Comments on dossiers proposing harmonised classification and labelling of substances with regard to peracetic acid (CAS 79-21-0, EC 201-186-8)

The Members of the Peracetic Acid Registration Group (PAR), managed by Steptoe & Johnson, with its registered office at Avenue Louise 489, 1050 Brussels, Belgium, hereby submit comments on dossiers proposing harmonised classification and labelling of substances with regard to peracetic acid (CAS 79-21-0, EC 201-186-8).

The members of PAR are Anti-Germ, Bioxal, CID Lines, Christeyns, Ecolab, Evonik Operations, Evonik Peroxide Spain, Hypred, ITW Novadan, Kemira, Promox, Quaron, Solvay, Sopura and Stockmeier Chemie.

General Comments - use this field for non-hazard class related comments

Section 1.1: The degree of purity (%) is only applicable if peracetic acid is used as an active substance in biocidal products. This purity specification is not applicable when peracetic acid is used for non-biocidal applications.

Section 2.1, Table 6: The classification for the hazard class "STOT SE 3 (H335)" should not only be mentioned in the column "Specific Conc. Limits, M-factors" but also in the columns for "Classification" and "Labelling".

Section 5 (Identified uses): Peracetic acid has not only biocidal uses but also non-biocidal uses. It has been registered under the REACH regulation with a total tonnage band of ≥ 1 000 to < 10 000 tonnes.

Comments on the open hazard classes: Acute toxicity:

Comments on the approach to classify a theoretical 100% substance (section 10.1.2, 10.2.2 and section 10.3.2, comparison with the CLP criteria):

Peracetic acid…% is currently classified in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation) as Acute Tox. 4* for the oral, dermal and inhalation route. The entry contains an asterisk (*) in the columns "classification" and "specific concentration limits and M-factors and Acute Toxicity Estimates (ATE)". The asterisk in the column "classification" indicates a minimum classification and the asterisk in the column "specific concentrations limits and M-factors and Acute Toxicity estimates (ATE)" indicates that the entry had specific concentration limits for acute toxicity under Directive 67/548/EEC.

The dossier submitter aims to remove the *(minimum classification) of peracetic acid from the harmonized classification under the Classification, Labelling and Packaging (CLP) Regulation ((EC) No 1272/2008) and to derive definitive ATE values for 100 % peracetic acid, which due to its high reactivity cannot exist in the pure state. For this purpose, ATE values were derived by linear extrapolation from LD_{50} values obtained from acute toxicity tests with equilibrium mixtures of peracetic acid (varying % peracetic acid and other ingredients) to a theoretical 100% peracetic acid for the purpose of classification.

Accordingly, the dossier submitter's proposal for adaption of the hazard classes acute toxicity – inhalation, dermal and oral - for peracetic % to Acute Tox. 3 oral (H301), Acute Tox. 2 inhalation (H330), and Acute Tox. 2 dermal (H310) is not triggered by actual acute toxicity test data for peracetic acid but is the result of a theoretical calculation approach considering the concentration of peracetic acid only. The potential impact of hydrogen peroxide, for example, which itself is classified into category 4 for acute oral and inhalation toxicity, was not considered by the dossier submitter for the derivation of ATE values with respect to the acute oral and inhalation toxicity of 100 % peracetic acid.

This approach is not a mandatory requirement of the CLP regulation and scientifically not justified for the following reasons:

There is no regulatory requirement that harmonised ATE values have to be established for a substance with a harmonised classification. According to the Guidance on the application of the CLP Criteria Version 5.0 – July 2017, chapter 1.5.3, harmonised Acute Toxicity Estimate (ATE) values may be included in Annex VI of CLP from 2016.

According to the classification, labelling and packaging (CLP) Regulation ((EC) No 1272/2008), *"the acute toxicity estimate (ATE) for the classification of a substance or ingredient in a mixture is derived using:*

- *The LD50/LC50 where available*
- *The appropriate conversion value from Table 3.1.2 that relates to the result of a range test*
- *The appropriate conversion value from Table 3.1.2 that relates to a classification category"*

Thus, the determination of a definitive ATE value is not mandatory and it is understood that it is only indicated when a LD_{50}/LC_{50} value is available for the respective substance.

