Committee for Risk Assessment

RAC

Annex 1

Background document

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

Formaldehyde …%

EC Number: 200-001-8
CAS Number: 50-00-0

CLH-O-0000007130-88-01/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:

Formaldehyde ...%

EC Number: **200-001-8**

CAS Number: **50-00-0**

Index Number: **605-001-00-5**

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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)	Formaldehyde
Other names (usual name, trade name, abbreviation)	formaldehyde gas, formaldehyde solution, methanal, formic aldehyde, methylene oxide, oxymethylene, methylaldehyde, oxomethane, formol, formalin, formalith, methylaldehyde, morbicid, oxomethane, paraform.
EC number (if available and appropriate)	200-001-8
EC name (if available and appropriate)	Formaldehyde
CAS number (if available)	50-00-0
Other identity code (if available)	-
Molecular formula	CH_2O
Structural formula	
SMILES notation (if available)	C=O
Molecular weight or molecular weight range	30.026 g/mol
Degree of purity (%) (if relevant for the entry in Annex VI)	100 % as gas Up to 55 % in aqueous 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)
Formaldehyde;CAS No.: 50-00-0	25 – 55	No information	

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
Formic acid; CAS No.: 64-18-6	≤ 0.04	Skin Corr. 1A – H314 SCL: C ≥ 90 % : Skin Corr. 1A; H314 10 % ≤ C < 90 % : Skin Corr. 1B; H314 2 % ≤ C < 10 % : Skin Irrit. 2; H315, Eye Irrit. 2; H319		No

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
Methanol; CAS No.:67-56-1	stabiliser	< 7	Flam. Liq. 2; H225 Acute Tox. 3 *; H331 Acute Tox. 3 *; H311 Acute Tox. 3 *; H301 STOT SE 1; 370** SCL: C ≥ 10 % : STOT SE 1; H370 3 % ≤ C < 10 % : STOT SE 2; H371		No

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5: Proposed harmonised classification and labelling of formaldehyde according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	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	605-001-00-5	formaldehyde …%	200-001-8	50-00-0	Acute Tox. 3* Acute Tox. 3* Acute Tox. 3* Skin Corr. 1B Skin Sens. 1 Muta. 2 Carc. 1B	H331 H311 H301 H314 H317 H341 H350	GHS05 GHS06 GHS08 Dgr	H331 H311 H301 H314 H317 H341 H350	-	Skin Corr. 1B; H314: C ≥25 % Skin Irrit. 2; H315: 5 % ≤C < 25 % Eye Irrit. 2; H319: 5 % ≤ C <25 % STOT SE 3; H335: C ≥ 5 % Skin Sens. 1; H317: C ≥ 0.2 %	*, B, D
Dossier submitters proposal					Modify: Flam. Gas 1B Acute Tox. 2 Acute Tox. 3 Acute Tox. 4 Skin Sens. 1A	Modify H221 H330 H311 H302 H317	GHS02 GHS05 GHS06 GHS08 Dgr	Modify: H221 H330 H311 H302 H317	Add: EUH071	<u>Add:</u> inhalation: ATE = 490 ppm (gases) dermal: ATE = 270 mg/kg bw Oral: ATE = 640 mg/kg bw <u>Modify:</u> Skin Sens. 1A; H317: C ≥ 0.2 %	Remove: *, D Add: F, T, 5
Resulting Annex VI entry if agreed by RAC and COM					Flam. Gas 1B Carc. 1B Muta. 2 Acute Tox. 2 Acute Tox. 3 Acute Tox. 4 Skin Corr. 1B Skin Sens. 1A	H221 H350 H341 H330 H311 H302 H314 H317	GHS02 GHS05 GHS06 GHS08 Dgr	H221 H350 H341 H330 H311 H302 H314 H317	EUH071	inhalation: ATE = 490 ppm (gases) dermal: ATE = 270 mg/kg bw Oral: ATE = 640 mg/kg bw STOT SE 3; H335: C ≥ 5 % Skin Corr. 1B; H314: C ≥ 25 % Skin Irrit. 2; H315: 5 % ≤ C < 25 % Eye Irrit. 2; H319: 5 % ≤ C < 25 %	B, F, T, 5

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

Hazard class	Reason for no classification	Within the scope of the general consultation
Explosives	*Data conclusive but not sufficient for classification*	**Yes**
Flammable gases	*Harmonised classification proposed*	**Yes**
Oxidising gases	*Data conclusive but not sufficient for classification*	**Yes**
Gases under pressure	*Data conclusive but not sufficient for classification*	**Yes**
Flammable liquids	*Data conclusive but not sufficient for classification*	**Yes**
Flammable solids	*Hazard class not applicable (gas/liquid)*	No
Self-reactive substances	*Data conclusive but not sufficient for classification*	**Yes**
Pyrophoric liquids		
Pyrophoric solids	*Hazard class not applicable (gas/liquid)*	No
Self-heating substances	*Data conclusive but not sufficient for classification*	**Yes**
Substances which in contact with water emit flammable gases	*Data conclusive but not sufficient for classification*	**Yes**
Oxidising liquids		
Oxidising solids	*Hazard class not applicable (gas/liquid)*	No
Organic peroxides	*Data conclusive but not sufficient for classification*	**Yes**
Corrosive to metals	*Data conclusive but not sufficient for classification*	**Yes**
Acute toxicity via oral route	*Harmonised classification proposed*	**Yes**
Acute toxicity via dermal route		
Acute toxicity via inhalation route		
Skin corrosion/irritation	*Hazard class not assessed in this dossier*	No
Serious eye damage/eye irritation		
Respiratory sensitisation		
Skin sensitisation	*Harmonised classification proposed*	**Yes**
Germ cell mutagenicity	*Hazard class not assessed in this dossier*	No
Carcinogenicity		
Reproductive toxicity		

Hazard class	Reason for no classification	Within the scope of the general consultation
Specific target organ toxicity-single exposure		
Specific target organ toxicity-repeated exposure		
Aspiration hazard		
Hazardous to the aquatic environment		
Hazardous to the ozone layer		

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

RAC general comment

Formaldehyde is produced industrially by catalytic oxidation of methanol. Pure formaldehyde is a colourless gas (boiling point −19 °C) with a pungent odour. Gaseous formaldehyde tends to polymerize at room temperature and normal pressure. Formaldehyde gas is flammable and the lower flammability limit is 7%.

Formaldehyde is not marketed as a gas and there is no Annex VI entry for gaseous formaldehyde. The current Annex VI entry reads "formaldehyde …%" and covers commercial aqueous solutions of formaldehyde known as formalin. Formalin is typically a saturated formaldehyde solution in water (37-40% by weight) containing (residual) methanol as a polymerization inhibitor and small amounts of formic acid as an impurity (oxidation product). In aqueous solutions formaldehyde exists predominantly as methylene glycol and its oligomers, but the polymerization slowly proceeds further to form poorly soluble paraformaldehyde (up to ≈100 monomer units) if methanol (stabiliser) is not present. Methanol concentrations in undiluted formalin range from <1% to 15%.

Formaldehyde is used for example as a preservative, disinfectant, in production of resins and adhesives, and can be present in many products including cosmetics, textiles and furniture. It is a common air pollutant as well as an endogenous substance in humans.

The current CLH proposal was triggered by the assessment of formaldehyde as a biocidal active substance. The reference specification under the Biocidal Products Regulation (Reg. 528/2012) was set at 22-55.5% formaldehyde in water and methanol content of ≤ 7% (Reg. 2020/1763; minimum purity of 87.5% with regard to formaldehyde translates into methanol concentration of ≤ 7%). During the CLH process one manufacturer clarified that the REACH registration dossier considers 30-60% solutions of formaldehyde in water with up to 3% methanol. The DS replied that they had checked that the classification of formaldehyde should not be influenced by a methanol content of up to 7% in an aqueous formaldehyde solution of 25-60% for toxicological and ecotoxicological endpoints. RAC considers the DS statement valid at least for the hazard classes evaluated in the current CLH process (physical hazards, acute toxicity, skin sensitisation).

RAC is however of the view that the Annex VI entry should cover the whole range of marketed formalin solutions, some of which have a methanol content up to 15%. This is proposed to be covered by taddition of Note F (cited below), which is particularly relevant for the hazard classes of flammability and STOT SE (the latter not being part of the current proposal).

"Note F: This substance may contain a stabiliser. If the stabiliser changes the hazardous properties of the substance, as indicated by the classification in Part 3, classification and labelling should be provided in accordance with the rules for classification and labelling of hazardous mixtures."

Marketed formaldehyde solutions not only "may" contain a stabiliser, they normally do contain one. This is specified in Note D (cited below), which is already part of the current Annex VI entry.

"Note D: Certain substances which are susceptible to spontaneous polymerisation or decomposition are generally placed on the market in a stabilised form. It is in this form that they are listed in Part 3. However, such substances are sometimes placed on the market in a non-stabilised form. In this case, the supplier must state on the label the name of the substance followed by the words 'non-stabilised'."

The DS proposed to remove Note D without providing a justification. In the absence of a reason for doing so, RAC does not support the proposed change and is of the view that **Note D should be retained.**

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Formaldehyde is an existing biocidal active substance approved in accordance with Regulation (EU) No 528/2012. The substance is also commercialised as a chemical. Classification of formaldehyde was inserted in the 1st ATP (1976) of Annex I of Directive 67/548/EEC and carcinogenicity classification was inserted in the 8th ATP in 1987. The classification for carcinogenicity and mutagenicity was re-evaluated under Regulation (EC) No 1272/2008 (CLP Regulation) and adopted with the 6th ATP of Annex VI. However, re-evaluation was targeted and did not exclude other human health hazard classes.

During re-assessment of the existing data in the context of the evaluation of formaldehyde as a biocidal active substance, the German CA noted that classification for Acute Toxicity needs to be updated. The current classification for Acute Toxicity was translated from Annex I of Dir 67/548/EEC. In addition, sub-classification for Skin Sensitisation was addressed. Updated harmonised classification is required by Regulation (EU) No 528/2012.

5 IDENTIFIED USES

According to information in the registration dossiers, formaldehyde is used at industrial sites, by professional workers and by consumers. It is used as a substance (either in pure state or diluted in water), in mixtures and in articles.

Consumer uses include: adhesives and sealants, paints and coating products, fillers, putties, plasters, modelling clay, inks and toners, polymers, fuels, biocides (e.g. disinfectants, pest control products), polishes and waxes, washing and cleaning products, cosmetics, personal care products, machine wash liquids/detergents, automotive care products, fragrances and air fresheners, metal, wooden and plastic construction and building materials, flooring, furniture, toys, textiles (e.g. curtains, carpet, clothing), footwear, leather products, paper and cardboard products, electronic equipment.

Formaldehyde can be found in complex articles with no release intended: machinery, mechanical appliances, electrical/electronic products not covered by the Waste Electrical and Electronic Equipment (WEEE) directive (e.g. large-scale stationary industrial tools).

Professional uses of formaldehyde include: adhesives and sealants, paints and coating products, polymers, laboratory chemicals, building and construction materials, textile, leather or fur, wood and wood products, pulp, paper and paper products, machine wash liquids/detergents, automotive care products, fragrances and air fresheners.

At industrial sites, formaldehyde is mostly used as intermediate in the production of chemicals, plastic products, textile, leather or fur, pulp, paper and paper products, mineral products (e.g. plasters, cement) and rubber products.

6 DATA SOURCES

Assessment Report Formaldehyde (PT02), October 2017, CA DE

Data from open literature

The dataset was checked against the information provided on the ECHA dissemination website and additional data that would have an impact on the classification proposal could not be identified.

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	colourless gas, pungent suffocating odour (formaldehyde gas) colourless liquid, irritating, pungent odour (formaldehyde solution (30-55 % w/w))	Merck (1996) Merck (1996), Synthide Ltd. 2005	
Melting/freezing point	-118 °C to -92 °C (formaldehyde gas) -15 °C (formalin (37 %))	CRC (2001) Kirk-Othmer (1994) L. Roth (1996)	
Boiling point	-19.5 °C (1013 hPa) (formaldehyde gas) 96 °C (formalin (37 w/w% aqueous solution, containing 10 -15 % methanol))	Merck (1996)	
Relative density	0.815 at –20 °C (formaldehyde gas) 1.1346 g/cm^3 at 25 °C (aqueous solution: 50 % formaldehyde, 7 % methanol)	CRC (2001) Synthite (2009)	
Vapour pressure	5490 hPa, 300 K (formaldehyde gas) 187 Pa, 25 °C (formalin (37 %))	CRC (2001) Ullmann (2005)	
Surface tension	**result**: 69.6 mN/m **concentration**: 1 mM **result**: 67.8 mN/m **concentration**: 10 mM **temperature**: No data formaldehyde is not surface active	Hasegawa et al. (1993)	Platinum hanging plate method with an Acoma Wilhelmy surface balance
Water solubility	up to 55 % (formaldehyde gas)	Merck (1996)	In aqueous solutions with a concentration > 55 % formaldehyde polymerize irrecoverably to paraformaldehyde. Polymerization occurs also at lower concentrations, the given value of up to 55

Property	Value	Reference	Comment (e.g. measured or estimated)
			% is based on the releasable formaldehyde content. Therefore, this is not a true solubility as this value is based on the polymerization effect.
Partition coefficient n-octanol/water	0.35 at 25 °C (formaldehyde gas)		KOWWIN v1.51, SRC-Log KOW for Microsoft Windows, Copyright; W. Melyan, 1993 – 1996, (The value was calculated according to the Atom/Fragment Contribution (AFC) method)
Flash point	For pure formaldehyde, the flash point does not need to be tested as the substance is a gas. For formaldehyde in aqueous solutions, the flash point value is above 50 °C and up to 85 °C. The flash point varies and depends on the concentrations of formaldehyde and methanol in the aqueous solution.	For details, see section 8.5.	
Flammability	The flammability of pure formaldehyde gas is derived from the explosive limits. Lower explosion limit: 7 vol% Upper explosion limit: 73 vol% Flammability of formaldehyde in aqueous solutions: Flammability is derived from flash point and boiling point. Based on chemical structure pyrophoric properties and flammability in contact with water are not to be expected.	DIN EN ISO/IEC 80079-20-1:2020-09 Expert statement	
Explosive properties	not explosive	Expert statement	Based on the theoretical assessment of the chemical structure.
Self-ignition temperature	Formaldehyde gas Auto-ignition temperature: 424 °C	DIN EN ISO/IEC 80079-20-1:2020-09 Registration from ECHA	

Property	Value	Reference	Comment (e.g. measured or estimated)
	Formaldehyde aqueous solution Auto-ignition temperature: 395 °C (DIN 51794, 55 % formaldehyde in aqueous solution)	dissemination website	
Oxidising properties	no oxidising properties	Expert statement	Based on the theoretical assessment of the chemical structure.
Stability in organic solvents and identity of relevant degradation products	**result:** At low temperatures soluble in all proportions in toluene, ether chloroform, ethylacetate **temperature:** No data	Ullmann (2005)	
Dissociation constant	pKa = 13.27 (of hydrate), 25 °C (aqueous solution of formaldehyde; measurement is usually performed with aqueous formaldehyde dilution (for gas or solution))	Serjeant and Dempsey (1979)	aqueous solution of formaldehyde measurement is usually performed with aqueous formaldehyde dilution (for gas or solution) FC
Viscosity	**result**: 2.1 mPas **temperature**: 25 °C (formalin 37 %)	Ullmann (2005)	

8 EVALUATION OF PHYSICAL HAZARDS

Introductory remark:
This section covers the assessment of physical hazards for Formaldehyde as a gas as well as for aqueous formaldehyde solutions. Anhydrous monomeric formaldehyde gas is not commercially available. In aqueous solution formaldehyde exists as methylene glycol ($HOCH_2OH$) and its oligomers, namely the low molecular mass poly(oxymethylene) glycols with the following structure $HO(CH_2O)nH$ (n = 1-8)). These compounds exist in equilibrium, depending on the concentration of formaldehyde and temperature. Monomeric, physically dissolved formaldehyde is only present in low concentrations of up to 0.1 wt% and the vapour pressure of formaldehyde solution is very low (187 Pa, 25 °C (formalin (37 %)).

8.1 Explosives

Formaldehyde gas: Hazard class not applicable. Gases are excluded per definition from the hazard class “Explosives” according to section 2.1 of Annex I to Regulation (EC) No 1272/2008.
Formaldehyde aqueous solution: see below

8.1.1 Short summary and overall relevance of the information provided on explosive properties

For Formaldehyde as aqueous solution no tests were performed because explosive properties of the substance can be excluded by an evaluation of the chemical structures:
The study does not need to be conducted because there are no chemical groups present in the molecule which are associated with explosive or self-reactive properties with reference to the screening procedures in Appendix 6 of the UN-MTC, see Tables A6.1 and A6.3.

8.1.2 Comparison with the CLP criteria

Formaldehyde aqueous solution: Data waiving is acceptable: A substance or mixture shall not be classified as explosive in accordance with section 2.1.4.3 of Annex I to Regulation (EC) No 1272/2008, if:
(a) There are no chemical groups associated with explosive properties present in the molecule. Examples of groups which may indicate explosive properties are given in Table A6.1 in Appendix 6 of the UN RTDG, Manual of Tests and Criteria; […]

8.1.3 Conclusion on classification and labelling for explosive properties

Formaldehyde aqueous solution: Classification is not required as the substance does not fulfil the criteria.

8.2 Flammable gases

Formaldehyde gas: see below
Formaldehyde aqueous solution: Hazard class not applicable (liquid).

Table 8: Summary table of studies on flammable gases

Method	Results	Remarks	Reference
Tabulated values in Annex B of the cited Standard	Lower explosion limit: 7 vol% Upper explosion limit: 73 vol%	Temperature/Pressure: at 20 °C / 101.3 kPa	DIN EN ISO/IEC 80079-20-1:2020-09
Tabulated value in Annex B of the cited Standard	Auto-ignition temperature: 424 °C	at 101.3 kPa	DIN EN ISO/IEC 80079-20-1:2020-09
Tabulated value of the cited Handbook	Gibbs Free Energy at 25 °C: -109.9 kJ/mol	CH_2O (g)	Ullmann (2012)

8.2.1 Short summary and overall relevance of the provided information on flammable gases

Experimental data on lower and upper explosion limit are 7 vol%- 73 vol%, which were stated in DIN EN ISO/IEC 80079-20-1:2020-09: Explosive atmospheres - Part 20-1: Material characteristics for gas and vapour classification - Test methods and data.

