective study	Oral, dermal, inhalation	formic acid conc. not known	Suicide Mean (SD) quantity consumed: 110 (78) mL The most common symptoms noted at presentation were: vomiting (78.5 %) abdominal pain (56.3% hematemesis (48.3%) respiratory distress (44 %) haematuria (30.1%) oliguria (24.5%) hypotension (24.5%) melena (22.2%) direct corneal injury (0.007%) Mean (SD) pH of all patients was 7.3 and the bicarbonate concentration was 19.2 (5.1) mEd/L. Leucocytosis was seen in 57.5% of the patients; liver enzymes (GOT, GPT) were elevated above normal values in 62.1% of the patients. The effectivity of medical treatment depends largely on the ingested dose and concentration of FA, the time delay after exposure. Low blood pH and bicarbonate concentration reflect the severity. The mortality rate was 35.4%. Bowel perforation, shock, and tracheoesophageal fistula were associated with 100% mortality. A higher blood pH was less likely to result in mortality. Dysphagia was noted in 154 patients, 98 of whom showed oesophageal stricture on evaluation, requiring repeat endoscopic dilatations after discharge. The prevalence of oesophageal stricture among the 195 patients who survived was 50.2%.	Prognosis depends on the exposure, rapid onset of treatment, proper examination, strict treatment regimen to counteract systemic and local effects. Dose is generally high in suicidal ingestion, resulting in high mortality rate (35%) Survivors show sequels of burns and corrosion in mouth and oesophagus Oesophageal stricture seen in 50% of survivors + dysphagia	Dalus D *et al.* (2013) Formic acid poisoning in a tertiary care center in south India : a 2-year retrospective analysis of clinical profile and predictors of mortality. J Emerg Med, v44 no2, 373-380 Summary: BPR: Ann II 8.12.5.01

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

A valid acute oral toxicity rat study is available (male and female Wistar rats, n=5m +5f per dose group) that was conducted according to the OECD TG 401 without deviations (Anonymous 1, 1985).
The animals received single doses of the undiluted test material (Formic acid, 99%) by oral gavage. Dose levels were 501, 631, 794, 1000 mg/kg bw (no control group included). During the 14 day observation period, animals were examined for clinical signs, body weight changes, and mortality. Necropsy was peformed on all animals that died or after sacrifice at the end of the observation period.
Clinical signs were noted 30 minutes after dosing. Symptoms included: unkempt fur, hunched posture, stagger, aggressiveness, dyspnea, sedation and ataxia, lateral and abdominal position, convulsions, bloody noses, blood in urine. At later times hypothermia, body weight loss and pale limbs were additionally noted.

Symptoms subsided and were absent in all animals but one which showed symptoms until the end of the observation period. Both mortality (0, 2, 1, 4/5 in males and 1, 2, 5, 4/5 in females at 501, 631, 794, 1000 mg/kg bw, respectively),seen within one to two days, and decrease in body-weight gain of survivors (56.1, 45.9 28.3 and -3.4 g at 501, 631, 794 and 1000 mg/kg bw, respectively) showed a clear dose-response relationship.

The clinical symptoms and pathological organ lesions (hyperemia of the stomach and intestines, congestion in spleens, mottled livers and kidneys, discoloration of kidneys and pancreas) are largely nonspecific and can be explained primarily by the local corrosive character of formic acid, and by associated secondary systemic effects. There may have been a trend of a higher sensitivity of female animals, but no significant difference between male and female animals was indicated in the report.

The combined oral LD50 value was 730 mg/kg bw (618 (in female) – 863 (in male) mg/kg bw) in this study.

An additional study (registration dossier (study report, Anonymous 2, 1969)), which not followed guideline or not GLP, mentioned a LD50 of 1100 mg/kg bw. This study is poorly reported and the results cannot be verified.

Several case reports report on fatal suicidal ingestion of formic acid (Westphal et al., 2001; Verstraete *et al.*, 1989; Rajan *et al.*, 1985; Naik *et al.*, 1980; Jefferys and Wiseman, 1980; von Muehledahl *et al.*, 1978; Dalus *et al.*, 2013). Due to the corrosivity of formic acid, local effects occur at all dose levels. The amount ingested and the concentration determine the grade and the location of the effects. Therefore, the observations range from moderate burns around the mouth to severe corrosion of the gastro-intestinal tract with destruction of the esophagus, perforation of the stomach, and corrosion of the small intestine together with massive bleeding and systemic toxicity. Systemic toxicity was seen after ingestion of 30 g formic acid or more. Prognosis is poor after massive oral ingestion (>45 to 200 g formic acid); prognosis is moderate after moderate oral ingestion (approx. 30 to 45 g); lesions, but low mortality, are expected in most cases with low amounts ingested (<30g); persistent lesions due to tissue corrosion must be expected in cases with >10 g formic acid ingested. Tissue destruction of the gastrointestinal tract may result in fatal bleeding, septic shock, or stricture which may require surgical treatment. Reversibility of effects was often seen in cases with low amounts ingested (<10 g formic acid).

