Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1); [HPT]

EC Number: -
CAS Number: -

CLH-O-0000001412-86-89/F

Adopted

4 December 2015

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CLH-O-0000001412-86-89/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 harmonized classification and labelling (CLH) of:

Chemical name: **Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1); [HPT]**

EC Number: **-**

CAS Number: **-**

The proposal was submitted by **Austria** and received by RAC on **12 December 2014.**

In this opinion, all classifications and labelling are given in accordance with the CLP Regulation; the notation of 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer provided.

PROCESS FOR ADOPTION OF THE OPINION

Austria 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 **20 January 2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **6 March 2015**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Agnes Schulte**

Co-rapporteur, appointed by RAC: **Michael Neumann**

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 harmonized classification and labelling was adopted on **4 December, 2015** by **a simple majority of all members present and having the right to vote.**

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

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	**No current Annex VI entry**										
Dossier submitters proposal	612-291-00-7	Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1); [HPT]	-	-	Carc. 1B Muta. 2 Skin Corr. 1B Skin Sens. 1A Aquatic Chronic 3	H350 H341 H314 H317 H412	GHS08 GHS07 GHS05 Dgr	H350 H341 H314 H317 H412			
RAC opinion	612-291-00-7	Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1); [HPT]	-	-	Carc. 1B Muta. 2 Acute Tox. 4 Acute Tox. 4 STOT RE 2 Skin Corr. 1C Eye Dam. 1 Skin Sens. 1A Aquatic Chronic 2	H350 H341 H332 H302 H372 (gastrointestinal tract, respiratory tract) H314 H318 H317 H411	GHS08 GHS07 GHS05 GHS09 Dgr	H350 H341 H332 H302 H372(gastrointestinal tract, respiratory tract) H314 H317 H411	EUH071		
Resulting Annex VI entry if agreed by COM	612-291-00-7	Reaction products of paraformaldehyde with 2-hydroxypropylamine (ratio 1:1); [HPT]	-	-	Carc. 1B Muta. 2 Acute Tox. 4 Acute Tox. 4 STOT RE 2 Skin Corr. 1C Eye Dam. 1 Skin Sens. 1A Aquatic Chronic 2	H350 H341 H332 H302 H372 (gastrointestinal tract, respiratory tract) H314 H318 H317 H411	GHS08 GHS07 GHS05 GHS09 Dgr	H350 H341 H332 H302 H372 (gastrointestinal tract, respiratory tract) H314 H317 H411	EUH071		

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

The biocidal active substance "*reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 1:1)*" is a UVCB substance prepared by the reaction of paraformaldehyde and 2-hydroxypropylamine. The active substance originally notified as α,α',α"-trimethyl-1,3,5-triazine-1,3,5(2H,4H,6H)-triethanol, shortened to HPT, according to the biocidal products Directive 98/8/EC, was renamed Reaction products of paraformaldehyde with 2-hydroxypropylamine (referred to throughout this document as RP 1:1).

UVCB substances are identified by their source and manufacturing process. In addition, the active substance is specified by the main identifier "*content of releasable formaldehyde*" which is typically 28% (range of 26 – 30% w/w). The active substance (RP 1:1) is applied in aqueous solutions where, depending on the environmental conditions, it hydrolyses completely to formaldehyde and 2-hydroxypropylamine. Also the active substance is expected to hydrolyse completely once the substance has entered the human or animal body.

The active substance and the biocidal products are handled and marketed as aqueous solutions which contain no organic solvents.

While this opinion covers RP 1:1, another closely related UVCB called "Reaction product of paraformaldehyde and 2-hydroxypropylamine (RP 3:2) is also produced and is of relevance to this evaluation by RAC

For several endpoints, data on RP 3:2, as well as the hydrolysis products formaldehyde and 2-hydroxypropylamine were also considered.

The CLP Regulation, Art. 9 and Annex 1, 1.1.1.3, support a weight of evidence evaluation of the available data. Where data on RP 1:1 are lacking, data on RP 3:2 and data on the hydrolysis products formaldehyde and 2-hydroxypropylamine were therefore considered. Regarding the toxic effects and the related mode of action information on the hazardous properties on these related substances are in general considered appropriate to predict the hazardous properties of RP 1:1. The quality and consistency of the information was also taken into account in reading across the data.

In this opinion, RAC documents the weight of evidence on the intrinsic properties of RP 1:1 in the order of data on RP 1:1 (the UVCB substance to be classified), data on RP 3:2 and finally, data on the hydrolysis products formaldehyde and and 2-hydroxypropylamine.

Available hydrolysis tests support qualitatively that hydrolysis will occur in contact with aqueous biological media in mucous membrans. Inhalation exposure to aerosolic RP 1:1 is expected to result in hydrolysis at the site of contact and toxicologically significant concentrations of formaldehyde could be reached on the surface of the mucous membranes in the respiratory tract, eye or upper gastrointestinal (GI) tract or skin. The inhalation exposure to gaseous formaldehyde that is released from RP 1:1 is assumed to contribute in addition to the toxic/carcinogenic effect resulting from the direct impact of hydrolysis products at the contact site.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

The DS included data on both reaction products of paraformaldehyde with 2-hydroxypropylamine (RP 1:1) and (RP 3:2). For RP 1:1 there is one oral rat study and two dermal rat studies. The LD_{50}'s were 960 mg/kg bw in the oral and above 2000 mg/kg bw for dermal. For RP 3:2 there were three oral rat studies and three dermal rat studies. The LD_{50}'s were 630 mg/kg bw for acute oral toxicity and 790 mg/kg for acute dermal toxicity. No data was available on inhalation toxicity.

Although the data could be considered to support classification, the DS stated that the effects were due to the corrosivity of the substance and therefore proposed no classification for acute toxicity.

Comments received during public consultation

Three Member State Competent Authorities (MSCA) suggested that classification for acute toxicity may be applied. Two MSCAs proposed that in addition to classification for skin corrosivity, RP 1:1 should be classified as: Acute Tox. 4 (oral); H302, Acute Tox. 3 (dermal); H311, Acute Tox. 4 (inhalation); H332.
Two MSCAs also proposed addition of the supplemental hazard information statement EUH071 (Corrosive to the respiratory tract) and one MSCA raised the possibility of adding EUH029 (Contact with water liberates toxic gas).

Assessment and comparison with the classification criteria

Acute oral toxicity

RP 1:1
An LD_{50} of 960 mg/kg bw was estimated in the acute oral toxicity study on RP 1:1 according to OECD TG 401 (Schülke & Mayr, 2000). Macroscopic findings such as 'congestion of stomach, intestine and lungs, mottling in liver' are mentioned in table 4.2-3 of the CLH report. Information on the severity and the dose-response of these effects is lacking, and whether the stomach lesions were likely to have contributed to the mortality remains unclear. Additional information in the document CLH-Rep_ATT_HPT Doc III A (further on cited as "RP 1:1 Doc III A") states that 'varying degree of mucosal congestion/erosion in the glandular part of the stomach and congestion/mucus exudation in small intestine, also emphysema/congestion of lungs and mottling in liver' were observed. In general, congestion is related to the premortal circulatory failure and is expected as a nonspecific premortal finding. Erosive lesions, if present due to the irritative properties of the substance (which is not known, as no microscopy has been done), should start in the forestomach and should also be most prominent in this region. Local erosions alone – unlike ulcerations – depending on the severity and progression of the lesion (in general) are unlikely to be lethal (and then only if of high severity after prolonged duration of exposure, illness delayed mortality may not be excluded). Other effects were reported in Doc III A6.1.1 as lethargy, abdominal breathing, gasping and piloerection at the day of dosing in all treatment groups. A slight decrease in body weight gain of survivors were seen.

Concerning the DS proposal not to classify for acute oral toxicity due to the classification as a corrosive substance, RAC does not find a general disclaimer on acute toxicity for non-classification of corrosive substances in the CLP Regulation. In addition, there are no data that clearly indicate that the mechanism of toxicity was corrosivity. No details on the macroscopic findings were given. Congestion may be concluded from reddening of the stomach mucosa, but congestion alone is not predictive of a corrosive/ulcerative event. How the finding 'erosion' was characterised, remains unclear, in particular as the macroscopic finding reported as 'congestion/erosion' in the glandular stomach was not verified by microscopy.

The lack of evidence for RP 3:2 to cause corrosive (ulcerative) effects in the forestomach region supports the interpretation that the mortalities of RP 1:1 are systemically induced.

RP 3:2
The oral LD_{50} of 630 mg/kg bw was derived from a study in accordance with OECD test guideline (TG) 423 where mortality at 2000 mg/kg bw was 100% and no effects were seen at 200 mg/kg bw (Bode Chemie, 2002). Local effects along the upper GI tract that could indicate corrosivity of the 10% test solution in corn oil were not reported for this study. Also two further oral studies (Schülke & May, 1977, 1979) did not show local effects at test concentrations of 8% and 10%, respectively, in aqueous 0.9% NaCl solution. The DS explicitely noted that surprisingly no local effects were detected in the oral studies. In both studies, the clinical effects in surviving rats were reversible within 24 hours.

In conclusion, an OECD TG 423 study on RP 3:2 revealed a LD_{50} value of 630 mg/kg bw and two other studies with a test design similar to OECD TG 401 resulted in oral LD_{50} values of 750 and 900 mg/kg bw. Thus, RAC concluded that the data warrants to classify RP 3:2 (based on the studies on RP 3:2) as Acute Tox. 4; H302 (Harmful if swallowed) according to CLP (oral LD_{50} guidance values for this category from 300 to 2000 mg/kg bw).

Formaldehyde
Formaldehyde has a minimum classification in CLP, Annex VI for Acute oral toxicity, in category 3; H301 (Toxic if swallowed).

2-Hydroxypropylamine
In the document CLH-REP_ATT_Appendix HPA_DV018252-32 (referred to as "Doc Appendix HPA" throughout this document) two studies were cited revealing an LD_{50} of 4260 mg/kg bw (Smyth *et al.*, 1949) and an LD_{50} of 2100 mg/kg bw (Carreon & Yakel, 1981).

There is no harmonised classification for 2-Hydroxypropylamine for this endpoint. Classification as Acute Tox. 4; H302 (Harmful if swallowed) is notified in the C&L Inventory.

RAC agrees to classify RP 1:1 (based on the oral study on RP 1:1 and consistent to RP 3:2) as **Acute Tox. 4; H302 (Harmful if swallowed)** according to CLP Regulation (oral LD_{50} guidance values for this category from 300 to 2000 mg/kg bw).