The auto-ignition temperature has been determined at 424 °C (DIN EN ISO/IEC 80079-20-1:2020-09) which excludes spontaneous ignition in air at a temperature of 54 °C or below.

Formaldehyde gas is not chemically unstable in the sense of the test method according to the UN Manual of Tests and Criteria, Part III, Section 35 "DETERMINATION OF CHEMICAL INSTABILITY OF GASES AND GAS MIXTURES". This can be derived from the thermodynamic data: The Gibbs Free Energy is -109.9 kJ/mol which means that it does not release energy but consumes it. Experimental testing can therefore be dispensed with.

8.2.2 Comparison with the CLP criteria

Flammable gas means a gas or gas mixture having a flammable range with air at 20 °C and a standard pressure of 101.3 kPa. The flammability range of a flammable gas is defined between the ''lower explosion limit'' (LEL) in air and the ''upper explosion limit'' (UEL) in air.

The criteria for category 1 have been amended by Regulation (EU) 2019/521 (12th ATP to CLP) as a new sub-classification in categories 1A and 1B of the hazard class "flammable gases. The CLP Regulation considers for flammable gases three categories 1A, 1B and 2. Category 1A is divided in four sub-categories: Flammable gas, Pyrophoric gas, Chemically unstable gas A and Chemically unstable gas B.

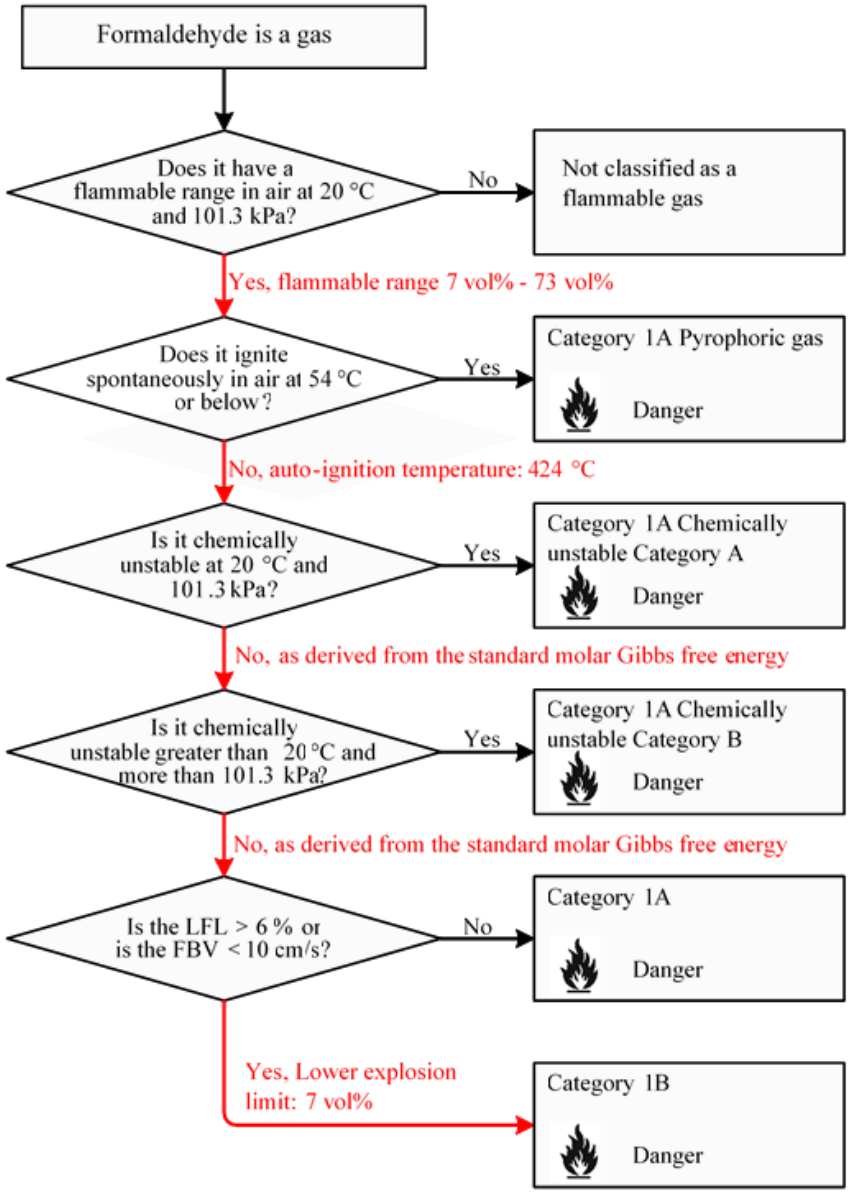
Criteria for categorization of flammable gases, which have been amended by Regulation (EU) 2019/521 (12th ATP to CLP):

Category			*Criteria*
1A	*Flammable gas*		*Gases, which at 20 °C and a standard pressure of 101,3 kPa are: (a) ignitable when in a mixture of 13 % or less by volume in air; or (b) have a flammable range with air of at least 12 percentage points regardless of the lower flammability limit unless data show they meet the criteria for Category 1B*
	Pyrophoric gas		*Flammable gases that ignite spontaneously in air at a temperature of 54 °C or below*
	Chemically unstable gas	*A*	*Flammable gases which are chemically unstable at 20 °C and a standard pressure of 101,3 kPa*
		B	*Flammable gases which are chemically unstable at a temperature greater than 20 °C and/or a pressure greater than 101,3 kPa*
1B	*Flammable gas*		*Gases which meet the flammability criteria for Category 1A, but which are not pyrophoric, nor chemically unstable, and which have at least either:*

		(a) a lower flammability limit of more than 6 % by volume in air; or *(b) a fundamental burning velocity of less than 10 cm/s;*
2	*Flammable gas*	*Gases, other than those of Category 1A or 1B, which, at 20 °C and a standard pressure of 101.3 kPa, have a flammable range while mixed in air.*

Due to the flammable range at 20 °C and a standard pressure of 101,3 kPa between 7 vol% and 73 vol%, pure formaldehyde gas fulfills the criteria for Category 1B as the lower explosion limit of more than 6 % by volume in air for Category 1B is meet. Within Category 1A, formaldehyde gas does not meet the criteria for classification as a pyrophoric and chemically unstable gas.

The classification procedure, in slightly modified form of the decision logic in section 2.3.3 in Figure 2.2.1


Formaldehyde is a gas
Does it have a flammable range in air at 20 °C and 101.3 kPa?
No
Not classified as a flammable gas
Yes, flammable range 7 vol% - 73 vol%
Does it ignite spontaneously in air at 54 °C or below?
Yes
Category 1A Pyrophoric gas
Danger
No, auto-ignition temperature: 424 °C
Is it chemically unstable at 20 °C and 101.3 kPa?
Yes
Category 1A Chemically unstable Category A
Danger
No, as derived from the standard molar Gibbs free energy
Is it chemically unstable greater than 20 °C and more than 101.3 kPa?
Yes
Category 1A Chemically unstable Category B
Danger
No, as derived from the standard molar Gibbs free energy
Is the LFL > 6 % or is the FBV < 10 cm/s?
No
Category 1A
Danger
Yes, Lower explosion limit: 7 vol%
Category 1B
Danger

8.2.3 Conclusion on classification and labelling for flammable gases

Formaldehyde gas: Due to the lower explosion limit of 7 vol% and the given criteria, Formaldehyde gas has to be classified as “Flam. Gas 1B, H221”. H221: Flammable gas.

8.3 Oxidising gases

Formaldehyde gas: see below
Formaldehyde aqueous solution: Hazard class not applicable (liquid).

8.3.1 Short summary and overall relevance of the provided information on oxidising gases

Hazard class not applicable as Formaldehyde gas is classified as a flammable gas.

8.3.2 Comparison with the CLP criteria

Oxidising gas means any gas or gas mixture that may, generally by providing oxygen, cause or contribute to the combustion of other material more than air does. Furthermore, it should be noted that if a substance contains oxygen, which is chemically bound only to carbon, oxidising properties can definitely be excluded.

8.3.3 Conclusion on classification and labelling for oxidising gases

Formaldehyde gas is a flammable gas thus it does not require classification as oxidising gas.

8.4 Gases under pressure

Formaldehyde gas: see below
Formaldehyde aqueous solution: Hazard class not applicable (liquid).

8.4.1 Short summary and overall relevance of the provided information on gases under pressure

Pure formaldehyde gas is not handled commercially because it tends to polymerize exothermally and may ignite. Formaldehyde is usually transported or stored as aqueous solutions.

8.4.2 Comparison with the CLP criteria

Gases under pressure are gases which are contained in a receptacle at a pressure of 200 kPa (gauge) or more at 20 °C, or which are liquefied or liquefied and refrigerated. They comprise compressed gases, liquefied gases, dissolved gases and refrigerated liquefied gases.

8.4.3 Conclusion on classification and labelling for gases under pressure

Formaldehyde gas does not get packaged or transported thus it does not require classification as “Gases under pressure”.

8.5 Flammable liquids

Formaldehyde gas: Hazard class not applicable (gas).
Formaldehyde aqueous solution: see below

Table 9: Summary table of studies on flammable liquids

Method	Results	Remarks	Reference
DIN EN 22719 Pensky-Martens closed cup method	Flash point: 84 °C (1013.25 hPa)	55 % formaldehyde in aqueous solution	Registration [1a]
DIN EN ISO 2719 Pensky-Martens closed cup method	Flash point: 85 °C (1013.25 hPa)	Analytical purity: 49.28 % formaldehyde, 1.57 % methanol in aqueous solution	Registration [1b]
closed cup method (not specified)	Flash point: 80.5 °C (1013.25 hPa)	Formaldehyde 37%, methanol-free	Registration [1c]
closed cup method (not specified)	Flash point: 50 °C (1013.25 hPa)	Formaldehyde 37%, 15% methanol	Registration [1c]
Closed cup method (not specified)	85 °C (37.2 % formaldehyde, 0.5 % methanol) 75 °C (37.2 % formaldehyde, 4.1 % methanol) 67 °C (37.1 % formaldehyde, 8.0 % methanol) 64 °C (37.2 % formaldehyde, 10.1 % methanol) 56 °C (37.1 % formaldehyde, 11.9 % methanol) 56 °C (37.5 % formaldehyde, 14 % methanol)		GisChem BG RCI [2]

[1a] Registration from ECHA dissemination website https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15858/4/12/?documentUUID=a1889247-a26a-450e-aa71-bcee37ba2fc1, accessed on 13/02/2018
[1b] Registration from ECHA dissemination website https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15858/4/12/?documentUUID=15c1000e-796b-489a-b44e-2ae42bb14c6b, accessed on 13/02/2018
[1c] Registration from ECHA dissemination website https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15858/4/12/?documentUUID=c644e5d6-3264-43ec-94d8-9f1bca8d8472 accessed on 10/05/2021
[2] Gefahrstoffinformationssystem Chemikalien (GisChem) der BG RCI und der BGHM, Data sheet „Formaldehyd“ published by the German Social Accident Insurance Institution for the raw materials and chemical industry (BG RCI) http://www.gischem.de/suche/dokument.htm?client_session_Dokument=173, Table on Flash points provided by BASF SE, accessed on 13/02/2018

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

The flash point varies and depends on the concentrations of formaldehyde and methanol in the aqueous solution.
No experimental data on flash point were provided for an aqueous solution of 55 % (w/w) formaldehyde with 7 % (w/w) methanol. Based on the available data, it can be concluded that formaldehyde solutions in water within the ranges of 25-55 % formaldehyde and 0-7 % methanol will have flash points above 60 °C.

8.5.2 Comparison with the CLP criteria

The criteria for the classification of flammable liquids are found in Annex I, Section 2.6 of CLP:
Flammable liquid means a liquid having a flash point of not more than 60 °C.
For flash point determination, a closed-cup method shall be used.
The reported data for formaldehyde solutions results in flash points above and below 60 °C.
Therefore, liquids with a flash point above 60 °C do not meet CLP classification criteria and will not be regarded as a flammable liquid. Formaldehyde solutions with a flash point ≥ 23 °C and ≤ 60 °C have to be classified as “Flam. Liq. 3, H226”. H226: Flammable liquid and vapour.

8.5.3 Conclusion on classification and labelling for flammable liquids

The flash point varies and depends on the concentrations of formaldehyde and methanol in the aqueous solution therefore, Note F is assigned to the entry.

8.6 Flammable solids

Formaldehyde gas: Hazard class not applicable (gas).
Formaldehyde aqueous solution: Hazard class not applicable (liquid).

8.7 Self-reactive substances

Formaldehyde gas: Hazard class not applicable (gas).
Formaldehyde aqueous solution: see below

8.7.1 Short summary and overall relevance of the provided information on self-reactive substances

Formaldehyde aqueous solution: DSC measurement showed two exothermic decomposition peaks at onset temperature of 220 °C and 280 °C with an energy of 350 J/g and 180 J/g respectively. Composition of test material, percentage of components: Formaldehyde 49.35 %; Methanol 1.84 %.
[1d] Registration from ECHA dissemination website https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15858/4/20/?documentUUID=95391e0f-3bfc-4718-a7d2-765d30b98a7e, accessed on 13/02/2018.

8.7.2 Comparison with the CLP criteria

In general, substances or mixtures classified as self-reactive substances and mixtures can decompose strongly exothermically when 50 kg are exposed to temperatures of 75 °C or lower depending on the Self-Accelerating Decomposition Temperature (SADT) of the substance or mixture.
However, because the decomposition temperature is above 200 °C, it can be assumed that their self-accelerating decomposition temperature (SADT) is greater than 75 °C for a 50 kg package. Therefore, the UN Test Series A to H for self-reactive substances and mixtures does not need to be conducted.
Furthermore, formaldehyde, aqueous solution (conc. ≥ 25 %, flash point. > 60 °C) is listed under UN number 2209 in Class 8, packing group III with classification code C9 according to the European Agreement concerning the International Carriage of Dangerous Goods by Road (ADR), 2017 edition. The transport classification requirements for self-reactive substances and mixtures are consistent to those of CLP/GHS. Therefore, it can be concluded, that Formaldehyde (aqueous solution) does not meet the classification criteria for this hazard class.

8.7.3 Conclusion on classification and labelling for self-reactive substances

Formaldehyde aqueous solution: Classification is not required, as the substance does not fulfil the criteria.

8.8 Pyrophoric liquids

Formaldehyde gas: Hazard class not applicable (gas).
Formaldehyde aqueous solution: see below

8.8.1 Short summary and overall relevance of the provided information on pyrophoric liquids

Formaldehyde aqueous solution: The study does not need to be conducted because the substance is known to be stable in contact with air at room temperature for prolonged periods of time (days) and hence, the classification procedure does not need to be applied.

8.8.2 Comparison with the CLP criteria

Data waiving is acceptable: The classification procedure for pyrophoric liquids need not be applied in accordance with section 2.9.4 of Annex I to Regulation (EC) No 1272/2008, when experience in manufacture or handling shows, that the substance or mixture does not ignite spontaneously on coming into contact with air at normal temperatures (i.e. the substance is known to be stable at room temperature for prolonged periods of time (days)).

8.8.3 Conclusion on classification and labelling for pyrophoric liquids

Formaldehyde aqueous solution: Classification is not required as the substance does not fulfil the criteria.

8.9 Pyrophoric solids

Formaldehyde gas: Hazard class not applicable (gas).
Formaldehyde aqueous solution: Hazard class not applicable (liquid).

8.10 Self-heating substances

Formaldehyde gas: Hazard class not applicable (gas).
Formaldehyde aqueous solution: see below

8.10.1 Short summary and overall relevance of the provided information on self-heating substances

According to Guidance on information requirements and chemical safety assessment, R7a, Endpoint specific guidance, R.7.1.10.7, indicated than in general, self-heating occurs only for solids in contact with air. The UN Test N.4, for self-heating substances and mixtures does not need to be conducted for liquids. The Guidance on the Application of the CLP Criteria, Version 5.0 – July 2017, section 2.11.4.2, gives detailed background information about this phenomenon: In general, the phenomenon of self-heating applies only to solids. The surface of liquids is not large enough for reaction with air and the test method is not applicable to liquids. Therefore, liquids are not classified as self-heating. However, if liquids are adsorbed on a large surface (e.g. on powder particles), a self-heating hazard should be considered.

Formaldehyde aqueous solutions are only liquids, which are not adsorbed on large surfaces, experimental testing can therefore be dispensed with.

8.10.2 Comparison with the CLP criteria

The classification of self-heating chemicals is based on tests described in Part III, Sub-section 33.4.6 of the UN Manual of Tests and Criteria (2019), Test N.4 “Test method for self-heating substances.” The test determines the ability of a chemical to undergo oxidative self-heating by exposure to air at temperatures of 100 °C, 120 °C or 140 °C in a 25 mm or 100 mm wire mesh cube sample container.

Substances or mixtures with a low melting point (< 160 °C) should not be considered for classification in this class since the melting process is endothermic and the substance-air surface is drastically reduced. In conclusion, the test method is not applicable to formaldehyde aqueous solutions with a boiling point of 96 °C (see Table 7) and in accordance to Guidance on the Application of the CLP Criteria.

8.10.3 Conclusion on classification and labelling for self-heating substances

Formaldehyde aqueous solution: Classification is not required as the substance does not fulfil the criteria.

8.11 Substances which in contact with water emit flammable gases

Formaldehyde gas: Hazard class not applicable (gas).
Formaldehyde aqueous solution: see below

8.11.1 Short summary and overall relevance of the provided information on substances which in contact with water emit flammable gases

Formaldehyde aqueous solution: The study does not need to be conducted because the substance is known to be soluble in water to form a stable mixture.