Most importantly, peracetic acid per se cannot exist as a stable isolated substance, but in an equilibrium mixture with hydrogen peroxide and acetic acid in aqueous solution. Pure peracetic acid is explosive and concentrations above 45% peracetic acid cannot be handled safely due to the explosive potential (CLH report for peracetic acid, version number 2.0, 24 June 2021, chapter 7, physicochemical properties). Accordingly, it is technically not possible to perform experimental studies with isolated PAA and acute toxicity data/definitive LD_{50}/LC_{50} values are not available for pure/isolated peracetic acid.

Acute toxicity data have been generated with mixtures containing different concentrations of peracetic acid in combination with varying amounts of hydrogen peroxide and acetic acid and in some instances further ingredients (e.g., sulphuric acid, stabilizers). Thus, it is not considered appropriate to extrapolate an ATE value (LD_{50}/LC_{50}) for a pure substance based on mixture test results. It has to be taken into account that other components/factors could impact the outcome of the acute toxicity tests (e.g., hydrogen peroxide is classified for acute oral toxicity and acute inhalation toxicity; damage of the dermal barrier due to severe corrosivity can lead to systemic availability of other mixture components). Thus, the extrapolation approach taken is expected to overestimate the peracetic acid-induced effect. Accordingly, application of the proposed ATE values in the additivity formula will eventually lead to over-classification of peracetic acid containing mixtures.

However, as no actual LD_{50}/LC_{50} values or results from range tests are available for isolated peracetic acid, results from the acute toxicity tests for peracetic acid containing mixtures can only be considered suitable to be used as surrogates for the determination of the appropriate classification category of peracetic acid and for similar peracetic equilibrium mixtures by expert judgement and application of the bridging

principles, but not to derive definitive ATE values for a 100% pure substance which can technically not exist.

Furthermore, the extrapolation approach is considered not to correctly reflect the mode of action of peracetic acid for acute toxicity. The primary mode of action of peracetic acid is characterized by local irritation/corrosion. Thus, acute toxic effects of peracetic acid containing mixtures were secondary to primary local effects (irritation/corrosion) for all exposure routes, reflecting the irritant/corrosive properties of the test material. Severity of effects depended on the combination of both, peracetic acid concentration and volume of the test dose applied. For all routes, and most noteworthy, also in a 90-day oral toxicity study (Assessment Report Peracetic Acid, Product types 1-6, November 2015, Finland) no adverse systemic effects were detected at non-corrosive concentrations. Accordingly, data obtained for peracetic acid-containing mixtures show no clear dose-response relationship.

Although not considered scientifically justified (extrapolation from mixture to pure substance), use of ATE values derived for the oral and inhalation route in the additivity approach leads to classification of the respective peracetic acid containing mixtures in the same acute toxicity hazard class as the actual test results.

However, for the dermal route, data do not substantiate the proposed acute toxicity category 2 classification and application of the proposed ATE value of 56.1 mg/kg bw leads to over-classification of peracetic acid containing mixtures at a concentration of equal or greater than 5.61 % peracetic acid (category 3 instead of the category 4 determined for a concentration of 11.89% peracetic acid). More details are included in the comments to endpoint “Acute toxicity-dermal route”.

Specific comments regarding evaluated health hazards “Acute toxicity – oral route” and “Acute toxicity – dermal route”:

The comments below refer to the endpoint **“Acute toxicity – oral route” (section 10.2 of the CLH report, page 15-27).**

Eighteen animal studies on acute oral toxicity are reported and three of them are evaluated as key studies. In the reliable studies no consistent gender-specific effect was observed. Females were more sensitive than males in most cases, but not in all studies (Anonymous (1998c) A6.1.1/05 – males are more sensitive: Anonymous (1982), A6.1.1/03 – comparable sensitivity were observed between males and females). Furthermore, a different pattern in gender -specificity was also observed for the different doses applied within one experiment (Anonymous (1985), A6.1.1/02 – no gender-difference was shown at 1260 mg/kg bodyweight).

In the section “Conclusion on classification and labelling for acute oral toxicity” (section 10.1.3) of the CLH report an Acute Tox. Category 3 classification for 100 % peracetic acid (H301: Toxic if swallowed) with an oral ATE value of 70 mg/kg bw is proposed for the classification of mixtures containing peracetic acid. The proposed ATE value is the lowest LD_{50} value determined for females as the more sensitive gender according to the CLH report. However, the above-mentioned points do not fully support the conclusion drawn that females are more sensitive than males. Due to the non-consistent gender sensitivities, a combined LD_{50} value (males and females) (i.e. 1700 mg/kg bw corresponds to 85.0 mg/kg bw of a theoretical 100% peracetic acid) for classification purposes as derived in the assessment report (AR) on

peracetic acid (PT1-6 and PT11/12) as well as on in situ generated peracetic acid (PT2-5) is considered more appropriate.

