Committee for Risk Assessment

RAC

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

Adopted

2 June 2022

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CLH-O-0000007130-88-01/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **Formaldehyde**

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

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

The proposal was submitted by **Germany** and received by RAC on **29 June 2021.**

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

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **9 August 2021**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **8 October 2021**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Michal Martínek**

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

The RAC opinion on the proposed harmonised classification and labelling was adopted on **2 June 2022** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	605-001-00-5	formaldehyde …%	200-001-8	50-00-0	Carc. 1B Muta. 2 Acute Tox. 3* Acute Tox. 3* Acute Tox. 3* Skin Corr. 1B Skin Sens. 1	H350 H341 H301 H311 H331 H314 H317	GHS05 GHS06 GHS08 Dgr	H350 H341 H301 H311 H331 H314 H317		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	605-001-00-5	formaldehyde …%	200-001-8	50-00-0	**Add** Flam. Gas 1B **Modify** Acute Tox. 4 Acute Tox. 3 Acute Tox. 2 Skin Sens. 1A	**Add** H221 **Modify** H302 H311 H330 H317	**Add** GHS02 **Retain** GHS06	**Add** H221 **Modify** H302 H311 H330 H317	**Add** EUH071	**Add** oral: ATE = 640 mg/kg bw dermal: ATE = 270 mg/kg bw inhalation: ATE = 490 ppm (gases) **Remove** Skin Sens. 1; H317: C ≥ 0,2 %	**Remove** D **Add** F, T, 5
RAC opinion	605-001-00-5	formaldehyde …%	200-001-8	50-00-0	**Modify** Acute Tox. 4 Acute Tox. 2 Skin Sens. 1A **Remove** Acute Tox. 3	**Modify** H302 H330 H317 **Remove** H311		**Modify** H302 H330 H317 **Remove** H311	**Add** EUH071	**Add** oral: ATE = 500 mg/kg bw inhalation: ATE = 100 ppm (gases) EUH071: C ≥ 25% **Remove** Skin Sens. 1; H317: C ≥ 0,2 %	**Retain** D **Add** F
Resulting Annex VI entry if agreed by COM	605-001-00-5	formaldehyde …%	200-001-8	50-00-0	Carc. 1B Muta. 2 Acute Tox. 4 Acute Tox. 2 Skin Corr. 1B Skin Sens. 1A	H350 H341 H302 H330 H314 H317	GHS05 GHS06 GHS08 Dgr	H350 H341 H302 H330 H314 H317	EUH071	oral: ATE = 500 mg/kg bw inhalation: ATE = 100 ppm (gases) 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 %	B, D, F

GROUNDS FOR ADOPTION OF THE OPINION

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**.

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**.

HUMAN HEALTH HAZARD EVALUATION

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.

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.

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 Basketter *et al.,* 2001	Substance: formalin (formaldehyde 37%) Vehicle: acetone/olive oil 4:1 Concentrations (corrected to formaldehyde): 0, 0.037, 0.19, 0.37, 1.9, 3.7%	EC_3 0.35%	No information on 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%	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

	Experiment conducted in 4 different laboratories		
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): intradermal induction 0.25%, topical induction 10%, challenge 2%	Response rate: 100% (9/9)	9 treated and 4 control animals No information on response rate in controls
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/cm²)**
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.

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ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

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