Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Reaction products of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2); [MBO]

EC Number: -
CAS Number: -

CLH-O-0000001412-86-95/F

Adopted

4 December 2015

4 December 2014

CLH-O-0000001412-86-95/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 (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 and 2-hydroxypropylamine (ratio 3:2); [MBO]**

EC Number: **-**

CAS Number: **-**

The proposal was submitted by **Austria** and received by RAC on **16 September 2014.**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonized System (GHS). The classification notation for 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 **9 December 2014**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **23 January 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	612-290-00-1	Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2)			Carc. 1B Muta. 2 Skin Corr. 1B Skin Sens. 1A Aquatic Chronic 3	H350 H341 H314 H317 H412	GHS05 GHS07 GHS08 Dgr	H350 H341 H314 H317 H412			
RAC opinion	612-290-00-1	Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2); [MBO]			Carc. 1B Muta. 2 Acute Tox. 4 Acute Tox. 3 Acute Tox. 4 STOT RE 2 Skin Corr. 1B Eye Dam. 1 Skin Sens. 1A Aquatic Chronic 2	H350 H341 H332 H311 H302 H373 (gastrointestinal tract, respiratory tract) H314 H318 H317 H411	GHS08 GHS06 GHS05 GHS09 Dgr	H350 H341 H332 H311 H302 H373 (gastrointestinal tract, respiratory tract) H314 H318 H317 H411	EUH071		
Resulting Annex VI entry if agreed by COM	612-290-00-1	Reaction product of paraformaldehyde and 2-hydroxypropylamine (ratio 3:2); [MBO]			Carc. 1B Muta. 2 Acute Tox. 4 Acute Tox. 3 Acute Tox. 4 STOT RE 2 Skin Corr. 1B Eye Dam. 1 Skin Sens. 1A Aquatic Chronic 2	H350 H341 H332 H311 H302 H373 (gastrointestinal tract, respiratory tract) H314 H318 H317 H411	GHS08 GHS06 GHS05 GHS09 Dgr	H350 H341 H332 H311 H302 H373 (gastrointestinal tract, respiratory tract) H314 H318 H317 H411	EUH071		

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

The substance is an biocidal active substance which has originally been notified under the name "3,3'-methylene-bis(5-methyl-oxazolidine)" (MBO) according to Directive 98/8/EC concerning the placing of biocidal products on the market. The evaluation of the dossier has shown that the active substance is a complex reaction mixture (UVCB Substance) with 3,3'-methylene-bis(5-methyloxazolidine) being only one of the constituents.

One of the by-products is α,α',α"-Trimethyl-1,3,5-triazine-1,3,5(2H,4H,6H)-triethanol (HPT) which is formed in the course of hydrolysis and is further hydrolysed to 2-hydroxypropylamine and formaldehyde. The active substance notified as MBO was renamed to "*reaction product from paraformaldehyde and 2-hydroxypropylamine (ratio 3:2)*" further referred to throughout this opinion as "*RP 3:2*".

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

According to the CLH report, the closely related substance RP 1:1 (see RAC opinion on *reaction product from paraformaldehyde and 2-hydroxypropylamine (ratio 1:1)),* contains about 28% (calculated) releasable formaldehyde while RP 3:2 contains about 45% (calculated) releasable formaldehyde per molecule. However, IND have argued (during public consultation) that ´free´(unbound) residual formaldehyde is present at very low concentrations.

From the data in the "Environmental hazard assessment" section of the CLH report, it can be concluded that substantial amounts of formaldehyde (or formaldehyde hydrate) can be released from RP 3:2 within 1 h at physiological pH. However, the extent of hydrolysis of RP 3:2 (and therefore release of formaldehyde from the substance) is highly dependent on the extent of dilution with water. As shown in Table 5.1.1.-3 of the CLH report, at a 1% (w/w) initial concentration of RP 3:2 (MBO; Grotan® WS), in a buffered aqueous solution at pH= 7 (at 25°C), the formaldehyde content reached 27% of the constituents within 1 h. The total concentration in the solution was very low, due to the low starting material concentration), and the formaldehyde formation rate appearing to plateau after this point. Separately it was shown that in an unbuffered solution of D_2O, at a 1% initial concentration of MBO (RP 3:2; Contram™ i.e apparently from another source) (at 20°C), formaldehyde hydrate content reached approximately 10% of the constituents (but only a low concentration in the solution, again due to the low concentration of starting material), but the time at which the sampling occurred was not stated (see table 5.1.1.-2 of the CLH report). Since the dossier submitter (DS) noted in the response to comments (RCOM) that the test material had a pH of around 9.0-10.0, the data seemed consistent with the findings in Table 5.1.1.-3, where in a buffered solution at pH = 9 the formaldehyde content reached approximately 7% after 33 min and 9% after 6.9 h. The highest degree of formaldehyde formation was seen at pH 4 (38% within 0.33 h, 42% within 6.8 h). For further details see the discussion under "RAC evaluation of environmental hazards", Section 5.1.1 of the CLH report and the RCOM.