The comments below refer to the endpoint **"Acute toxicity – dermal route" (section 10.2 of the CLH report, page 28-34).**

Two acute dermal toxicity studies in rabbits are reported as key studies which were conducted by the same laboratory under similar conditions. Key study Anonymous 1996c was conducted with Proxitane AHC (4.89 % peracetic acid, 19.72 % hydrogen peroxide and 10 % acetic acid) and the study resulted in acombined acute dermal LD_{50} value of 1147 mg/kg bw corresponding to an extrapolated LD_{50} value of 56.1 mg/kg for a theoretical 100 % peracetic acid solution. However, key study Anonymous 1996d conducted with Proxitane WW12 (11.69 % peracetic acid, 18.05 % hydrogen peroxide and 20 % acetic acid) resulted in a combined acute dermal LD_{50} value of 1957 mg/kg bw corresponding to an extrapolated acute dermal LD_{50} value of 228.8 mg/kg bw for a theoretical 100 % peracetic acid solution. Thus, the study with the product with the higher peracetic acid concentration (Proxitane WW12) resulted in a lower acute dermal toxicity (9/10 animals dead at 2020 mg/kg bw and 2/10 animals dead at 500 mg/kg bw for 4.89% peracetic acid in contrast to 6/10 animals dead at 2020 mg/kg bw and 0/10 animals dead at 500 mg/kg bw). Acknowledging that peracetic acid is the only component classified with respect to acute dermal toxicity in the tested equilibrium mixtures, Proxitane WW12 (11.69 % peracetic acid) would be expected to reveal a higher acute dermal toxicity due to its higher peracetic acid content when compared to Proxitane AHC (4.89 % peracetic acid). The observed discrepancy could be explained by the corrosivity of both products. Toxic effects depend on the corrosive damage inflicted which can be expected to result in a certain randomness of effects, reducing overall reliability of acute dermal toxicity test results.

As studies were conducted under comparable conditions (same test laboratory, same test method, same skin area treated, similar volumes of test material applied on a mL/kg bw basis), the results underline that acute toxicity effects of peracetic acid do not show a clear dose-response but depend on the extent of corrosive damage caused to skin and tissue of the individual test animals. Both products were tested undiluted and corrosive effects were observed as clinical signs. Air (Air bubbles), probably indicative of gas embolism (oxygen in blood vessels, generated by degradation of peracetic acid equilibrium solutions) and a possible cause of death, was observed in blood vessels, heart, and pericardium of test animals (section 10.2, table 15, Summary table of animal studies on acute dermal toxicity) which died during the studies. In contrast, no pathological findings were observed in test animals which survived the studies and were necropsied after 14 days.

After destruction of the skin barrier due to corrosivity, the tested mixture would be expected to become systemically available. Noteworthy, further substances contained in the tested mixture could act as confounding factors (influence the severity of effects observed) in addition to peracetic acid. Thus, differences in the severity of corrosive effects between animals of one tested dose group (e.g., due to higher volume of test substance concentrated in a test region, unnoticed damage of the skin due to clipping of the hair, different stability of peracetic acid in the tested solutions) could explain the observed differences.

The high reactivity and associated local mode of action of peracetic acid need to be taken into account as well in order to explain the effects observed after acute dermal dosing:

Peracetic acid is highly reactive, and therefore rapidly degraded upon contact with organic matter such as skin or mucous membranes of the gastrointestinal or respiratory tract. The toxicity of peracetic acid is

mainly triggered by local irritation/corrosion at the site of first contact (portal-of-entry-effects). Hence, it is generally accepted that peracetic acid does not become systemically available upon contact with skin or mucous membranes of the gastrointestinal or respiratory tract. It is also evidenced by in vitro studies showing a rapid degradation of peracetic acid in rat blood. In rat blood diluted 1000 times, the half-life of peracetic acid was less than 5 minutes. For this reason, distribution of peracetic acid in the body is expected to be very limited, unless higher amounts of peracetic acid solutions can reach tissue and blood vessels through severely damaged skin.