8.11.2 Comparison with the CLP criteria

Data waiving is acceptable: The classification procedure for this class need not be applied in accordance with section 2.12.4 of Annex I to Regulation (EC) No 1272/2008, if:

(a) the chemical structure of the substance or mixture does not contain metals or metalloids; or
(b) experience in production or handling shows that the substance or mixture does not react with water, e.g. the substance is manufactured with water or washed with water; or
(c) the substance or mixture is known to be soluble in water to form a stable mixture.

8.11.3 Conclusion on classification and labelling for substances which in contact with water emit flammable gases

Formaldehyde aqueous solution: Classification is not required as the substance does not fulfil the criteria.

8.12 Oxidising liquids

Formaldehyde gas: Hazard class not applicable (gas).
Formaldehyde aqueous solution: see below

8.12.1 Short summary and overall relevance of the provided information on oxidising liquids

Formaldehyde aqueous solution: No tests were performed because oxidizing properties of the substance can be excluded by an evaluation of the chemical structures:
All constituents in the aqueous solution, which could be chemically relevant, contain oxygens chemically bonded only to carbon and hydrogen.

8.12.2 Comparison with the CLP criteria

Data waiving is acceptable: For organic substances or mixtures the classification procedure for this class shall not apply in accordance with section 2.13.4 of Annex I to Regulation (EC) No 1272/2008, if:

(a) the substance or mixture does not contain oxygen, fluorine or chlorine; or
(b) the substance or mixture contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen.

8.12.3 Conclusion on classification and labelling for oxidising liquids

Formaldehyde aqueous solution: Classification is not required as the substance does not fulfil the criteria.

8.13 Oxidising solids

Formaldehyde gas: Hazard class not applicable (gas).
Formaldehyde aqueous solution: Hazard class not applicable (liquid).

8.14 Organic peroxides

Formaldehyde gas: Hazard class not applicable (gas).
Formaldehyde aqueous solution: see below

8.14.1 Short summary and overall relevance of the provided information on organic peroxides

Formaldehyde aqueous solution: The study does not need to be conducted because the product does not fall under the definition of organic peroxides according to GHS and the relevant UN Manual of tests and criteria.

8.14.2 Comparison with the CLP criteria

Data waiving is acceptable in accordance with the given definition of organic peroxides in section 2.15.1.1 of Annex I to Regulation (EC) No 1272/2008:
Organic peroxides mean liquid or solid organic substances, which contain the bivalent -O-O- structure and may be considered derivatives of hydrogen peroxide, where one or both of the hydrogen atoms have been replaced by organic radicals. The term organic peroxide includes organic peroxide mixtures (formulations) containing at least one organic peroxide. Organic peroxides are thermally unstable substances or mixtures, which can undergo exothermic self-accelerating decomposition. In addition, they can have one or more of the following properties:

i. be liable to explosive decomposition;
ii. burn rapidly;
iii. be sensitive to impact or friction;
iv. react dangerously with other substances.

8.14.3 Conclusion on classification and labelling for organic peroxides

Formaldehyde aqueous solution: Classification is not required as the substance does not fulfil the criteria.

8.15 Corrosive to metals

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

Values for formaldehyde aqueous solution (formalin) are published in the DECHEMA Corrosion Handbook (online 2021):

Corrosion rate:
Aluminum (non-clad type): 0.22 mm/a @ 35 °C
Steel (carbon steel): 0.81 mm/a @ 65 °C

Expert statement on Formaldehyde aqueous solution with regard to the hazard class “corrosive to metals” (Bäßler, R. (2021):
The values given the DECHEMA Corrosion Handbook for the corrosion rates for aluminum and carbon steel allow a statement on the classification as corrosive to metals. The evaluation of corrosivity has to distinguish between Corrosion resistance and in terms of classification as “corrosive to metals”.
Since the corrosion resistance of materials is determined by analogy with the test method of the UN Manual of Tests and Criteria, but with much lower limits, it can be concluded that classification criteria is not met, as the corrosion rate is much lower than the criterion of 6.25 mm per year.

8.15.2 Comparison with the CLP criteria

Definition of corrosive to metals according to section 2.16.1 of Annex I:
A substance or a mixture that is corrosive to metals means a substance or a mixture, which by chemical action will materially damage, or even destroy, metals.

Classification criteria according to section 2.16.2 of Annex I:
Substances and mixtures of hazard class corrosive to metals are classified in a single hazard category by using the UN Test C.1 (UN-MTC, Part III, sub-section 37.4), if the corrosion rate on either steel or aluminum surfaces exceeding 6.25 mm per year at a test temperature of 55 °C when tested on both materials.

8.15.3 Conclusion on classification and labelling for corrosive to metals

Formaldehyde aqueous solution: Classification is not required, as the substance does not fulfil the criteria.

RAC evaluation of physical hazards

The physical hazards section of the CLH report contains classification proposals for both the gas and the aqueous solution. As the Annex VI entry in the scope of the CLH proposal (605-001-00-5, "formaldehyde …%") covers only formaldehyde solutions in water, the RAC assessment is limited to aqueous solutions.

Consequently, **RAC does not support** the DS proposal to classify "formaldehyde …%" as **Flam. Gas 1B nor** the related proposal to add **Note T**.

"Note T: This substance may be marketed in a form which does not have the physical hazards as indicated by the classification in the entry in Part 3. If the results of the relevant method or methods in accordance with Part 2 of Annex I of this Regulation show that the specific form of substance marketed does not exhibit this physical property or these physical hazards, the substance shall be classified in accordance with the result or results of this test or these tests. Relevant information, including reference to the relevant test method(s) shall be included in the safety data sheet."

Summary of the Dossier Submitter's proposal

Explosives

The DS proposed no classification based on absence of chemical groups associated with explosive properties.

Flammable liquids

Classification is triggered when the flash point is ≤ 60 °C. According to the data presented in the CLH report, shown in the table below, the flash point of formalin solutions varies from ca. 85 to 50 °C mainly depending on the concentration of methanol.

Flash point of formalin with varying methanol and formaldehyde content		
Test substance composition	**Flash point**	**Reference**
Formaldehyde 37.2%, methanol 0.5%	85 °C	GisChem BG RCI [2]
Formaldehyde 37.2%, methanol 4.1%	75 °C	GisChem BG RCI [2]
Formaldehyde 37.1%, methanol 8.0%	67 °C	GisChem BG RCI [2]
Formaldehyde 37.2%, methanol 10.1%	64 °C	GisChem BG RCI [2]
Formaldehyde 37.1%, methanol 11.9%	56 °C	GisChem BG RCI [2]
Formaldehyde 37.5%, methanol 14.0%	56 °C	GisChem BG RCI [2]
Formaldehyde 55% (methanol not mentioned)	84 °C	Registration [1a]
Formaldehyde 49.3%, methanol 1.6%	80.5 °C*	Registration [1b]
Formaldehyde 37%, methanol-free	85 °C*	Registration [1c]
Formaldehyde 37%, methanol 15%	50 °C	Registration [1c]

* According to the online registration dossier (the two values were swapped in the CLH report)

According to the DS, it can be concluded that the flash point of a 25-55% aqueous solution of formaldehyde containing up to 7% methanol is > 60 °C. Therefore, no classification has been proposed. Still, the DS proposed to add Note F to indicate that the substance contains a stabiliser potentially changing the hazardous properties.

Self-reactive

In general, substances or mixtures classified as self-reactive substances and mixtures can decompose strongly exothermically when 50 kg are exposed to temperatures of 75 °C or lower depending on the Self-Accelerating Decomposition Temperature (SADT) of the substance or mixture. The waiving criteria include absence of structural alerts or a heat of decomposition below 300 J/g.

A DSC test with aqueous formaldehyde solution (formaldehyde 49.4%, methanol 1.8%)

showed two exothermic decomposition peaks at onset temperatures of 220 °C and 280 °C with energies of 350 J/g and 180 J/g respectively. Based on the decomposition temperature above 200 °C in the DSC test the DS concluded that the SADT is greater than 75 °C for a 50 kg package. Furthermore, the DS pointed out that formaldehyde aqueous solution (conc. ≥ 25%, flash point > 60 °C) is listed in ADR (entry 2209) without a classification as self-reactive.

Pyrophoric liquids

The DS proposed no classification based on experience in handling.

In contact with water emitting flammable gas

The DS proposed no classification as the substance is known to be soluble in water to form a stable mixture.

Oxidising liquids

The DS proposed no classification based on structure (oxygen bonded only to carbon and hydrogen).

Corrosive to metals

The DS presented results of a test with formalin reporting corrosion rates of 0.81 mm/year for steel (at 65 °C) and 0.22 mm/year for aluminium (at 35 °C). Based on these results the DS concluded that the classification criterion of > 6.25 mm/year (at 55 °C) is not met and classification is not warranted.

Comments received during consultation

Comments were received from industry and from 1 MSCA. Industry comments related to relevance of the proposed classification of formaldehyde as flammable gas to aqueous formaldehyde solutions.

The commenting MSCA raised two issues:

- Self-reactive: the heat of decomposition is above 300 J/g and a DSC

measurement in a small vessel cannot be extrapolated to a 50 kg package. Therefore, this endpoint should be considered inconclusive.

- Corrosive to metals: it should be clarified if the handbook data presented in the CLH report were obtained in compliance with the UN C.1 method. If this is not the case, the endpoint should be considered inconclusive.

As to self-reactivity, the DS explained that, as an empirical rule, it is assumed that if the decomposition starts above 200 °C, the SADT can be estimated to be above 75 °C. They further mentioned the extensive experience in handling formaldehyde and pointed out that fsolutions are classified as corrosive or flammable (and corrosive) but not as self-reactive in the UN Model Regulations on Transport of Dangerous Goods.

The DS acknowledged that the testing method on metal corrosion is not specified in the handbook. Still, they believed that the method employed was one of the standard ones and the results can be used for classification under CLP.

Assessment and comparison with the classification criteria

Explosives, Pyrophoric liquids, In contact with water emitting flammable gas, Oxidising liquids

RAC agrees with **no classification** and the DS's assessment.

Flammable liquids

RAC agrees with the DS that aqueous formaldehyde solutions with methanol content of ≤ 7% have a flash point above 60 °C and **do not meet the classification criteria**. RAC also agrees with the DS proposal to **add Note F** to cover formaldehyde solutions with a methanol content above 7%, some of which will meet the classification criterion of a flash point ≤ 60 °C.

Self-reactive

Formaldehyde does not contain any groups associated with explosive or self-reactive properties. Therefore, RAC agrees with the DS's proposal of **no classification**.

Spontaneous polymerization of formaldehyde occurs particularly in non-stabilized aqueous solutions. However, polymerizing substances do not fulfil the criteria for classification as self-reactive (Guidance on the application of the CLP criteria, version 5.0, 2.8.4.3.3). The tendency to polymerize is highlighted in Note D.

Corrosive to metals

The structures of formaldehyde, of the related species formed by its hydration and polymerization in aqueous solutions and of methanol do not raise concern about corrosivity to metals (no acidic or basic groups, no halogens, no complexing agents). However, formalin contains small amounts of corrosive formic acid as an impurity. The documentation submitted for the purpose of approval of formaldehyde as a biocidal active substance contains a statement that aqueous formaldehyde is corrosive to carbon steel.

The DS presented corrosion data from a handbook (DECHEMA Corrosion Handbook). The corrosion rate of steel was 0.81 mm/year at 65 °C, the corrosion rate of aluminium was 0.22 mm/year at 35 °C. Although the classification criterion (6.25 mm/year at 55 °C) is not met, the negative result is associated with significant deficiencies:

- A sufficiently detailed description of the test methods, test results and the test substance is not available. In particular, it is not clear whether the test substance represented worst case regarding formic acid content.
- The test with aluminium was conducted at a markedly lower temperature (35 °C) than the standard one (55 °C). Reaction rate (corrosion rate) generally decreases with decreasing temperature.
- No information on localised corrosion has been provided.

Because of these deficiencies, RAC proposes **no classification due to inconclusive data**.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 8: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Systemic availability, non-guideline, non-GLP Route: Oral Species, strain, sex, number: (1) Rat and (2) mouse; strain, sex and number of animals not reported Dose levels, duration of exposure: (1) 7 mg/kg bw, single administration (2) dose not reported, single administration	(1+2) Oral absorption (^{14}C): 100 % (1) Rapid and wide ^{14}C tissue distribution, lowest in blood and highest in bone marrow at 12 h, 50 % ^{14}C elimination within 12 h via exhaled air (40 %), urine (10 %) and faeces (1 %) (2) ^{14}C residues 20 % at 24 h and 10 % at 96 h	^{14}C formaldehyde, conc. and purity unknown;	Buss et al., 1964, Naunyn Schmiedebergs Arch Exp Pathol Pharmakol 247: 380-381 non-English (German), conference abstract
Systemic availability, non-guideline, non-GLP Route: Inhalation Species, strain, sex, number: (1) Rat: Fischer 344; males; n = 8/group (exposed and unexposed) (2) Human: n = 6 volunteers; 4 men, 2 women Dose levels, duration of exposure: (1) 14.4 ± 2.4 ppm formaldehyde (nose-only) for 2 hours (2) 1.9 ± 0.1 ppm for 40 minutes	No significant difference in blood formaldehyde levels (mean ± std. error) in both experiments (1) 2.25 ± 0.07 µg/g blood in formaldehyde-exposed male rats measured immediately after end of 2-h exposure vs. 2.24 ± 0.07 µg/g blood in unexposed male rats (2) 2.61 ± 0.14 µg/g blood before exposure vs. 2.77 ± 0.28 µg/g blood after exposure	GC-MS analysis using pentafluorophenylhydrazones (PFPH) Inhaled dose: 1) ~ 1.45 µg/g bw 2) ~ 0.01 µg/g bw	Heck et al., 1985. Am Ind Hyg Assoc J 46:1-3
Systemic availability, non-guideline, non-GLP Route: Inhalation Species, strain, sex, number: Rhesus monkeys; n = 3/group (exposed vs. unexposed); sex not reported Dose levels, duration of exposure: 6 ppm for 6 hours/day, 5 days/week for 4 weeks	No significant difference in blood formaldehyde levels between exposed monkeys (1.84 ± 0.15 and 2.04 µg/g blood measured at 7 min and 45 h after last exposure, respectively) and unexposed control monkeys (2.42 ± 0.14 µg/g blood)	GC-MS analysis using PFPH method Inhaled dose: 0.9 µg/g bw	Casanova et al., 1988, Food Chem Toxicol 26:715-6.
Distribution, non-guideline, non-GLP Route: Inhalation (whole body) Species, strain, sex, number: (1) Rat, F344, M, 3 (2) Mouse, B6C3F1, M, 3 Dose levels, duration of exposure:	(1+2) ^{14}C widely distributed; highest ^{14}C levels in nasal cavity, trachea, lung, GI tract	^{14}C-formaldehyde	Chang et al., 1983, Toxicol Appl Pharmacol 68: 161-176

Method	Results	Remarks	Reference
18 µg/L (15 ppm) for 6 hours pre-treated group: 18 µg/L for 6 hours/day for 4 days			
Distribution, non-guideline, non-GLP Route: Inhalation (head only) Species, strain, sex, number: Rat, F344, M, 4 Dose levels, duration of exposure: (1) 5.4-12-18-29 µg/L for 6 hours (pre-treated group: 18 µg/L for 6 hours/day for 9 days) (2) 0.76-16 µg/L for 6 hours (plus 70 h post-exposure)	(1) Highest ^{14}C levels in nasal mucosa >> oesophagus, kidney, liver, intestine, lung > spleen, heart, plasma > brain, testes, erythrocytes (2) ^{14}C excretion via air (40 %, mainly within 12 h), urine (17 %) and faeces (4-5 %); 35-39 % ^{14}C remaining in tissues & carcass at 70 h	^{14}C-formaldehyde	Heck et al., In: Gibson, 1983, Formaldehyde toxicity, Hemisphere Publishing Corporation: 26-37
Toxicokinetics, non-guideline, non-GLP Route: (1) Inhalation (2) Intravenous Species, strain, sex, number: Rat, F344, M, 1 Dose levels, duration of exposure: 1) 9.6 µg/L for 6 hours 2) single injection; unknown dose	(1) C_{MAX}: 2.4 µg/mL ^{14}C-HCHO-equiv., t_{MAX}: 6 h, $t_{1/2}$ (^{14}C): 55 h (2) plasma $t_{1/2}$ (^{14}C): ~50 h for formaldehyde and formate	(1+2) ^{14}C formaldehyde (2) ^{14}C-sodium formate	Heck et al., In: Gibson, 1983, Formaldehyde toxicity, Hemisphere Publishing Corporation: 26-37
Metabolism/Toxicokinetics, non-guideline, non-GLP Route: Intraperitoneal Species, strain, sex, number: Rat, Sprague-Dawley, M, 3 Dose levels, duration of exposure: 4-40 mg/kg bw	^{14}C exhaled as CO_2 within 12 h: 70-66 %, within 48 h: 82-78 %; ^{14}C eliminated with urine within 12 h: 5.5-9 %, within 48 h: 7.5-11 %; urinary metabolites: formate (55-80 %), hydroxymethyl-/ bishydroxymethyl-/ polymethylenurea (20-45 %)	^{14}C-formaldehyde thiazolidine-4-carboxylate formed from cysteine with formaldehyde or urea adducts	Mashford & Jones, 1982, Xenobiotica 12(2): 119-124
Metabolism/Toxicokinetics, non-guideline, non-GLP Route: Rectal Species, strain, sex, number: Dog, Mongrel, M/F, 3 Dose levels, duration of exposure: 1500 mg (~ 100 mg/kg bw)	Serum formic acid ↑, levels [mg/L] at 15 min: 130, at 45 min: 180, at 3 h: 140 (control range: 0-12)	Other parameters not determined	Myers et al., 1997, World J Surg 21:886-9