10.1.2 Comparison with the CLP criteria

According to the criteria of the CLP Regulation, substances should be classified as acute tox. 4, H302 when the oral LD_{50} is between 300 and 2000 mg/kg bw. Formic acid is of moderate toxicity via the oral route when tested in the rat. Oral LD_{50} = 730 mg/kg bw.

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Proposed classification and labelling for formic acid: acute oral Tox. Cat. 4; H302

10.2 Acute toxicity - dermal route

Hazard class not assessed in this dossier.

10.3 Acute toxicity - inhalation route

Also see § 3.3 of the Confidential Annex I to this CLH report.

Table 12. Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, , form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** **LC_{50}**	**Reference**
Comparable to OECD TG 403 GLP: no (not compulsory at the time the study was conducted) Key study Reliability 1	Rat Sprague-Dawley m+f 10/sex/group	Formic acid purity 98% vapour	2.82, 6.60, 8.08, 10.6, 14.7 mg/l (analytical); 4 hours whole body	7.4 mg/l (m+f) Males: 7.3 mg/l Females : 7.5 mg/l Clinical signs (in all treated groups): Closed lids, snout swiping, discharge from the nose and eye, corrosion of nose and eyes, salivation, corneal opacity, loss of pain reflex, dyspnea, respiration sounds, flatulence, apathy, hunched posture, unsteady gait Symptoms persisted until d14 after treatment (except for the 2.82 mg/l group: symptom free at d11) Mortality: within 7 days post exposure (inflated lungs, dilated hearts). BW at d7: dose-dependent decrease	REACH registration dossier, Anonymous 3, 1980
OECD TG 403 Not GLP	Rat / Wistar / both sexes 6 animals	Formic acid (purity unknown)	Saturated atmosphere (nominal saturated concentration : 44168ppm) Duration of exposure : 10min	All animals died Clinical signs : ocular nasal irritation, gasping, increased salivation Pupils of eyes opaque after 3-4min	REACH Registration dossier (Anonymous 4, 1982)
OECD TG 403 Not GLP	Rat / Wistar Both sexes	Formic acid Purity : > 99%	Saturated atmosphere Duration of	Mortality was of 75% after 3min of exposure	REACH Registration dossier

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, , form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
	18 animals	Inhalation (nose only) Vehicle : air	exposure : 3, 10 and 116min	100% after 10min of exposure Most death occurred within 24h after treatment	(Anonymous 5, 1981)

Table 13. Summary table of human data on acute inhalation toxicity

Human case reports on accidental and suicidal inhalation exposure to formic acid are available.

Species Sex, No/group	Route of exposure	Test substance	Observations	Result	Reference
1 male, 39-year-old Case report	Inhalation	Formic acid 98%	Accidental spray (aerosol) into the face with concomitant inhalation (occupational) Clinical signs: facial burns (3% of total body surface), dyspnea Nasopharyngoscopy: mild supraglottic erythema, normal vocal cords Skin: second-degree burns Pulmonary function tests: Vital capacity reduced on d1, recovered largely within 14 days. Complains of dyspnea till d15 <u>Day 1</u> FVC (L): 3.74 (79% predicted) FEV_1 (L): 2.86 (73% predicted) FEV_1/FVC: 76.38 (92% predicted) $FEF_{25\%-75\%}$ (l/sec): 2.32 (56% predicted) <u>Day 15</u> FVC (L): 4.35 (92% predicted) FEV_1 (L): 3.62 (92% predicted) FEV_1/FVC: 83.09 (101% predicted) $FEF_{25\%-75\%}$ (l/sec): 3.82 (92% predicted)	Reversible Pulmonary dysfunction: Reactive Airway Dysfunction Syndrome	Yelon *et al.*, (1996). Formic acid inhalation injury: a case report. J. Burn Care Rehab. 17, 241-242. BPD ID A6.12.2_10 Summary : BPR: Ann II 8.12.2.10
(1) 1 male, 22-year-	inhalation	Fumes from formic acid	Suicide by mixing formic acid with concentrated sulphuric	External chemical	Bakovic M, *et al.* (2015) Suicidal chemistry: combined