Due to the underlying mechanism, which is characterized by direct chemical reactivity without primary systemic effects and metabolism, the observed acute dermal toxicity is considered dependent on the corrosive potential of the applied peracetic acid concentration (% in vehicle) and the applied volume rather than on the body dose (mg/kg body weight).

Accordingly, no systemic toxicity was observed for mixtures tested at non-irritant concentrations and only a temporary weight loss in some animals when tested at slightly irritant but non-corrosive concentrations as seen in key study number three, 0.89% peracetic acid (Anonymous (1994) A6.1.2/05). However, peracetic acid is rapidly absorbed through damaged skin when the skin barriers are destroyed due to the corrosivity of peracetic acid solutions (JACC Report 40 – Peracetic Acid and its Equilibrium Solutions (2001). This may explain why no systemic toxicity is observed at non-corrosive concentrations of peracetic acid containing mixtures.

In the section “Conclusion on classification and labelling for acute dermal toxicity” (section 10.2.3) of the CLH report the key study with Proxitane AHC (4.89 % peracetic acid) in rabbits is used to propose an acute dermal ATE value and classification for peracetic acid. An Acute Tox. Category 2 classification for 100 % peracetic acid (H310: Fatal in contact with skin) with a dermal ATE value of 56.1 mg/kg bw for the classification of mixtures containing peracetic acid is proposed.

We propose that this approach (i.e. solely concentration-dependent extrapolation from the lowest LD_{50} value obtained) shall be reconsidered based on expert judgement considering the toxicological profile/local mode of action of peracetic acid and the missing dose/concentration-response relationship of the observed effects.

Moreover, it is noteworthy that peracetic acid is classified as skin corr. 1(A); H314 and based on its chemical characteristics and the fact that it has no potential for dermal absorption at non-corrosive conditions upon contact with skin, testing of corrosive peracetic acid containing mixtures would nowadays no longer be performed due to animal welfare reasons, and the acute dermal toxicity study would be waived instead. With a view to waiving of acute toxicity tests reference is made to the OECD “Guidance Document on Considerations for Waiving or Bridging of Mammalian Acute Toxicity Tests”, ENV/JM/MONO(2016)32, where under point 8 it is stated that “if an acute dermal toxicity waiver is granted on the basis of the test chemical being corrosive, the label would need to reflect the potential for corrosivity of the test chemical by the dermal route.” In point 14 it is further explained that “A dermal toxicity study may be waived if the test chemical is corrosive or severely irritating to skin (GHS Category 1). The determination of corrosion is based on in vivo, validated and/or accepted in vitro or other data, or in the absence of any other information, when the test chemical has a pH less than or equal to 2 or greater than or equal to 11.5”. When strictly following this guidance, only labelling of peracetic acid as skin corr. 1(A); H314 “Causes severe skin burns and eye damage“ would be warranted and a classification with respect to acute dermal toxicity would not be required when taking into account especially the

requirements as set out in point 14 of the OECD guidance document which are completely fulfilled by the intrinsic properties of peracetic acid.

Accordingly, it is recognized that a number of strong acids (such as sulphuric, phosphoric, nitric or hydrochloric acid) or substances acting by a mode of action similar to that of peracetic acid (such as sodium hypochlorite or perchloric acid) are classified for their key toxic effect, i.e. as corrosive to skin but are not classified for acute dermal toxicity.

Taken together, all these facts do not warrant classifying peracetic acid into an even more stringent hazard category for acute dermal toxicity on the basis of a putative ATE value of 56.1 mg/kg bw (i.e. worst case LD_{50} value). Furthermore, it is also not reasonable that the extrapolated ATE value of 56.1 mg/kg bw (i.e. worst case LD_{50} value) shall be used for ATE calculations when classifying mixtures containing peracetic acid, due to the reasons listed below.

1. The second key study, conducted with Proxitane WW12 (11.69 % peracetic acid) revealed a much higher extrapolated ATE value of 228.8 mg/kg bw. This ATE value is a factor of 4 higher and this should be taken into account as Proxitane WW12 contains a higher concentration of peracetic acid which is the only component classified for acute dermal toxicity.