Available hydrolysis tests support qualitatively that hydrolysis will occur in contact with aqueous biological media in mucous membranes. 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 evaporating from RP 1:1 is assumed to contribute to the toxic/carcinogenic effect resulting from the direct impact of hydrolysis products at the contact site.

The CLP Regulation, Art. 9 and Annex 1, 1.1.1.3, supports a weight of evidence evaluation of the available data. Where data on RP 3:2 are lacking, data on RP 1:1 and data on the hydrolysis products formaldehyde and 2-hydroxypropylamine were therefore considered. Regarding the

quality of the available data and the consisitency of information on the toxic effects and the related mode of action, information on hazardous properties on these 'source' substances are in general considered appropriate to predict the hazardous properties of RP 3:2.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

The DS included data on reaction products of paraformaldehyde with 2-hydroxypropylamine for both 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} were 960 mg/kg bw for acute oral toxicity and above 2000 mg/kg bw for acute dermal toxicity. For RP 3:2 there were three oral rat studies and three dermal rat studies. The LD_{50} 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 for acute toxicity, the DS stated that the effects were due to the corrosive effect of the substance and therefore proposed no classification for acute toxicity.

Comments received during public consultation

Two MSCAs suggested that classification for acute toxicity may be applicable. One MSCA also proposed addition of the supplemental hazard information statement EUH071 (corrosive to the respiratory tract) and 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
Local effects in the GI tract were seen in the acute oral toxicity study on RP 1:1 (Schülke & Mayr, 2000). However, its severity, dose-response relationship and whether it contributed to the mortality remains unclear. The LD_{50} value for RP 1:1 was 960 mg/kg bw.

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

2-Hydroxypropylamine
In the document CLH-REP_ATT_Appendix HPA_DV018252-32 (hereafter referred to as "Doc Appendix HPA") 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.

RP 3:2
The oral LD_{50} of 630 mg/kg bw was derived from a study according to OECD technical 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.

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.

In conclusion, an OECD TG 423 (acute toxic class method) study on RP 3:2 revealed an 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 agrees to classify RP 3:2 (based on the studies on RP 3:2) as **Acute Tox. 4; H302 (Harmful if swallowed)** according to the CLP Regulation (ATE guidance values for this category are from > 300 to $\leq$ 2000 mg/kg bw).

Acute dermal toxicity

RP 1:1
Two acute dermal studies on RP 1:1 revealed LD_{50} values > 2000 mg/kg bw.

Formaldehyde
Formaldehyde has a harmonised classification in CLP, Annex VI for Acute dermal toxicity, category 3; H311 (Toxic in contact with skin).

2-Hydroxypropylamine
In Doc Appendix HPA, an LD_{50} of 1640 mg/kg bw was calculated in the study of Smyth *et al.* (1949) 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 3:2
Corrosivity was not observed after dermal application of undiluted test substance in two studies on RP 3:2 with a comparable design to OECD TG 402. Slight skin reddening (Draize score 1, 10-24 h) seen at ≥ 5.04 mL/kg was obviously not the cause of death in the study of Schülke & Mayr (1977) with LD_{50} at 6000 mg/kg bw. Local eryhema (6 h post application and local scale formation at study termination (14 days post exposure) were observed in another study of Schülke & Mayr (2000). This study revealed an LD_{50} of 1400 mg/kg bw. At study termination (14 days post exposure) skin histopathology of surviving rats at ≥ 1000 mg/kg bw showed (non-reversible) effects such as local cellular debris and necrotic tissue (scab), leucocyte infiltration and epidermal cyst. However, no information could be found on the severity and extension of the skin lesions. Necrotic tissue (scab formation) was only reported for the survivors at study termination and was likely not the cause of mortalities.

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.

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

RAC agrees 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 ATE guidance values for this category are 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.

Acute inhalation toxicity

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

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

During public consultation one MSCA suggested that read across to formaldehyde could be justified. This MSCA noted that the level of formaldehyde emission may not be constant over time and proposed classification on acute inhalation toxicity as Acute Tox. 4; H332 (Harmful if inhaled) for RP 3:2.

The CLP Guidance, 3.1.2.3.3 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 appropriate for RP 1:1 and RP 3:2 based on the read across from formaldehyde vapour to released mist with 28% formaldehyde content. RAC emphasises that the correct amount of releasable formaldehyde for RP 3:2 is 45%.

RAC considers that read across to formaldehyde is justified as RP 3:2 contains 45% releasable formaldehyde. Using the data supporting formaldehyde classification (Cat. 3) and taking the maximum amount of releasable formaldehyde into account, Acute Tox. 4 is considered as justified assuming that the total amount of 45% formaldehyde is indeed released. This is consistent with the observation that acute toxicity values for the oral route demonstrated lower potency of RP 3:2 than formaldehyde to cause acute toxic effects. As hydrolysis data in contact with biological tissues are lacking, RAC discussed the uncertainties with regards to the actual emitted concentrations in air (as gaseous phase or aqueous solution), and futher uncertainties that may result from unstable intermediates which could also contribute to the acute inhalation toxicity. For RP 3:2 a LC_{50} of about 1.3 mg/L (factor of 2.2 applied on a LC_{50} of 0.6 mg/L (4h) for formaldehyde) would result. For mists, this is equivalent to Cat. 4 (ATE guidance values from >1 to ≤5 mg/L).

