ECHA
EUROPEAN CHEMICALS AGENCY

Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

L-(+)-lactic acid; (2S)-2-hydroxypropanoic acid

EC Number: 201-196-2
CAS Number: 79-33-4

CLH-O-0000001412-86-191/F

Adopted

9 March 2018

Corrigendum
3 December 2019

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CLH-O-0000001412-86-191/F

9 March 2018

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

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

Chemical name: **L-(+)-lactic acid; (2S)-2-hydroxypropanoic acid**

EC Number: **201-196-2**

CAS Number: **79-33-4**

The proposal was submitted by **Germany** and received by RAC on **20 February 2017.**

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

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **14 March 2017**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **28 April 2017**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Sonja Kapelari**

Co-Rapporteur, appointed by RAC: **Bert-Ove Lund**

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

The RAC opinion on the proposed harmonised classification and labelling was adopted on **9 March 2018** by **consensus**.

CORRIGENDUM

The statements referring to the GCL of 1% for skin corrosion/irritation and serious eye damage/eye irritation have been removed from the opinion. Formulators of mixtures containing L-(+)-lactic acid are requested to follow the CLP Regulation, to correctly classify their mixtures.

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 and ATE	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitters proposal	TBD	L-(+)-lactic acid; (2*S*)-2-hydroxypropanoic acid	201-196-2	79-33-4	STOT SE 3 Skin Irrit. 2 Eye Dam. 1	H335 H315 H318	GHS05 GHS07 Dgr	H335 H315 H318			
RAC opinion	TBD	L-(+)-lactic acid; (2*S*)-2-hydroxypropanoic acid	201-196-2	79-33-4	Skin Corr. 1C Eye Dam. 1	H314 H318	GHS05 Dgr	H314	EUH071		
Resulting Annex VI entry if agreed by COM	TBD	L-(+)-lactic acid; (2*S*)-2-hydroxypropanoic acid	201-196-2	79-33-4	Skin Corr. 1C Eye Dam. 1	H314 H318	GHS05 Dgr	H314	EUH071		

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

L-(+)-lactic acid and lactate form an integral part of normal mammalian intermediary metabolism, as they are produced by the reduction of pyruvate. Total normal lactate turnover at rest has been determined as 1.6 to 2 g/kg bw/d in humans, 4.9 to 8.1 g/kg bw/d in rats and 2.3 to 3.5 g/kg bw/d in dogs (Connor and Woods, 1982).

However, it should be noted that the classification proposal concerns lactic acid, with concentrated lactic acid having a typical concentration of 92.95% (Background document [BD], table 6) and a pH of about 1.85.

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

The Dossier Submitter (DS) did not propose any classification for physical-chemical hazards for L-(+)-lactic acid. However, due to lack of data for the hazard class "Corrosive to metals", they recommended testing according to UN Manual of Test and Criteria.

The vapour of the substance contains more than 99% water and is not ignitable, therefore no flash point was determined up to 100 °C. Pure crystalline solid L-(+)-lactic acid is not a flammable solid. Since the melting point of pure lactic acid is low (53 °C), the substance will in fact melt as the flammability test (as described in Part III, sub-section 33.2.1.4.3.1, of the UN Manual of Test and Criteria [UN-MTC]) is carried out.

Experience in handling and use indicates that L-(+)-lactic acid is neither pyrophoric nor does it react with water to liberate flammable gases. Testing showed that no spontaneous ignition was observed below 400 °C. Consideration of the structure indicates further that L-(+)-lactic acid does not have explosive or oxidising properties.

Comments received during public consultation

The only comment on these hazard classes was submitted by a company/manufacturer, who provided a new study which had been completed in December 2015. Based on this study, L-(+)-lactic acid (purity: 88.2%) is not corrosive to steel and aluminium specimens according to the UN Manual of Test and Criteria (ST/SG/AC.10/11/Rev5, 2009); Test C.1.

Assessment and comparison with the classification criteria.

The outcome of the study provided during the public consultation, which was performed according to UN-MTC criteria, showed that L-(+)-lactic acid (88.2%) was not corrosive to metals. Therefore, RAC concludes that the substance does not require classification for corrosivity to metals.

Regarding the other physical hazard classes, RAC agrees with the DS that **L-(+)-lactic acid does not warrant any classification** according to CLP criteria.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

The DS did not propose classification for acute toxicity as all relevant LD_{50}/LC_{50} values were above the thresholds for classification for all routes of exposure.

Comments received during public consultation

There were no comments provided in the public consultation regarding this hazard class.