Acute dermal toxicity

RP 3:2
The lowest LD_{50} of 760 mg/kg bw was estimated for female rats (males and females combined LD_{50} 790 mg/kg bw) (Bode Chemie, 2002). No local skin effects were observed in all animals at this dose. At 2000 mg/kg bw (test substance was undiluted at this dose), 1/5 males had erythema and slight oedema (5/5 males died on day 1-7), 4/5 females had slight to severe erythema and slight to severe oedema (5/5 females died on day 1-7). As no indication on skin necrosis and scab formation was reported in only 2/5 female animals at 2000 mg/kg bw and 4/5 males died without any skin effects, the mortalities observed can not be explained by corrosive effects.

RAC proposes that based on the lowest acute dermal LD_{50} value of 760 mg/kg bw in female rats, RP 3:2 should be classified as Acute Tox. 3; H311 (Toxic in contact with skin) according to CLP (dermal LD_{50} guidance values for this category from 200 to 1000 mg/kg bw). As mortalities occurred without local skin effects or scab formation due to necrotic precursor lesions were seen in the surviving animals at the end of the 14 day observation time, skin lesions are unlikely to be the cause of mortalities.

Formaldehyde
Formaldehyde is classified in CLP, Annex VI as acute dermal toxicity, category 3; H311 (Toxic in contact with skin).

2-Hydroxypropylamine
In Doc Appendix HPA the study of Smyth et al. (1949) calculated an LD_{50} of 1640 mg/kg bw and the study of Carreon & Yakel (1981) identified an LD_{50} of 1850 mg/kg bw, both in rabbits.

There is no entry in CLP, Annex VI for acute dermal toxicity. Some self-classifications as Acute Tox. 4; H312 (Harmful in contact with skin) are available.

RP 1:1
Two dermal acute studies on RP 1:1 revealed LD_{50} values > 2000 mg/kg bw when undiluted test substance was dermally applied. The study of Becker Chemie (2002), conducted according OECD TG 402, is taken as the most informative study. No deaths were observed at 2000 mg/kg bw in a preliminary test on two female rats. One out of 5 females was found dead at this dose level on day 4 in the main (limit dose) study with clinical signs of reduced activity, abdominal position, paleness, piloerection as well as reduced body and abdominal tone. No effects were seen in other rats. Black colouration was reported as local effects in this female.

Skin reaction (slight to well defined erythema and yellowish disclouration after patch removal, in 3 rats additional hardening with dark discolouration) were reported (assumed by the RAC to have been observed at the end of the 24 h exposure time). Erythema was still present up to 24 h after patch removal. Over the following days discolouration, hardening and desquamation was observed which was not fully reversible up to day 14.

No mortality and no other effect (bw, clinical signs) were recorded in the OECD TG 402 study of Schülke & Mayr (2002). Skin reactions were not recorded.

The DS identified in the CLH report a classification for acute dermal toxicity as Acute Tox. 4; H311 as appropriate. Based on the DS's interpretation that the effects are secondary to corrosivity, the final proposal was to not classify for acute dermal toxicity.

RAC agrees with the view of three MSCA that corrosivity does not cover the acute toxicity classification. RAC noted that a read across to RP 3:2 and to formaldehyde would support a classification as Acute Tox 3; H311. However based on the available studies for RP 1:1 it appears that the potential of dermal toxicity differs from RP 3:2 and formaldehyde and RAC gives more weight to the studies on RP 1:1. RAC concludes that **classification of RP 1:1 for dermal acute toxicity is not warranted**.

Acute inhalation toxicity

RP 3:2
Studies on acute inhalation toxicity were not available on RP 3:2.

Formaldehyde
There are acute inhalation studies (see Formaldehyde Core Document) suggesting that corrosive effects in the upper respiratory effects may contribute (possibly in addition to other effects) to lethality: histopathological examination revealed excessive mucus secretion, mucociliary dysfunction, single cell necrosis, and discontinuous nasal epithelium with erythrocyte leakage following 4 h of exposure of rats to formaldehyde gas concentrations of 12 µg/L (Bhalla *et al.*, 1991). Higher concentrations (0.6-1.7 mg/L) resulted in haemorrhage and oedema of the lung as well as oedema in liver and kidneys and hepatocyte necrosis (Skog, 1950). The Formaldehyde Core Document indicates a LC_{50} of 0.6 mg/L (4 h).
Formaldehyde is classified in CLP, Annex VI as acute inhalation toxicity, category 3; H331 (Toxic if inhaled).

2-Hydroxypropylamine
According to the information in Doc Appendix HPA no mortality was found in rats exposed for 8 h to saturated vapour (Smyth *et al.*, 1949; post exposure observation period 14 days, no further data available). Twelve rats were exposed for 8 h to air saturated with 2-hydroxypropylamine at 20°C. No clinical symptoms were detected and no effects were seen at necropsy (no further details; BASF AG, 1965 cited in Greim, 1994).
There is no entry in CLP, Annex VI for acute inhalation toxicity.

RP 1:1
Studies on acute inhalation toxicity were not available on RP 1:1.

The CLP Guidance (version 4.1, 2015), 3.1.2.3.2 states that 'Corrosive substances (and mixtures) may be acutely toxic after inhalation to a varying degree and by different modes of action. Therefore, it is not possible to estimate the acute inhalation toxicity from the corrosivity data alone.

The DS considered acute inhalation toxicity, category 4 (H332) for RP 1:1 based on the read across from formaldehyde vapour to released mist with 28% formaldehyde content, but found the classification for acute (inhalation) toxicity redundant for corrosive substances.

RAC considers read across to formaldehyde justified as RP 1:1 contains 28% releasable formaldehyde and agrees on Acute Tox. 4 (as suggested by two out of three MSCA supporting classification for acute inhalation toxicity) based on the formaldehyde classification (Cat. 3) and taking the maximum amount of releasable formaldehyde into account.

Acute Tox. 4 is considered justified assuming that the acute inhalation toxicity of RP 1:1 is totally dependent on 28% releasable formaldehyde. For RP 1:1 the LC_{50} of about 1.8 mg/L (factor of 3 applied on a LC_{50} of 0.6 mg/L (4h) for formaldehyde) for RP 1:1 would result. For mists, this is equivalent to Cat. 4. RAC thus agrees to classify RP 1:1 as **Acute Tox. 4; H332 (Harmful if inhaled)**

This is consistent with the observation that acute toxicity values for the oral and dermal route demonstrated lower potency of RP 1:1 than formaldehyde to cause acute toxic effects. RAC discussed uncertainties that remain with regards to the actual emitted concentrations in air (in the gaseous phase or aqueous solution) as hydrolysis data in contact with biological tissues are lacking, and uncertainties that may result from nonstable intermediates which could also contribute to the acute inhalation toxicity.

EUH071

The supplemental labelling with the hazard statement EUH071 – Corrosive to the respiratory tract – was proposed by two MSCA. If in addition to classification for inhalation toxicity, data are available that indicate that the mechanism of toxicity is corrosivity (CLP, Note 1 in Table 3.1.3), EUH071 could be assigned.

RAC notes that the CLP criteria on EUH071 are not clearly defined. EUH071 can also be applied to inhaled corrosive substances not tested for acute inhalation toxicity. According to CLP, Annex II, ,1.2.6 (which states *'For substances and mixtures in addition to classification for skin corrosivity, if no acute inhalation test data are available and which may be inhaled.'*) EUH071 may then be appropriate whithout a corresponding classification for acute inhalation toxicity.

In line with previous RAC recommendations where EUH071 has been assigned in addition to the classification on acute inhalation toxicity, **RAC agrees to assign EUH071**.

EUH029

The labelling EUH029 – Contact with water liberates toxic gas – was suggested for consideration by one MSCA. CLP, Annex II, 1.2.1 defines that substances and mixtures which in contact with water or damp air, evolve gas classified for acute toxicity in category 1, 2 or 3 in potentially dangerous amounts should be labelled with this phrase.

RAC discussed that the liberation of toxic gas after contact with water will not be the main concern as sufficiently high amounts of toxic gase may not immediately be produced. Formaldehyde will also be generated and released without contact with water as aqueous conditions are given under normal room air conditions in contact with mucous membranes (of the eye, the respiratory tract and the upper GI tract) and in contact with sweaty skin. It is also of note that the CLP, Annex 11, 1.2.1 foresees the additional labelling with EUH029 only for substances classified for acute toxicity in category 1, 2 or 3 and not for Acute Tox. 4 substances.

RAC agrees that EUH029 is not warranted.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier submitter's proposal

The DS argued that there is no evidence for effects justifying STOT SE 1 or 2 and that STOT SE 3; is not appropriate as the substance is corrosive.

Comments received during public consultation

One MSCA remarked that the classification STOT SE is not covered by the classification for skin corrosivity. With regards to STOT SE, this MSCA agreed that no classification is required.

Assessment and comparison with the classification criteria

RP 3:2
There is no proposal to classify RP 3:2 for STOT SE 1, 2 or 3.

Formaldehyde
For formaldehyde, there is no entry in Annex VI on STOT SE; some notifiers self-classified for STOT SE (1 or 3).

2-Hydroxypropylamine
There is no entry in Annex VI on STOT SE. There is no robust information to judge on STOT SE.

RP 1:1
Based on the acute toxicity studies on RP 1:1 there were no effects beyond those covered by the classifications on acute oral and inhalation toxicity that would justify STOT SE 1 or 2.

There are no experimental/other data that justify an additional classification as STOT SE 3 (H335) for respiratory tract irritation, and the CLP guidance 3.8.2.5 should be considered that states as follows

> *'In general, a classification for corrosivity is considered to implicitly cover the potential to cause RTI and so the additional Category 3 is considered to be superfluous, although it can be assigned at the discretion of the classifier. The Category 3 classification would occur only when more severe effects in the respiratory system are not observed.'*

Following the CLP criteria STOT SE 3 should be considered as covered by Skin Corr. 1B.

RAC agrees with the DS that **no classification on STOT SE is warranted**, and that the potential for respiratory tract irritation is covered by the classification of RP 1:1 as corrosive.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

There are two rabbit OECD TG 404 (or comparable) studies on RP 1:1 and three on RP 3:2. The DS also included discussion on the hydrolysis products of the substance, formaldehyde and 2-hydroxypropylamine. The results suggested strong irritant to corrosive properties. The DS found subcategorization difficult based on the data, but, as Skin Corr. 1 without subcategorization is not yet possible, proposed Skin Corr. 1B. In arriving at this decision more weight was put on the more recent studies.

Comments received during public consultation

Comments in agreement with proposed classification for Skin Corrosivity Cat. 1 without subcategorisation were submitted by three MSCA.