RAC, therefore agrees to classify RP 3:2 as Acute Tox. 4 (Harmful if inhaled).

EUH071
The supplemental labelling with the hazard statement EUH071 – Corrosive to the respiratory tract – was proposed by one MSCA. If in addition to classification for inhalation toxicity, data are available that indicates 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 MS. 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 gas 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 to 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 concludes 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 STOT SE 3; H335 is not appropriate as the substance is corrosive.

Comments received during public consultation

Two MSCAs remarked that the classification STOT SE is not (generally) covered by the classification Skin Corr. and one MSCA wished to consider data on formaldehyde for classification as STOT SE. One MSCA agreed that no classification for STOT SE 3 is required.

Assessment and comparison with the classification criteria

RP 1:1
There is no proposal to classify RP 1:1 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.

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

RP 3:2
Based on the acute toxicity data on RP 3:2 there were no effects beyond those covered by the classifications on acute dermal and oral 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, 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 also 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 3:2 as corrosive to the skin.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

Two rabbit OECD TG 404 (or comparable) studies on RP 1:1 and three on RP 3:2 were summarised in the CLH report. The DS also included discussion on the hydrolysis products of the substance, formaldehyde and 2-hydroxy-propylamine. The results suggested strong irritant to corrosive properties. The DS found subcategorisation difficult based on the data, but, as Skin Corr. 1 without subcategorisation 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 the proposed classification for Skin corrosivity category 1 without subcategorisation were submitted by three MSCA.

Assessment and comparison with the classification criteria

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 minutes and 1 hour were also tested in the study of Becker Chemie (2002) and these revealed only well defined erythema at 4 h postexposure.

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 3:2
Skin corrosion and strong irritation was observed in two studies on RP 3:2, one of which (with 4 h exposure time) was in full compliance with OECD TG 404 (Bode Chemie, 2002). In this study brown discolouration, necrotic tissue, and demarcation was reported as non-reversible in 2/3 rabbits on day 7, on day 14, on day 21 (2 animals had granulation tissue, synonymous with scar formation following necrosis), and on day 28 (scarring was seen in 2 animals) (see study report in Doc III A6.1.4/03).

RAC notes that the DS proposed Skin Corr. 1 without a subcategory in chapter 4.4. of the CLH report and revised the proposal to Skin Corr. 1B following the response from one MSCA. The CLP Regulation does not foresee a classification for skin corrosion without subcategorisation. In contrast to the DS argumentation in the CLH report, it is RAC's view that the available data enable a decision to be made on the subcategory. The translation rules of Annex II may give general guidance (but does not reflect the quantitive aspects needed for subcategorisation), but more emphasis is given by RAC on the study information on RP 3:2 and studies on RP 1:1 and formaldehyde were taken as additional information.

Corrosive effects were seen in 2/3 animals in the study of Bode Chemie (2002). The earliest time point, when brown discolouration (interpreted as indicative for epidermal cell destruction as brown discolouration and necrotic tissues was reported from day 7 onwards for this and the second rabbit) was observed, was after 1 hour (of 4 h exposure time) in one animal. The same lesions were reported for the second rabbit beginning after 48 h. According to the CLP criteria (Annex I, Table 3.2.1) the subcategory 1B is appropriate when corrosive effects appeared during the 14 day observation time after exposure for > 3 min and ≤ 1 h. Although exposure periods of less than 4 h were not tested on RP 3:2, the first reading was done after 1 h in the study of Bode Chemie (2002). As corrosive effects in this study began after 1 hour exposure duration, RAC proposes to assign subcategory 1B based on the 1 h observation and taking read across to formaldehyde and 2-hydroxlpropylamine into account.

Irritant and corrosive effects were also reported for all animals of the second study (Schülke & Mayr, 1979) using a 24 h exposure period. The report on the study results does not allow a subcategorisation due to the extended exposure period and limited readings (only at 24 and 72 h, see Doc III A6.1.4/02).

As RP 3:2 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 3:2 itself has corrosive properties or that a sufficiently rate of hydrolysis will occur within a short period of exposure (within 1 h) that caused corrosive effects by the hydrolysis products (formaldehyde and 2-hydroxypropylamine).

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 and read across to the corrosive hydrolysis products, **RAC agrees on the classification as Skin Corrosive 1B; H314 (Causes severe skin burns and eye damage)**.

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 studies indicate that the substance is eye corrosive.

Comments received during public consultation

Comments in agreement with the DS proposal were submitted by one MSCA. It was pointed out by another MSCA that although no labelling is required as the substance is also skin corrosive the substance should be classified for Eye damage category 1.

Assessment and comparison with the classification criteria

RP 1:1
A guideline conforming acute eye irritation study on RP 1:1 resulted in irreversible cornea lesions at day 21.

Formaldehyde
The Annex VI entry on formaldehyde do not include eye irritation/damage, however the majority of notifiers have self-classified the substance as Eye Dam. 1.
The formaldehyde Core Dossier summarises that although no guideline-conforming 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 covering eye irritation/damage on 2-hydroxypropylamine, but the majority of notifiers classify the substance as Eye Dam. 1.