old Case report		(85%) and carbon monoxide (concentration not known)	acid in a confined space Death due to CO intoxication; corrosion/irritation of skin, trachea, lungs, stomach due to formic acid fumes.	burns Internal injuries mainly to the respiratory tract. Injury to the oropharyngeal area and trachea, pulmonary edema, and subpleural petechiae Complete lack of the respiratory epithelium of the trachea, edema of mucosa, and submucosa of the trachea, thrombi, and hemolysis inside the small vessels of the trachea, pulmonary edema, hemolysis, and thrombosis in the lung vessels	intoxication with carbon monoxide and formic acid. Int. J Legal Med FA_BPR_Ann_II_8_12_2_11
(2)1 male, 26-year-old Case report	inhalation	Fumes from formic acid (concentration not reported, amount 950 ml) and carbon monoxide (concentration not known)	Suicide by mixing formic acid with concentrated sulphuric acid in a confined space. Death. The body showed pronounce bright pink-red lividity. The autopsy was otherwise unremarkable.	See observations, no further info on formic acid effects	Lin PT and Dunn (2014) Suicidal Carbon Monoxide Poisoning by Combining Formic Acid and Sulfuric Acid Within a Confined Space. J. Forensic Science, January 201, Vol 59, No. 1 FA_BPR_Ann_II_8_12_2_12
(3)1 male, 26-year-old; 1male, 53-year-old, 1 female, 53-year-old Case report	inhalation	Fumes from formic acid (98-100%) and carbon monoxide (concentration not known)	Suicide by mixing formic acid with concentrated sulphuric acid in a confined space 26-year-old: death. No autopsy 53-year-old father: coma, hypoxemia, metabolic acidosis, and a carboxyhemoglobin level of 45.8%. Developed acute respiratory distress syndrome. Transient ulceration of vocal cords. 53-year-old mother: dizziness, headache, carboxyhemoglobin level of 23.0%	See observations. In addition to the toxicities of carbon monoxide, concomitant inhalation of formic acid fumes can cause severe lung injury, which may complicate the management	Yang CC et *al.* (2008) Formic acid: A rare but deadly source of carbon monoxide poisoning. Clinical Toxicology, 46:4, 287-289 FA_BPR_Ann_II_8_12_2_13

				of carbon monoxide poisoning.	

Table 14. Summary table of other studies relevant for acute inhalation toxicity

Species Sex, No/group	**Method**	**Test substance**	**Route dose levels duration of exposure**	**Result**	**Reversi-bility**	**Reference**
Rat, Fischer 344/N, m + f 10/sex Supportive data Rel 1	In accordance with OECD TG 413 (Subchronic inhalation toxicity : 90-day study)	Formic acid purity 95%	0, 15, 30, 61, 122, 244 mg/m^3 6h/d, 5d/wk, 13 weeks Vapour, whole body	No clinical signs Local effects: nasal irritation, squamous metaplasia of the respiratory epithelium, olfactory degeneration, severity minimal to mild. Respiratory epithelium squamous metaplasia: mg/m³ 0 15 30 61 122 244 male 0 0 0 0 0 9 female 0 0 0 0 0 6 Olfactory epithelium degeneration: minimal to mild mg/m³ 0 15 30 61 122 244 male 0 0 0 0 0 9 female 0 0 0 1 1 5	NOAEL$_{local}$: 30 mg/m^3 LOAEL$_{local}$: 61 mg/m^3	Thompson M (1992) NTP Technical Report on Toxicity Studies of Formic Acid. Administered by inhalation to F344/N rats and B6C3F$_1$ mice. US Department of Health and Human Services, Public Health Service, National Institutes of Health NIH, Toxicity Report Series No: 19, NIH Publication No: 92-3342, July 1992 (published). BPD ID A6.4.3_01 Summary: BPR: Ann II 8.9.2.03
Mice B6C3F$_1$ m + f 10/sex Supportive data Rel 1	In accordance with OECD TG 413 (Subchronic inhalation toxicity : 90-day study)	Formic acid purity 95%	0, 15, 30, 61, 122, 244 mg/m^3 6h/d, 5d/wk, 13 weeks Vapour, whole body	No clinical signs Local effects: nasal irritation, olfactory degeneration, severity minimal but dose-related. Olfactory epithelium degeneration: minimal mg/m³ 0 15 30 61 122 244 male 0 0 0 0 0	NOAEL$_{local}$: 61 mg/m^3 LOAEL$_{local}$: 122 mg/m^3	BPD ID A6.4.3_02 Thompson, 1992 (see above)

				2 TG female 0 0 0 0 2 5		

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

In a rat inhalation study, male and female Wistar rats (10 per sex and dose level) were exposed in a whole body exposure chamber in groups of 5 to formic acid vapours at concentrations of 2820, 6600, 8080, 10600, 14700 mg/m³ (analytical) (Zeller & Klimisch, 1980). The exposure period was 4 hours. The concentration levels were measured using IR photometry. The observation period was 14 days.

Clinical signs (Closed lids, snout swiping, discharge from nose and eye, corrosion of nose and eyes, salivation, corneal opacity, loss of pain reflex, dyspnea, respiration sounds, flatulence, apathy, hunched posture, unsteady gait) were noted in al treated groups and persisted until termination except the animals at 2.82 mg/L which were free of symptoms on day 11. Deaths occured within 7 days post treatment. Pathology revealed heart dilatation, hyperemia, and inflated lungs. Further, corneal opacity and corrosion of the dorsal nose was seen in some cases. Body weights were dose-dependently depressed in all survivors on day 7. Body weight gain was noted in the second week after treatment. Animals of the groups at 8.08 mg/l did not reach the initial weight.

Clinical signs indicated corrosive properties of the test substance, evidenced by the occurrence of corneal opacity and corrosion of the dorsal nose in some cases. Inflated lungs and dilated hearts were seen in animals that died; gross pathology revealed no changes in animals sacrificed at termination. The LC50 was 7.4 mg/L (m+f) in this study (males: 7.3 mg/L; females 7.5 mg/L).