Assessment and comparison with the classification criteria

Acute toxicity: oral

There are three studies in rats and one in guinea pigs. Two of the rat studies were performed according to EPA´s OPP (Office of Pesticide Programs) test guidelines (1982). The other two studies are pre-guideline studies, conducted in 1941.

The lowest LD_{50} value in rats is 3543 mg/kg bw (see CLH report, Table 11), whereas the LD_{50} in guinea pigs reported in the 1941 study was 1810 mg/kg bw. Although the latter study would support a classification as Acute Tox. Cat. 4, RAC agrees not to classify lactic acid because the guinea pig study covered many substances with focus on glycols and their esters and suffer from several deficiencies (e.g. necropsy and individual data were not reported). Therefore, RAC does not consider the guinea pig study relevant for classification, especially as there are two rat studies showing LD_{50} values > 3500 mg/kg that are both GLP-compliant and are similar to OECD guidelines (see CLH report, Table 11).

RAC notes that the guideline rat studies are conducted with 80% L-(+)-lactic acid instead of 93% (the highest obtainable concentration of the active substance, according to the CLH dossier). Although a higher concentration is likely to be more toxic (irritative/corrosive), the oral LD_{50} values caused by the 80% lactic acid were so much higher than the threshold for classification that it is not expected that a higher concentration than 80% would fulfil the criteria. Therefore, **RAC does not propose a classification for acute toxicity via the oral route.**

Acute toxicity: inhalation

In one rat study conducted according to EPA´s OPP test guidelines (1985) and similar to OECD TG 403, the acute inhalation LC_{50} value was > 7.94 mg/L/4h (the only dose level tested, 1/10 animals died at this dose level) with a concentration of 76.5-83.5% lactic acid in the aerosol. The limit for classification for acute toxicity 4 via inhalation route (mists) is 1.0 mg/L/4h < ATE ≤ 5.0, therefore RAC supports the DS´s view that no classification is warranted, although the concentration of the test substance was 80% instead of 93% (see above).

Acute toxicity: dermal

In one rabbit study conducted according to EPA´s OPP test guidelines (1982) by Wingard & Barnes (1983), the acute dermal LC_{50} value is > 2000 mg/kg bw. RAC agrees with the DS that **no classification is justified**, although the concentration of the test substance was 80% instead of 93% (see above) as no mortality was observed in the tested animals.

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

Summary of the Dossier Submitter's proposal

The DS proposed classification with STOT SE 3 (respiratory tract irritation), H335, based on transient rapid and shallow breathing and eye tearing in an acute inhalation study where rats were exposed for four hours to an aerosol consisting of 76.5-83.5% lactic acid.

Comments received during public consultation

Three industry organisations disagreed with the proposed classification for STOT SE 3. Their arguments focused on lack of human data, uncertain animal data, and that respiratory irritation is covered by classification for skin irritation and serious eye damage.

Assessment and comparison with the classification criteria

Concentrated lactic acid has a pH < 2. Substances and mixtures with a pH < 2 can be predicted to be irritating or corrosive to skin (CLP 3.2.2.1.2.3. and CLP 3.2.3.2.1.1.) and eyes (CLP 3.3.2.2.4.). Similar effects could be expected on epithelia of the respiratory system. Accordingly, the acute inhalation study in rats indicates transient respiratory effects, such as rapid and shallow breathing occurring shortly after exposure.

However, as there are neither any specific human data nor any pathological findings at necropsy in the acute inhalation toxicity rat study (histopathological evaluation was not performed) unequivocal evidence of transient irritation of the upper or lower respiratory tract has not been provided. **RAC, therefore, concludes that the DS´s proposal to classify L-(+)-lactic acid for STOT SE 3 is not justified on the basis of the available data.**

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The DS proposed to classify L-(+)-lactic acid for skin irritation/corrosion, category 2, H315 (Causes skin irritation), based on human data which are considered to provide the key information for classifying L-(+)-lactic acid according to CLP criteria.

Comments received during public consultation

In the only comment received for this hazard class, a MSCA suggested to classify lactic acid as a corrosive substance (Skin Corr. 1C) based on the rabbit study by van Beek (1986). In addition, the MSCA pointed out that such a classification would warrant the EU supplementary hazard statement EUH071, "corrosive to the respiratory tract".

Assessment and comparison with the classification criteria

Irritation/corrosivity was tested *in vitro* with a biobarrier/chemical detection system and in a skin organ culture model with rabbit and human skin and *in vivo* in rabbits, guinea pigs, pigs and humans. More recently, three studies have been published where lactic acid has been studied using five different *in vitro* skin models (Catarino *et al*., 2018; Desprez *et al*., 2015; Alépée *et*

al., 2014). Although the studies have not been analysed in detail by RAC (they were not included in the CLH proposal), they are suggestive of corrosive effects of lactic acid in *in vitro* skin models.