Assessment and comparison with the classification criteria

RP 3:2
Based on the study of Bode Chemie (2002) on RP 3:2 and the observation that the signs of corrosivity were already noticed at the first reading after 1 hour, RAC proposes classification as Skin Corrosive category 1B; H314 (Causes severe skin burns and eye damage).

Formaldehyde
Formaldehyde is classified in CLP, Annex VI as Skin Corr. 1B; H314 (Causes severe skin burns and eye damage).

2-Hydroxypropylamine
2-Hydroxypropylamine is classified in CLP, Annex VI as Skin Corr. 1B; H314 (Causes severe skin burns and eye damage).

RP 1:1
Irritant and corrosive properties were observed for RP 1:1 in two studies conducted according to OECD TG 404 (Becker Chemie, 2002, Schülke & Mayr, 2000). Exposure periods of 3 min and 1 h were also tested in the study of Becker Chemie (2002) and revealed only well defined erythema at 4 h post-exposure. Some evidence for damage of deeper skin layers such as induration, discolouration, scab formation and desquamation was noted after 4 h exposure; the effects were not reversible.
The study of Schülke & Mayr (2000) resulted after 4 hours exposure in destruction of skin tissue (eschar formation) that was observed at day 7 in 2 rabbits. The effects were reversible on Day 14. Additional information on the exposure duration originated from Doc HPT Doc III A.

The DS relied on the translation rules that suggested to translate corrosive substance (R34) to Skin Corr. Cat. 1B and to read across to formaldehyde, also classified in Cat. 1B.

As RP 1:1 was tested for skin irritation/corrosion in undiluted form which should not contain relevant concentrations of formaldehyde or 2-hydroxypropylamine, the observation of corrosivity supports either that RP 1:1 itself has corrosive properties or that a sufficiently rate of hydrolysis will occur within a short period of exposure (within 4 h) that caused corrosive effects by the hydrolysis products (formaldehyde and 2-hydroxlpropylamine).

Based on the available studies on RP 1:1, RAC proposes classification for skin corrosivity. RAC gives more weight on the available studies on RP 1:1 than only on the read across and general recommendations from the translation period. Based on the observation that exposure durations up to 1 h did not induce corrosive effects and 4 h did (Becker Chemie, 2002), RAC agrees on the **classification as Skin Corrosive 1C; H314 – Causes severe skin burns and eye damage** (according to Table 3.2.1, CLP Guidance).

RAC evaluation of serious eye damage/irritation

Summary of the Dossier submitter's proposal

For a skin corrosive substance eye irritation studies should normally not be conducted. However, a number of such studies were submitted by the applicant in the biocide process and these were summarised in the CLH report. One study with each substance (RP 1:1 and RP 3:2) was OECD TG 405 compliant (or comparable). In addition, one supportive non-guideline study was included.

The DS concluded that the studies indicate that the substance is eye corrosive.

Comments received during public consultation

It is pointed out by one MSCA although no labelling is required as the substance is also skin corrosive the substance should be classified as Eye Dam. 1.

Assessment and comparison with the classification criteria

RP 3:2
RAC recommends to classify for Eye Dam. 1 as for corrosive substances the risk for severe eye damage is implicit and has been demonstrated in animal studies. A separate labelling with H318 is not needed.

Formaldehyde
There is no Annex VI entry on a separate classification for eye irritation/damage on formaldehyde, however the majority of notifiers have self-classified the substance as Eye Dam. 1.

The Formaldehyde Core Document summarises that although no guideline-conform testing has been conducted, testing on dilutions (up to 15%) indicate severe irreversible eye damage that would justify the classification as Eye Dam. 1.

Due to specific concentration limits assigned to the existing Annex VI entry, mixtures containing formaldehyde at concentrations within the range 5% ≤ C < 25% are classified as Eye Irrit. 2; H319.

In humans, indications of eye irritation such as increased eye blink frequency and conjunctival redness were seen from gaseous concentrations of 600 µg/m³ (WHO 2010).

2-Hydroxypropylamine
Studies reporting corrosive properties to eyes were documented in Doc Appendix HPA.
There is no Annex VI entry on a separate classification for eye irritation/damage on 2-hydroxypropylamine, but the majority of notifiers classify the substance as Eye Dam. 1.

RP 1:1
The eye irritation study of Schülke & Mayr (2000) according to OECD TG 405 revealed non-reversible cornea lesions of RP 1:1 that support the classification as Eye Dam. 1.

The DS noted that the irreversible eye damage would support Eye Dam. 1, but considered a separate classification as not required as the labelling for H314 – Causes severe skin burns and eye damage already mentions the eye damage.

CLP guidance (version 4.1, 2015) stipulates in section 3.3.2.4:

> *A skin corrosive substance is considered to also cause serious eye damage which is indicated in the hazard statement for skin corrosion (H314: Causes severe skin burns and eye damage). Thus, in this case both classifications (Skin Corr. 1 and Eye Dam. 1) are required but the hazard statement H318 'Causes serious eye damage' is not indicated on the label because of redundancy (CLP Article 27).*

Also, CLP Guidance in section 3.3.2.6 indicates in step 0 that:

> *if the substance is classified as a skin corrosive, the substance is classified for serious eye damage but not labelled for serious eye damage.*

However, CLP guidance is not clear with regards to a separate classification for corrosive effects on the eye. The first sentence of CLP guidance, section 3.3 recommends:

> *It should be noted that if a substance or mixture is classified as Skin corrosive category 1 then serious damage to eyes is implicit and there is no need to proceed with classification for eye effects.*

In previous cases of corrosive substances, RAC decided not to propose a separate classification on serious eye damage. For RP 1:1, RAC agrees to classify as Eye Dam. 1. Although for corrosive substances the risk for severe eye damage is implicit (and testing should be avoided), in this case severe eye damage has been demonstrated in an animal study on RP 1:1 and **justifies a separate classification as Eye Dam. 1. However, separate labelling with H 318 is not needed**.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

The DS included five GPMT tests in the dossier which were conducted in accordance with or were comparable to OECD TG 406; two studies used RP 1:1 and three used RP 3:2. For RP 1:1 one study resulted in > 60% sensitisation at 1% induction concentration but it was concluded that the study was unreliable. For RP 3:2, one study with a very low intradermal induction dose (0.01%) was negative and two where positive; the effect rates were 60% at a 1% induction dose and > 90% at a 5% induction dose, respectively. In addition there is human data described for RP 3:2, in which 3.1% of 1786 patients showed sensitivity. The DS proposed to classify Skin Sens. 1A; H317.

Comments received during public consultation

Comments in agreement with skin sensitisation 1A by two MSCA.

Assessment and comparison with the classification criteria

RP 3:2
A total of 3.1% or 55 patients out of 1786 patients showed positive reaction to RP 3:2 (Geier et al., 1997). A more recent study (DeGroot et al., 2010) reviewed five patch test studies on patients who were metalworkers with suspected contact dermatitis and who had contact with metal working fluids containing RP 3:2. Positive reactions were found in 2.3 to 6.7% of metal workers (see Table 2 in this publication). These relatively high frequency meets the criteria (selected workers with known exposure or dermatitis is ≥1.0%) for a subcategorization a as skin sensitisation Cat. 1A.
In addition animal data support subcategory 1A (≥60% responding at >0.1% to ≤1% intradermal induction dose based on results from the study of Anderson et al., 1984).

Formaldehyde
The existing classification of the hydrolysis product formaldehyde in Annex VI is Skin Sens. 1; H317.

2-Hydroxypropylamine
There is no evidence for sensitizing properties in human studies with limited documentation The Doc Appendix HPA documented summaries on two patch test series in volunteers with 0.2 ml 2% aqueous solution of hydroxypropylamine negative. A questionnaire to workers exposed to 2-hydroxypropylamind revealed that 5 of 15 randomly selected individuals reported contact dermatitis. Study considered of limited validity, presumably due to irritant effects observed after direct contact with 2-hydroxypropylamine.

RP 1:1
Human data on RP 1:1
No information available.

Animal data on RP 1:1
A GPMT study according to OECD TG 406 (with some contradictory observations related to the irritative effects in the preliminary and main studies) (Lubirzol Corporation, 2001) is available supporting skin sensitization Cat. 1A due to 90% positive response to 1% induction concentration.

Another GPMT study was considered as of limited validity for several reasons. Intradermal injection of 1% test substance in distilled water resulted in discrete or pathy erythema, no local effects was observed after topical application of undiluted test material (while strong irritation was expected). A 40% positive response at 24 h was observed with an intradermal induction dose of 1%, which would support a classification for Skin Sens. Cat. 1B.

Based on the evidence from the GPMT study of Lubrizol Corporation (2001) (criteria ≥60% responding at >0.1% to ≤1% induction dose) and on the supporting human/animal evidence from read across to RP 3:2 and formaldehyde, RAC agrees with the proposal by the DS to classify RP 1:1 for skin sensitisation, as **Skin Sens. 1A; H317 (May cause an allergic skin reaction).**

RAC evaluation of specific target organ toxicity– repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal

A number of oral studies in the rat were available for both RP 1:1 and RP 3:2. No dermal or inhalation studies were available. Although some effects are below the guidance values, these effects are concluded to be due to the corrosivity of the test compound and thus, according to the DS, no classification is warranted.

Comments received during public consultation

No comments received.

Assessment and comparison with the classification criteria

Oral route

RP 3:2

The most relevant study is a 90-day study (Bode Chemie, 2002, in accordance with OECD TG 408, version 1998) on 10 male and 10 female rats which resulted in mortalities of 3 males (day 49-75) and 5 females (day 49-79) that received 180 mg/kg bw/d (high dose, reduced to 120 mg/kg at week 12). No mortalities were seen in the low- and mid dose groups (mid dose 60 mg/kg bw/d). These doses corresponded to concentrations of 0.4%, 1.2% and 3.6/2.4% in corn oil for the low, mid and high dose groups, respectively. It is to be noted that effects at these concentrations would not lead to classification as skin irritant as the concentrations are below 5%.

The study has some weaknesses as the stomach and the bone marrow were the only organs examined for histopathological effects at the low and mid doses. Histopathology findings were reported (see Doc III A6.4.1/02) without any grading of severity and with lack of information such as whether all animals that showed ulcerative gastritis had also peritonitis.

All males and females of the high dose groups showed long-lasting piloerection from day 35 onwards. Ataxia was noted in one female. Reduced pupil size was detected in 3/7 male and 5/5 female survivors. Clinical abnormalities from the functional observational battery give some indications on abnormal neuromotor and sensory functions at 180/120 mg/kg bw/d. Gait impairment in one female and reduced pupil size (miosis – loss of capacity to adapt to darkness due to permanently contracted pupils) were seen in 3/7 males and 5/5 female survivors. The study authors interpreted these effects as being of unclear toxicological relevance that occurred at doses greater than the maximum tolerated dose (MTD).
The view of RAC is that a neurotoxic effect could not totally be excluded, as the effects were seen in surviving animals (after week 11) and miosis is not considered to be associated with gastritis. However, as the dose of 180 mg/kg bw/d during the first 11 weeks is above the guidance values for classification as STOT RE (100 mg/kg bw/d for a 90-day study), these effects do not warrant classification.