Method	Results	Remarks	Reference
Metabolism, non-guideline, non-GLP Route: *Ex vivo* Species, strain, sex, number: Rat, F344, M, 8 Dose levels, duration of exposure: 10 µM to 2.4 mM	Nasal epithelium: oxidation by glutathione - dependent and independent dehydrogenases, K_M ~ 3 µM and 550 µM, resp.; Liver: similar activity	*ex vivo* evaluation of tissue homogenates	Casanova-Schmitz et al., 1984, Biochem Pharmacol 33: 1137-1142
Metabolism, non-guideline, non-GLP Route: Inhalation (nose only) Species, strain, sex, number: Rat, F344, M, 9-15 Dose levels, duration of exposure: 1.1-2.4-4.8-7.2-12 µg/L for 3 hours (correspond to 0.9-2-4-6-10 ppm, respectively)	GSH depletion in nasal epithelium: DNA cross-links ↑ ($^3H/^{14}C$ ratio), ^{14}C incorporation ↓ (0.15 vs. 0.3-0.6 %); in bone marrow: ^{14}C incorporation ↓ (18 vs. 24 %)	GSH depletion by 300 mg/kg bw phorone i.p. 2 h pre-exposure, ^{14}C- and ^3H-form-aldehyde	Casanova & Heck, 1987, Toxicol Appl Pharmacol 89: 105-121
Absorption, non-guideline, non-GLP Route: Dermal (non-occluded) Species, strain, sex, number: (1) Rat, F344, ≥ 3 M + 5 F (2) Guinea pig, Dunkin-Hartley, ≥ 5 M + 5 F Dose levels, duration of exposure: (1+2) 0.1-11.2 mg/animal for 72 h (10 µL 1 % solution or 40 µL 37 % solution per 2 cm^2 skin area)	(1+2) 100 % total absorption ^{14}C under occluded conditions likely; relative to applied dose: 21-28 % ^{14}C evaporated, 29-36 % ^{14}C absorbed systemically (blood: 0.1 %, liver: 0.2 %, carcass: 22-28 %, urine: 5-10 %, faeces: 1-2 %, exhaled CO_2: ~1 %), 16 % to 3-4 % ^{14}C (low to high dose, respectively) retained at applied site	60-73 % recovery	Jeffcoat et al., In: Gibson, 1983, Formaldehyde toxicity, Hemisphere Publishing Corporation: 38-50
Absorption, non-guideline, non-GLP Route: Dermal (occluded) Species, strain, sex, number: Rabbit, New Zealand White, M, 8 Dose levels, duration of exposure: 0.37-3.7-37 mg/animal for 4 hours (1 mL aqueous solution per 120 cm^2 skin area)	Blood: ~ 0.1 %, CO_2: ~ 0.3 %, liver: ~ 0.2 %, kidneys: ~ 0.1 %, application site: ~ 65 %, unaccounted: ~ 1/3 of dose, (all data as ^{14}C)	Systemic absorption within 4 h: less than 1/3 of dose (^{14}C)	Robbins et al., 1984, J Toxicol Environ Health 14: 453-463
Absorption, non-guideline, non-GLP Route: Dermal and *ex vivo* Species, strain, sex, number: Human skin Dose levels, duration of exposure:	Flux: 16.7 and 319 µg/cm^2/h at 3.7% and 37 %, respectively Skin associated: 0.23/1.75 mg/cm^2	^{14}C-formaldehyde added to formalin, diluted in phosphate buffer (3.7 % only)	Loden, 1986, Acta Pharmacol Toxicol 58 : 382-389

Method	Results	Remarks	Reference
3.7-37 %, 21/15 h			

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

It has been shown that formaldehyde is readily absorbed after oral or inhalation exposure but to a lesser degree after dermal exposure. Gastrointestinal absorption of ^{14}C-formaldehyde in rats and mice was reported to be rapid and virtually complete, resulting in detectable radioactivity throughout the animal tissues within 5 min. As a highly water soluble gas, inhaled formaldehyde readily passes over into the lining mucosa; however, the site of deposition and absorption is dependent on species specificities in nasopharyngeal anatomy, mucous clearance and breathing pattern (see also https://echa.europa.eu/de/information-on-chemicals/biocidal-active-substances/-/disas/factsheet/1306/PT02 and A6.2_HCHO-add.pdf from doc_IIIA_TaskForce.zip). Analysis of dermal absorption of ^{14}C-formaldehyde *in vivo* was complicated by significant evaporation of the active substance from its aqueous solution and poor recovery. Systemic bioavailability from dermal exposure may be delayed and/or limited by covalent binding, most likely to abundant SH- and/or NH_2-groups, at the site of application.

Formaldehyde is rapidly metabolised. Upon the initial site of contact, formaldehyde can be metabolised via formaldehyde dehydrogenase to yield formate. Formate can subsequently undergo further oxidation to generate carbon dioxide or be incorporated into amino acids, purines, thymidine via tetrahydrofolate-dependent one-carbon biosynthetic pathways. Formaldehyde can also react non-enzymatically with a range of sulfhydryl- and amino-compounds to form adducts, some of which can at least in part dissociate or decompose to release formaldehyde again. However, experimental evidence suggests that the spontaneous reaction of formaldehyde with glutathione to generate S-hydroxymethylglutathione is the dominant pathway at least in the nasal mucosa of the rat (Casanova-Schmitz et al., 1984, Casanova & Heck, 1987).

Taking this information into context, formaldehyde as the parent compound is not expected to undergo wide systemic distribution (i.e. to more distant organs such as kidney or spleen) or to be stored in any tissue of the body. This is supported by studies that demonstrated no significant difference in blood formaldehyde levels between exposed and control rats, monkeys or human volunteers (Heck et al., 1985; Casanova et al., 1988). Aside from its incorporation as formate into metabolic pathways, formaldehyde can be excreted either in the urine – primarily as formic acid – or in exhaled air as carbon dioxide.

It is worth mentioning that exposure to formaldehyde can also occur endogenously. Endogenous formaldehyde is normally formed from the amino acid metabolism, such as that of serine, glycine, methionine, metabolism of choline as well as demethylation of N-, S- and O-methyl compounds (ATSDR, 1999).

For the proposed health hazard classifications (primarily for acute toxicity), it is relevant to know that formaldehyde can rapidly be metabolised to formate or react with other compounds to yield adducts at the site of contact. Formaldehyde at high doses or concentrations beyond the body's metabolic capacity to remove the parent compound might trigger health effects but primarily acts at the site of contact.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Table 9: 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
Acute oral toxicity (gavage), non-guideline, non-GLP, deviations: F not tested, no pathology, no clinical examinations	Rat, Wistar, M, ≥ 8/group	4 % (w/w) formaldehyde solution prepared from special-grade paraformaldehyde (polymer of formaldehyde; purity not specified)	300, 400, 520, 675, 875, 1140 mg/kg bw	640 mg/kg bw (min-max of 551-742 mg/kg bw) (based on data pooled from two experiments)	Tsuchiya et al., 1975, Keio J Med 24: 19-37
Acute oral toxicity (gavage), non-guideline, non-GLP deviations: F not tested, no pathology, no clinical examinations	Rat, Wistar, M, 10/group	Max. 2 % (w/w) aqueous solution of formaldehyde (purity not specified)	Not reported	800 mg/kg bw (95 % C.I.: 730-870 mg/kg bw)	Smyth et al., 1941, J Ind Hyg Toxicol 23: 259-268
Acute oral toxicity (gavage), non-guideline, non-GLP deviations: no pathology, no clinical examinations	Guinea Pig, M/F, 10/group	Max. 2 % (w/w) aqueous solution of formaldehyde (purity no specified)	Not reported	260 mg/kg bw (95 % C.I.: 220-300 mg/kg bw)	Smyth et al., 1941, J Ind Hyg Toxicol 23: 259-268

Table 10: Summary table of human data on acute oral toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Case report	37 % (v/v) solution of formaldehyde (no further information specified on the other components, concentration probably w/w but	Accidental poisoning from ingestion of formaldehyde (45 mL) of a 26-year-old female in India	Endoscopy results at 96 h after poisoning showed severe oesophageal burns, hyperemia and superficial ulceration of the distal stomach and antrum. Four weeks later, oesophagus showed recovery, whereas the distal part of the stomach was cicatrised (i.e. healing with scar).	Kochhar et al., 1986, Human Toxicol 5, 381-382

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
	indicated as v/v by authors.)			
Case report and literature review	Formalin. Containing approx. 40 % (w/w) formaldehyde (no further information specified on other components)	Attempted suicide of a 28-year-old male in Japan by ingestion of formalin (150 mL) Literature search and review identified 26 cases of formalin ingestion since 1950.	Admitted to the hospital 2 hours after ingestion; observed erosions of the oropharyngeal mucosa and respiratory stridor; developed acute respiratory distress syndrome; endoscopy results 4 days after admission showed oesophageal erosion, diffuse corrosive gastric ulcers and intact duodenum; about 132 days after admission, stomach had regenerated mucosa with scattered linear scars. Literature review showed stomach lesions and complications from ingestion of formalin.	Yanagawa et al., 2007, Clinical Toxicology 45(1):72-76

Table 11: Summary table of other studies relevant for acute oral toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Review	Formalin	Focus on the toxicity of ingested formalin (no specifics given on the composition of the solution) in humans	Ingestion of formaldehyde may cause burning in the mouth and oesophagus, nausea and vomiting of tissue and blood or coffee ground material, abdominal pain, and diarrhoea. Furthermore, it can cause liver and kidney damage, leading to jaundice, albuminuria, haematuria and anuria, acidosis and convulsions or central nervous system depression and lead to unconsciousness and death resulting from cardiovascular failure. The fatal dose in humans is about 60-90 mL formalin containing approx. 40% formaldehyde (w/w).	Pandey et al. 2000, Hum Exp Toxicol 19: 360-366

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

Two studies are available describing the acute oral toxicity of formaldehyde solutions in male rats and male and female guinea pigs (Tsuchiya et al., 1975; Smyth et al., 1941). In the study of Tsuchiya et al. (1975), male Wistar rats were given a single oral administration of formaldehyde (as 4 % (w/w) solution) at doses ranging from 300 to 1140 mg/kg bw and observed up to 1 week after administration. Table 13 shows mortality data from this study. This study reported an average LD_{50} of 640 mg/kg bw (min-max 551-742 mg/kg bw) in male rats.

Table 12: Mortality from acute oral exposure to formaldehyde in male rats from the Tsuchiya et al. (1975) study (based on data pooled from two experiments)

Dose [mg/kg bw]	N (total)	N (dead)	Mortality [%]	Mean body weight [g]
1140	8	8	100	104.0
875	16	13	81.3	106.3
675	16	9	56.2	106.8
520	16	2	12.5	110.1
400	16	3	18.7	113.1
300	8	0	0	111.8

The study of Smyth et al. (1941) determined LD_{50} values and dose-mortality curves from acute oral exposure to 60 glycols and glycol derivatives - formaldehyde being one of them - in male Wistar rats and guinea pigs of both sexes. Limited information on the study design is reported in this study, but the study reported LD_{50} values of 800 mg/kg bw (95 % CI: 730-870 mg/kg bw) and 260 mg/kg bw (95 % CI: 220-300 mg/kg bw) for rats and guinea pigs, respectively. The acute oral LD_{50} value in rats is in line with the findings from the Tsuchiya et al. (1975) study, which also concluded that the LD_{50} of formaldehyde by oral administration in rats ranges between 500 and 800 mg/kg bw. For both studies, no clinical examination or pathology assessment was provided, and the cause of death was not determined.

It is worth mentioning that additional information on the acute oral toxicity of formaldehyde was provided in a IUCLID dataset (ECB, 2000; OECD, 2002), which reported a LD_{50} of 42 mg/kg bw in mice. However, evaluation of the original study report revealed that the LD_{50} cited in this dossier was derived for formaldehyde monomethylhydrazone (with the chemical formula of C2H6N2) rather than for formaldehyde. In addition, the mentioned reference (Keller et al., 1983) could not be found. Therefore, this value is not used for classification purposes of formaldehyde.

Available human data of oral exposure to formaldehyde pertain to cases of poisoning from formalin, an aqueous solution containing about 40 % (w/w) formaldehyde and methanol (5-13 %) as a stabiliser to prevent polymerisation. The study of Yanagawa et al. (2007) identifies 26 published cases of formalin ingestion since 1950.

Table 13 provides an overview of these 26 cases.

Table 13: Cases of hospitalised patients who ingested formalin as reported in Yanagawa et al. (2007)

Country	Age	Gender	Estimated amount of ingested formalin (mL)	Formaldehyde (%)	Shock on arrival	Complications of stomach	Gastrectomy	Outcome
Japan	65	M	150	40	+	Cicatrical gastric stenosis	-	Survive
Japan	28	M	150	40	-	Cicatrical gastric stenosis	-	Survive
Japan	48	M	30	38	-	Hemorrhage	-	Survive
Japan	57	F	30	38	-	?	-	Death (Respiratory failure)
USA	41	M	240	37	-	Cicatrical gastric stenosis	+	Survival
India	26	F	45	37	-	Cicatrical gastric stenosis	-	Survival
Japan	55	M	30	37	-	Cicatrical gastric stenosis	-	Survive
Japan	74	F	30	37	+	Gastritis	-	Death
Japan	48	M	30	37	-	Cicatrical gastric stenosis	+	Survive
Japan	34	M	150	35	-	Cicatrical gastric stenosis	-	Survive
Japan	50	M	100	35	+	Hemorrhage	+	Survive
Japan	48	M	50	35	+	Hemorrhage and gastritis	-	Death
Japan	30	F	30	35	-	Gastritis	-	Survive
Japan	59	M	20	35	-	Cicatrical gastric stenosis	-	Survive
Japan	62	M	20	35	-	None	-	Survive
USA	46	F	120	10	+	Cicatrical gastric stenosis	+	Survival
USA	?	?	40	1.6	-	None	-	Survival
Japan	19	M	6	2	-	Cicatrical gastric stenosis	-	Death (gastric stenosis)
Japan	19	F	150	?	-	Hemorrhage and leathery change	-	Death
USA	38	F	120	?	-	Cicatrical gastric stenosis	+	Survival
USA	14	M	120	?	-	Perforation	+	Survival
USA	58	M	118	?	+	Hard and leathery change	-	Death
France	46	F	50-100	?	+	None	-	Death
Germany	55	F	?	?	+	Hemorrhage	+	Death
Germany	34	M	?	?	+	Perforation	-	Death
India	40	M	?	?	?	Cicatrical gastric stenosis	-	Survival

Gastrointestinal (GI) tract irritation and lesions, e.g. cicatrical gastric stenosis, are the most reported local effects from acute oral exposure to formalin in humans due to the ability of formalin of fixing the tissue upon exposure (Kochhar et al., 1986; Pandey et al., 2000; Yanagawa et al., 2007). In addition to GI effects, systemic effects such as respiratory distress as well as liver and kidney damage have been observed from formalin ingestion. Death due to health complications from formalin ingestion, such as malnutrition induced by cicatrical gastritis, respiratory or cardiovascular failure, has also been reported (Pandey et al., 2000; Yanagawa et al., 2007). A key limitation to the evaluation of the human data for acute oral toxicity is that the presence of methanol in formalin. Methanol (CAS number 67-56-1) is also classified in CLP, Annex VI as acute oral toxicity, category 3, and consequently, the presence of methanol may confound the acute oral toxicity effects of formaldehyde. Therefore, the human data on acute oral toxicity of formalin/formaldehyde is used as supporting information.

Overall, the acute oral toxicity study of Tsuchiya et al. (1975) was taken as the key study for the proposal of acute oral toxicity classification of formaldehyde under CLP criteria. Even though the study was not performed in accordance with OECD test guideline (but this is due to the fact that the study was performed before the publication of the test guidelines) or under GLP compliance, the study is considered well conducted (e.g. single oral administration via gavage, 6 doses tested, at least 8 animals per dose examined). The determined acute oral LD_{50} for male rats of 640 mg/kg bw is also lower (and thus more conservative for classification) than the respective LD_{50} of 800 mg/kg bw determined in the Smyth et al. (1941) study. While the acute oral LD_{50} of formaldehyde in guinea pigs (260 mg/kg bw) as reported in Smyth et al. (1941) study is lower than that in male rats, there is minimal information available on the study design and methods (e.g. tested doses, health status or housing conditions of the animals, approach to derive LD_{50}) that limits its eligibility as a key study for classification. Therefore, the Smyth et al. (1941) study can only be used as supporting information. No clinical examination or pathology assessment was provided in the two animal studies, but poisoning cases in humans have shown that the effects from single exposure to formalin are primarily localised in the GI tract with a few reports of systemic effects resulting in death. However, it cannot be determined whether these effects are solely attributable to formaldehyde as formalin contains methanol, which is also classified as an acute oral toxicant under CLP.

Altogether, the available data warrant a health risk classification of formaldehyde for acute oral toxicity as category 4 ("Harmful if swallowed", H302) based on an oral LD_{50} value of 640 mg/kg bw in male rats. According to the lowest observed LD_{50} value in a reliable study, the ATE (oral exposure) for formaldehyde can be set at 640 mg/kg bw.