In the acute dermal toxicity study in rabbits (using 80% L-(+)-lactic acid), in two acute dermal irritation/corrosion tests on rabbits (using 88% (pH not stated) and 80-85% (pH 1.83) L-(+)-lactic acid) irritative and corrosive effects such as necrosis, formation of scar tissue and blanching could be observed. The CLP and OECD TG compliant rabbit study by van Beek (1986) using 50% L-(+)-lactic acid (pH not stated) showed very slight to slight ischaemic necrosis, moderate to severe haemorrhage and slight oedema after an exposure duration of four hours. After 3 weeks slight to severe incrustation, formation of scar tissue and disturbed hair growth could be observed. In addition, 88% L-(+)-lactic acid was also corrosive *in vitro* on rabbit skin.

A non-GLP, non-guideline *in vitro* Corrositex assay by Harbell (1994) revealed a biobarrier (artificial biomembrane) break through time of 31 minutes of 90% L-(+)-lactic acid, which would correspond to corrosive 1B/1C.

Neither irritation nor corrositivity, however, was found in two studies in pigs and in one study in guinea pigs, testing L-(+)-lactic acid in concentrations up to 88%. All these three studies were GLP and OECD compliant.

York *et al.* (1996), conducted an *in vitro* (Transcutaneous electrical resistance, TER) corrosivity test on human skin and a Patch Test on 26 volunteers using 88% lactic acid (pH not known but assumed to be < 2). The substance was corrosive in the *in vitro* test. In the Patch Test (0.2 mL applied in a Plain Hill Top Chamber), reversible irritative effects were seen after application times of 2, 3 and 4 hours in 21 out of 26 volunteers. However, it is acknowledged that the exposure was stopped as soon as signs of irritation were observed. Thus, the study is not really designed to assess corrosion (further information on this study is provided in the section "Supplemental information – in depth analyses by RAC").

Overall, RAC is of the opinion that for L-(+)-lactic acid (pH 1.83) a classification for **Skin Corrosion Category 1C, H314** is justified due to the outcome of the rabbit study by van Beek (1986), finding corrosive effects of 50% L-(+)-lactic acid after 4 hours exposure, supported by two studies showing corrosion after exposure to concentrated lactic acid (Barnes 1983; Wingard and Barnes 1983). Category 1C applies when corrosion has been observed after an exposure duration of 1-4 hours. Corrosive effects at high concentrations are also demonstrated in the Corrositex assay and the human *in vitro* TER assay. Category 1C might also be supported by the human patch test, where effects only were observed when the exposure time exceeded 1 hour.

In addition, RAC agrees that the supplementary labelling with **EUH071 "corrosive to the respiratory tract"** is warranted, based on the fact that the substance is corrosive and based on the possibility of exposure to aerosols (see chapter 3.2.4.2. of Guidance on the Application of the CLP Criteria).

~~The GCL was discussed, and it was noted that whereas the GCL for corrosive 1C is normally 5%, the GCL for substances with a pH ≤ 2, which is the case for concentrated lactic acid, is 1%.~~

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The DS proposed to classify L-(+)-lactic acid for serious eye damage, Category 1, H318, based on the pH < 2 of concentrated L-(+)-lactic acid and on the outcome of an *in vitro* Chicken Enucleated Eye Test (CEET).

Comments received during public consultation

The three comments received were in favour of the proposed classification. However, one commenter by an industrial association recommended to propose a specific concentration limit (SCL) of 10% for eye damage since the outcome of a new *in vitro* Bovine Corneal opacity and Permeability (BCOP) tests suggested no effects up to a concentration of 10% lactic acid.

DS replied that the Guidance on the Application of the CLP Criteria states that, while the possibility to use in vitro test methods as a basis for setting SCLs have not yet been explored, an SCL should apply to any mixture containing the substance. However, in this case the available data refer only to a specific solvent and not different solvents, and hence cannot be used for setting of an SCL.

The Chicken CEET is an alternative to the Draize eye irritation test with albino rabbits. According to the above mentioned Guidance, this test is one of four *in vitro* test methods adopted for the identification of substances inducing serious eye damage.

In OECD TG 437 it is clearly stated that the BCOP test is considered to evaluate the eye hazard potential of a test chemical. However, it is known that the BCOP test method can only identify correctly 31% of the chemicals that do not require classification for eye irritation or serious eye damage.