In principle, the mortalities at 180/120 mg/kg bw/d that occurred at day 49 or later could be relevant for classification for STOT RE, as they could not be seen as acute toxic effects. As the toxic effects at the high dose (including the ulcerative gastritis, peritonitis and a shift to higher relative numbers of neutrophilic granulocytes and reactive bone marrow granulopoiesis) occurred at above the upper limit of the guidance values (100 mg/kg bw/d for a 90-day study), they do however not justify classification. Granulocytosis and increased granulopoiesis are likely to be secondary systemic effects to the chronic inflammantory and ulcerative processes in the stomach and peritonitis.

Local effects in the stomach were also observed in about half the animals (6 males, 5 females) treated at 60 mg/kg bw/d (1.2% in corn oil), increased medullary granulopoiesis was also seen in 4 males and 1 female at this dose. Repeated exposure to low concentrations that are not irritant at single exposure conditions may lead to exacerbations of adverse effects which over time may result in toxicologically significant effects. These chronic lesions could be relevant for classification for STOT RE. The DS argued that 60 mg/kg bw/d is more than half an order of magnitude lower than the dose mediating the acute toxicity and that the local effects are sufficiently be addressed by classification for corrosion/irritation.

The CLP guidance does not suggest that effects along the administration routes resulting from repeated exposures are covered by classification for corrosion, while it gives some recommendation concerning Annex I 3.9.1.6, when STOT SE might be more appropriate than STOT RE:

> *"Where the same target organ toxicity of similar severity is observed after single and repeated exposure to a similar dose, it may be concluded that the toxicity is essentially an acute (i.e. single exposure) effect with no accumulation or exacerbation of the toxicity with repeated exposure. In such a case classification with STOT-SE only would be appropriate."*

In addition section 3.9.2.5.1 gives guidance on the doses, as follows:

> *"If the dose is more than half an order of magnitude lower than that mediating the evident acute toxicity (corrosivity) then it could be considered to be a repeated-dose effect distinct from the acute toxicity."*

For RP 3:2 the dose at which the effects in the stomach and bone marrow occurred in the 90-day study was much lower than the oral acute toxic doses (LD_{50} 630 mg/kg bw). The local effects in the stomach were not observed in three oral acute toxicity studies (at much higher test concentrations of 8% - 10%, highest dose tested 2000 mg/kg bw). RAC, in line with comments received from some MSCA during the public consultation, does not agree with the DS view that the local irritant effects are mechanistically sufficiently addressed with the classification for corrosion and should not support the classification for STOT RE.

The toxic effects in the GI tract are considered as chronic toxic effects that resulted from prolonged/repeated exposure to low concentrations/doses of RP 3:2. The effects are considered as reflecting repeated exposure toxicity and not just acute toxicity. Because they occurred within the range of guidance values (CLP regulation, Table 3.9.2-a, ≤ 100 mg/kg bw/d for an oral 90-day study) and the effective dose is considerably lower than the acutely toxic dose, RP 1:1 should be classified for STOT RE. Local effects in the GI tract (like chronic oesophagitis, gastritis) after repeated/prolonged exposure are toxicogically relevant as they impair not only the morphology and/or function of the locally targeted organ, but also bear the potential to impair adherent tissues/organs by transmural extension of the chronic inflammation (e.g. peritonitis, pleuritis) or to cause delayed mortalities (after ulceration into body cavities). Thus, RAC propose to classify RP 3:2 as STOT RE 2; H373 - May cause damage to (gastrointestinal tract) through prolonged or repeated exposure.

Formaldehyde

There is no harmonised classification on formaldehyde for STOT RE.

Lesions related to the irritancy in the stomach are - similar to RP 3:2 - the main effects after repeated oral administration of formaldehyde. However, available studies suggest that the lesions were seen at comparatively higher doses or occurred with lower severity grades compared to RP 3:2.

After 12 months exposure to 300 mg/kg bw/d, forestomach squamous cell hyperplasia/hyperkeratosis, glandular hyperplasia and erosion/ulceration of the glandular stomach were seen (Tobe *et al.*, 1989, Doc III A6.3.1). No local effects in the GI tract were observed in a 90-day study in rats receiving formaldehyde in drinking water at concentrations up to 1000 mg/L (150 mg/kg bw/d) (Johannsen *et al*., 1986). A 4-week oral study in rats (Til *et al.*, 1988, Formaldehyde Core Document III A6.3.1) receiving 0, 5, 25, 125 mg/kg bw/d with drinking water revealed, at 125 mg/kg bw/d, very slight to moderate hyperkeratosis of the forestomach (all animals) and very slight to moderate gastritis (3/10 males, 5/10 females) of the glandular stomach. A focal papillomatous hyperplasia was observed in one female. None of the available studies conducted were fully compliant with the relevant test guidelines.

2-Hydroxypropylamine
A NOAEL of 600 mg/kg bw/d was estimated in a 90-day feeding study (with limitations) that was conducted in rats long before the OECD standards on testing were developed (Smyth *et al.*, 1951). Alterations (without further details) in kidney and liver were observed at 2200 mg/kg bw/d.

RP 1:1
The DS indicated the 90-day study of Lubrizol Deutschland GmbH (2002) to be of higher relevance than the second 90-day study of Schülke & Mayr (2002), both conducted in accordance with OECD TG 408.

In the first gavage 90-day study on 10 male and 10 female rats/dose groups that received 0, 12, 30, 80 or 150 mg/kg bw/d RP 1:1 (concentrations 0, 0.48, 1.2, 3.2 or 6% in peanut oil) (Lubrizol Deutschland GmbH, 2002), 2 males died after the first dose of 200 mg/kg bw/d which was then reduced to 150 mg/kg bw/d. Lesions in this region were found at this dose in both males and in 1 male that died at day 52 and in 1 female that died at day 75.

Abnormal breathing sounds were noted in animals at 80 mg/kg bw/d (1 female that died on day 68, 3 males (including 1 male which died on day 68 with pharyno-laryngeal lesions), at week 5 or later) and 150 mg/kg bw/d (4 males, 3 females starting at week 2). From the latter dose, 2 males and 2 females showed poor general condition and reduced activity. Reduced motor activity was observed in 1 female and 1 male at 30 mg/kg bw/d and in 1 female at 150 mg/kg bw/d.

Histopathology on animals which died during the exposure period revealed laryngitis in 1/1 male at 80 mg/kg and in 2/3 males and 1/1 female at 150 mg/kg bw/d, ulcerative laryngitis in 1/3 males at 150 mg/kg bw/d and pharyngitis in 1/3 males at 150 mg/kg bw/d and oesophagus lesions (mural inflammation and myopathy) in 3/9 females and mural inflammation only in 1/9 females at 150 mg/kg bw/d.
In surviving animals at 150 mg/kg bw/d, purulent rhinitis was observed in 1/7 males and 1/9 females and stomach submucosal inflammation in 1/7 males.

No treatment-related findings were seen at 30 mg/kg bw/d except in 1 female that died on day 38 with reduced activity, reduced skin turgor, reduction of bw and enlarged submandibular lymph node and 1 surviving female rat which showed nose bleeding, corneal opacity of a bloody left eye and a hairless region around the eye.

Systemic arteritis observed at 12, 30, and 80 mg/kg bw/d, each in one female rat that died on day 24, 38 and 25, respectively, and was not considered to be treatment-related. Slightly reduced food consumption and 9-10% lower body weight gain in comparison to control values were observed in male rats at 150 mg/kg bw/d, while no treatment-related effect on the body weight was seen on any of the female dose groups. These findings do not indicate non-specific toxic effects.

This study is difficult to interpret as the day of death is not given for all decedents and as the toxicity/mortalities occurred without a clear dose response relationship. As far as the data are reported, the lesions in the laryngo-pharyngeal regions were seen in animals that died on day 1, 52 and 75 of treatment. Either all the effects from 30 mg/kg bw/d onwards were considered substance related or interpreted as being related to the pre-gastric (mal-)administration (at least of parts of the applied dose) of the high concentration of RP 1:1, in the absence of a clear dose-relationship of the observed clinical and histopathological effects and considering the small incidences and the pharyngeal/oesophageal sites (lesions due to assumed irritative properties following a gavage administration would be expected to occur in the forestomach) affected in animals that died.

The test substance concentration at 150 mg/kg bw/d was 6% in peanut oil.

It is the opinion of RAC that for RP 1:1 no clear conclusion on oral repeated dose toxicity can be drawn from this study.

The pharynx/larynx was also examined in the second 90-day study (Schülke & Mayr, 2001). The DS interpreted this study as not valid as the MTD was not clearly reached and no local GI tract effects were seen. The absence of local effects in the upper GI tract after gavage administration with doses up to 180 mg/kg bw/d at concentrations up to 2.5% in water as the vehicle, may be related to the less concentrated test material and/or to the lack of maladministration.
No treatment-related mortality was observed at 0, 40, 100 or 250 mg/kg bw/d. High dose females showed a decreased motor activity (measured). Food consumption was significantly lower in males of the mid and high dose group at week 11, a slight dose-dependent decrease in bw gain was seen during the last 3 weeks of the treatment period for the high dose males (-9%) and mid and high dose females (-8%). Several effects on haematology, clinical chemistry and organ weights were reported. However, the study seems to be of limited value due to varying degree of pneumonic changes with histopathological characteristic of mycoplasal pneumonia that was indicated in the study report according to a note of the Rapporteur Member State (RMS).

No conclusion with regards to the classification for STOT RE can be drawn from two range-finding 14-day studies (Becker Chemie, 2002; Schülkie & Mayr, 2002).

As no valid information on oral repeated dose is available on RP 1:1, read across on RP 3:2 is proposed based on the same constituents of UVCB at a slightly lower concentration of releasable formaldehyde (28% from RP 1:1 versus 45% formaldehyde from RP 3:2). The read across to RP 3:2 is in line with the argumentation in the RP 1:1 Doc IIIA, where the applicant suggested using the data on RP 3:2.

Consistent with RP 3:2, RAC proposes to classify RP 1:1 as **STOT RE 2; H373 - May cause damage to (gastrointestinal tract) through prolonged or repeated exposure.**

Dermal route

RP 3:2
No repeated dose study using the dermal route is available.