2. An acute dermal ATE value of 56.1 mg/kg bw does not correctly predict the acute dermal toxicity of certain mixtures containing peracetic acid. For example, the calculated ATE value of Proxitane WW12 (11.69 % peracetic acid) is 100/(11.69/56.1) = 479 mg/kg bw and this would be equivalent with a category 3 classification (H311 Toxic in contact with skin). However, the reliable study results obtained with Proxitane WW12 (Anonymous 1996d) revealed an LD_{50} of 1957 mg/kg bw (factor 4 higher) and this is equivalent with a category 4 classification (H312 Harmful in contact with skin). This plausibility check clearly shows that the proposed acute dermal ATE value of 56.1 mg/kg bw needs revision as it does not correctly calculate the acute dermal toxicity category of Proxitane WW12 for which a valid acute dermal toxicity study is available. The results of the second key study overrules the outcome of the calculation method.

3. For acute oral toxicity the proposed ATE value is 70 mg/kg bw and the resulting classification is acute oral toxicity category 3 (H301: Toxic if swallowed). For acute dermal toxicity the proposed ATE value is 56.1 mg/kg bw and the resulting classification is acute dermal toxicity category 2 classification (H310: Fatal in contact with skin). This results in a more severe classification for acute dermal toxicity and this further supports the conclusion that the derived ATE value of 56.1 mg/kg bw for acute dermal toxicity does not reflect correctly the acute toxicity hazard potential by the dermal route.

According to the Guidance Document on Considerations for Waiving or Bridging of Mammalian Acute Toxicity Tests, ENV/JM/MONO(2016)32, point 16/17, dermal toxicity is unlikely to result in a more severe classification than the corresponding oral hazard. In addition, in an older Sanco guidance document on dermal absorption it is stated that “Based on theoretical grounds and supported by a comparison of oral and dermal absorption data available for 12 pesticides, it is assumed that dermal absorption will not exceed oral absorption established by means of bile duct cannulation (unpublished data).” (Sanco/222/2000 rev. 7, 19 March 2004). Thus, it is not plausible, that the acute dermal toxicity especially for a non-systemically available substance is higher than its acute oral toxicity.

Accordingly, a moderate oral toxicity has been concluded for peracetic acid and dermal toxicity was considered lower in a previous hazard assessment for peracetic acid (JACC Report 40 – Peracetic Acid and its Equilibrium Solutions (2001). Furthermore, test results from acute oral toxicity studies (reliability 2, not key studies) presented in the CLH report support this conclusion.

Based on the proposed oral ATE value of 70 mg/kg bw mixtures are classified in category 3 for acute oral toxicity if the peracetic acid concentration is 23 % or higher (no other ingredient contributing to acute oral toxicity). However, based on a dermal ATE of 56.1 mg/kg bw mixtures are classified in category 3 for dermal toxicity if the peracetic acid concentration is 5.61 % or higher (no other ingredient classified for acute dermal toxicity). This shows a large and inappropriate difference in the cut off value for an acute toxicity category 3 classification between the oral and dermal route considering in parallel that the acute dermal toxicity of a substance is usually never more severe than its acute oral toxicity.

The discrepancy between the calculated ATE value of 56.1 mg/kg bw and the acute dermal hazard potential of peracetic acid containing solutions is also reflected in the CLH dossier, where it is stated that "based on the results obtained in rabbits, classification of the aforementioned formulations (PAA conc. 5-15 %) as Acute Tox. 4 with the hazard statement H312: "Harmful in contact with skin" in accordance with the criteria of the CLP Regulation (reference value 1000 < ATE 2000 ≤ mg/kg bw) is warranted". However, application of the proposed ATE value in the additivity formula would result in a category 3 classification for product with a concentration equal to or higher than 5.61 % peracetic acid (assuming that no other ingredient is classified for acute dermal toxicity).

Based on the presented argumentation, the conclusion in section 10.2.3 of the CLH dossier that there is sufficient evidence to remove the asterisk from the classification for the dermal route and to apply a dermal ATE value of 56.1 mg/kg bw is not considered conclusive.

It is not considered justified to derive a definitive ATE for the dermal route based on the available data, and thus it is proposed to keep the current classification with Acute Tox. 4*; H312 for the dermal route to avoid over-classification of peracetic containing mixtures. Peracetic acid is classified with Skin corrosion 1A, and this hazard class is considered to be most appropriate hazard class to characterize the hazard potential of peracetic acid containing solutions upon contact with skin.