RP 3:2
The DS noted that the irreversible eye damage would support classification for Eye damage category 1, but considered a separate classification as not required as the labelling for H314 (Causes severe skin burns and eye damage) already covers eye damage.

The study of Schülke & Mayr (1979) demonstrated severe effects (iris lesions after 24 hours, mean 2.0 (which means haemorrhage, gross destruction, or no reaction to light according to OECD TG 405) that were considered as irreversible. Animals were sacrificed due to the severity of ocular reactions 24 h after instillation.

The CLP guidance 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, the 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, the 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 for serious eye damage. For RP 3:2 RAC agrees to classify as Eye Dam. 1. Although for corrosive substances the risk for severe eye damage is implicit (and testing should not be avoided), in this case severe eye damage has been demonstrated in animal studies (conducted in 1978 and 1979) and **justifies a separate classification as Eye Dam. 1. Separate labelling with H318 is not needed**.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

The DS included five Guinea Pig Maximisation Test (GPMT) tests in the CLH report 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 rate was 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 as Skin Sens. 1A; H317.

Comments received during public consultation

Two MSCAs submitted comments in agreement with the DS's proposal.

Assessment and comparison with the classification criteria

Animal data on RP 1:1
A GPMT study (Lubirzol Corporation, 2001) is available supporting Skin sensitisation category 1A due to a positive response to a 1% induction concentration in 90% of animals.

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

2-Hydroxypropylamine
There is no evidence for sensitizing properties in available 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 as negative. A questionnaire to workers exposed to 2-hydroxypropylamind revealed that 5 of 15 randomly selected individuals reported contact dermatitis. This study was considered of limited validity, presumably due to the irritant effects observed after direct contact with 2-hydroxypropylamine.

RP 3:2

Human data on RP 3:2
In a study on contact allergy, numerous formaldehyde releasers were tested and among these the highest frequency was observed for RP 3:2 (Geier *et al.*, 1997, Doc III A6.12/01).
Epicutaneous testing in 1786 patients (from 35062 patients in 24 hospitals) exposed to RP 3:2 for 24 h or 48 h revealed allergic skin reactions in 55 patients (3.1%). In this study,
46 out of 1406 patients tested with formaldehyde and in separate experiments with RP 3:2 showed positive reaction to RP 3:2. As only 13 out of these 46 patients were also positive to formaldehyde, it was concluded that the positive results might primarily result from the UVCB substance and not only from released formaldehyde.

DeGroot *et al.* (2010) reviewed five patch test studies on patients who were metal workers with suspected contact dermatitis, and who had contact with metal working fluids containing RP 3:2, and found positive reactions in 2.3% to 6.7% of the exposed workers (see Table 2 in this publication).

According to the CLP Guidance, 3.4.2.2.3 on the evaluation of human data, frequencies of 2.3% to 6.7% as reported for the metal workers correspond to the high frequency level (Table 3.4.2-b, the guidance level for high frequency in selected workers with known exposure or dermatitis is ≥ 1.0%) and supports a subcategorisation as Skin Sens. 1A.

Regarding the exposure level and its relevance for subcategorisation, no data were included in the CLH report to enable human exposure to be estimated for sub-categorisation in accordance the CLP Guidance.

Animal data on RP 3:2
In the GPMT for RP 3:2, the intradermal induction dose of 0.5% resulted in 60% positive animals after challenge with a 1% solution (Anderson *et al.*, 1984).

A positive sensitisation response > 90% was observed in another GPMT study by Schülke & Mayr (2001). This study can not be used for subcategorisation as a high induction dose (5%) was applied, and a decision concerning whether to classify in Cat. 1A or 1B, requires induction concentrations below 1% to have been tested.

The results of the Anderson *et al.* (1984) study meet the criteria for subcategory 1A (≥60% responding at >0.1% to ≤1% intradermal induction dose). RAC concludes that the information from the animal testing is supportive of subcategory 1A.

RAC agrees with the DS's proposal to classify RP 3:2 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 seen 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

Two MSCA did not agree that STOT RE is covered by the classification for corrosion and asked for this classification to be considered or, if data are lacking, to refer to formaldehyde.
One MSCA proposed STOT RE 2, referring to the provision of section 3.9.2.5.1 of the CLP Regulation stating that if repeated dose effects occur at doses more than half an order of magnitude lower than the acute toxicity, classification for STOT RE should be considered.

In addition to comparing repeated oral toxicity with acute oral toxicity, the stomach lesions in rats treated with RP 3:2 in the OECD TG 415 study at 45 mg/kg bw over 70 days of treatment support classification as STOT RE.

Assessment and comparison with the classification criteria

Oral route

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 to OECD TG 408.

In the first gavage 90-day study with 10 male and 10 female rats per dose group 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 one male that died at day 52 and in one female that died at day 75.

Abnormal breathing sounds were noted in animals at 80 mg/kg bw/d at week 5 or later (in one female that died on day 68, 3 males, including one male which died on day 68 with pharyno-laryngeal lesions,) 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 one female and one male at 30 mg/kg bw/d and in one 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 bw/d 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. The summary table in the HPT Doc III A gives the impression that a microscopic examination on the larynx, pharynx and oesophagus was limited to the intermittent deaths.