Formaldehyde
No valid dermal repeated dose study seems to be available (see core document on formaldehyde). There are several long-term studies with unusual application regime (twice weekly for 60 wks, thrice weekly for 26 wks, 2-3 weeks with documentation on the application frequency in the CLH report) on formaldehyde at concentrations of 0.1 to 10% that revealed mild to moderate irritation from concentrations of 0.5% onwards. Whether systemic effects (full list of examined organs as required in guideline studies) were examined in these studies, is neither documented in the CLH Report nor in the Formaldehyde Core Document.

2-Hydroxpropylamine
No repeated dose study using the dermal route is available.

RP 1:1
No repeated dose study using the dermal route is available.
Taking the data from formaldehyde into account, the overall database is not sufficient to take any decision on classification for STOT RE for this route.

Inhalation route

RP 3:2
No repeated dose study using the inhalation route is available.

Formaldehyde
Due to the lack of data on RP 1:1, data on formaldehyde were assessed for STOT RE:

Classification on effects from repeated inhalation exposure may be considered if doses are much lower than those that induce acute irritant or corrosive effects.

As explained for the oral route, the CLP guidance does not indicate whether effects along the administration routes resulting from repeated exposures are covered by a classification for corrosion, while it gives some recommendation in Annex I 3.9.1.6, regarding when STOT SE might be more appropriate than STOT RE:

> *"Where the same target organ toxicity of similar severity is observed after single and repeated exposure to a similar dose, it may be concluded that the toxicity is essentially an acute (i.e. single exposure) effect with no accumulation or exacerbation of the toxicity with repeated exposure. In such a case classification with STOT-SE only would be appropriate."*

In addition, Section 3.9.2.5.1 gives guidance on the relevant doses

> *"Substances (or mixtures) classified as corrosive may cause severe toxicological effects following repeated exposure, especially in the lungs following inhalation exposure. In such cases, it has to be evaluated whether the severe effect is a reflection of true repeated exposure toxicity or whether it is in fact just acute toxicity (i.e. corrosivity). One way to distinguish between these possibilities is to consider the dose level which causes the toxicity. If the dose is more than half an order of magnitude lower than that mediating the evident acute toxicity (corrosivity) then it could be considered to be a repeated-dose effect distinct from the acute toxicity."*

In short, if doses are considerably lower than those being acutely toxic/irritant and these low doses induce serious health damage after repeated inhalation with accumulation/exacerbation of repeated exposure, classification for STOT RE should be considered.

For formaldehyde, the acute inhalation LC_{50} was reported to be 0.6 mg/L (600 mg/m³) by Nagorny *et al*. (1979) (see Formaldehyde Core Document II, Table 3-2). Taking the adverse effect concentration (AEC) of 0.12 mg/m³ from human data into account, the surrogate effect for repeated inhalation toxicity occurs at concentrations 5000-fold below the acute toxic dose, thus indicating that a classification for repeated inhalation effects is warranted.

There are no human study that examined chronic non-neoplastic lesions in the respiratory tract in humans under controlled exposure conditions. Instead existing limit values were derived from surrogate data on sensory irritation effects on eyes, nose and throat as these effects are considered as the most sensitive adverse (non-neoplastic) effects. The Scientific Committee on Consumer Safety (SCCS) (2014) in their evaluation considered eye irritation as the most sensitive effect:

> *"Eye irritation was revealed as most sensitive adverse endpoint. In susceptible individuals, slight discomfort due to eye irritation occurred at 0.25 ppm but dose-dependent increases in eye irritation were not observed below 1 ppm. Objective ratings for eye irritation (conjunctival redness and eye blinking frequency) have been investigated in healthy volunteers and a NOAEL of 0.5 ppm (without exposure peaks) and 0.3 ppm (with exposure peaks of 0.6 ppm) was established."*

However data on sensory irritation can not be used to decide on classification for chronic toxic effects.

From repeated dose inhalation studies in animals, dose-dependent non-neoplastic lesions in the nasal cavity that increased in severity and extension with exposure time and dose (for review see SCCS 2014; BfR, 2006) were reported. Following inhalation exposure up to 24 months, squamous metaplasia was observed in rats at 6 ppm formaldehyde. Epithelial hypertrophy, hyperplasia and metaplasia, mixed inflammatory cell infiltrates, turbinate adhesions were seen at 10 ppm, in addition destructed turbinate architecture occurred at 15 ppm (Monticello et al., 1996, cited from BfR, 2006). While lesions of the respiratory epithelium in the nasal cavity were not reported after 6 weeks exposure up to 2 ppm (Monticello *et al*., 1991; Formaldehyde Core document IIIA), inhalation exposure of ≥12 months to ≥2 ppm (2.456 mg/m³) formaldehyde caused purulent rhinitis, epithelia dysplasia and squamous metaplasia at level I of the nasal cavity (Kerns *et al*., 1983 a, b, cited from BfR, 2006). At concentrations above 2 ppm, lesions extended to more posterior parts (level I to III) of the nose and reached the trachea at 14.3 ppm. Monticello (1989, cited from RAC Opinion on Formaldehyde) has demonstrated that inhalation of 6 ppm formaldehyde for 1 or 6 weeks induced loss of cilia, inflammatory response, epithelial hyperplasia and squamous metaplasia and increased cell proliferation in the nasal passages of Rhesus monkeys. Like in rats, lesions in monkeys showed an anterior-posterior gradient and duration-related increase in severity and extension, but these were more widespread than in rats. Inhalation of 3 ppm formaldehyde over 26 weeks induced squamous metaplasia and hyperplasia in the nasoturbinates in 6/6 Rhesus monkeys, while no effects were observed at 0.2 and 1 ppm (Rusch *et al*., 1983, see SCCS, 2014).

Taking 2 ppm formaldehyde as a robust LOAEC for chronic inflammatory and meta/hyperplastic lesions secondary to initial cytotoxicity in the nasal mucosa from repeated/prolonged inhalation and using the Haber's rule standard extrapolation from 12 months to 90-day exposure to compare with the guidance values, 2 ppm for 12 months corresponds to 8 ppm (9.824 mg/m³ = 0.01 mg/L) in a 90-day study. This is clearly below the guidance concentration of 50 ppm and would justify a classification of formaldehyde as STOT RE 1.

<u>2-Hydroxypropylamine</u>
There are no repeated dose inhalation studies with test guideline conformity.

Bronchopneumonia and rhinitis were observed in two 11-day inhalation studies in rats and mice. The same effects seen in the control groups invalidate these studies (Doc Appendix HPA).

<u>RP 1:1</u>
No repeated dose study using the inhalation route is available.

The DS suggested read across to the hydrolysis product formaldehyde on which a local inhalative AEC of 0.12 mg/mg³ was based on human data on eye irritation.

Referring to the CLP Regulation, 3.9.2.10.3, RAC agrees with the DS on the read across to formaldehyde as data on repeated inhalation toxicity of RP 1:1 are lacking. However RAC does not agree that effects from repeated inhalation are covered by the classification for corrosion.

The absence of an entry for formaldehyde for STOT RE in CLP, Annex VI does not by itself justify non-classfication for RP 1:1.

The DS informed that RP 1:1 contains about 28% releasable formaldehyde. Assuming that under prolonged inhalation exposure conditions RP 1:1 would continuously release the maximal releasable amount of 28%, a factor of 3.6 should be applied to correct for the content of releasable formaldehyde.
As the human AEC was based on eye irritation, an acute receptor-mediated sensory irritation effect (without obvious cytotoxicity and infiltration of inflammatory cells) as surrogate for the lowest adverse effect in humans, animal data on repeated inhalation toxicity may be more appropriate to conclude on the classification for STOT RE.

For RP 1:1, the LOAEC for repeated inhalation exposure is based on the formaldehyde LOAEC of 2 ppm (2.456 mg/m³) derived from a rat 12-month study (Kerns *et al*., 1983 a,b) which would correspond to 8 ppm (9.824 mg/m³ = 0.01 mg/L) in a 90-day inhalation study based on Haber's rule. The 8 ppm LOAEC, corrected for the maximal amount of releasable formaldehyde (28%) from RP 1:1 with a factor of 3.6, results in a (corrected) concentration of 0.036 mg/L for RP 1:1 which is close to the lower boundary of the guidance value for STOT RE 2 (0.02<C ≤0.2 mg/L). As inhalation exposure to the aerosol is expected to be the main concern for RP 1:1, the guidance values for the gaseous form were not considered.

If the chronic toxicity occurred at the same dose level as the acute inhalation toxicity, chronic toxicity would be covered by the classification for acute toxicity. The inhalative LC_{50} was unknown for RP 1:1 (and RP 3:2) as no acute inhalation study is available. As a substitute information on the difference between the level of the inhalation LC_{50} and the LOAEC for chronic effects for formaldehyde is considered. The Formaldehyde Core Document indicates an LC_{50} of 0.6 mg/L (4 h) which is markedly higher than the LOAEC for chronic effects (2 ppm = 2.456 mg/m³). Thus, the acute toxicity classification does not cover the classification for STOT RE.

It is noted that the formation of formaldehyde as hydrolysis product may depend on several factors (e.g. temperature, pH, dilution). The RMS raised uncertainties (Doc II-A 2.12) that exposure conditions or hydrophobic formulations may reduce the rate of hydrolysis, but may theoretically enhance deeper respiratory tract exposure and may also increase irritation properties due to their effect on membranes.

Repeated inhalation exposure to RP 1:1 generates the hydrolysis products formaldehyde and 2-hydroxypropylamine. Whether 2-hydroxypropylamine may exert additive effects to those expected from formaldehyde, remains unknown.

Based on the read across from data on formaldehyde (see above), RAC proposes to classify RP 1:1 with regards to target organ toxicity from repeated inhalation as STOT RE 2; H373 (May cause damage to the respiratory tract through prolonged or repeated exposure).

All routes/Overall classification on STOT RE

When classification for STOT RE is proposed based on data from several routes with different target organs, the final labelling should consider all the relevant target organs. RAC agrees that classfication of RP 1:1 is warranted as **STOT RE 2, H373 – May cause damage to the respiratory tract and the gastrointestinal tract through prolonged or repeated exposure.**

No specific route should be indicated.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

The DS proposed to classify RP 1:1 as a caterory 2 mutagen based on the existing harmonised classification of its hydrolysis product formaldehyde.