Evidence of respiratory tract irritation is found in the histopathological data of the nasal cavity of the repeated dose inhalation toxicity studies performed with formic acid vapours (13-week inhalation, rat, mouse). Testing was conducted at concentrations of 0, 15, 30, 61, 122, 244 mg/m³ in rats and mice (Thompson, 1992). Both in the rat and the mouse, the inhalation of formic acid did not result in clinical effects. In the rat, microscopic changes occurred in the respiratory and olfactory epithelium of the nose. In the mouse, microscopic changes were limited to the degeneration of the olfactory epithelium of the nose. Both in the rat and the mouse the upper respiratory tract was the major target for toxicity.

Human case reports on acute accidental or suicidal inhalation exposure are rather rare. Besides local effects and respiratory tract irritation, patients suffered and recovered rapidly from metabolic acidosis following accidental inhalation (Yelon *et al.*, 1996). Inhalation of fumes created by mixing formic acid with concentrated sulphuric acid leads to injuries to the respiratory tract from formic acid, and deadly carbon monoxide intoxication (Bakovic *et al.*, 1996; Lin & Dunn, 2014; Yang *et al.*, 2008).

10.3.2 Comparison with the CLP criteria

According to the criteria of the CLP Regulation, substances should be classified as acute tox. Cat. 3, H331 when the inhalation (vapour) LC_{50} is between 2,0 and 10,0 mg/l. In the Zeller H and Klimisch H-J (1980) study, the LC is of 7.4 mg/l and thus fulfilled the criteria of the category 3. Additionally, the EUH071 phrase is proposed, as the corrosive properties determine the toxicity of formic acid (CLP Regulation Annex II, point 1.2.6).

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Proposed classification and labelling for formic acid: acute inhalation Tox. Cat. 3 (vapour); H331.

Since data are available that indicate that the mechanism of toxicity is corrosivity, formic acid shall also be labelled as EUH071: 'corrosive to the respiratory tract'.

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute oral toxicity

The DS presented animal and human data. They proposed classification as Acute Tox. 4 based on an LD_{50} of 730 mg/kg bw from an acute oral toxicity study in rats.

Acute inhalation toxicity

The DS proposed classification as Acute Tox. 3 based on a 4-hour LC_{50} of 7.4 mg/l (vapours) from an acute inhalation toxicity study in rats. They additionally proposed labelling with EUH071 as the toxicity of formic acid was considered to be caused by its corrosive properties.

Comments received during consultation

Two MSCAs supported the DS's proposal. One of them recommended adding the respective ATE values.

A manufacturer (BASF) asked to raise the LC_{50} value of the key acute inhalation toxicity study from 7.4 mg/l to 7.85 mg/l based on an amendment of the study report (see 'additional key elements' below). The DS disagreed.

One individual proposed H300 and H330 due to the experience of formic acid causing serious skin burns.

Additional key elements

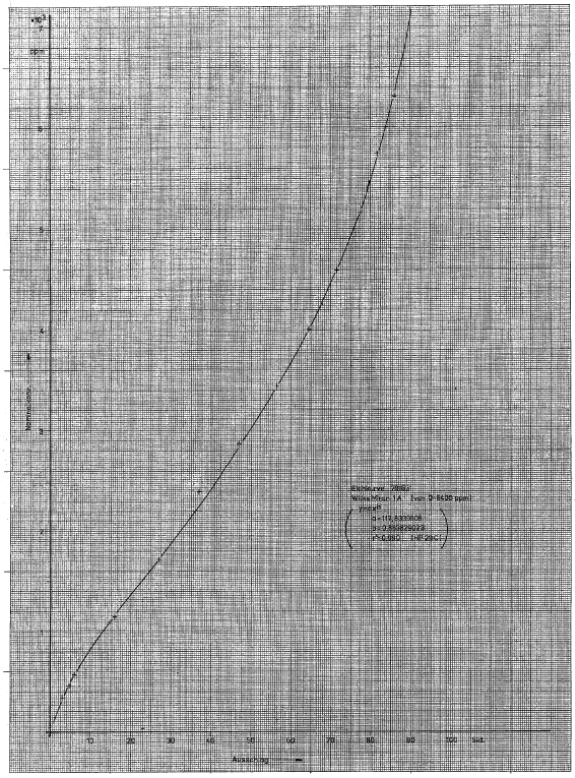
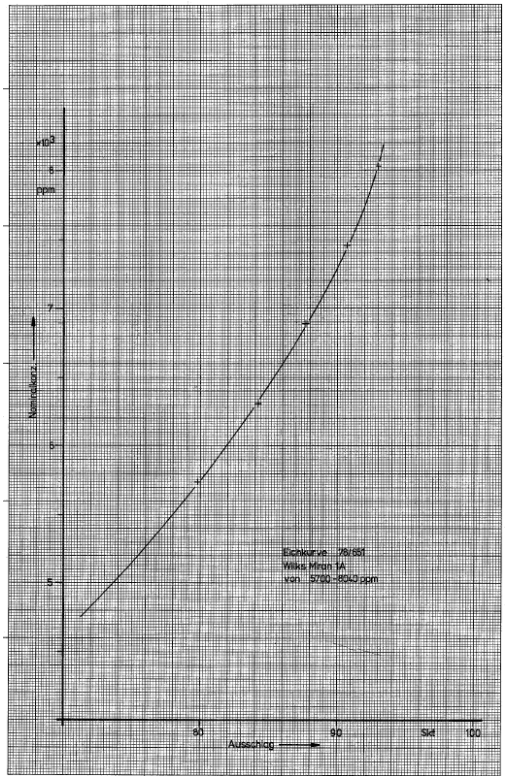
Re-analysis of the key acute inhalation toxicity study in rats (1980)