Assessment and comparison with the classification criteria

The CEET was performed with three different formulations:

a) powder consisting of 60% L-(+)lactic acid and 40% Ca-lactate,

b) 88% L-(+)-lactic acid (pH 2) and

c) a buffered solution containing 73-84% L-(+)-lactic acid and sodium lactate.

Results for corneal thickness expressed in swelling, for corneal opacity and fluorescein retention were reported. The overall test outcome described different corneal effects for each of the test substance from slight corneal effects (with the buffered solution) to severe corneal effects with the 88% concentration of L-(+)-lactic acid.

Table: *Summary of the maximum mean scores for corneal swelling, opacity and fluorescein retention and the irritation categories assigned (see table 20 in the BD).*

Test material	Maximum mean score for[1]:			Categories according to OECD TG 438[1]	Classification
	Swelling	Opacity	Flurescein		
a)	17	2.0	2.0	II/III/III moderate corneal effects	No prediction can be made
b)	28	4.0	3.0	III/IV/IV severe corneal effects	H318
c)	6	0.5	1.0	II/I/II slight corneal effects	No classification

[1]The criteria can be found in OECD TG 438.

Although not mentioned in the CLH report, the REACH registration dossier mentions a published ocular tolerance study (Guillot et al., 1982) of humectants and moisturizers used in cosmetics, which included tests of lactic acid. According to the registration dossier, the test showed that 10% and 20% lactic acid provoked a significant ocular irritation in the rabbit eye, only with the lesion caused by 10% lactic acid being reversible within 7 days.

Based on the pH value of < 2, on the outcome of the CEET assay using 88% L-(+)-lactic acid, and supported by the study by Guillot, RAC is of the opinion that a classification for serious eye damage, Category 1, H318 is warranted.

With regards to setting a specific concentration limit (SCL), four new GLP-compliant BCOP tests, compliant with OECD TG 437, were submitted by industry. While a concentration of 10% of lactic acid did not induce eye irritation, concentrations of 20% and 40% resulted in mild and severe irritation, respectively. However, RAC is of the opinion that only three concentrations tested in one type of assay, using only one solvent, does not justify the setting of a SCL. ~~The GCL for eye damage (category 1) is 3%, but in the event that the pH is ≤ 2 the GCL will be 1% (CLP Regulation, table 3.3.4).~~

Overall, RAC agrees to classify L-(+)-lactic acid as **Eye Dam. 1~~, with an GCL of 1%~~.**

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Based on the results of a modified Buehler test, in which none out of 10 tested animals showed sensitising effects, the DS concluded that 80% L-(+)-lactic-acid does not meet the criteria for classification for skin sensitisation according to the CLP Regulation.

Comments received during public consultation

There were no comments provided in the public consultation regarding this hazard class.

Assessment and comparison with the classification criteria

In a Guinea Pig study conducted according to EPA´s OPP test guidelines (1982) and similar to OECD TG 406, 80% L-(+)-lactic acid was selected for induction as the range-finding trials revealed very slight erythema and oedema at this concentration after one single application. However, as after two topical induction applications this concentration proved to be highly irritating (grade 4), the test site of the animals was changed and the concentration of the test substance was reduced to 24% L-(+)-lactic acid for the subsequent seven induction applications.

The reactions observed after 24 and 48 hours after the challenge (pinpoint pitting of the skin and eschar formation, very little redness) were very similar to those observed during the induction phase and occurred in up to six animals and in up to eight naïve control animals.

Due to the fact that the same type of effects, including scab formation, were observed in the test and control animals, RAC agrees with the DS that these effects should be considered as irritation reactions. Thus, no conclusions as to the sensitising potential of L-(+)-lactic acid can be drawn from this study. However, a sensitising potential of this endogenous substance is not expected. Based on lack of relevant data, **RAC supports no classification for skin sensitisation**.

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

Summary of the Dossier Submitter's proposal

The DS did not propose any classification for STOT RE as no effects were observed in an oral subchronic toxicological study in rats.

Comments received during public consultation

There were no comments provided in the public consultation regarding this hazard class.

Assessment and comparison with the classification criteria

The only available subchronic study in rats is a non-guideline, non-GLP study using calcium lactate pentahydrate (used as food additive and as an antacid and as a medicine to treat calcium deficiencies). According to information in the CLH dossier, the solubility of calcium lactate is 50 g/L and calcium lactate is likely to dissociate in solution to lactic acid and calcium. The results of this study can be used for lactic acid, but calcium effects also have to be considered.

In the first setting of the study, five males and five females per group were treated with a concentration of 0, 0.3, 0.6, 1.25, 2.5 and 5% of calcium lactate pentahydrate in drinking water for 13 weeks. No effects were observed.