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 one female that died on day 38 with reduced activity, reduced skin turgor, reduction of bw and enlarged submandibular lymph node and one surviving female rat which showed nose bleeding, corneal opacity of a bloody left eye, and a hairless region around the eye.

Systemic arteritis was 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 nonspecific 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. 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 Maximum Tolerable Dose (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; Schülke & Mayr, 2002).

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 drinking water with formaldehyde up to concentrations of 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 Doc 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 guidelines.

2-Hydroxypropylamine

The NOAEL of 600 mg/kg bw/d was estimated in a 90-day feeding study with limitations, being 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 3:2

The most relevant study is a 90-day study (Bode Chemie, 2002, in accordance to 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. It is to be noted that effects at these concentrations would not lead to classification as skin irritant as the concentration is below 5%.

The study has weaknesses as the stomach and the bone marrow were the only organs examined for histopathological effects in the low and mid doses. Histopathology findings were reported (Doc III A6.4.1/02) without any grading of severity and with lack of information, such as whether all animals with 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 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. As the dose of 180 mg/kg bw/d during the first 11 weeks is above the guidance value limit for classification as STOT RE (100 mg/kg bw/d for a 90-day study), these effects do however 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 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 with 60 mg/kg bw/d (1.2% in corn oil). In addition, increased medullary granulopoiesis was seen in 4 males and one 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 leading to the acute toxicity and that the local effects are sufficiently 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, section 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, the CLP Guidance, 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."*

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). 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 was 2000 mg/kg bw). RAC, in line with comments received during the public consultation from some MSCAs, does not agree with the DS' view that the local irritant effects are mechanistically sufficiently addressed with the classification for corrosion and therefore should not support 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 to reflect 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 3:2 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 agrees with the proposal from an MSCA during public consultation to classify RP 3:2 as **STOT RE 2; H373 (May cause damage to the GI tract through prolonged or repeated exposure)**.

Dermal route

RP 1:1
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 treatment regimens (twice weekly for 60 weeks, three times weekly for 26 weeks, 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 core document on formaldehyde.

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

RP 3:2
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 1:1
No repeated dose study using the inhalation route is available.

Formaldehyde
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 say that effects along the administration routes resulting from repeated exposures are covered by classification for corrosion, while it gives some recommendation in 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 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 causing acute toxicity/irritation 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.

In 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, and 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, epithelial dysplasia and squamous metaplasia at level I of the nasal cavity (Kerns *et al.*, 1983a, b, cited from BfR, 2006). At higher concentrations than 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 a 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 days exposure when comparing with the guidance values, 2 ppm for 12 months corresponds to 8 ppm (9.824 mg/m³ = 0.01 mg/L) for a 90-day study. This is clearly below the guidance concentration for gases 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 3:2</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 dose inhalation toxicity of RP 3:2 are lacking. However, RAC does not agree that effects after repeated inhalation exposure 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-classification for RP 3:2.

The DS informed that RP 3:2 contains about 45% releasable formaldehyde. Assuming that under prolonged inhalation exposure conditions RP 3:2 would continuously release the maximal releasable amount of 45%, a factor of 2.2 should be applied to correct for the lower content of 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 3:2, the LOAEC for repeated inhalation exposure is based on the LOAEC of 2 ppm for formaldehyde (2.456 mg/m³, derived from a rat 12-month study; Kerns et al., 1983 a,b) which corresponds to 8 ppm (9.824 mg/m³ = 0.01 mg/L) for a 90-day inhalation based on Haber's rule. The 8 ppm LOAEC corrected for the maximal amount of releasable formaldehyde from RP 3:2 (45%) with a factor of 2.2 results in a (corrected) concentration of 0.02 mg/L for RP 3:2 which is at the lower boundary of the guidance value (for mists) for STOT RE 2 ($0.02 < C \leq 0.2$ mg/L). As inhalation exposure to the aerosol is expected to be the main concern for RP 3:2, 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 3:2 (and RP 1:1) 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 a LC_{50} of 0.6 mg/L (4 h) which is markedly higher than 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 some uncertainties related to the data(Doc II A 2.12), namely 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 to RP 3:2 generates the hydrolysis products formaldehyde and 2-hydroxypopylamine. Whether 2-hydroxypropylamine may exert additive effects to those expected from formaldehyde, remains unknown.

Based on the read across from data on formaldehyde, RAC agrees to classify RP 3:2 for the effects on the respiratory system as STOT RE 2; H373

All routes/Overall classification on STOT RE

If 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 classification of RP 3:2 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 3:2 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 3:2. Predominantly, clastogenic effects were induced in cells of mammalian cell cultures whereas bacterial gene mutations tests were weakly positive (one test) or negative (two tests). Regarding the *in vivo* testing, a negative *in vivo* micronucleus test and an *in vivo* chromosomal aberration test, which was assessed as equivocal by the DS, are available. The *in vivo* data provide no clear evidence for the induction of

mutagenic effects since there is limited information that the active substance reached the bone marrow cells in relevant concentrations.