10.1.2 Comparison with the CLP criteria

Exposure route	**Classification category or experimentally obtained acute toxicity range estimate**	**Toxicology results (LD_{50})**
Oral (mg/kg bw)	0 < Category 1 ≤ 5	
	5 < Category 2 ≤ 50	
	50 < Category 3 ≤ 300	
	300 < Category 4 ≤ 2000	640 mg/kg bw in male rats (Tsuchiya et al., 1975)

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Acute oral toxicity: Category 4, "Harmful if swallowed", H302, ATE = 640 mg/kg bw

10.2 Acute toxicity - dermal route

Table 14: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Value LD_{50}	Reference
Acute dermal toxicity, guideline- and GLP-conformity unknown (secondary literature, no original study report available)	Rabbit No further information on strain, sex and number of animals used	Formaldehyde (composition unknown)	No details of the study reported	270 mg/kg bw	Lewis and Tatken, 1980, Registry of toxic effects of chemical substances, Cincinnati, Ohio, National Institute for Occupational Safety and Health, Vol. 1, p. 695
Acute dermal toxicity (subcutaneous), non-guideline, non-GLP, limited details on study outcomes (e.g. no data on body weight or incidence of observed effects)	White rat, n = 64 (8/group); sex and specific strain not indicated	35.5 % (w/w) formaldehyde (obtained from Baker's 35.5 % solution)	300-640 mg/kg (10 or 15 % interval difference between doses)	420 mg/kg bw	Skog, 1950, Acta Pharmacol 6: 299-318
Acute dermal toxicity (subcutaneous), non-guideline, non-GLP, limited details on study outcomes (e.g. no data on body weight or incidence of observed effects)	White mouse, n = 72 (8/group); sex and specific strain not indicated	2 % (w/w) formaldehyde (obtained from Baker's 35.5 % solution)	150-460 mg/kg (10 or 15 % interval difference between doses)	300 mg/kg bw	Skog, 1950, Acta Pharmacol 6: 299-318

Table 15: Summary table of human data on acute dermal toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available				

Table 16: Summary table of other studies relevant for acute dermal toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data available				

10.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

There are two old references on acute dermal toxicity of formaldehyde in rabbits, rats and mice available for evaluation (Lewis and Tatken, 1980; Skog, 1950). The Lewis and Tatken (1980) reference is a report from the US's Registry of Toxic Effects of Chemical Substances and provided a dermal LD_{50} of 270 mg/kg bw in rabbits (the preferred species for dermal toxicity testing; see OECD test guideline 404: Acute Dermal Irritation/Corrosion). No further information on the study design and assessment was provided in this reference.

Skog (1950) investigated the acute toxicity of lower aliphatic aldehydes including formaldehyde in rodents. The acute dermal toxicity of formaldehyde in both rats and mice was conducted via subcutaneous injection. Even though this study was not performed in accordance with OECD test guideline (e.g. OECD test guideline 404) or under GLP compliance as it was performed much earlier before the introduction of OECD test guidelines or GLP, it is considered well-conducted (e.g. 8-9 doses tested, 8 animals per dose examined, clinical and histological examinations performed) and suitable for evaluation. LD_{50} values (determined via the probit method) were calculated to be 420 mg/kg for rats and 300 mg/kg for mice. Lethality occurred within 68 hours for rats and within 20 minutes for mice. Clinical observations showed that animals became listless and exhibited lacrimation as well as increased nasal secretion. Systemic effects such as bronchitis, slight hyperaemia and small haemorrhages around some vessels of the lungs as well as hyperaemia of liver and kidneys were reported in this study. However, it is not clear if these effects are specific to formaldehyde exposure due to lack of reporting of incidence or dose-response relationship of these systemic effects.

Overall, notwithstanding the limitations of both references, the reported LD_{50} values for all three species are similar within the range of 270-420 mg/kg, which fits in the acute dermal toxicity, category 3. The classification for acute dermal toxicity of formaldehyde is proposed taking a weight-of-evidence approach, and in this case, no change in the existing classification of formaldehyde as acute dermal toxicity, category 3 ("Toxic in contact with skin", H311) is required. Since the lowest LD_{50} is 270 mg/kg bw, the ATE for formaldehyde (dermal exposure) can be set at 270 mg/kg bw. It should be mentioned that formaldehyde is classified in CLP, Annex VI as skin corrosive, category 1B (Skin Corr. 1B), and for animal welfare reasons, further *in vivo* testing on acute dermal toxicity should be avoided (refer to OECD test guideline 404).

10.2.2 Comparison with the CLP criteria

Exposure route	**Classification category or experimentally obtained acute toxicity range estimate**	**Toxicology results (LD_{50})**
Dermal (mg/kg bw)	0 < Category 1 ≤ 50	
	50 < Category 2 ≤ 200	
	200 < Category 3 ≤ 1000	270 mg/kg bw in rabbits (Lewis and Tatken, 1980) 300 mg/kg bw in mice (Skog, 1950) 420 mg/kg bw in rats (Skog, 1950)
	1000 < Category 4 ≤ 2000	

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

Acute dermal toxicity: Category 3, Toxic in contact with skin", H311, ATE = 270 mg/kg bw

10.3 Acute toxicity - inhalation route

Table 17: 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
Acute inhalation toxicity, non-guideline, non-GLP: no details about test substance, exposure and analytical methods (secondary literature)	White rat, males, 6-10/group, specific strain not indicated	Formaldehyde (purity of test substance not indicated), gas	0.28-0.94 mg/L (233-783 ppm; 21 concentrations tested) 4 hours	0.588 mg/L (490 ppm) [a]	Nagorny et al., 1979, Gig. Truda Profzabol. 7, 27-30 cited in OECD (2002) OECD HPV Chemicals programme, SIDS Dossier approved at SIAM 14 (26-28 March 2002)
Acute inhalation toxicity, non-guideline, non-GLP: no details about test substance, exposure and analytical methods (secondary literature)	White mouse, M/F, 6-8/group, specific strain not indicated	Formaldehyde (purity of test substance not indicated), gas	0.079-1.008 mg/L (14 concentrations tested; 66-840 ppm) 2 hours	0.505 mg/L (421 ppm) [a]	Nagorny et al., 1979, Gig. Truda Profzabol. 7, 27-30 cited in OECD (2002) OECD HPV Chemicals programme, SIDS Dossier approved at SIAM 14 (26-28 March 2002)
Acute inhalation toxicity (whole body), non-guideline, non-GLP: limited details on study outcomes (e.g. no data on body weight or incidence of observed effects)	White rat, n = 72 (8/group); sex and specific strain not indicated	35.5 % formaldehyde (obtained by vapourising the Baker's 35.5 % solution), gas	0.6-1.7 mg/L (9 concentrations tested; 500-1417 ppm), 30 minutes	1 mg/L (833 ppm) [a]	Skog, 1950, Acta Pharmacol 6: 229-318
Acute local inhalation toxicity (nose-only), non-guideline, non-GLP: no details on clinical signs and other effects (e.g. body weight); no histopathological assessment other than nose performed	Rat, Sprague-Dawley, M, n = 10 (2/control and 3/formaldehyde-exposed; 2 time points examined)	Formaldehyde (obtained by passing dry, purified nitrogen through paraformaldehyde), gas	0.012 mg/L (10 ppm), 4 h	No LC_{50} LOAEC (local): ≤ 0.012 mg/L (10 ppm) [a]	Bhalla et al., 1991, J Toxicol Environ Health 33: 171-188

[a] 1 ppm = 1.2 mg/m^3 (0.0012 mg/L) at 1013.25 hPa and 20 °C

Table 18: Summary table of human data on acute inhalation toxicity

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
See Table 20 below.				

Table 19: Summary table of other studies relevant for acute inhalation toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Reviews	Formaldehyde	Reviews from international and national agencies, covering health effects of formaldehyde, among others, including acute inhalation exposure to formaldehyde in humans. The overall findings of at least 15 controlled exposure human studies of formaldehyde have been summarised in these reviews.	Human studies of acute controlled exposure (generally ranging between 30 minutes to 4 hours) to formaldehyde at concentrations up to 3 ppm revealed [1] local, reversible irritation of the nose, throat and eyes, [2] indications of nasal epithelium irritation (altered nasal lavage fluid contents) and [3] subtle modulation in pulmonary function variables.	ATSDR, 1999. Toxicological Profile for Formaldehyde. OECD (2002) OECD HPV Chemicals programme, SIDS Dossier approved at SIAM 14 (26-28 March 2002)

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

Nagorny et al. (1979) (study published in Russian but evaluated and summarised in OECD, 2002) investigated the acute inhalation toxicity of formaldehyde in male white rats. Twenty-one concentrations from 0.28-0.94 mg/L (equivalent to 233-783 ppm) were tested with 6-10 rats per concentration. Concentrations from 0.39 mg/L (325 ppm) onwards were reported to lead to mortality and a LC_{50} value of 0.588 mg/L (490 ppm) was determined following exposure for 4 hours. Clinical symptoms such as restlessness, excitation, laboured breathing, gasping and assuming a lateral position before death were observed (Nagorny et al., 1979; OECD, 2002).

Even though there was no accompanying histopathological assessment provided from the Nagorny et al. (1979) study, histopathological examination of another study revealed excessive mucus secretion, mucociliary dysfunction, single cell necrosis, and discontinuous nasal epithelium with erythrocyte leakage following 4-hour inhalation exposure to 0.012 mg/L (10 ppm) formaldehyde in male rats (Bhalla et al., 1991). Furthermore, an earlier study of Skog (1950) reported a higher LC_{50} value of 1 mg/L (833 ppm) in rats following shorter exposure for 30 minutes, which is in alignment with the outcomes from the Nagorny et al. (1979) study. From this study, exposure to formaldehyde at higher concentrations (0.6-1.7 mg/L; 500-1417 ppm) resulted in haemorrhage and oedema of the lung as well as oedema in liver and kidneys and hepatocyte necrosis (Skog, 1950). Altogether, evidence shows that the respiratory tract is the primary target organ of formaldehyde toxicity from inhalation exposure in animals.

Effects of acute inhalation exposure (generally ranging between 30 minutes to 4 hours) to formaldehyde in humans have been mainly identified from controlled exposure studies of healthy volunteers with formaldehyde concentrations ranging from 0.25-3 ppm (0.0003-0.0036 mg/L), which is much lower than the reported LC_{50} from animal studies. At the highest reported concentration of 3 ppm, transient irritation of the eyes and respiratory tract along with slightly altered pulmonary function variables have been observed (ATSDR, 1999; OECD, 2002). No human studies of inhalation exposure to higher concentrations of formaldehyde were identified for classification purposes.

In accordance with CLP, Annex I, Section 3.1, the preferred test species for evaluation of acute inhalation toxicity is the rat and classification for acute inhalation toxicity should be related to a 4-hour experimental period. With this considered, the study of Nagorny et al. (1979) is the most appropriate key study for classification purposes. Findings from the Skog (1950) and Bhalla et al. (1991) studies are in alignment with the key study and provide supporting information regarding target organ (respiratory tract). Altogether, the available data on acute inhalation toxicity warrant a classification of formaldehyde in acute inhalation toxicity (gases), Category 2 ("Fatal if inhaled", H330) based on LC_{50} value of 0.588 mg/L (490 ppm) from 4-hour exposure in rats. Since the lowest LC_{50} is 0.588 mg/L / 490 ppm, the ATE (inhalative exposure) can be set at 490 ppm.

10.3.2 Comparison with the CLP criteria

Exposure route	**Classification category or experimentally obtained acute toxicity range estimate**	**Toxicology results (LC_{50})**
inhalation; gases (ppmV)	0 < Category 1 ≤ 100	
	100 < Category 2 ≤ 500	490 ppm (Nagorny et al., 1979; OECD, 2002)
	500 < Category 3 ≤ 2500	
	2500 < Category 4 ≤ 20000	

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Acute inhalation toxicity: Category 2, Fatal if inhaled, H330, ATE = 490 ppm V (gases)

According to CLP, Annex I, section 3.1.2.3.3, in addition to classification for inhalation toxicity, if data are available that indicates that the mechanism of toxicity is corrosivity, the substance or mixture shall also be labelled as EUH071: 'corrosive to the respiratory tract'. Formaldehyde is classified under CLP, Annex VI as Skin Corr. 1B and therefore warrants the EUH071 labelling.

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Acute oral toxicity

There are several published acute oral toxicity studies and a number of human poisoning cases. The DS proposed classification as Acute Tox. 4; H302 with an ATE of 640 mg/kg bw based on an acute oral toxicity study in rats (Tsuchyia *et al.* 1975).

Acute dermal toxicity

The DS proposed Acute Tox. 3; H311 with an ATE of 270 mg/kg bw based on a rabbit LD_{50} value found in literature (no information about the study is available). A subcutaneous study in rats and mice was used as supporting information.

Acute inhalation toxicity

The DS proposed Acute Tox. 2; H330 with an ATE of 490 ppm based on an acute inhalation study in rats (Nagorny *et al.*, 1979). They further proposed to add EUH071 ('Corrosive to the respiratory tract.') due to classification as Skin Corr. 1B and

evidence of respiratory tract irritation in animal and human studies.

The DS also proposed to add Note 5: *"The concentration limits for gaseous mixtures are expressed as volume per volume percentage."*

Comments received during consultation

Comments were received from 2 industry representatives and 1 individual.

The industry commenters supported the DS proposals for acute toxicity (all routes), noting that the inhalation studies were old and non-guideline. They submitted a recent acute inhalation toxicity study in rats (Anonymous, 2015; see "Additional Key elements" in the Background Document) showing 100% mortality at 463 ppm. No revision of the classification proposal was made by the DS in response to this study.

Additional key elements

Acute inhalation study in rats (Anonymous, 2015)

In this GLP study, male and female Wistar rats (5/sex) were exposed (whole body) to formaldehyde vapour for 4 hours at a single concentration of 463 ppm (analytical concentration; the target concentration was 500 ppm). Formaldehyde vapour was generated from a non-stabilised aqueous solution (formaldehyde 10%) using a thermostat vaporiser (40 °C), the vapour was then diluted with air to achieve the desired concentration. The temperature in the exposure chamber was 23 °C.

All animals died within 2 days. Clinical signs included gasping, respiration sounds, breathing in stretched position, closed eyelids, red nasal discharge, poor general condition and salivation. During necropsy all animals showed dilated stomach filled with gaseous content. Four males and four females additionally showed similar findings in the intestine. Two males showed effusion (clear fluid) in the thoracic cavity.

The study was conducted according to OECD TG 403. RAC notes a deviation in the choice of exposure concentrations: unless conducted as a limit test (which is not the case here), at least three concentrations should be tested and their choice should preferably be based on a sighting study.

Assessment and comparison with the classification criteria

Acute oral toxicity

Formaldehyde currently has a minimum classification as Acute Tox. 3*, translated from the Dangerous Substances Directive (DSD) classification of T; R25. The criterion for T; R25 was 25 mg/kg bw < LD_{50} ≤ 200 mg/kg bw. This classification was already present in the entry from 1976 (Dir. 76/907/EEC). The available records from the meetings of the Working Group on Classification and Labelling of Dangerous Substances held in 1986 contain a claim that ingestion of 10 g of formalin, corresponding to a formaldehyde dose of 50 mg/kg bw, can be lethal to humans. This human ATE was obviously used to derive the concentration limit of 25% in the ATP of 1987 (Dir. 87/432/EEC). As the source of the human information is not provided in the records, this rather low ATE cannot be verified by RAC and is not considered further.

The database presented in the CLH report comprises two relatively old animal studies (Tsuchyia *et al.*, 1975; Smyth *et al.*, 1941) and a summary of human case reports.

Acute oral toxicity study in rats (Tsuchyia et al., 1975)

The authors performed several acute toxicity experiments in male rats (strain not specified) with aqueous solutions of formaldehyde (methanol-free prepared from paraformaldehyde) and with formalin (methanol content above 10%). The concentration of formaldehyde in the dosing solutions was 2% or 4%, the number of animals per group was 6 to 16. The observation period was only 1 week, but the deaths occurred mostly within 24 hours (some by the 3rd day).

The main experiment with methanol-free formaldehyde (dosed as a 4% aqueous solution) yielded an LD_{50} of 640 mg/kg bw. Mortality rates at the individual dose levels can be found in Table 12 of the CLH report.

No mention of clinical signs or necropsy findings can be found in the publication. The investigators apparently focused mainly on derivation of a robust LD_{50} value. Despite the limitations and the age of the study (the experiments took place in 1957-58), the abovementioned LD_{50} value is considered sufficiently reliable for classification purposes.

Acute oral toxicity study in rats and guinea pigs (Smyth et al., 1941)

The authors of the publication determined rat LD_{50} values for about 60 substances including formaldehyde ("of the usual commercial grade", purity and methanol content not specified). Most substances, including formaldehyde, were tested also in guinea pigs. The investigators used about 10 animals per group (male Wistar rats or guinea pigs of mixed sex), the post-exposure observation period was 14 days. Dose levels, clinical signs and necropsy findings are not reported. Formaldehyde concentration in the dosing solutions was ≤ 2%.

The LD_{50} for formaldehyde was 800 mg/kg bw in rats and 260 mg/kg bw in guinea pigs. It is noted that guinea pigs were more sensitive than rats to most of the compounds tested in both species.

The rat LD_{50} for methanol in the same study was 12900 mg/kg bw (guinea pigs not tested). Thus, the impact of methanol content in formalin on the rat LD_{50} value for formaldehyde was probably minimal.

Despite the poor reporting, the age of the study and the lack of information on purity, the reliability of the LD_{50} values is considered just sufficient for inclusion in the dataset.

Human data

The DS presented a list of human poisoning cases from formalin ingestion as summarized by Yanagawa *et al.* (2007). RAC has additionally used information from reviews of formalin and/or methanol poisonings by ATSDR (1999), Hovda *et al.* (2017) and US EPA (2013), as well as case reports by Eells *et al.* (1981) and Burkhart *et al.* (1990).

Formaldehyde is highly irritating to mucosal tissues and formalin ingestion results in severe stomach lesions. After absorption, formaldehyde is rapidly metabolised to formic acid. The systemic toxicity of formaldehyde is thought to primarily result from

the accumulation of formic acid and the ensuing metabolic acidosis. The symptoms after formalin ingestion include severe abdominal pain, vomiting, hypotension and shock, difficulty breathing, seizures, coma and anuria. Death due to the failure of multiple organ systems can occur within 24 h.

As to the lethal dose in humans, the patient in the case described by Eells *et al.* (1981) (a 41-year-old woman, bw ca. 60 kg) ingested 120 ml formalin containing 37% w/v formaldehyde, 12.5% v/v methanol, and no formic acid. The patient was admitted to hospital 30 minutes after ingestion and died 28 hours after admission, despite treatment (including ventilation, gastric lavage, intravenous bicarbonate). The lethal dose in this case can be estimated at < 740 mg/kg bw ("less than" because part of the formalin was removed by gastric lavage). A similar amount of formalin (exact composition unknown) was ingested in the fatal case described by Burkhart *et al.* (1990). Fatal cases after ingestion of formalin volumes as low as 30 ml are mentioned in the review by Yanagawa *et al.* (2007; the primary sources are in Japanese), this would correspond to lethal doses of formaldehyde in the order of 200 mg/kg bw.