There are several mutagenicity studies *in vitro* and *in vivo* for RP 1:1. Predominantly clastogenic effects are induced in cells of mammalian cell cultures whereas bacterial gene mutations tests are weakly positive (one test) or negative (one test). Regarding the *in vivo* testing, a negative result was obtained in an *in vivo* chromosomal aberration test after repeated gavage exposure to RP 1:1. After single i.p. injection of RP 1:1 an *in vivo* micronucleus test was negative whereas an *in vivo* chromosomal aberration test was positive. The positive result seems to be of questionable relevance due to deficiencies in the study (e.g. no statistical evaluation of the data).

The DS additionally provided information on similar results of *in vitro*/*in vivo* mutagenicity tests for the substance RP 3:2. (To avoid a confusion it should be noted that the corresponding references in the Tables 4.8-2 and 4.8-5 were taken from the CLH report for RP 3:2. They are not part of the reference list of the CLH report for RP 1:1.)

The DS also argued that due to the rapid hydrolysis of RP 1:1 to formaldehyde at contact with biological tissues, an induction of local genotoxic effects is to be expected at the site of first contact *in vivo*. Therefore the DS referred to the classification of formaldehyde, classified as Muta. 2, based on the induction of genotoxic effects *in vivo* on somatic cells at site of contact and supported by positive results in numerous *in vitro* mutagenicity and genotoxicity tests. The other hydrolysis product 2-hydroxypropylamine is of very minor toxicological relevance.

Due to the mechanistic considerations of formaldehyde release from RP 1:1 the DS proposed to classify the substance RP 1:1 as a Muta. 2 on the basis of its hydrolysis product formaldehyde.

Comments received during public consultation

One MSCA expressed support for the proposed classification. One individual disagreed with the proposed classification as a category 2 mutagen due to the lack of relevant mutagenicity data.

Assessment and comparison with the classification criteria

RP 3:2
RAC takes note of the additional information from the DS that RP 3:2 induces similar results in mutagenicity tests *in vitro* and *in vivo* as RP 1:1.

Formaldehyde
RAC agrees with the approach of the DS to take into account the classification of formaldehyde as a category 2 mutagen for justification of the classification of RP 1:1.

2-Hydroxypropylamine
The DS noted that no indication for mutagenicity of 2-hydroxypropylamine has been detected in available bacterial studies and no relevant structural alerts are present.

RP 1:1
The evaluation of the mutagenicity data of RP 1:1 by the DS and RAC does not differ. RAC also comes to the conclusion that a proposal for classification of RP 1:1 as category 2 mutagen is justified.

In vitro data
The available bacterial gene mutation tests are weakly positive with S9-mix (Lubrizol Corporation, 2000, see Doc III A6.6.1/02) or negative (Schülke and Mayr, 2000, see Doc III A6.6.1/01). The negative results are not conclusive because the tested concentrations were below the highest concentration (5000 µg/plate or relevant cytotoxic concentration) recommended by the respective test guideline.
Two mouse lymphoma assays (Lubrizol Corporation, 2001 see Doc III A6.6.3/01; Schülke and Mayr, 2002, Doc III A6.6.3/02) are positive with and without S9-mix. In the analysis of the colony sizes predominantly small colonies were found, which indicate clastogenic activity of RP 1:1.
A chromosomal aberration test was positive in CHL cells with and without S9-mix (Lubrizol Corporation, 2001, Doc III A6.6.2).

In vivo data
Three studies are available that are able to detect systemic chromosome mutagenic activity in bone marrow cells of mice.

An *in vivo* chromosomal aberration was negative after repeated oral administration (gavage) of RP 1:1 up to the highest tested dose of 425 mg/kg bw (Schülke and Mayr, 2000 (DocIIIA6.6.4/03)). Neither cytotoxic effects nor clinical signs were induced. Thus the highest

tested doses did not correspond to the MTD nor was it in accordance with highest guideline recomended dose.

In two further *in vivo* tests RP 1:1 was injected once intraperitoneally. In a negative *in vivo* micronucleus test, the highest tested dose of 100 mg/kg bw induced cytotoxic effects (reduced PCE/NCE ratio) as well as minor clinical signs (Becker Chemie, 2002a (Doc III A6.6.4/01)). An *in vivo* chromosomal aberration test (Becker Chemie, 2002b (Doc III A6.6.4/02)) was positive at the highest tested doses of 50 and 100 mg/kg bw but the result seems to be of questionable relevance because there are deficiencies in the study (e.g. no statistical evaluation of the data).

The quantity of test data for RP 1:1 is limited and the available mutagenicity studies are not published. Thus, only the data given by the applicant in the biocide registration dossier are available. These data allow neither a detailed test evaluation nor they do allow to assess whether a test performance is fully in accordance with the corresponding guideline. But despite these limitations the following conclusion can be drawn: in bacteria as well as in somatic cell cultures mutagenic effects are induced. For RP 1:1 there is no reliable evidence for a systemic mutagenic effect. An *in vivo* micronucleus test in bone marrow cells of mice was negative after i.p. injection. The results of two *in vivo* chromosomal aberration tests are of limited relevance due to methodological deficiencies.

Formaldehyde, which is quickly released from RP 1:1 on contact with biological tissues, is classified as a category 2 mutagen based on the induction of local genotoxic effects *in vivo* on somatic cells at the site of contact and are supported by positive results in numerous *in vitro* mutagenicity and genotoxicity tests. Although it seems likely that the amount of formaldehyde may vary depending on different uses, the inherent potential of RP 1:1 to release formaldehyde is a critical factor.

Testing of the *in vitro* mutagenicity of RP 1:1 shows that the observed positive effects are consistent with those known from formaldehyde alone. Uncertainties remain due to the relevance of the available (negative) *in vivo* studies. However, it is assumed that RP 1:1 – like formaldehyde - has a poor systemic availability *in vivo* due to its rapid hydrolysis. Therefore it seems unlikely that genotoxic effects would be induced at a site distant from first contact.

Although no distinct criteria is noted on reaction products from UVCBs in the CLP Regulation, (likewise for CMR substances in mixtures, Art. 6.3 and 1.6.3.1 of the CLP Guidance) the information on the hydrolysis product is used to assess the mutagenic potential of RP 1:1.

RAC discussed that due to its reactivity, poor systemic availability is expected for RP 1:1 and therefore, the induction of systemic genotoxic effects is unlikely. However, a local genotoxic effect produced by the hydrolysis product formaldehyde is expected and RAC considers read across to formaldehyde (which is classified as a mutagen category 2 based on its local genotoxic action) justified. Some RAC members expressed the view that the guidance relates only to classification of substances that causes germ cell mutations. This view is reflected in a minority position supported by three RAC members. RAC recognised that according to the CLP Guidance, Section 3.5.1, classification is also warranted if there is evidence of only somatic cell genotoxicity that leads to classification in Category 2 if genotoxic substances are only acting locally.

RAC agrees with the proposal of the DS to classify RP 1:1 as a **Germ cell mutagen, category 2; H341 (Suspected of causing genetic defects)** based on the properties of its hydrolysis product formaldehyde.

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

No cancer bioassay or human data were available for either RP 1:1 or RP 3:2. The DS discussed arguments that the classification should relate to the substance itself (consider only free formaldehyde) and not to potentially released or degraded substances (proposal 2, p. 48 of the

CLH report). Also, arguments supporting a classification based on the hydrolysis to formaldehyde are reflected and in the end taken forward.

Comments received during public consultation

Three MSCAs agreed and four industry commenters disagreed with the classification proposal. Some industry commenters suggested to classify RP 1:1 on the basis of the content of free (unbound) formaldehyde. Since the formaldehyde content is below 0.1% no classification was found to be justified.

Assessment and comparison with the classification criteria

RP 3:2
No carcinogenicity studies are available on RP 3:2.

Formaldehyde
The hydrolysis product formaldehyde is classified in CLP, Annex VI for carcinogenicity, category 1B.

2-Hydroxypropylamine
No information on the carcinogenic potential of 2-hyroxypropylamine is available.

RP 1:1
There are no reliable human data. Two medical letter reports in Doc III A stated that no adverse effects have been documented from annual medical screenings that could be ascribed to employees in the manufacturing of products containing formaldehyde releasing biocides or with the active substance RP 1:1. No information is given on the details of the level, duration, frequency and conditions of exposure, on the substances the workers were exposed to or on the details of the medical examinations and results.

No studies on carcinogenicity or prolonged/repeated inhalation exposures are available for RP 1:1. The non-submission of data was justified by a read across to formaldehyde, and the probable carcinogenic effects of RP 1:1 are considered by the biocide applicant to be related to the hydrolysis product formaldehyde (Doc III A6.7).

It is expected that RP 1:1 exerts similar effects as formaldehyde such as cytotoxicity, hyperplasia, metaplasia, tumours and local mutagenic effects at the sites of contact - on the epithelium of the respiratory tract following prolonged inhalation - as formaldehyde is one of the main hydrolysis products.
It is assumed for RP 1:1 that, similar to formaldehyde, systemically increased bioavailability and a concern for systemic carcinogenic responses are not to be expected.

Although it is noted that the amount of formaldehyde released may vary depending on different uses, the reaction product of paraformaldehyde and 2-hydroxypropylamine is intended to release formaldehyde in aqueous solutions. RP 1:1 is expected to hydrolyse completely under aqueous environmental conditions or when the substance has entered the human or animal bodies (Doc II A1.4.3). Both hydrolysis products, formaldehyde and 2-hydroxypropylamine, are considered to be slightly volatile from aqueous solutions.

The following is presented as clarification of the objectives of the classification proposal and in response to some comments received during public consultation. Exposure to formaldehyde may result from inhalation or dermal exposure to RP 1:1 as an active substance. This can result from exposure to the undiluted UVCB substance and (as considered in the CLH report) the contact with biological tissues/media then generates hydrolysis products (including formaldehyde). Similarly, exposure to RP 1:1 in aqueous solution (such as diluted formulations or products on the market) can result in contact with hydrolysis products from the dilution and with those directly generated following contact with biological media. Coinciding with the above can be exposure to the gaseous form after evaporation of formaldehyde from the undiluted or diluted RP 1:1.

Formaldehyde is classified based on its carcinogenic potential at the sites of exposure, primarily on the nasopharyngeal tumours observed in man and rodents after prolonged inhalation[1].

The CLP Guidance, Section 3.6.2.2.7 states that:

> *"A substance that has not been tested for carcinogenicity may in certain instances be classified in Category 1A, Category 1B or Category 2 based on tumour data from a structural analogue together with substantial support from consideration of other important factors such as formation of common significant metabolites, e.g. for benzidine congener dyes."*

The CLP Guidance (section 1.4.3) explicitly foresees the read across of information from 'source' substances to predict the same hazard for another 'target' substance. For RP 1:1, it is not about the similarity of source and target substance, but RP 1:1 should be classified as a carcinogen based on the release of the *identical* substance (formaldehyde) resulting from hydrolytic transformation of RP 1:1.