The DS additionally provided information on similar results of *in vitro*/*in vivo* mutagenicity tests for the substance RP 1:1. (To avoid a confusion it should be noted that the corresponding references in the tables 4.8-1 and 4.8-4 were taken from the CLH report for RP 1:1. They are not part of the reference list of the CLH report for RP 3:2).

The DS also argued that due to the rapid hydrolysis of RP 3:2 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 refers to the classification of formaldehyde that is classified as a category 2 mutagen based on the induction of genotoxic effects *in vivo* on somatic cells at the 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 3:2 the DS proposed to classify RP 3:2 as a Muta. 2 on the basis of its hydrolysis product formaldehyde.

Comments received during public consultation

Two MSCAs expressed their support for the proposed classification. One individual commenter disagreed with the proposed classification as Muta. 2 due to the lack of relevant mutagenicity data.

Assessment and comparison with the classification criteria

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

Formaldehyde
RAC agrees with the approach of the DS to take into account the classification of formaldehyde as a category 2 mutagen in the justification of the classification of RP 3:2.

Formaldehyde that is rapidly released from RP 3:2 on contact with biological tissues is classified as a category 2 mutagen based on the induction of genotoxic effects *in vivo* on somatic cells at the site of contact, 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 the use, the inherent potential of RP 3:2 to release formaldehyde is a critical factor.

Testing of the *in vitro* mutagenicity of RP 3:2 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 3:2 has poor systemic availability *in vivo* due to its rapid hydrolysis. Therefore it seems unlikely that genotoxic effects are induced at a site distant from first contact.

Although no distinct rule is noted on 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) the information on the hydrolysis product was used to assess the mutagenic potential of RP 3:2.

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 3:2

The evaluation of the mutagenicity data of RP 3:2 by the DS and RAC does not differ. RAC also comes to the conclusion that a proposal for classification of RP 3:2 as a category 2 mutagen is justified.

In vitro data

The available bacterial gene mutation tests are weakly positive with and without S9-mix (Lubrizol Corporation, 2000, see Doc III A6.6.1/03) or negative (Schülke and Mayr, 1997, Doc IIIA 6.6.1/01; Schülke and Mayr, 2000, Doc III A6.6.1/02). It is not possible to conclude on the relevance of the negative results 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, Doc III A6.6.3/02; Schülke and Mayr, 2002, Doc III A6.6.3/01) were positive with and without S9-mix. At the analysis of the colony sizes, predominantly small colonies were found, which indicate clastogenic activity of RP 3:2.
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

Two studies are available that are able to detect systemic chromosome mutagenic activity in bone marrow cells of mice:
- One *in vivo* micronucleus was negative after single gavage up to the highest tested dose of 300 mg/kg bw, which induced clinical symptoms (Bode Cemie, 2002 (DocIIIA6.6.4/02)). Due to the lack of cytotoxic effects (reduction of PCE/NCE ratio) and due to the lack of detailed information on the nature and severity of clinical symptoms, no conclusion can be drawn as to whether the MTD was reached.
- One *in vivo* chromosomal aberration test after repeated gavage of RP 3:2 at the highest tested dose of 367 mg/kg bw, in which an increase of the chromosome aberration frequency was observed (not statistically significant; Schülke and Mayr (Doc III A6.6.4/01), 2002). Neither cytotoxic effects nor clinical symptoms were induced. Thus the highest tested doses did not correspond to the MTD nor was it in accordance with highest guideline recomended dose.

The quantity of test data for RP 3:2 is limited and the 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 test guideline. But despite these limitations, the following conclusion can be drawn: in bacteria as well as in somatic cell cultures, mutagenic effects are induced. The results from an *in vivo* micronucleus test as well as from an *in vivo* chromosomal aberration test are of limited relevance due to obvious methodological deficiencies.

RAC discussed that due to its reactivity a poor systemic availability is expected for RP 3:2 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 Muta. 2 based on its local genotoxic action, justified. Some RAC members expressed that the CLP guidance text relates only to classification of substances that caused germ cell mutations. This view is reflected in a minority position supported by three RAC members. RAC recognised that according to the guidance, section 3.5.1, classification is also warranted if there is evidence of only somatic cell genotoxicity leading to classification in category 2 if genotoxic substances are only acting locally.

RAC agrees with the proposal of the DS to classify RP 3:2 for **Germ cell mutagenicity, 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. The proposal iwas to classify in line with formaldehyde

Comments received during public consultation

Three MSCA agreed and four industry commenters disagreed with the classification proposal.

Assessment and comparison with the classification criteria

RP 1:1
No carcinogenicity studies are available on RP 1:1.

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 3:2
There are no reliable human data. Two medical letter reports in Doc IIIA stated that no adverse effects have been documented from annual medical screenings of employees in the manufacturing of products containing formaldehyde releasing biocides or with the active substance RP 3:2. No information is given on the details of the level, duration, frequency and conditions of exposure, the substances the workers were exposed to or the details of the medical examinations and results.