The presence of methanol in the ingested formalin solutions may have contributed to the observed toxicity to some extent. Methanol does not produce local effects. After absorption it is slowly metabolized first to formaldehyde and then rapidly to formic acid. The systemic effects of methanol are, as in the case of formaldehyde, attributed mainly to metabolic acidosis due to accumulation of formic acid (although some contribution of formaldehyde produced from methanol directly in tissues cannot be excluded). The intoxication symptoms include impaired vision, nausea, tremors, convulsions and dyspnea, the patient may develop coma and respiratory and circulatory failure. The lethal dose of methanol is variably given as 30-240 ml, with 1000 mg/kg bw (1.2 ml/kg) as the best estimate (Hovda *et al.*, 2017).

Conclusion on classification

The LD_{50} values from the rat (Tsuchyia *et al.*, 1971; Smyth *et al.*, 1941), the preferred species for acute oral toxicity classification, are above 300 mg/kg bw and therefore correspond to Category 4. A well-described case report of human poisoning (Eells *et al.*, 1981) also provides a lethal dose in excess of 300 mg/kg bw. On the other hand, there is limited human information (Yanagawa *et al.*, 2007) indicating human lethal doses below 300 mg/kg bw, and a guinea pig LD_{50} of 260 mg/kg bw (Smyth *et al.*, 1941). It is noted that the formaldehyde concentrations in the human poisoning cases were corrosive while those used in the animal studies probably caused only mild local effects. Local effects in the gastrointestinal tract might have decreased the threshold for lethality in humans.

As the information indicating an LD_{50} in humans below 300 mg/kg bw is not sufficiently detailed and the rat is the preferred species for acute oral toxicity studies (OECD TG 420, 423, 425; CLP, Annex I, 3.1.2.2.1), RAC agrees with the DS's proposal of Category 4. However, given the possibly higher sensitivity of humans to the toxicity of formaldehyde and unknown human relevance of the guinea pig data, RAC prefers the somewhat lower converted ATE of 500 mg/kg bw (CLP, Annex I, Table 3.1.2) to the DS proposal of 640 mg/kg bw (the lowest rat LD_{50}).

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

Acute dermal toxicity

The current minimum classification Acute Tox. 3* has been translated from the DSD classification of T; R24. The criterion for R24 was 50 mg/kg bw < LD_{50} ≤ 400 mg/kg bw.

The DS presented one acute dermal toxicity study in rabbits from a secondary source (Lewis and Tatken, 1980) reporting an LD_{50} of 270 mg/kg bw. Lewis and Tatken (1980) refer to Union Carbide Data Sheet from 1967 as the source of this information. No further details are available.

The DS further presented an acute subcutaneous toxicity study (Skog, 1950) reporting an LD_{50} of 420 mg/kg bw for rats and 300 mg/kg bw for mice. However, relevance of this information for acute dermal toxicity classification is low as subcutaneous injection is not dermal exposure.

No other acute dermal toxicity data is available. While the biocidal assessment report presents the rabbit LD_{50} of 270 mg/kg bw, the online REACH registration dossier contains only a waiver. Indeed, formaldehyde has a harmonized classification as Skin Corr. 1B, and no acute dermal toxicity studies are required under REACH (nor under the Biocidal Products Regulation) for substances classified as corrosive to the skin.

Conclusion on classification

The current classification is Acute Tox. 3* and, in the original DSD process, it was supported by the same study that was presented by the DS (Lewis and Tatken ,1980). Although a dermal LD_{50} value is available, details of the study needed for its evaluation are lacking.

Formaldehyde has a harmonised classification as Skin Corr. 1B and substances classified as corrosive to the skin do not generally need to be tested for acute toxicity under REACH and BPR. Waiving of acute dermal toxicity testing for substances classified as corrosive is also envisaged in the relevant OECD documents (TG 402, GD 237).

Given the unknown reliability of the available data and the possibility of waiving, RAC recommends to **remove the classification for acute dermal toxicity** from the Annex VI entry.

Acute inhalation toxicity

The substance in the scope of Annex VI entry is an aqueous solution of formaldehyde, whereas the substance tested in acute toxicity studies was formaldehyde vapour. Formaldehyde is relatively volatile and partial pressure of formaldehyde in formalin solutions at 20-25 °C is in the order of 200 Pa, corresponding to 2000 ppm, or 0.2% vol. (the exact value differs considerably between sources, see the online registration dossier). Therefore, toxic effects via inhalation of formaldehyde vapour up to ca. 2000 ppm are considered relevant for the classification of formalin.

The current classification as Acute Tox. 3* is a translation from the DSD classification of T; R23. The criterion for T; R23 was 0.5 mg/l < LC_{50} ≤ 2 mg/l, for formaldehyde this is equivalent to 420 ppm < LC_{50} ≤ 1700 ppm. Although the justification of this DSD classification is not available to RAC, it is noted that the classification is consistent

with the results of the acute inhalation studies by Nagorny (1979) and Skog (1950) presented in the CLH report.

The available information comprises of several acute inhalation studies in rodents. Besides the classification, the role of local effects in acute inhalation toxicity of formaldehyde has to be discussed in the context of the proposed labelling with EUH071.

Acute inhalation toxicity study in rats and mice (Nagorny, 1979)

Male rats (6-10/group) were exposed to formaldehyde for 4 hours at concentrations from ca. 230 to >750 ppm (21 concentration levels). The 4-hour rat LC_{50} was 490 ppm, mortality started around 340 ppm. Lethality mainly occurred 1-2 days after exposure, clinical signs included restlessness and laboured breathing.

Male and female mice (6-8/group) were exposed to formaldehyde for 2 hours at concentrations from 66 to 840 ppm (14 concentration levels). The 2-hour mouse LC_{50} was 421 ppm.

Acute inhalation toxicity study in rats (Skog, 1950)

Rats (8/group) were exposed to formaldehyde for 30 minutes at concentrations from 0.6 to 1.7 mg/l (9 concentration levels). The post-exposure observation period was 3 weeks. The 30-min rat LC_{50} was 1 mg/l, which corresponds to ca. 830 ppm. Clinical signs included lachrymation, nasal secretion, respiratory sounds and gasping. Pathology of decedents showed lung edema. Although the majority of deaths occurred within the first 3 days, there were also delayed mortalities (up to day 15).

Acute inhalation study in rats (Anonymous, 2015)

Five male and 5 female Wistar rats were exposed for 4 hours to a single concentration level of 463 ppm. All animals died within 2 days. Respiratory symptoms included gasping, respiratory sounds and breathing in stretched position. Necropsy showed dilated stomach and intestines, respiratory tract findings were limited to effusion in the thoracic cavity in two males. Unfortunately, the choice and number of exposure concentrations did not follow any of the applicable OECD test guidelines (403, 433, 436). As a result, classification in Category 1 (LC_{50} < 100 ppm) cannot be excluded unless results of other studies are taken into account.

Local effects in the respiratory tract

A number of rodent studies reported damage of epithelial tissue in the upper respiratory tract after single or short-term exposure to concentrations around 10 ppm (ATSDR, 1999). Lung effects were observed close to the LD_{50}. A single 6-hour exposure to ca. 130 and 300 ppm was reported to lead to pulmonary edema in rats (Kamata *et al.*, 1996b, as cited in ATSDR, 1999). Pulmonary edema was also observed in decedents in the study by Skog (1950). It is therefore plausible that the mortalities in the acute toxicity studies were at least partly due to local effects. On the other hand, no strong evidence of lung damage was reported in the recent acute study by Anonymous (2015), and respiratory symptoms (secondary to metabolic acidosis) have been also observed in human oral poisoning cases. Still, formalin is classified as corrosive to the skin and, besides the local effects after inhalation of high concentrations of formaldehyde vapour, there is a possibility of inhalation exposure to

formalin aerosol. Therefore, addition of EUH071 ('Corrosive to the respiratory tract') is considered justified.

Although EUH071 is not currently part of the Annex VI entry, local effects in the respiratory tract are already addressed there. Risk phrase R37, 'Irritating to the respiratory system', has been part of the harmonised classification of formaldehyde since 1976 (Dir. 76/907/EEC) with a concentration limit of 5%. The corresponding hazard statement, STOT SE 3; H335 ('May cause respiratory irritation') with a specific concentration limit of ≥ 5% is still part of the entry (in the second last column). In the later DSD entries (from 1987) R37 applied up to 25%, from which concentration the solution was considered corrosive (R34). However, there is no upper limit for respiratory tract irritation (STOT SE 3; H335) in the current Annex VI entry. This will lead to overlap between EUH071 and STOT SE 3.

As STOT SE was not evaluated in the CLH report and was not open for third-party consultation, the overlap between EUH071 and STOT SE 3 cannot be resolved by RAC within the current process. Still, RAC will outline a possible solution to this problem.

The proposed labelling as EUH071 is mainly related to inhalation of formalin in the form of aerosol. Classification of aqueous solutions of formaldehyde as Skin Corr. 1B. applies from ≥ 25%. Between ≥ 5% and < 25% the solutions are classified as Skin Irrit. 2 and Eye Irrit. 2. The current limit for STOT SE 3; H335 of ≥ 5% is identical to the lower limit for skin and eye irritation.

The available records from the discussions on formaldehyde by the Working Group on Classification and Labelling of Dangerous Substances in 1986 show that the reasoning behind the concentration limits for eye/respiratory irritation (R36/37) of 5% and for acute toxicity (R23/24/25) of 30% was not available to the experts at that time. The reduction of the cut-off for "corrosive" (R34 vs R36/37/38) and "toxic" (R23/24/25 vs R20/21/22) from 30% to 25% agreed in 1986-87 was not triggered by data on local effects but by considerations related to the ATE for acute oral toxicity.

In the absence of data on the threshold concentration (as % formaldehyde in aqueous solution) for respiratory tract corrosion, a practical solution could be to apply the existing limits for skin irritation/corrosion to respiratory irritation/corrosion, that is:

- EUH071: C ≥ 25%
- STOT SE 3; H335: 5% ≤ C < 25%

Conclusion on classification

The substance in the scope of the Annex VI entry is aqueous solution of formaldehyde. This solution can release toxic formaldehyde gas. Since anhydrous formaldehyde is completely gaseous at room temperature, the acute toxicity classification of formaldehyde has to follow the criteria for gases (as opposed to vapours; see CLP, Annex I, 3.1.2.3.1). Classification in Category 2 is warranted for gases with a 4-hour LC_{50} of > 100 ppm and ≤ 500 ppm.

The recent acute inhalation toxicity study in rats by Anonymous (2015) reported 100% mortality after a 4-hour exposure to 463 ppm. Lower concentrations were not tested in this study. The pre-guideline study by Nagorny (1979) reported a 4-hour rat LC_{50} of 490 ppm; no mortality occurred below 300 ppm and 100% mortality from 750 ppm. These two studies, when considered together, point towards classification in Category

2 rather than Category 1. However, they do not allow derivation of an exact ATE.

Where the available data allow to conclude on classification but not on the ATE, RAC normally proposes a converted ATE from Table 3.1.2 of Annex I to the CLP. The converted ATE for Category 2 is 100 ppm. RAC notes that 100 ppm lies not only at the border of Category 1 (ATE ≤ 100 ppm) but actually within the range for Category 1. Although this may cause confusion, RAC can only use the converted value as it is.

In conclusion, RAC proposes classification as **Acute Tox. 2; H330 with an ATE of 100 ppmV (gases).**

RAC further agrees with the DS's proposal to **assign EUH071** based on classification of the substance as Skin Corr. 1B and on effects in the respiratory tract observed in animal acute inhalation studies. The overlap between STOT SE 3; H335 (in the second last column of the current entry) and EUH071 cannot be resolved by RAC within the current process because STOT SE was not open for third-party consultation. RAC suggest that a possible way forward could be to apply the existing limits for skin irritation/corrosion to respiratory irritation/corrosion, that is:

- EUH071: C ≥ 25%
- STOT SE 3; H335: 5% ≤ C < 25%

RAC does not support the DS's proposal to add Note 5: *"The concentration limits for gaseous mixtures are expressed as volume per volume percentage."* because the classification is for aqueous solutions of formaldehyde.

10.4 Skin corrosion/irritation

Health hazard not assessed in this dossier.

Formaldehyde is classified in CLP, Annex VI as skin corrosive, category 1B; H314 (causes severe skin burns and eye damage).

10.5 Serious eye damage/eye irritation

Health hazard not assessed in this dossier.

Formaldehyde is classified as skin corrosive, category 1B, and according to CLP Guidance, Section 3.3, "*serious damage to eyes is implicit as reflected in the hazard statement (H314: causes severe skin burns and eye damage)*". Therefore, a separate classification of formaldehyde for serious eye damage/eye irritation is not necessary.

10.6 Respiratory sensitisation

Health hazard not assessed in this dossier.

10.7 Skin sensitisation

Table 20: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
Similar to OECD 406 (GPMT), GLP compliance not mentioned, fewer number of animals tested than suggested in guideline	Guinea pig, Dunkin Hartley, 9 tested and 4 control, sex not specified	Formalin (diluted in physiological saline; no further information on composition provided)	Induction 0.25 % (v/v) formalin (corr. to 0.09 % (w/w) formaldehyde; a series of 6 intradermal injections) 10 % (v/v) formalin (corr. to 3.7 % (w/w) formaldehyde; occluded patch applied on the same site 6-8 days later for 48 h) Challenge 2 % (corr. to 0.74 % formaldehyde; occluded patch applied on different site 12-14 days after last induction for 24 h)	Sensitising All 9 tested animals showed positive response; mean erythema score was 1.7 out of 3.	Kimber et al., 1991, Toxicol Lett 55: 203-213
Similar to OECD 406 (GPMT), GLP compliance not specified	Guinea pig, Dunkin Hartley, 10 tested and 5 control, sex not clearly specified	Formalin (containing 37 % formaldehyde; diluted in physiological saline)	Induction 0.25 % (v/v) formalin (corr. to 0.09 % (w/w) formaldehyde; a series of 6 intradermal injections) 10 % (v/v) (corr. to 3.7 % (w/w) formaldehyde; occluded patch applied on the same site 6-8 days later for 48 h) Challenge 2 % (v/v) (corr. to 0.74 % (w/w) formaldehyde; occluded patch applied 12-14 days after last induction for 24 h)	Sensitising All 10 tested animals showed positive response. In control animals (without induction) no skin reaction was detected following the challenge phase.	Hilton et al., 1996, Food Chem Toxicol 34: 571-578
Similar to OECD 429 (LLNA); GLP compliance not mentioned	Mouse, CBA/Ca, females, 4/group	Formalin (containing 37 % formaldehyde; diluted either in acetone or DMF)	0, 0.25, 0.5, 1.0, 2.5, and 5 % (v/v) formalin (corr. to 0; 0.09; 0.19; 0.37; 0.93, and 1.9 % (w/w) formaldehyde); Daily exposure for 3 consecutive days	Formaldehyde was shown to be sensitising. EC_3: ~0.33 % (w/w) (110 mM in DMF) ~0.54 % (180 mM in acetone)	Hilton et al., 1998, Am J Contact Dermat 9(1): 29-33
Similar to OECD 429 (LLNA); GLP compliance not mentioned	Mouse, CBA/Ca, female, 4/group	Formalin (containing 37 % formaldehyde; diluted in 4:1 acetone/olive	0.1, 0.5, 1, 5, 10 % (v/v) formalin; Daily exposure for 3 consecutive days	Formaldehyde was shown to be sensitising (increasing stimulation index with increasing	Basketter et al., 2001, Contact Dermat 45: 89-94

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
		oil)		concentration). EC_3: 0.35 % (w/w) formaldehyde (corresponding to 0.93 % (v/v) formalin)	
Similar to OECD 429 (LLNA), GLP compliance not mentioned, Deviation: Mice were pretreated with 1 % SDS on the dorsum of the ears 1 hour before formaldehyde exposure in order to enhance possible low responses of weak sensitisers	Mouse, Balb/c, females, 3 tested and 6 control	Formaldehyde (dissolved in 4:1 acetone/olive oil)	0; 0.06; 0.23; 0.92, and 1.85 % (w/w); Daily exposure for 3 consecutive days	Formaldehyde was shown to be sensitising. EC_3: 0.96 % (w/w)	De Jong et al., 2007, J Immunotoxicol 4:239-246
GPMT, GLP compliance not specified	Guinea pig, Hartley, females, 10 animals	Formalin (37 % (w/w) aqueous formaldehyde)	5 % (v/v) (corr. to 1.85 % (w/w) formaldehyde) used throughout the experiment Induction: 3 sets of 2 intradermal injections (0.1 mL); dermal application on day 7 (0.5 mL) Challenge: Dermal application on day 21 for 24 hours and observed 1 and 2 days after challenge	Three rounds of experiments conducted: Round 1: 2/8 with reaction Round 2: 1/10 with reaction Round 3: 2/10 with reaction Cumulative: 5/28 animals with reaction	Marzulli and Maguire, 1982, Food Chem Toxicol 20: 67-74
Draize guinea pig technique, GLP compliance not specified	Guinea pig, Hartley, females, 10 animals	Formalin (37 % (w/w) aqueous formaldehyde; diluted in saline)	0.1 % (v/v) formalin used throughout the experiment Induction: 10 intradermal injections (3 times a week) Challenge: 1 intradermal injection given 2 weeks after the last (10^{th}) injection	Three rounds of experiments conducted: Round 1: 6/10 with reaction Round 2: 1/10 with reaction Round 3: 3/10 with reaction Cumulative: 10/30 animals with reaction	Marzulli and Maguire, 1982, Food Chem Toxicol 20: 67-74
Split-adjuvant technique, GLP compliance not specified	Guinea pig, Hartley, females, 10 animals	Formalin (37 % (w/w) aqueous formaldehyde)	5 % (v/v) (corr. to 1.85 % (w/w) formaldehyde) used throughout the experiment Induction: 4 dermal applications (0.2 mL) given every 2-3 days for 9 days; CFA injection given on day 4 Challenge: Day 22 using	Three rounds of experiments conducted: Round 1: 2/10 with reaction Round 2: 0/10 with reaction Round 3: 0/10 with reaction	Marzulli and Maguire, 1982, Food Chem Toxicol 20: 67-74