Endpoints, on which data on RP 1:1 are available, show that effects were consistent with those known from formaldehyde alone. With regards to the oral repeated toxicity, with the observation that the toxicity may be more severe for RP 3:2 when comparing the dose levels or the severity of effects observed with formaldehyde, no valid study was available for RP 1:1. However uncertainties remain due to the lack of studies with full guideline compliance and as an additional contribution of the other hydrolysis product 2-hydroxypropylamine to the effects by formaldehyde are unknown.

As mentioned by the DS, from a quantitative aspect, the hydrolysis rate of RP 1:1 to formaldehyde depends on several environmental factors (increase at higher temperature, lower pH, and at higher dilution). At all tested pH levels the hydrolysis half-life was less than 1 h. However, water contact or dilution of RP 1:1 with aqueous solutions are not a necessary condition for exerting toxic effects of RP 1:1, for the aerosol aqueous conditions were given at contact sites (mucous membranes with oral & inhalation exposure, sweaty skin with dermal exposure) and as demonstrated by similar toxic effects with lipid vehicles. The CLH report stated that the equilibrium of RP 1:1 (or RP 3:2) shifts towards formaldehyde (by dilution and) by the reaction of formaldehyde with biological media.

With regards to the Industry representative comments during public consultation that a classification of RP 1:1 as a carcinogen is not justified based on the end use 'diluted metalworking fluid' containing less than 0.05% of 'free, unbound' formaldehyde and the slow rate of formaldehyde release during its use, the DS replied that the uses and different dilutions that are on the market are not relevant for the decision on the hazard of the substance itself.

The Industry representative stated that evidence is lacking that sufficient formaldehyde will be released during exposure to workers to cause a carcinogenic risk. RAC considers the lack of observations in annual medical screenings of the type presented here not to be robust information. RAC notes that the CLP Regulation states that a classification is based on the intrinsic hazards of a substance and does not take the exposure conditions and the exposure to mixtures containing the substance of concern into account.

The option to classify RP 1:1 as a carcinogen in category 2 in order to account for uncertainties for substances that are unstable, showing equilibrium behaviour and having half-lives depending on dilution, temperature and pH as discussed in the CLH report is not supported by RAC. By weighing the evidence from read across to the specific substance (and hydrolysis product) that is known to have carcinogenic properties (formaldehyde), no reasons (such as uncertainty about structural similarity or qualititative differences in the mechanistic aspects) could be identified to justify

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1 http://echa.europa.eu/opinions-of-the-committee-for-risk-assessment-on-proposals-for-harmonised-classification-and-labelling?search_criteria_name=Formaldehyde&search_criteria_ecnumber=200-001-8&search_criteria=Formaldehyde

category 2 and RAC considers that the data supports category 1B. Hydrolysis tests indeed have demonstrated that high concentrations of formaldehyde are generated within short time periods.

These hydrolysis tests support qualitatively that hydrolysis will occur in contact with aqueous biological media on mucous membrans. Inhalation exposure to aerosolic RP 1:1 is expected to result in hydrolysis at the site of contact and toxicologically significant concentrations of formaldehyde could be reached on the surface of the mucous membranes in the respiratory tract, eye or upper GI tract or skin. The inhalation exposure to gaseous formaldehyde that evaporated from RP 1:1 is assumed to contribute in addition to the toxic/carcinogenic effect resulting from the direct impact of hydrolysis products at the contact site. Demonstrating that the room concentrations of released gaseous formaldehyde are rather low would not be sufficient to discount the hazardous potential that may result from the aerosol exposure to RP1:1.
As no data are available to demonstrate that a sufficiently high concentration of formaldehyde cannot (meaning: has not the potential to) be reached, there is no evidence to justify a lower classification. This prerequisite of evidence, and the fact that CLP is hazard based, is in contrast to the opinion of some commenters during public consultation, who argued that the classification is only justified if evidence from exposed workers demonstrates that sufficient formaldehyde will be released and have caused tumours.

Although no specific mention is made on classification of reaction products from UVCBs in the CLP Regulation, (likewise for CMR substances in mixtures, Art. 6.3 of the CLP Regulation and section 1.6.3.1 of the CLP Guidance) information on the hydrolysis product is used here to assess the hazardous properties including the carcinogenic potential of RP 1:1. More guidance is given in REACH, Annex XI, 1.5.2 that specifies that similarities to substantiate the read across may be based on common precursors or common breakdown products via physical or biological processes, which results in structurally similar chemicals.

RAC agrees with the proposal of the DS to classify RP 1:1 as **Carc. 1B; H350 (May cause cancer)**.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

No reprotoxicity study are available for RP 1:1. For RP 3:2 there is one developmental (OECD TG 414) and one fertility study (OECD TG 415). The resuls of these studies do not support classification for either sexual function and fertility or development, according to the DS.

Comments received during public consultation

One MSCA requested further information and argumentation.

Assessment and comparison with the classification criteria

RP 3:2

Effects on fertility
From the available data on repeated dose studies and a 1-generation study with 70 days of premating treatment, no indication is given of adverse effects on the male sexual function or fertility of the male rat.

Based on the 1-generation study in rats it was concluded that RP 3:2 induced reduced pup survival at first litter check (Day 0/1) in the mid and high dose groups. Although the increase appeared to be dose related, the overall increase on a per litter basis was limited. This finding did not correspond to the effects on pup survival seen at Day 1-4 where no clear dose response was observed. The number of dead pups on Day 1-4 were higher in the low dose than in the mid dose and unusual high numbers of pups died (mainly on Day 2/3) in the control groups. During the

discussion, RAC questioned the reliability of the study and found the observed effects as borderline and not sufficient to justify a classification for this endpoint.

In conclusion, in agreement with the DS' s proposal RAC agreed that a classification of RP 3:2 for the endpoint fertility is not warranted.

Developmental toxicity
A developmental study conducted according to OECD TG 414 on rabbits gavaged with 0, 5, 35, 90 or 135 mg/kg bw/d RP 3:2 did not reveal adverse effects on the development or increased rates of malformations that require classification. A dose of 135 mg/kg bw/d resulted in severe maternal toxicity (decrease in body weight, increased mortality and abortions). Total implantation loss was observed in 3 dams out of 22 dams. Since the mortality rate at this high dose is high, 11 dams out of 24 died premature, the CLP guidance criteria (Annex I: 3.7.2.4.4) is fulfilled that data for a dose level should not be considered if mortality is excessively increased, e.g. higher than 10%.

Based on the available data RAC concludes that no classification is warranted for developmental effects.

Formaldehyde

The Formaldehyde Core Document summarised that repeated (14-day or 90-day) inhalation studies on rats revealed testis atrophy, reduced sperm counts and motility and increased sperm abnormalities or reduced serum testosterone at doses which influenced food consumption and body weight gain. As no quantitative information on the reduction in food consumption and bw gain is reported, no conclusion can be drawn. Studies with intraperitoneal application confirmed advers effects on sperm.

No teratogenic effects were observed in inhalation or oral developmental studies according to OECD TG 414. Fetotoxic effects (lower bw and retardations) were observed at the high dose with maternal toxicity (bw loss)

2-Hydroxypropylamine

No data on fertility and developmental toxicity available.

Effects on fertility
No studies on sexual function and fertility are available on RP 1:1.

RP 3:2 hydrolyses to the 1:1 reaction product, the data on RP 3:2 are relevant for RP 1:1.

From the available data on RP 3:2 on repeated dose studies and a 1-generation study with 70 days of premating treatment no indication is given on adverse effects on the male sexual function or fertility of the male rat. In addition no concern was identified for RP 1:1 from the available 90-day studies that were of limited validity.

Based on the same hydrolysis products (although with a lower maximum concentration of releasable formaldehyde) read across to the 1-generation study on RP 3:2 is proposed.
RAC concludes for RP 1:1 that **no classification is warranted for fertility effects**.

Developmental toxicity
No developmental studies are available on RP 1:1.

RP 3:2 hydrolyses to the 1:1 reaction product, the data on RP 3:2 are relevant for RP 1:1.

A developmental study conducted according to OECD TG 414 on rabbits gavaged with 0, 5, 35, 90 or 135 mg/kg bw/d RP 3:2 did not reveal adverse effects on the development or increased rates of malformations that require classification. A dose of 135 mg/kg bw/d resulted in severe maternal toxicity (decrease in body weight, increased mortality and abortions). Total implantation loss was observed in 3 dams out of 22 dams. Since the mortality rate at this high dose is high, 11

dams out of 24 died prematurely, the CLP guidance criteria (Annex I: 3.7.2.4.4) are fulfilled that data for a dose level should not be considered if mortality is excessive e.g. greater than 10%.

Based on the available read across consideration to RP 3:2 RAC concludes that **no classification is warranted for developmental effects**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier submitter's proposal

The substance "Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 1:1)" (RP 1:1) is a formaldehyde-releasing UVCB substance with bactericidal and fungicidal properties and is employed as a biocidal active substance.

Degradation
The dossier submitter proposed to consider RP 1:1 as rapidly degradable because one out of two studies on ready biodegradability (both performed according to the OECD TG 301D (Closed-Bottle-Test)) showed 62.7% degradation after 28 days.

Aquatic Bioaccumulation
According to the dossier submitter, RP 1:1 does not meet the CLP criteria for bioaccumulation. There are no experimental data on bioaccumulation of RP 1:1 available, however, based on the hydrolysis products formaldehyde ($logK_{ow}$ = 0.48) and 2-hydroxypropylamine ($logK_{ow}$=0.61) the potential for bioaccumulation of RP 1:1 was considered low.

Acute Toxicity
The dossier submitter proposed to not classify RP 1:1 as acutely hazardous to the aquatic environment. The basis for this proposal is that $L(E)C_{50}$ values for all three trophic levels are >1 mg/L and the lowest $L(E)C_{50}$ value was derived for algae with E_rC_{50} = 2.9 mg/L.

Chronic Toxicity
The dossier submitter proposed to classify RP 1:1 as Aquatic Chronic 3 (H412) based on rapid degradability and the lowest chronic toxicity in algae (*Pseudokirchneriella subcapitata*, E_rC_{10} = 0.148 mg/L). Algae have been shown to be the most sensitive throphic level in aquatic acute toxicity tests. The NOEC was determined in the study report (Dunett´s test using individual replicate values) to be <0.05 mg/L. Based on the flat dose-response curve and the observed difference (factor of 9) between biomass and growth rate, an E_rC_{10} of 0.148 mg/L (corrected for 76% recovery) was derived. In a second study on algae (*Desmodemus subspicatus*) a 72h-NOE_rC of 0.9 mg/L was derived and supports the proposed classification. For *Daphnia* no chronic study is available, however a read-across to the chronic *Daphnia* study with RP 3:2 resulted in a NOEC of 1.3 mg/L based on mean survival of the offspring. For fish no chronic study is available.