The original study conducted in a BASF laboratory in 1980 reported an LC_{50} for combined sexes of 7.4 mg/l. In 2014 this laboratory issued Amendment no. 1 (the authors were different from those of the initial report), changing the LC_{50} value to 7.85 mg/l. The reasons for this change are not fully explained in the amendment itself but are elaborated in a position paper (2021) submitted by BASF in the third-party consultation. Industry also submitted raw data from the 1980 study. The documentation has been analysed by RAC and the outcome of this analysis is presented below.

In the 1980 study the rats were exposed to formic acid in the form of a vapour. Concentration of formic acid in the breathing zone of the animals was determined by infrared spectroscopy. In order to convert the signal from the IR analyser to a concentration in ppm, two calibrations were prepared; one (calibration 1) covering concentrations from 0.6 to 11.9 mg/l and the other (calibration 2) from 10.8 to 15.1 mg/l. Data from both calibrations are shown in the following table.

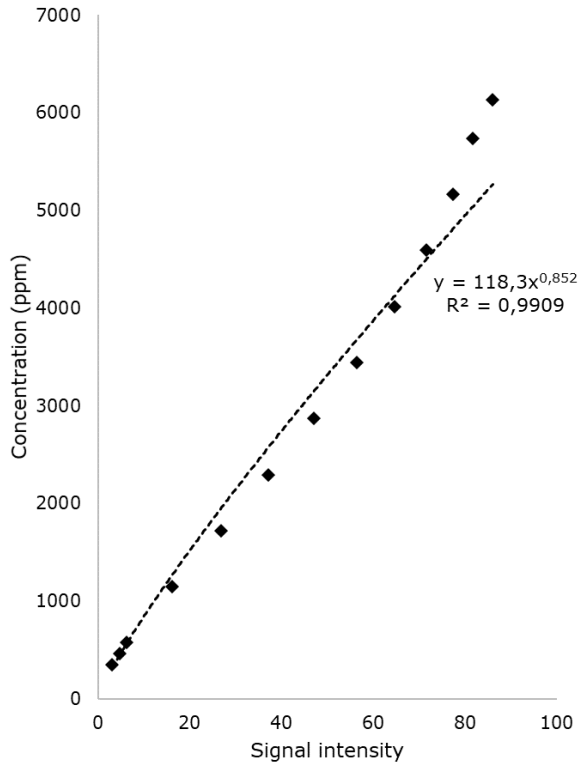
Calibration 1			Calibration 2		
Concentration		Signal intensity	Concentration		Signal intensity
ppm	mg/l		ppm	mg/l	
344	0.6	3.1			
459	0.9	4.7			
574	1.1	6.3			
1148	2.2	16.2			
1722	3.2	26.8			
2295	4.3	37.2			
2869	5.4	47.0			
3443	6.5	56.5			
4017	7.6	64.6			
4591	8.6	71.6			
5164	9.7	77.4			
5738	10.8	81.8	5738	10.8	79.8
6312	11.9	86.1	6312	11.9	84.2
			6886	13.0	87.7
			7459	14.0	90.7
			8033	15.1	93.0

The data points from the tables were plotted on millimetre paper and calibration curves were drawn.

Calibration 1	Calibration 2
	

The millimetre paper with calibration 1 additionally contains, in brackets on the right-hand side, the following equation: $y = ax^b$, $a = 117.8339908$, $b = 0.853829023$, $r^2 = 0.990$. Such a power function, however, shows a rather poor fit, as can be seen in the graph below (created by RAC), and this function was not used by the study authors. The original study authors used the curve drawn in the millimetre paper above; RAC agrees with this choice.

Calibration 1: regression mentioned in the graph but not used by the authors in 1980



Signal intensities at the five exposure concentrations were measured and converted to concentrations using the two graphs on millimetre papers. RAC confirms that the concentrations were read from the graphs correctly by the original authors. The signal intensity of 81.0 falls into the ranges of both calibrations. In 1980 the laboratory used calibration 1, leading to a slightly lower concentration (10.6 mg/l) than calibration 2 (11.1 mg/l). This choice is considered appropriate as it leads to a lower (more conservative) LC_{50} value. The concentrations used for the calculation of the original LC_{50} are shown in bold.