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance	Dose levels duration of exposure	Results	Reference
			GPMT method (applied for 24 hours and observed 1 and 2 days after challenge)	Cumulative: 2/30 animals with reaction	
Cyclophosphamide/CFA bioassay, GLP compliance not specified	Guinea pig, Hartley, females, 10 animals	Formalin (37 % (w/w) aqueous formaldehyde)	5 % (v/v) (corr. to 1.85 % (w/w) formaldehyde) used throughout the experiment Cyclophosphamide (150 mg/kg bw) given 3 days before induction Induction: 4 dermal applications (0.2 mL) given daily for first 4 days and once on day 9 for 6 hours; 2 CFA injections given on day 4 Challenge: Day 22 using GPMT method	Three rounds of experiments conducted: Round 1: 4/8 with reaction Round 2: 0/10 with reaction Round 3: 0/10 with reaction Cumulative: 4/28 animals with reaction	Marzulli and Maguire, 1982, Food Chem Toxicol 20: 67-74
Similar to OECD 406 (Buehler test), GLP compliance not specified	Guinea pig, Hartley, females, 10 animals	Formalin (37 % (w/w) aqueous formaldehyde; diluted in saline)	Induction: 5 % (v/v) (corr. to 1.85 % (w/w) formaldehyde); applied for 6 hours on day 1, 7 and 14 Challenge: 2 % (w/w) formaldehyde, 24 h occlusive patch applied on day 28	Three rounds of experiments conducted with 0/30 animals showing reaction In control animals (without induction) no skin reaction was detected. Formaldehyde was not sensitising in this Buehler assay.	Marzulli and Maguire, 1982, Food Chem Toxicol 20: 67-74
Similar to OECD 406 (Buehler test), GLP compliance not mentioned, fewer number of animals tested than suggested in guideline	Guinea pig, Dunkin-Hartley, 10 tested and 5 control, sex not clearly specified	Formalin (containing 37 % (w/w) formaldehyde; diluted in saline)	Induction: 5 % (w/v) formaldehyde (patch-exposed for 6 hours; occurred once a week for 3 weeks) Challenge: 1 % (w/v) formaldehyde (patch-exposed for 6 hours; occurred 12-14 days after induction)	Sensitising (70 % positive response)	Hilton et al., 1996, Food Chem Toxicol 34: 571-578
Similar to OECD 429 (LLNA), GLP compliance not mentioned	Mouse, CBA/Ca, 4/group/lab (study replicated in 4 labs), sex not specified	Formalin (diluted in 4:1 acetone/olive oil; no further information on composition provided)	Formalin concentrations: 0, 5, 10, 25 % (presumably v/v) Daily exposure for 3 consecutive days	Sensitising potential demonstrated with all tested doses and all 4 independent laboratories (stimulation index ranging from 3.7-11.9)	Kimber et al., 1991, Toxicol Lett 55: 203-213
Similar to OECD 429 (LLNA), GLP compliance not mentioned	Mouse, BALB/c, female, 4/group	Formalin (containing 37 % (w/w) formaldehyde; diluted in DMF)	0, 10, 25, 50 % (w/v) formalin Daily exposure for 3 consecutive days	Sensitising potential demonstrated with all tested doses (stimulation index of 8.58, 9.72 and 9.04 with 10, 20 and 50%, respectively)	Hilton et al., 1996, Food Chem Toxicol 34: 571-578

Table 21: Summary table of human data on skin sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Modified human Draize predictive test; summary only	Formalin (37 % (w/w) aqueous formaldehyde)	Induction: 5 % formalin Challenge: 1 % formalin	Four out of 52 volunteers (7.7 %) showed reaction.	Marzulli and Maguire, 1982, Food Chem Toxicol 20: 67-74
Diagnostic patch test; published report	Formaldehyde 1 % and 2 % (aqueous solution, w/w)	Patches were applied for 2 days, and results were read at day 2, 3, 4 and 7.	From 3734 patch tested patients, 121 (3.2 %) gave a positive reaction to 1 % and/or 2 % formaldehyde in water. There was no statistically significant difference between 1 and 2 % with respect to allergic reactions, but 2 % gave significantly more irritant reactions.	Trattner et al., 1998 Contact Dermatitis 38, 9-13
Patch tests; results from the European Surveillance System on Contact Allergy (ESSCA); published report	Occupational allergens including formaldehyde	The analysis included data from the years 2002-2010 from 11 European countries; patients aged 16-68 years (engaged in working life) were considered for the analysis.	Contact allergy to formaldehyde was most commonly found in personal care and related workers (5.7 %, 95 % CI 3.08–9.59) and machine tool setters and setter-operators (4.2 %, 95 % CI 1.95–7.87). Among the 9986 workers positive for occupational contact dermatitis (OCD), 3.04 % (95 % CI 2.69-3.4) had positive sensitisation reaction from formaldehyde exposure. Among 23564 workers negative for OCD, 1.82 % had positive sensitisation reaction from formaldehyde exposure.	Pesonen et al. 2015 Contact Dermatitis, 72, 154-163
Patch test; published report Subjects: 20 formaldehyde-sensitive patients (i.e. those who had a positive patch test to 1 % aqueous formaldehyde but negative test results to other chemicals such as paraben mix and rubber) and 20 healthy volunteers from Denmark	Formaldehyde (solution)	Occluded and non-occluded patch test with formaldehyde solutions at 25, 50, 250, 500, 1000, 5000 and 10000 ppm (corresponding to 0.0025, 0.005, 0.025, 0.05, 0.1, 0.5 and 1 % (w/w), respectively)	Dose-response relationship between formaldehyde exposure and positive skin sensitisation observed in the occluded patch testing (2 days). All patients had positive reactions to 10000 ppm (1%) formaldehyde. 5000 ppm: 9/20 patients with reaction 1000 ppm: 3/20 patients with reaction 500 ppm: 2/20 patients with reaction 250 ppm: 1/20 patient with reaction 25 and 50 ppm: 0 patient with reaction No positive results in the non-occluded patch test.	Flyvholm et al., 1997 Contact Dermatitis, 36:26-33
Standardised patch test (TRUE Test™) and patch test with Finn	Formaldehyde	Group 1: 0.12, 0.57 and 1.12 mg/cm^2 formaldehyde for TRUE Test™	Group 1: 5/9 and 2/9 patients with irritant reactions to the 1.12 mg/cm^2 and 0.57 mg/cm^2 TRUE test patches, respectively. Group 2: Dose-response rates for elicitation were reported for 25 patients	Fischer et al., 1995 Curr Prob Dermatol

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
chambers; published report Five studies (groups): Group 1: 9 healthy volunteers (3 women and 6 men) Group 2: 25 patients with previously positive reaction to formaldehyde Group 3: 120 patients with contact dermatitis Group 4: 24 patients with previously positive reaction to formaldehyde Group 5: 255 patients (96 males and 159 females) with contact dermatitis		Group 2: 0.02, 0.03, 0.04, 0.08, 0.12 and 0.15 mg/cm^2 formaldehyde for TRUE Test™ 0.015, 0.032, 0.063, 0.13, 0.25, 0.5 and 1 % (w/w) aqueous formaldehyde using Finn chambers Group 3: 0.01, 0.02, 0.04, 0.08, 0.12, 0.15 mg/cm^2 formaldehyde for TRUE Test™ 1 % (w/w) aqueous formaldehyde using Finn chambers Group 4: 0.15, 0.20, 0.26, 0.33 mg/cm^2 formaldehyde for TRUE Test™ 0.1, 0.3 and 1 % (w/w) using Finn chambers Group 5: 0.11, 0.19, 0.26, 0.33 mg/cm^2 formaldehyde using TRUE Test™ 1 % (w/w) aqueous formaldehyde using Finn chambers A TRUE Test patch with 0.81 mg/cm^2 N-hydroxymethylsuccinimide (HMS; a pro-allergen) contains 0.19 mg/cm^2 formaldehyde and exposes the skin to the same amount of formaldehyde as a Finn chamber test with 15 µL 1 % (w/w) formaldehyde solution.	with known formaldehyde sensitivity as follows: 4 / 8 / 20 / 36 / 68 / 76 and 88 % at concentrations of 0.015 / 0.032 / 0.063 / 0.13 / 0.25, 0.5 and 1.0 % (w/w), respectively, in water. Two groups of contact dermatitis patients exposed to a 1.0 % (w/w) formaldehyde showed response rates of 2.5 % (3/120; Group 3) and 3.5 % (9/255; Group 5). Group 4: 13/24 patients with previously positive reaction to formaldehyde demonstrated positive reactions to both TRUE Test™ and test with Finn chambers.	22:24-30.
Patch test; published report Subjects: 35 formaldehyde-allergic patients;	Formaldehyde (solution)	0.1, 0.3 and 1 % (w/w) aqueous formaldehyde	Dose-response relationship between formaldehyde exposure and allergy reaction. Patients allergic to formaldehyde 1.0 % only: 19/35 (54 %)	De Groot et al., 1988 Contact Dermatitis, 18:197-201

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
limited information on test methods			0.3 and 1 %: 8/35 (23 %) 0.1, 0.3 and 1%: 8/35 (23 %)	

Table 22: Summary table of other studies relevant for skin sensitisation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Formaldehyde (MAK value documentation, 2010); Assessment report	Formaldehyde	Formaldehyde is labelled as "Sh" (sensitising to the skin).	Allergic contact dermatitis from formaldehyde exposure in humans is frequently diagnosed, and numerous animal studies have shown mostly positive results. The key studies included in the MAK documentation are evaluated in the dossier. Frequencies of formaldehyde sensitisation in the general population in Europe were 0.3-0.9 %.	DFG (2000)
Review article	Formaldehyde		Formaldehyde is a common cause of contact allergy. In Europe, 2–3 % of patients suspected of contact dermatitis have positive patch test reactions. Allergic contact dermatitis caused by formaldehyde is often chronic, presumably because it is difficult to avoid exposure to the allergen completely. Patients allergic to formaldehyde are often women with hand eczema with/without facial dermatitis. This is explained by the hands being exposed to household cleansing agents (e.g. washing-up liquids) where formaldehyde is often found in combination with detergents that impair barrier function and increase penetration. Hand eczema from formaldehyde sensitivity is also found more often in nurses and other medical professions (paramedicals) and in metalworkers.	De Groot et al. 2009 Contact Dermatitis 61(2):63-85

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

Formaldehyde is a known primary skin sensitiser inducing Type IV allergic contact dermatitis (WHO, 1989; ATSDR, 1999; OECD, 2002). Concentrations of 1 % or less induced positive reaction in ca. 2 % of all patients tested throughout the world in dermatology clinics, higher concentrations used for challenge might be irritant (WHO 1989, ATSDR, 1999). Generally, it is difficult to distinguish between irritant and sensitising effects at higher concentrations (IARC 1995). In occluded patch tests on 20 healthy volunteers (non-sensitised controls) 1 % formaldehyde resulted in no irritant effects (ATSDR, 1999). In the OECD documentation (2002), a threshold for the challenge concentration in patch tests on formaldehyde-sensitised subjects was reported: 30 ppm (0.003 %) in aqueous solution and 60 ppm (0.006 %) for products containing

formaldehyde. However, other data on concentration-response relationships for skin allergic reaction in formaldehyde-sensitive patients induced by dermal exposures to formaldehyde suggested a positive reaction to formaldehyde is rare below concentrations of 0.025-0.05 % (ATSDR, 1999). A threshold concentration for induction has been estimated to be less than 5 % aqueous solution (OECD 2002).

The sensitising properties of formaldehyde are confirmed by a large number of tests in laboratory animals, including the guinea pig maximization test (GPMT) according to Magnusson & Kligman (Kimber et al., 1991; Hilton et al., 1996). Both studies, conducted similarly to OECD Guideline 406 (Skin Sensitisation), exposed 9-10 guinea pigs to 0.25 % formalin (corresponding to 0.09 % formaldehyde) via intradermal injection as the induction phase followed by 2% formalin (0.74 % formaldehyde) as the challenge phase. All exposed animals showed positive sensitising response to formalin (formaldehyde) exposure. Both studies are considered as key studies for the sub-category classification for skin sensitisation of formaldehyde, and the results of both studies meet the criteria for sub-category 1A ("≥ 30 % responding at ≤ 0.1 % intradermal induction dose" in the GPMT).

Local lymph node assays (LLNA) in mice also demonstrated skin sensitisation potential of formaldehyde as determined by lymphocyte proliferation in draining lymph nodes following dermal exposure (Kimber et al., 1991; Hilton et al. 1998; Basketter et al., 2001, de Jong 2007). The LLNA study by Basketter et al. (2001) determined the EC_3 (percent concentration required to elicit a stimulation index of 3 and a value that can be used for the sub-category classification) as approx. 0.35 % formaldehyde diluted in 4:1 acetone/olive oil vehicle. This result is comparable to the results obtained by Hilton et al. (1998), who determined EC_3 values of approximately 0.33 % and 0.54 % formaldehyde in dimethylformamide (DMF) and in acetone, respectively. De Jong et al. (2007) showed an EC_3 of approximately 0.96 % and calculated a stimulation index of 6.99 for repeated exposure (treatment at day 0-2; 7, 14, 21, 28, 35, 42, 49, and 56-58) with 0.6 % formaldehyde. However, mice were pretreated with 1 % SDS on the dorsum of the ears 1 hour before formaldehyde exposure in order to enhance possible low responses of weak sensitisers. Nevertheless, the studies by Basketter et al. (2001) and Hilton et al. (1998) are considered as key studies for the sub-category classification, and the results of both studies [as well as that from De Jong et al. (2007)] meet the criteria for sub-category 1A ("$EC_3 \leq 2$ %").

Buehler tests in guinea pigs produced equivocal results (Marzulli and Maguire, 1982; Hilton et al., 1996); however, this test has been reported to yield a high frequency of false negative findings when compared with findings in human predictive skin sensitisation testing (Marzulli and Maguire, 1982).

A substantial database on allergic skin reactions to formaldehyde in humans is available as the 1 % aqueous solution has been included in the European baseline patch test series. Pesonen et al. (2015) analysed data collected by the European Surveillance System on Contact Allergy (ESSCA) network between 2002 and 2010 from 11 European countries. Patients were workers of both sexes aged 16–68 years. Patch test results showed that 3.04 % and 1.82 % of workers with (n=9986) and without (n=23564) occupational contact dermatitis, respectively, had positive skin sensitising reactions to formaldehyde. Another patch test study by Trattner et al. (1998) reported that out of 3734 patients, 121 (3.2 %) had positive skin sensitising reactions to 1 % and/or 2 % formaldehyde.

In addition, dose-response data are available from three published studies and used as supporting evidence for classification. In the study by Flyvholm et al. (1997), 20 formaldehyde-sensitive patients (14 women, 6 men; age 32-71 years) were exposed to concentrations from 0.0025 % (w/w; 25 ppm) to 1 % (w/w; 10000 ppm) formaldehyde in occluded/diagnostic patch test. At 0.5 % (5000 ppm), 6 out of 9 positively tested patients had moderate to strong reactions, decreasing to response rates of 3/9 (33 %) and 2/9 (22 %) at 0.1 and 0.05 % formaldehyde, respectively. Similarly, the study by De Groot (1988) included patch testing of 35 patients known to be allergic to formaldehyde, and 8 out of 35 (23 %) patients showed reactions towards aqueous solution of 0.1 % (w/w) formaldehyde. At 0.3 and 1.0 % formaldehyde, allergic response rates were 8/35 (23 %) and 19/35 (54 %). The study by Fischer et al. (1995) reported results from 5 different studies using two different patch tests (a standardized TRUE Test™ and patch test using Finn chambers), various concentrations of formaldehyde (concentration ranging from 0.015-1%) and patients with or without previously sensitising reaction to formaldehyde. Dose-response relationship was consistently demonstrated between formaldehyde and skin-sensitising/allergic reactions.

Altogether, the available animal and human data on skin sensitisation support the sub-category classification of formaldehyde as Category 1A ("May cause an allergic skin reaction", H317).

With regard to assessment of potency, higher weight is given to the LLNA studies with EC_3 values of 0.33-0.54 % (w/w), according to which formaldehyde qualifies as a "strong" skin sensitiser, resulting in a GCL of 0.1 %. Data supporting the existing SCL of 0.2 % could not be identified.

10.7.2 Comparison with the CLP criteria

Sub-category	**Type of data**	**Assay**	**Criteria**	***Results***
1A	Animal	LLNA	$EC_3 \leq 2$ %	EC_3 0.33-0.54 % (w/w) (Hilton et al., 1998; Basketter et al., 2001)
		GPMT	≥ 30 % responding at ≤ 0.1 % intradermal induction dose or ≥ 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose	100 % positive at 0.25 % intradermal induction dose of formalin (equivalent to 0.09 % (w/w) formaldehyde) (Kimber et al., 1991; Hilton et al., 1996)
		Buehler assay	≥ 15 % responding at ≤ 0.2 % topical induction dose or ≥ 60 % responding at > 0.2 % to ≤ 20 % topical induction dose	
	Human	Repeated Insult Patch Test & Maximization Test	Positive responses at ≤ 500 µg/cm^2	
		Diagnostic patch test data	relatively high frequency of skin sensitisation occurrence in a defined population in relation to relatively low exposure	121 out of 3734 patch-tested patients (3.2 %) gave positive reaction to 1-2 % formaldehyde (Trattner et al., 1998)
		Other epidemiological evidence	relatively high frequency of allergic contact dermatitis in relation to relatively low exposure	
1B	Animal	LLNA	EC_3 value > 2 %	
		GPMT	≥ 30 % to < 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose or ≥ 30 % responding at > 1 % intradermal induction dose	
		Buehler assay	≥ 15 % to < 60 % responding at > 0.2 % to ≤ 20 % topical induction dose or ≥ 15 % responding at > 20 % topical induction dose	
	Human	Repeated Insult Patch Test & Maximization Test	positive responses at > 500 µg/cm^2	
		Diagnostic patch test data	relatively low but substantial frequency of skin sensitisation occurrence in a defined population in relation to relatively high exposure	
		Other epidemiological evidence	relatively low but substantial frequency of allergic contact dermatitis in relation to relatively high exposure	

10.7.3 Conclusion on classification and labelling for skin sensitisation

Criteria for Skin Sensitisation Category 1A, "May cause an allergic skin reaction", H317 are met.
LLNA data indicate a "strong" potency for skin sensitisation with a GCL of 0.1 %.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The current classification of formaldehyde is Skin Sens. 1 with an SCL of 0.2%. The DS proposed subcategorization as Skin Sens. 1A mainly based on LLNA and GMPT data, although human data are also mentioned in the justification. As the EC3 values from the most reliable LLNAs correspond to strong potency, the DS proposed to apply the generic concentration limit of 0.1%.