No studies on carcinogenicity or prolonged/repeated inhalation exposures are available for RP 3:2. The non-submission of data was justified by a read across to formaldehyde and probable carcinogenic effects of RP 3:2 are considered by the applicant in the biocide process to be related to the hydrolysis product formaldehyde (Doc III A6.7).

It is expected that RP 3:2 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 3:2 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 may vary depending on different uses, the reaction product of paraformaldehyde and 2-hydroxypropylamine is intended to release formaldehyde in aqueous solutions. In aqueous solutions RP 3:2 is expected to hydrolyse completely under environmental conditions or when the substance has entered the human or animal bodies (Doc IIA1.4.2). 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 3:2 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 3:2 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. Exposure to the gaseous form after evaporation of formaldehyde from the undiluted or diluted RP 3:2 can coincide with the above.

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:

> *"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 3:2, it is not about the similarity of source and target substance, but RP 3:2 should be classified as a carcinogen based on the release of the *identical* substance (formaldehyde) resulting from hydrolytic transformation of RP 3:2.

Endpoints, on which data on RP 3:2 are available, show that effects were consistent with those known from formaldehyde alone. Similar effects were noted e.g. for the oral repeated dose toxicity, with the observation that the toxicity may be more severe for RP 3:2 when comparing with the dose levels or the severity of effects observed with formaldehyde. 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 3:2 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 3:2 with aqueous solutions are not a necessary condition for exerting toxic effects of RP 3:2, 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 3:2 (or RP 1:1) shifts towards formaldehyde with dilution and with the reaction of formaldehyde with biological media.

To the industry representative comment during public consultation that a classification of RP 3:2 as a carcinogen is not justified based on the end use 'diluted metal working fluid' containing less than 0.1% of 'free, unbound' formaldehyde and the slow rate of formaldehyde release during its use, the DS replied that the end uses and different forms of the substance that are on the market are not relevant for the decision on classification.

The industry representative further stated that evidence is lacking that sufficient formaldehyde will be released during exposure to workers to cause a carcinogenic risk. RAC notes that the CLP Regulation states that classification is based on intrinsic hazards of a substance and does not take the exposure conditions into account.

The option to classify RP 3:2 as carcinogen, in category 2, in order to account for uncertainties for substances that are unstable, showing equilibrium behaviour and having half-lives depending on

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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

dilution, temperature and pH (as was discussed in the CLH report) is not supported by RAC. Taking into account 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 a downgrading of the classification into category 2.

Hydrolysis tests 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 membranes. Inhalation exposure to aerosolic RP 3:2 is expected to result in hydrolysis at the site of contact and toxicologically significant concentrations of formaldehyde could be reached on 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 3:2 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 inhalation exposure to RP 3:2 aerosol.

As no data are available to demonstrate that a sufficiently high concentration of formaldehyde can not (meaning never) be reached, there is no evidence to justify classification in a lower category. This prerequisite of evidence, and the fact that CLP is hazard based, is in contrast to the opinion of some commenters who found that the classification is only justified if evidence from exposed workers demonstrates that sufficient formaldehyde will be released and has 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 3:2. 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 3:2 as **Carcinogen, category 1B; H350 (May cause cancer).**

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

One developmental toxicity (OECD 414) and one fertility study (OECD 415) were available which had been conducted using RP 3:2. According to the DS, these studies did not support classification for either sexual function and fertility or development. No reprotoxicity study are available for 1:1.

Comments received during public consultation

One MSCA commented that the DS's interpretation of implantation loss and post-natal deaths at the high dose as being secondary to the maternal effects was not substantiated and suggested conducting a comparison of individual dam and fetal/pup effects.

RP 3:2

<u>Effects on fertility</u>

The documentation of the results of the 1-generation study in the CLH report was not sufficiently detailed to enable a conclusion to be reached on whether the fertility effects are direct or secondary effects or whether or not classification is justified.

To strengthen the database, more details from the MBO Doc III A and from the original study report are given in the BD.

Assessment and comparison with the classification criteria

Formaldehyde

The Formaldehyde Core Document summarised repeated dose inhalation studies (14 days or 90 days) with rats, which 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 or bw gain was reported, no conclusion can be drawn on the implications of these findings. Studies with intraperitoneal application confirmed the adverse effects on sperm.

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

Effects on fertility

The available data from repeated dose toxicity studies and from a 1-generation study with 70 days of premating treatment gave no indication of adverse effects on sexual function or fertility in male rats.

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 at the low dose than at the mid dose and an unusual high numbers of pups died (mainly on Day 2/3) in the control groups. RAC questioned the reliability of the study and found the observed effects to be borderline and not sufficient to justify a classification for this endpoint.

In conclusion, in agreement with the DS' s proposal RAC agrees that a **classification of RP 3:2 for 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. The mortality rate in dams at this high dose was high; 11 dams out of 24 died prematurely. The CLP Regulation criteria states (in Annex I: 3.7.2.4.4) that data for a dose level should normally not be considered if mortality is excessive e.g. greater than 10%.

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

Thus, RAC concludes overall that no classification for reproductive toxicity is warranted for RP 3:2.