Signal intensity	Concentration from Calibration 1		Concentration from Calibration 2	
	ppm	mg/l	ppm	mg/l
22.3	1500	2.8		
57.1	3480	6.6		
68.0	4280	8.1		
81.0	5600	10.6	(5880)	(11.1)
91.9			7720	14.7

The amendment (2014) and the industry position paper (2021) present three main claims:

1. Industry claims that the signal intensity of 81.0 does not correspond to 5600 ppm and the reading from the calibration curves was incorrect. RAC however found

that the original reading was correct; the controversy lies in the choice of the calibration (calibration 1 vs 2).

2. Industry claims the ppm values for calibration 1 should have been determined from the power function $y = 117.8 \cdot x^{0.8538}$ rather than from the curve on the millimetre paper. However, visual comparison of both curves shows that the curve drawn on the millimetre paper has a much better fit than the function.

3. Industry pointed out the difference in signal intensities between calibration 1 and calibration 2 for the two common points, i.e. 5738 and 6312 ppm. The signal intensities in calibration 2 were by about 2 units lower than in calibration 1 (79.8 vs 81.8, 84.2 vs 86.1). They claim the signal intensities at the 3 lowest exposure concentrations should be increased by 2. However, industry has not provided any argument as to why one calibration should be better than the other. RAC is of the view that both calibrations should be taken as they are and used for their respective calibration ranges. Where the two ranges overlap, the more conservative option should be chosen, as was also done by the original authors in 1980.

Application of the new industry proposals described in points (2) and (3) would lead to slightly higher exposure concentrations, see the table below. To further support their case, the laboratory rebuilt the original equipment and provided new measurements, the concentrations from this technical trial are also shown in the table.

Concentrations (mg/l)				Mortality	
Nominal, 1980 and 2014	Analytical, 1980, original report	Analytical 1980, amendment 2014	Analytical, technical trial 2014	males	females
4.0	2.8	3.4	3.2	0/10	0/10
8.5	6.6	7.3	7.1	2/10	1/10
10.6	8.1	8.4	9.0	8/10	8/10
13.4	10.6	11.1	11.1	10/10	10/10
17.9	14.7	14.7	15.8	10/10	10/10

RAC concludes that the original study report from 1980 is correct. The data manipulations proposed in the amendment from 2014 are unjustified and the 2014 amendment should not be accepted.

Assessment and comparison with the classification criteria

Acute oral toxicity

The key information consists of a guideline-compliant acute oral toxicity study in rats (1985) and human case reports. The CLH report further mentions an LD_{50} of 1100 mg/kg bw from a poorly reported mouse study (1969).

Acute oral toxicity study in rats (1985)

Wistar rats (5/sex/group) were dosed with undiluted formic acid (purity 99%) via gavage at dose levels of 501, 631, 794 and 1000 mg/kg bw. Post-exposure observation period was 14 days.

LD_{50} was 863 mg/kg bw for males, 618 mg/kg bw for females and 730 mg/kg bw for combined sexes. Mortality rates are presented in the following table. Females appear slightly more sensitive than males.

Mortality in the acute oral toxicity study (1985)		
Dose (mg/kg bw)	Mortality	
	males	females
501	0/5	1/5
631	2/5	2/5
794	1/5	5/5
1000	4/5	4/5

Clinical signs included hunched posture, dyspnea, sedation, convulsions, blood in urine, hypothermia, body weight loss and pale limbs. Gross pathology of decedents showed hyperemia of the stomach and intestines.

Human case reports

Table 11 of the CLH report summarises several case reports and reviews. Of particular relevance for classification are well-described fatal cases where the ingested amount was known at least approximately; these are listed in the table below. All four cases in the table had a fatal outcome despite intense treatment (e.g. ventilation, transfusion, dialysis). The estimated dose ranged between 200 and 1700 mg/kg bw.

Human case reports		
Reference	Subject; ingested material, amount; dose of formic acid (estimated by RAC)	Brief description of the case (in all cases medical treatment, not described in the table)
Verstraete *et al.* (1989)	39-year old female Approx. 200 ml of a descaling product (pH 1.97) containing 50% formic acid Ca. 1700 mg/kg bw	Main findings: pain, vomiting of blood, shock, severe metabolic acidosis, hemolysis, severe lesions of the esophagus and stomach, severe gastrointestinal bleeding, pneumonia, acute tubular necrosis, respiratory distress syndrome, peritonitis, sepsis Died 6 weeks after admission in multiorgan failure Pre-existing conditions: Cushing syndrome with hypertension and diabetes
Naik *et al.* (1980), case 1	35-year old female 3 mouthfuls of a 40% formic acid solution	Main findings: vomiting of blood, massive bleeding per rectum, abdominal pain, clotting defect, hemolysis, profound metabolic acidosis, anuria,