Comments received during consultation

Two industry commenters supported the DS's proposal.

Assessment and comparison with the classification criteria

The current classification as Skin Sens. 1 is a translation from the DSD classification R43. Sub-categorisation was not possible under DSD. Harmonised classification of formaldehyde for skin sensitisation was introduced in 1981 (81/957/EEC) with a concentration limit of 5%. The concentration limit was decreased to 1% in 1987 (87/432/EEC), and then further down to 0.2% in 1996 (96/54/EC). For comparison, the generic concentration limit under the Dangerous Preparations Directive (1999/45/EC) was 1%.

Animal data

The LLNAs, GPMTs and Buehler assays presented in the CLH report are summarised in the table below. In addition, several non-standard tests in guinea pigs (Marzulli and Maguire, 1982) can be found in Table 20 of the CLH report.

Animal data on skin sensitisation			
Study; reference	**Method**	**Results**	**Remarks, deviations from OECD TG**
LLNA Hilton *et al.,* 1998	Substance: formalin (formaldehyde 37%) Vehicle: DMF or acetone Concentrations (corrected to formaldehyde): 0, 0.093, 0.19, 0.37, 0.93, 1.9%	DMF: EC_3 0.33% Acetone: EC_3 0.54%	No information on irritation threshold
LLNA	Substance: formalin	EC_3 0.35%	No information on

Basketter *et al.,* 2001	(formaldehyde 37%) Vehicle: acetone/olive oil 4:1 Concentrations (corrected to formaldehyde): 0, 0.037, 0.19, 0.37, 1.9, 3.7%		irritation threshold
LLNA Hilton *et al.,* 1996	Substance: formalin (formaldehyde 37%) Vehicle: DMF Concentrations (corrected to formaldehyde): 0, 3.7, 9.3, 19%	EC_3 < 3.7% SI at 3.7%: 8.6	EC_3 could not be determined due to inappropriate concentration selection No information on irritation threshold
LLNA Kimber *et al.,* 1991	Substance: formalin (formaldehyde content not specified) Vehicle: acetone/olive oil 4:1 Concentrations (formalin, not corrected to formaldehyde): 0, 5, 10, 25% Experiment conducted in 4 different laboratories	EC_3 < 5% (as formalin) SI at 5% (as formalin): 9.0, 3.7, 6.8 and 4.6 in laboratory A, B, C and D respectively	EC_3 could not be determined due to inappropriate concentration selection No information on irritation threshold
LLNA De Jong *et al.,* 2007	Substance: formaldehyde Vehicle: acetone/olive oil 4:1 Concentrations (formaldehyde): 0, 0.06, 0.23, 0.92, 1.9%	EC_3 0.96%	SLS pre-treatment 3 animals per concentration No information on irritation threshold
GPMT Hilton *et al.,* 1996	Substance: formalin (formaldehyde 37%) Concentrations (reportedly formaldehyde[a]): intradermal induction 0.25%, topical induction 10%, challenge 2%	Response rate: 100% No reaction in controls	10 treated and 5 control animals
GPMT Kimber *et al.,* 1991	Substance: formalin (formaldehyde content not specified) Concentrations (formalin, not corrected to formaldehyde):	Response rate: 100% (9/9)	9 treated and 4 control animals No information on response rate in controls

	intradermal induction 0.25%, topical induction 10%, challenge 2%		
GPMT Marzulli and Maguire, 1982	Substance: formalin (formaldehyde 37%) Concentrations (corrected to formaldehyde): intradermal induction 1.9%, topical induction 1.9%, challenge 1.9%	Response rate: 18% (5/28)	Rationale for concentration selection not provided, the same concentration for topical induction and challenge No information on positive control
Buehler assay Hilton *et al.,* 1996	Substance: formalin (formaldehyde 37%) Concentrations (reportedly formaldehyde[a]): induction 5%, challenge 1%	Response rate: 70% No reaction in controls	10 treated and 5 control animals
Buehler assay Marzulli and Maguire, 1982	Substance: formalin (formaldehyde 37%) Concentrations (corrected to formaldehyde): induction 1.9%, challenge 1.9%	Response rate: 0% (0/30)	Rationale for concentration selection not provided, the same concentration for induction and challenge No information on positive control

[a] The table in the publication states that the test concentrations are expressed as 'formaldehyde' for the GPMT and Buehler assay, while tables with for other assays (*e.g.* LLNA) report the concentrations of 'formalin'. The DS obviously considered the concentrations for the GPMT (but not Buehler test) to represent concentrations of 'formalin' and corrected them with a factor of 0.37.

Three reliable LLNAs (Hilton *et al.*, 1998; Basketter *et al.*, 2001) reported EC3 values between 0.33% and 0.54%. This corresponds to subcategory Skin Sens. 1A (EC3 ≤ 2%) and strong potency (0.2% < EC3 ≤ 2%). This subcategorization is further supported by the EC3 of 0.96 from a non-standard LLNA by De Jong *et al.* (2007) and by four standard LLNAs reported by Kimber *et al.* (1991). Although EC3 values could not be derived from the latter four assays, all SI values at 5% formalin (probably corresponding to ca. 2% formaldehyde) were above 3.

The results of two reliable GPMTs (Hilton *et al.*, 1996; Kimber *et al.*, 1991) and one reliable Buehler assay (Hilton *et al.*, 1996) also correspond to Skin Sens. 1A. Subcategory 1A is warranted if ≥ 60% of animals respond at ≤ 1% intradermal induction for GPMT or at ≤ 20% topical induction for Buehler. The cut-off between strong and extreme potency at ≥ 60% response is 0.1% intradermal and 0.2% topical for GPMT and Buehler respectively. While the Buehler assay by Hilton *et al.* (1996) clearly corresponds to strong potency (induction concentration above 0.2%), no conclusion can be made for the GPMTs as the intradermal concentrations are known only approximately (either 0.25% or 0.09% in Hilton *et al.*, 1996; probably around 0.09% in Kimber *et al.*, 1991) and are close to 0.1%. The studies by Marzulli and Maguire (1982) are considered of low

reliability due to questionable concentration selection and lack of positive control.

Overall, the reliable animal data are consistent with Skin Sens. 1A and a strong potency.

Human data

Human repeated insult patch tests

The DS presented one human repeat insult patch test (HRIPT) with formalin at an induction concentration of 5% (equivalent to 1.9% formaldehyde; Marzulli and Maguire, 1982). This test was part of a concentration series described in Marzulli and Maibach (1974). The authors tested a number of substances using a Draize test, described as follows: The studies conducted on normal male subjects, aged 21-50 years. During the 3½-week induction period the test material (0.5 g) was applied to upper arm and covered with an occlusive patch (Johnson & Johnson Square Band Aid, without perforations) for 48 or 72 hours. 10 applications were administered successively at the same site. Following a rest period of approximately 2 weeks, the challenge patch was applied for 72 hours, after which the reaction was read. The challenge was done at a non-irritant concentration. Generally, reactions showing erythema and oedema (at least grade 2) were accepted as positive. To verify reproducibility, positives were retested a week or two later. Most grade 1 (erythema only) subjects were retested approximately weekly; if the severity of the reaction decreased on re-testing, the subjects were considered to have an irritant response.

The results for formaldehyde (water used as a vehicle) are summarised in the table below. The positive result at 0.37%, corresponding to ca. 290 µg/cm^2, meets the criterion for subcategory 1A (i.e. positive response at ≤ 500 µg/cm^2).

HRIPTs by Marzulli and Maibach (1974)				
Induction concentration[a] (%)	**Challenge concentration[a] (%)**	**Response (no. positive/total no. of subjects)**	**Response (%)**	**Dose per surface area[b] (µg/cm^2)**
0.037	0.37	0/45	0	29
0.37	0.37	4/89	4.5	290
1.1	0.37	5/88	5.7	860
1.9	0.37	4/52	7.7	1400
3.7	0.37	8/102	7.8	2900

[a] administered as formalin, the concentrations in the table are corrected for the concentration of formaldehyde in formalin (37%)

[b] as provided in OECD (2021)

Diagnostic patch tests

Formaldehyde is a well-known contact allergen in humans and a great amount of published diagnostic patch test data is available. Two diagnostic patch test results presented in the CLH report (Trattner *et al.*, 1998; Pesonen *et al.*, 2015) and studies summarized by De Groot *et al.,* 2009; are listed in the table below (full references can be found in De Groot *et al.*, 2009; test concentration 1% in water except Trattner *et al.*, 1998, who used 1% and 2%). The European studies show a relatively consistent sensitisation frequency of about 2-3%, which is qualified as 'high' according to the

criteria in the Guidance on the application of the CLP criteria (CLP guidance), Table 3.2 in section 3.4.2.2.3. An even higher frequency (7-9%) was found in the USA in the same period.

Human diagnostic patch tests				
Reference	**Country**	**Time period**	**Number of patients**	**Positive**
Trattner *et al.,* 1998	Denmark	1992-1996	3734	3.2%
Pesonen *et al.,* 2015	Europe	2002-2010	Workers with occupational contact dermatitis: 9986	3.0%
			Workers without occupational contact dermatitis: 23564	1.8%
Jong *et al.,* 2007	UK	2004-2005	6958	2.0%
Carlsen *et al.,* 2007	Denmark	1985-2005	14980	2.9%
Worm *et al.,* 2005	Germany, Austria, Switzerland	2001-2004	31045	1.7%
Uter, 2008	Europe	2004	9956	2.0%
Uter *et al.,* 2005	Europe	2002-2003	9213	2.0%
Hasan *et al.,* 2005	Finland	2000-2002	11798	2.5%
Machovcova *et al.,* 2005	Czech Republic	1997-2001	12058	4.1%
Bruynzeel *et al.,* 2005	Europe	1996-2000	26210	2.3%
Lindberg *et al.,* 2007	Sweden	2000	3790	2.6%
Britton *et al.,* 2003	UK	2000	2063	2.1%
Brasch *et al.,* 2001	Germany	1993-1999	32779	1.9%
Goossens *et al.,* 1998	Belgium	1995-1997	8521	0.9%
Hasan *et al.,* 2005	Finland	1995-1996	9378	3.0%
Schnuch *et al.,* 1997	Germany, Austria	1990-1995	36786	2.1%
Kränke *et al.,* 1996	Austria	1992-1993	11516	0.9%
Perrenoud *et al.,* 1994	Switzerland	1989-1990	2295	5.7%
Akyol *et al.,* 2005	Turkey	1992-2004	1038	1.3%
Lazarov, 2006	Israel	1998-2004	2156	1.8%
Freireich-Astman *et al.,* 2007	Israel	1999-2000	943	1.9%
Davis *et al.,* 2008	USA	2001-2005	3836	9.0%

Pratt *et al.,* 2004	USA	2001-2002	4909	8.4%
Wetter *et al.,* 2005	USA	1998-2000	1321	7.9%
Marks *et al.,* 2003	USA	1998-2000	5830	9.2%
Marks *et al.,* 2000	USA	1996-1998	3440	9.3%
Albert *et al.,* 1999	USA	1988-1997	927	6.8%
Marks *et al.,* 1998	USA	1994-1996	3111	9.2%
Marks *et al.,* 1995	USA	1992-1994	3526	7.8%
Liu *et al.,* 1997	China	1988-1996	1135	4.1%

Exposure

The DS has not attempted characterization of exposure level. Dermal exposure to formaldehyde occurs from a variety of sources, including cosmetics, household cleaners, textiles, glues or metalworking fluids. Use of formaldehyde in cosmetic products will be presented as an example, no attempt at exposure characterisation for other sectors has been made by RAC. Formaldehyde was allowed in the EU as a preservative in cosmetic products at concentrations up to 0.2% until 2019 (Dir. 76/768/EEC; Reg. 1223/2009). Although it was banned then from use in cosmetics due to carcinogenic properties (Reg. 831/2019), formaldehyde releasers are still allowed in cosmetics at concentrations up to 0.6% (see also De Groot *et al.*, 2010a). Typical formaldehyde concentrations in products at releaser concentrations meeting the limits appear to range between ca. 0.001% and 0.1% (De Groot *et al.*, 2010b).

Given the widespread exposure to formaldehyde and formaldehyde releasers, the number of exposures as well as frequency of exposure (as per CLP guidance, 3.4.2.2.3.1, Table 3.3) are relatively high. The information on exposure concentrations in cosmetics indicate levels below 1%. This results in an overall exposure score of 4 (0 for concentration, 2 for repeated exposure, 2 for number of exposures). Score range of 1-4 corresponds to a 'relatively low' exposure. Thus, diagnostic patch test data show a high incidence of reactions in relation to relatively low exposure at least for the use in cosmetics.

Elicitation threshold

Although not directly relevant for subcategorization, the DS also presented some information on dose-response relationship for elicitation. Fischer *et al.* (2011) have used the data from Flyvholm *et al.* (1997) to derive an ED_{10} of 20.1 µg/m^2, corresponding to ca. 0.07%. SCCS recently proposed (SCCS, 2021) to decrease the cut-off for labelling of cosmetic products with 'contains formaldehyde' from 0.05% to 0.001% formaldehyde based on a repeated open application test with a formaldehyde releaser; the method involved SLS pre-treatment to induce irritant dermatitis.

Human data on dose-response relationship for elicitation (patch tests)			
Reference; type of study	**Number of subjects**	**Formaldehyde concentration**	**Response rate**
Flyvholm *et al.,* 1997	20 formaldehyde-sensitive	1%	19/20
		0.5%	9/20
		0.1%	3/20

		0.05%	2/20
		0.025%	1/20
		0.005%	0/20
	20 healthy controls		No reaction to any concentration
Fischer *et al.,* 1995	25 formaldehyde-sensitive	1%	22/25[a]
		0.5%	19/25
		0.25%	17/25
		0.13%	9/25
		0.063%	5/25
		0.032%	2/25
		0.015%	1/25
De Groot *et al.,* 1988	35 formaldehyde-sensitive	1%	35/35
		0.3%	16/35
		0.1%	8/35

[a] The publication shows a list of concentrations tested, and for each concentration the number of patients for whom this was the minimal concentration eliciting a positive response. The incidences in this table have been derived on the assumption that each patient also reacted to all concentrations above his/her elicitation threshold.

Conclusion on classification and concentration limit

Both animal and human data clearly demonstrate the skin sensitisation potential of formaldehyde. Reliable animal studies (LLNA, GPMT, Buehler assay) are consistent with subcategory 1A and strong potency. A HRIPT showed a positive result at a surface dose below 500 µg/cm^2, which also meets the criteria for subcategory 1A. The diagnostic patch tests show a high frequency of sensitisation; the corresponding exposure level appears to be relatively low, but no firm conclusion can be made due to limited exposure information (no exposure information presented by the DS, only some information related to the use in cosmetics retrieved by RAC).

In conclusion, RAC agrees with the DS's proposal of **Skin Sens. 1A** based on animal and human data. Since there is no clear indication of extreme potency, the GCL of 0.1% applies.

10.8 Germ cell mutagenicity

Health hazard not assessed in this dossier

In 2012, the RAC adopted the opinion on the proposed harmonised classification and labelling of formaldehyde as germ cell mutagenicity, category 2; H341 (suspected of causing genetic defects) based on scientific studies that demonstrated that formaldehyde induces genotoxic effects *in vivo* on somatic cells at site of contact.

10.9 Carcinogenicity

Health hazard not assessed in this dossier.

In 2012, the RAC adopted the opinion on the proposed harmonised classification and labelling of formaldehyde as carcinogenicity, category 1B; H350 (may cause cancer). This adopted classification is based on limited evidence of carcinogenicity in humans (positive association of nasopharyngeal tumours in industrial cohorts) and sufficient evidence of carcinogenicity from animal studies (dose-related increase in nasal tumours of the upper respiratory tract in rats).

10.10 Reproductive toxicity

Health hazard not assessed in this dossier.

10.11 Specific target organ toxicity-single exposure (STOT-SE)

Health hazard not assessed in this dossier.

There is no harmonised classification of formaldehyde in CLP, Annex VI for STOT SE. However, based on the acute toxicity studies and reports on formaldehyde, the effects from single exposure to formaldehyde occur at the site of contact (e.g. stomach for oral and respiratory tract for inhalation exposure), and there have been no clear effects observed beyond the site of contact that would justify STOT-SE 1 or 2 classification of formaldehyde. Classification for STOT SE 3 is not required, as the potential for respiratory tract irritation is already covered by the Skin Corr. 1B classification. Therefore, classification additional for STOT SE is not assessed.

10.12 Specific target organ toxicity-repeated exposure (STOT-RE)

Health hazard not assessed in this dossier.

There is no harmonised classification of formaldehyde in CLP, Annex VI for STOT RE. Data on oral or dermal exposure to formaldehyde is limited and considered not suitable for STOT RE classification. Formaldehyde is classified as skin corrosive, category 1B, and, as stated in the CLP Guidance, Section 3.9.2.5.1, corrosive substances may cause severe toxicological effects in the lungs following repeated inhalation exposure. Therefore, additional classification for STOT RE is not assessed.

10.13 Aspiration hazard

Health hazard not assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not assessed in this dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Not assessed in this dossier.

13 ADDITIONAL LABELLING

Formaldehyde is classified under CLP, Annex VI as Skin Corr. 1B and therefore warrants the EUH071 labelling.

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