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 3:2)" (RP 3:2) 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 3:2 as rapidly degradable. The basis for this proposal was that although Contram^{TM} MBO and GrotaMar 71 is proven to be not readily biodegradable, it is demonstrated that for RP 3:2 primary abiotic degradation via hydrolysis in the aquatic environment has a half-life <16 days (corresponding to a degradation of >70 % within 28 days) and the degradation products do not fulfil the criteria for classification as hazardous to the aquatic environment.

Aquatic Bioaccumulation

According to the dossier submitter, RP 3:2 does not meet the CLP criteria for bioaccumulation. There are no experimental data on bioaccumulation of RP 3:2 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 3:2 was considered low.

Acute Toxicity

The dossier submitter proposed to not classify RP 3:2 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} =2.4 mg/L.

Chronic Toxicity

The dossier submitter proposed to classify RP 3:2 as Aquatic Chronic 3 (H412) based on rapid degradability and the lowest chronic toxicity in algae (*Desmodemus subspicatus*) with a NOE_rC of 0.5 mg/L. Algae have been shown to be the most sensitive species in aquatic acute toxicity tests. Two studies with the same species showed comparable results (E_rC_{50} of 2.4 and 5.7 mg/L) and a third study on marine algae confirmed the findings from the freshwater algae tests (E_rC_{50} of 3.8 mg/L). The chronic Daphnia study according to OECD Guideline 211 resulted a NOEC of 1.3 mg/L based on reproduction. For fish no chronic study was available.

Comments received during public consultation

Three MSCA commented the ENV part of the classification dossier.

One commenting MSCA questioned the scientific significance of the information on hydrolysis rate and considered that further information is needed to verify the conclusion on hydrolysis. Another MSCA 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. One commenting MSCA requested a new algae study.

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

RAC notes that RP 3:2 (Contram™ MBO and GrotaMar 71) has proven in two tests according to OECD TG 301D (Closed-Bottle-Test) to be not readily biodegradable. It was also shown that RP 3:2 was not toxic to the microorganisms. Both hydrolysis products formaldehyde and 2-hydroxypropylamine alone on their own. Consequently, the observation that the UVCB substance RP 3:2 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 might be an indication. Overall no further explanation of the negative test result is given which would question the reliability of the study for classification purposes.

RAC also takes note of a test on biodegradation in seawater according to the OECD TG 306 (Closed-Bottle-Method) with two test concentrations tested. In the higher test concentration only 54% degradation was observed after 28 days supporting the negative test results from the TG 301D tests. Only in the lower test concentration a degradation of 69% seem to indicate a limited potential for primary degradation but may not be used as indication of ultimate degradation of all constituents of the UVCB-substance RP 3:2.

RP 3:2, 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 3:2 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 3:2 the positive test result of the TG 306 test in only one concentration may not be evaluated as a consistent positive test result superseding the negative test results from two 301D tests and one test concentration in the 306 test.

In a weight of evidence approach, taking all available information into account, RAC concludes that the UVCB-substance RP 3:2 is not readily biodegradable. This is in line with the assessment of the UVCB-substance RP 1:1.

Hydrolysis

It has been demonstrated in a laboratory test that RP 3:2 hydrolyses to formaldehyde and 2-hydroxypropylamine at rather low concentrations within a few hours. RAC notes that hydrolysis of RP 3:2 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 3:2 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 3:2 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) "*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, data from*

hydrolysis studies could be considered." While it has been demonstrated that RP 3:2 hydrolyses to the degradations products formaldehyde and 2-hydroxypropylamine, it was questioned in the 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 3:2 is a formaldehyde-releasing UVCB substance with bactericidal and fungicidal properties and it is scientifically well understood that the ecotoxicological properties are cause mainly by the hydrolysis product formaldehyde. Algae are the most sensitive species for the formaldehyde releaser RP 3:2, RP 1:1.

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 a *Daphnia* sp. 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 3:2. Acute toxicity data show that fish are up to 12 times and invertebrates up to 6 times more sensitive against formaldehyde than against RP 3:2, while the sensitivity of algae is nearly identical. The chronic toxicity data for invertebrates 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 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 <u>not</u> been sufficiently demonstrated that the two relevant hydrolysis products (formaldehyde and 2-hydroxypropylamine) and in particular 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 <u>not</u> 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. In

the case of RP 3:2, 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 3:2 does not fulfil the criteria on aquatic bioaccumulation.

Acute Toxicity

RAC agrees with the dossier submitter to not classify RP 3:2 as acutely hazardous to the aquatic environment.

Chronic Toxicity

RAC agrees with the dossier submitter that the lowest chronic toxicity of RP 3:2 was derived for algae with a NOE_rC of 0.5 mg/L. However, in contrast to the dossier submitter RAC considers RP 3:2 to be not rapidly degradable for the purpose of classification. This would result in a classification of RP 3:2 as Aquatic Chronic 2 (H411). RAC also applied the surrogate approach since adequate studies on chronic fish toxicity using RP 3:2 as the test substance were not available. The surrogate approach results (the substance not rapidly degradable and the fish LC_{50} of 58 mg/L) in a classification of RP 3:2 as Aquatic Chronic 3 (H412). Since the most severe outcome is chosen, as indicated by the guidance, **RAC concludes concludes that RP 3:2 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).