	(bath stain remover) Ca. 500 mg/kg bw	pulmonary complications, ulceration throughout the esophagus and stomach, acute tubular necrosis Died on day 14 after shock and massive vomiting of blood (blood-filled stomach and small bowel)
Naik *et al.* (1980), case 2	66-year old female 50-100 ml of kettle descaler containing 55% formic acid Ca. 500-1000 mg/kg bw	Main findings: vomiting, shock, tachycardia, ulceration of mouth and pharynx, profound metabolic acidosis, aspiration pneumonia, cardiac and respiratory arrest, pulmonary edema, hemolysis, gross clotting defect, hematuria, acute renal failure and anuria, hypotension, extensive erosion of the esophagus, stomach and duodenum Died 5 days after admission Pre-existing conditions: ischemic heart disease, brain stem vascular insufficiency
Naik *et al.* (1980), case 3	56-year old male A mouthful of kettle descaler containing 55% formic acid Ca. 200 mg/kg bw	Main findings: pain, vomiting, tachycardia, hypotension, cyanosis, anuria, sloughing of the mucosa of the soft palate and oropharynx, acute respiratory distress, intravascular coagulation, tubular necrosis Died on day 11 due to circulatory failure Pre-existing conditions: asbestosis, duodenal ulceration

In addition, Jefferys and Wiseman (1980) briefly reviewed 45 cases of formic acid poisoning from ingestion of descaling agents (formic acid content 44-60%). Ingestion of 5 to 30 g of formic acid produced no deaths, and the majority of subjects developed minor burns only. Ingestion of 30-45 g produced more serious effects; of the 6 patients recorded, one died, and the rest developed serious conditions such as acute renal failure, hematemesis, intravascular conditions and oesophageal strictures. Ingestion of 45 to 200 g of formic acid was recorded from 16 patients, of whom 14 died, the majority from corrosive perforations of the abdominal viscera, gastrointestinal haemorrhage or acute renal failure. The consumption of 60 g or more of formic acid (approx. 100 ml of the descaling fluid) produced death in all cases. 45 g of formic acid corresponds to ca. 700 mg/kg bw if assuming a body weight of 65 kg.

The available human information indicates that doses around 500 mg/kg bw may be lethal in humans despite treatment.

Conclusion

Both animal and human data are consistent with Category 4 (300 mg/kg bw < ATE ≤ 2000 mg/kg bw). The lowest animal LD_{50} is 620 mg/kg bw (rounded-off) from females in the rat study, mortality started at 500 mg/kg bw/d. Human data indicate a similar threshold for mortality but a somewhat higher sensitivity cannot be excluded as all the cases underwent intense medical treatment (such as intravascular bicarbonate, dialysis, ventilation). Due to this uncertainty about human sensitivity, RAC prefers the somewhat lower converted ATE of 500 mg/kg bw (CLP, Annex I, Table 3.1.2).

In conclusion, RAC proposes classification as **Acute Tox. 4; H302** with an **ATE** of **500 mg/kg bw**.

Acute inhalation toxicity

The key study is a guideline-compliant acute inhalation toxicity study in rats (1980). The DS further presented non-guideline acute studies, repeated dose studies and human data.

Acute inhalation toxicity study in rats (1980)

Sprague-Dawley rats (10/sex/group) were exposed (whole body) to vapours of formic acid for 4 hours at concentrations of 2.8, 6.6, 8.1, 10.6 and 14.7 mg/l. Post-exposure observation period was 14 days.

RAC notes the Amendment no. 1 to the study report, issued in 2014, changing the exposure concentrations and the LC_{50}. However, after examination of the documentation RAC concluded that this amendment is unjustified and should not be accepted (for details see 'additional key elements'). The original study report from 1980 remains valid.

LC_{50} was 7.3 mg/l for males, 7.5 mg/l for females and 7.4 mg/l for combined sexes. Mortality rates are presented in the following table. Since there was no significant difference in susceptibility between sexes, the combined LC_{50} of 7.4 mg/l is considered to represent an appropriate overall ATE from this study.

Mortality in the acute inhalation toxicity study (1980)

Concentration (mg/l)	Mortality	
	males	females
2.8	0/10	0/10
6.6	2/10	1/10
8.1	8/10	8/10
10.6	10/10	10/10
14.7	10/10	10/10

Clinical signs included discharge from nose and eye, corneal opacity, loss of pain reflex, dyspnea, respiration sounds, hunched posture and unsteady gait. Pathology of decedents showed corneal opacity, corrosion of the dorsal nose, inflated lungs and dilated hearts.

Other information

In two non-standard acute studies (registration dossier, studies dated 1981 and 1982) rats were exposed to a saturated atmosphere of formic acid (concentration presumably in the range of 80 mg/l) for 3 to 116 min. All animals exposed for ≥ 10 minutes died. These studies do not provide information useful for classification mainly because they used a single very high and poorly defined concentration.

In a set of NTP studies (Thompson, 1992) rats and mice were exposed for formic acid vapours for 2 or 13 weeks (6 hours/day, 5 days/week). The top concentration in the 2-week studies was 500 ppm (0.94 mg/l), at this concentration all 10 mice died within the first week and 4 out of 10 rats died on day 10. Clinical signs included nasal discharge, laboured breathing and corneal opacity. Histopathological examination of the respiratory tract revealed necrosis of the nasal epithelium in most of the top concentration animals of

both species, mice additionally showed changes in the larynx, pharynx and trachea. The top concentration in the 13-week studies was 128 ppm (0.24 mg/l), histopathological changes were minimal and limited to the nasal cavity. Overall, these studies showed (mainly upper) respiratory tract irritation after repeated exposure.