Comments received during public consultation

Three MSCAs commented on the environmental hazards and one of them supported the dossier submitter's proposal.

One commenting MS questioned the scientific quality of the study on ready biodegradability and wether it was carried out under GLP. Also the use of potassium hydrogen phthalate as a reference substance and the use of river water as the inoculum were questioned and noted that it is not possible to rule out adaption to the test item. The same commenting MS highlighted that for the

two hydrolysis degradation products 2 –hydroxypropylamine and formaldehyde it is unclear if additional data for an environmental hazard classification are available.

Another commenter requested further explanations on the hydrolysis and on the degradation of the hydrolysis products.

Assessment and comparison with the classification criteria

Degradation

RAC notes that degradability tests on UVCB substances may only be considered relevant if it has been shown that the UVCB substance only contains structurally similar constituents that are expected to behave in the same way in the tests. RAC in general prefers the assessment of degradation via a testing approach where relevant constituents of a UVCB substance are first subjected to screening assessment individually. If certain constituents represent the worst case with regard to degradability, these "defined constituents" may be used for further testing and for assessing the entire UVCB substance.

Ready biodegradability

The potential for biotic degradation of RP 1:1 was investigated in two studies on ready biodegradability both performed according to the OECD TG 301D (Closed-Bottle-Test). In one test the pass level for ready biodegradability was clearly not reached. It was also shown that RP 1:1 was not toxic to microorganisms. Both hydrolysis products formaldehyde and 2-hydroxypropylamine on their own seem to be readily biodegradable. Consequently, the observation that the UVCB substance RP 1:1 is not readily degradable may indicate that it might include constituents which biodegrade at a slower rate or biodegradation products are formed which degrade more slowly. The fact that the 10-day window is not fulfilled may indicate that some compounds are not readily degradable. Overall no further explanation of the negative test result is given which would question the reliability of the study for classification purposes.

The second test showed 62.7% degradation after 28 days which is close to the threshold criterion in CLP. The dossier submitter rated this study with Klimisch score 2. One commenting MSCA CA questioned its scientific quality and reliability. RAC notes that the study appears to have been carried out under GLP. Adaption of the inoculum to the test item however could not be ruled out.

For comparison, RAC notes that the closely related RP 3:2 (Contram^{TM} MBO and GrotaMar 71) has been shown in two tests to be not readily biodegradable.

RP 1:1, being an UVCB-substance, might contain constituents which are not sufficiently similar with regard to the property tested. Consequently, the degree of ultimate degradation (mineralisation to CO_2) of each of the various constituents and degradation products remains unknown in standard screening tests such as OECD 301D. It seems not possible to calculate a ThOD for RP 1:1 and a more careful consideration of the nitrification is recommended when measuring the COD. It is known that ready biodegradability tests may sometimes fail because of the stringent test conditions and that consistent positive test results should generally supersede negative test results. However, in the case of the UVCB substance RP 1:1 the borderline positive test result in one of the two OECD TG 301D tests may not be evaluated superseding the negative test. There is clear evidence from three tests, that RP 3:2 and RP 1:1 are not ready biodegradable and an adaptation of the inoculum cannot be ruled out. The weight of evidence approach by RAC incorporates that it has not been demonstrated for RP 3:2 and RP 1:1 that all constituents are sufficiently similarly degradable.

Based on the weight of the available evidence, including supporting data from RP 3:2, RAC concludes that RP 1:1 is not readily biodegradable. This is in line with the evaluation of RP 3:2.

Hydrolysis

It has been demonstrated in a laboratory test that RP 1:1 hydrolyses to formaldehyde and 2-hydroxypropylamine at rather low concentrations within a few hours. RAC notes that hydrolysis of RP 1:1 is rather the establishment of an equilibrium than irreversible hydrolysis. Consequently, the hydrolysis rate may not be taken as and abiotic degradation half-life as such. A more careful consideration of the hydrolysis is recommended. In addition, it has been demonstrated that hydrolysis of RP 1:1 is strongly dependent on its concentration in water and complete hydrolysis may only be assumed at very low concentrations. The CLP guidance requires that hydrolysis has to be demonstrated under relevant environmental conditions. Since RP 1:1 is a UVCB substance, degradation may not follow single first order kinetics. Both degradation rate independent from concentration and degradation following first order kinetics, are required to extrapolate laboratory results to relevant environmental conditions (see guidance IR R.7b). At the 32th meeting of ECHA's Member State Committee (MSC-32) it was agreed that relevant environmental conditions include 12°C temperature. Although, the hydrolysis half-life DT_{50} under relevant environmental conditions (temperature, concentration, and pH) was not calculated, it may be reasonable to consider that the primary degradation half-life would be shorter than 16 days.

Rapid degradability

Following the guidance on the application of the CLP criteria (version 4.1, June 2015, II.2.3.8 Hydrolysis) to demonstrate rapid degradability data from hydrolysis studies could be considered "*only when it can be satisfactorily demonstrated that the hydrolysis products formed do not fulfil the criteria for classification as hazardous for the aquatic environment*". While it has been demonstrated that RP 1:1 hydrolyses to the degradation products formaldehyde and 2-hydroxypropylamine it was questioned during PC if it has been sufficiently demonstrated that the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment.

RP 1:1 is a formaldehyde-releasing UVCB substance with bactericidal and fungicidal properties and it is scientifically well understood that the ecotoxicological properties are mainly related to the hydrolysis product formaldehyde. Algae are the most sensitive species for the formaldehyde releasers RP 1:1 and RP 3:2.

For the hydrolysis product formaldehyde, ecotoxicity data have been assessed during the Biocides Review Programme in 2012 ("Formaldehyde Core Dossier"). All three trophic levels, fish, invertebrates and algae have been tested for acute aquatic toxicity. The sensitivity is at the same level, i.e. around 5.7 mg/L and above the CLP criteria to classify for aquatic acute hazard. However, no long-term study on fish is available. The algae study is only available as a literature publication without any raw data or concentration-response curves. Only the 72h E_rC_{50} of 5.7 mg/L was published. Consequently, the literature data does not allow the derivation of a NOE_rC, nor an E_rC_{10} or an E_rC_{20} and thus from this study no information on the chronic algae toxicity of formaldehyde is available. A second algae study was requested by several MSCA during the Biocides Review Programme and by one commenting MSCA during PC, but up to date has not been provided. For daphnia a NOEC of 1.04 mg/L was derived, which is close to the criterion (<1 mg/L) for classification.

There is evidence that formaldehyde is slightly more toxic than RP 1:1. Acute toxicity data show that fish are up to 23 times and invertebrates up to 5 times more sensitive to formaldehyde than to RP 1:1, while the sensitivity of algae is nearly identical. The chronic toxicity data for invertebrates (read-across to RP 3:2) show a slightly higher sensitivity to formaldehyde.

In 2012 RAC adopted its opinion on the proposal submitted by France for a harmonised classification and labelling at EU level of formaldehyde. However, the endpoint and classification as hazardous to the aquatic environment were not part of the dossier and have not been evaluated by RAC.

For the second relevant hydrolysis product 2-hydroxypropylamine an OECD assessment dated 2011 summarises acute ecotox data and QSAR estimations for all three trophic levels. The

available information seems to indicate that 2-hydroxypropylamine to not fulfil the CLP criteria for aquatic acute toxicity. However, none of the available information was considered to be a reliable key study by the dossier submitter. No additional information and none of the original study reports or scientific article were provided. Chronic toxicity of 2-hydroxypropylamine was not available in the CLH report. RAC concludes that the data do not sufficiently demonstrate that the hydrolysis product 2-hydroxypropylamine, does not fulfil the criteria for classification as hazardous to the aquatic environment.

The CLH report shows in Figure 5.1.1-1 that at least one other known degradation product and a number of unknown compounds may be formed by hydrolysis (depending on the initial concentrations) and no information on them is presented and it is not possible to know if they do not fulfil the criteria for classification as hazardous for the aquatic environment.

In summary, RAC considers RP 1:1 to be not ready biodegradable but hydrolysable. RAC agrees with the commenting MSCA that it has not been sufficiently demonstrated that the two relevant hydrolysis products (formaldehyde and 2-hydroxypropylamine) and other potential hydrolysis products do not fulfil the criteria for classification as hazardous to the aquatic environment. As consequence, RAC considers RP 1:1 to be not rapidly degradable for the purpose of classification.

Aquatic Bioaccumulation

RAC notes that a UVCB substance may only be considered to be one chemical substance for the purpose of assessing and testing the potential to bioaccumulate, if a clear case is made in the assessment for why all constituents are sufficiently similar with regard to the property tested. This has not been demonstrated for RP 1:1. RAC agrees with the dossier submitter that, although there are no experimental data about bioaccumulation available, in view of the rapid hydrolysis, it may be assumed that RP 1:1 does not fulfil the criteria on aquatic bioaccumulation.

Acute Toxicity

RAC agrees with the dossier submitter to not classify RP 1:1 as acutely hazardous to the aquatic environment (lower EC_{50} = 2.9 mg/L for *P. subcapitata*).

Chronic Toxicity

RAC agrees with the dossier submitter that the lowest chronic toxicity of RP 1:1 was derived for algae (*P. subcapitata*) with an E_rC_{10} of 0.148 mg/L. However, in contrast to the dossier submitter RAC considers RP 1:1 to be not rapidly degradable for the purpose of classification. This would result in a classification of RP 1:1 as Aquatic Chronic 2 (H411). RAC also applied the surrogate approach since adequate studies on chronic fish and invertebrate toxicity using RP 1:1 as test substance were not available. The surrogate approach results (the substance not rapidly degradable and the *Daphnia magna* EC_{50} of 29 mg/L) in a classification of RP 1:1 as Aquatic Chronic 3 (H412). Since the most stringent outcome should be chosen, **RAC concludes that RP 1:1 should be classified as Aquatic Chronic 2 (H411).**

Additional references

Additional references not included in the CLH report

De Groot A, Geier J, Flywholm M-A, Lensen G, Doenraads P-J (2010) Formaldehyde-releasers: relationship to formaldehyde contact allergy. Metalworking fluids and remainder. Part 1. Contact Dermatitis 63:117-128.

BfR, 2006. Assessment of the carcinogenicity of formaldehyde. http://www.bfr.bund.de/cm/350/assessment_of_the_carcinogenicity_of_formaldehyde.pdf

SCCS 2014 http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_164.pdf

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).