The DS further summarised several reports of suicidal attempts where the subjects mixed formic acid and sulphuric acid to generate toxic carbon monoxide. The involvement of CO and lack of exposure quantification precludes their use for classification. Nevertheless, the respiratory tract injuries (including lack of the respiratory epithelium of the trachea, pulmonary edema) in the case described by Bakovic *et al.* (2015) were attributed to formic acid and could be used as supporting evidence for EUH071.

Conclusion

The 4-hour LC_{50} of 7.4 mg/l from a guideline-compliant rat study corresponds to Category 3 (2.0 mg/l < ATE ≤ 10.0 mg/l). RAC agrees with the DS's proposal of **Acute Tox. 3; H331** with an **ATE** of **7.4 mg/l (vapours)** based on the guideline-compliant acute inhalation toxicity study.

The substance is classified as corrosive to the skin. While the available animal data indicate irritation of the respiratory tract after inhalation of formic acid vapours, it is not clear whether the deaths were mainly due to local effects. Still, formic acid can also be inhaled in the form of aerosol, which would most likely lead to serious respiratory tract corrosion. Therefore, RAC agrees to add **EUH071**.

10.4 Skin corrosion/irritation

Existing harmonised classification; hazard class not assessed in this dossier.

10.5 Serious eye damage/eye irritation

10.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

No eye irritation study reports are available on formic acid itself. Due to the inherent properties of formic acid (strong acid), the substance has been classified as corrosive (C, R 35) in the EU (12th ATP to Directive 67/548/EEC). The European Union concludes that a similar effect (corrosivity) is expected for the eyes, and that no further testing is required. Corrosivity to the eyes may thus be assumed from the low pH-value of formic acid. Specific concentration limits for preparations have been set by the European Union. No caustic effect is assumed by concentrations below 10% (R36, irritant to the eye).

10.5.2 Comparison with the CLP criteria

N.A.

10.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

The current GHS classification is Skin corrosive cat. 1A, H314 at C≥90%, and 1B, H314 at 10% ≤C<90%.

According to the CLP regulation Annex I point 3.3.2.3, skin corrosive substances shall be considered as leading to serious damage to the eyes as well (Category 1).

In accordance with the footnote to Table 3.3.5 of the CLP regulation, formic acid at concentrations requiring classification as skin corrosion 1A or 1B (C≥10%) need not be labelled with H318.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

No test data are presented in the CLH report. The substance has a harmonised classification as corrosive to the skin with an SCL of ≥ 10% (more specifically, Skin Corr. 1A at C ≥ 90%, Skin Corr. 1B at 10% ≤ C < 90%). According to the CLP (Annex I, 3.3.2.2.2), skin corrosive substances shall be considered as leading to serious eye damage (Category 1). Therefore, the DS proposes to add a classification as Eye Dam. 1 with an SCL of ≥ 10%.

Comments received during consultation

One MSCA supported the DS's proposal.

Assessment and comparison with the classification criteria

Classification as Eye Irrit. 2 is already part of the Annex VI entry with SCLs identical to those for Skin Irrit. 2, that is 2% ≤ C < 10%. Only a skin corrosion classification is included in the current entry with an SCL of ≥ 10%, obviously because in the past, when a substance was classified as corrosive, the eye hazard was considered to be implicit. According to the current interpretation of the CLP regulation (Annex I, 3.3.2.2.2), Eye Dam. 1 should be part of the classification in addition to the classification for skin corrosion, but H318 is omitted from the labelling (CLP, Annex III).

In conclusion, RAC agrees with the DS's proposal to add **Eye Dam. 1; H318** with an **SCL** of **≥ 10%**.

10.6 Respiratory sensitisation

Hazard class not assessed in this dossier.

10.7 Skin sensitisation

Hazard class not assessed in this dossier.

10.8 Germ cell mutagenicity

Hazard class not assessed in this dossier

10.9 Carcinogenicity

Hazard class not assessed in this dossier

10.10 Reproductive toxicity

Hazard class not assessed in this dossier

10.11 Specific target organ toxicity-single exposure

Hazard class not assessed in this dossier

10.12 Specific target organ toxicity-repeated exposure

Hazard class not assessed in this dossier

10.13 Aspiration hazard

Hazard class not assessed in this dossier

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Parameter not assessed in this dossier.

11.2 Environmental fate and other relevant information

Parameter not assessed in this dossier.

11.3 Bioaccumulation

Parameter not assessed in this dossier.

11.4 Acute aquatic hazard

Hazard class not assessed in this dossier.

11.5 Long-term aquatic hazard

Hazard class not assessed in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

Hazard class not assessed in this dossier

13 ADDITIONAL LABELLING

Not assessed in this dossier

14 REFERENCES

Anonymous 1, 1985: see Confidential Annex I to CLH report

Anonymous 2, 1969: see Confidential Annex I to CLH report

Anonymous 3, 1980: see Confidential Annex I to CLH report

Anonymous 4, 1996: see Confidential Annex I to CLH report

Anonymous 5, 1981: see Confidential Annex I to CLH report

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15 ANNEXES

Confidential ANNEX I to CLH report