In second setting, the same number of rats per group was fed with a concentration of 0, 5, 10, 20 and 30% of the substance in food for 13 weeks. Nephrocalcinosis was observed, but the findings were even more pronounced in the controls. It was shown that it was the feed used in the experiment that caused nephrocalcinosis and not calcium lactate.

A 2-year study where rats were given 0, 2.5, or 5% calcium lactate pentahydrate via the drinking water showed a slightly decreased body weight gain, but no other effects, at the top dose (in the CLH report stated to be 880 mg/kg bw/day, but in the REACH registration dossier 880 mg/kg bw/day in males and 930 mg/kg bw/day in females).

As calcium lactate pentahydrate caused no effects at doses much higher than the guidance value for STOT RE, RAC agrees **not to classify L-(+)-lactic acid for specific target organ toxicity – repeated exposure (STOT RE)**.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

The mutagenicity potential of L-(+)-lactic acid was tested in several *in vitro* studies, covering gene mutation and chromosomal damage endpoints. Six out of eight studies were clearly negative. A chromosomal aberration assay (Moriat *et al.* 1990) showed cytotoxicity and clastogenic effects at a pH of 5.7-6.7 in Chinese hamster ovary cells and a non-guideline, non-GLP study by Demerec *et al.* (1951) showed some cytotoxic and mutagenic effects in the absence of S9 mix.

Based on the test results (the Moriat study was considered to be "pseudo-positive" due to the unphysiological pH used) the DS proposed not to classify L-(+)-lactic acid as germ cell mutagen.

Comments received during public consultation

There were no comments provided in the public consultation regarding this hazard class.

Assessment and comparison with the classification criteria

There are three Ames tests (all three are similar to OECD TG 471 but two of them were not GLP-compliant) - with and without S9 mix - which did not reveal any genotoxic potential of L-(+)-lactic acid. The doses of L-(+)-lactic acid were up to 2.4 mg/plate in one test, up to 5000 µg/plate in the other and up to 10 mg/plate in the third study.

Two out of three OECD-compliant chromosomal aberration assays were also negative. One of these negative assays was performed in human lymphocytes with a test dose up to 901 µg/mL for 3 hours as well as for 24 and 48 hours. The other negative study was performed in Chinese hamster fibroblasts with a test dose up to 1 mg/mL. In the third study, using Chinese hamster ovary cells under an unphysiological low pH, cytotoxicity and clastogenicity was observed. The study lacks details but the authors came to the conclusion that the observations should be considered as pseudo-positive due to the low pH.

The study by Demerec *et al*. (1951) was not described in detail in the CLH dossier but it is pointed out that cytotoxicity was observed even at the lowest dose as well as weak mutagenic effects at some doses, but not dose-dependently.

The last of the eight studies provided in the CLH dossier, is an OECD- and CLP-compliant mammalian cell gene mutation assay, in which mouse lymphoma cells were exposed to L-(+)-lactic acid dissolved in RPMI medium at concentrations up to 901 µg/mL. In none of the tested concentrations - with and without metabolic activation - was the induced mutation frequency increased compared to the controls.

Summing up, the results of the *in vitro* studies and the fact that there is high background exposure on L-(+)-lactic acid via food and endogenous metabolism indicate that L-(+)-lactic acid, as proposed by the DS and agreed by RAC, **does not warrant a classification for mutagenicity** according to CLP criteria.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

According to the information provided in a summary of an oral chronic non-guideline, non-GLP rat study, using the food additive calcium lactate (pH 6.0-8.0) dissolved in distilled drinking water, decreased food intake and decreased body weight gain but no significant dose-related increase in the incidence of any specific tumour was observed.

Based on the limited information in the study summary, the absence of genotoxic potential of L-(+)-lactic acid and based on the high background exposure levels on L-(+)-lactic acid via food and endogenous metabolism in mammals and humans, the DS concluded that L-(+)-lactic acid do not meet the criteria to be classified for carcinogenicity according to the CLP criteria.

Comments received during public consultation

There were no comments provided in the public consultation regarding this hazard class.

Assessment and comparison with the classification criteria

In the long-term carcinogenicity study by Maekawa *et al*. (1991), 50 male and 50 female F344 rats were treated with a concentration of 0, 2.5 and 5% of calcium lactate in drinking water *ad lib*. for two years.

According to information in the CLH dossier, the solubility of calcium lactate is 50 g/L, and calcium lactate is likely to dissociate in solution to lactic acid and calcium. The results of this study can be used for lactic acid but calcium effects also have to be considered.

At week 113, the surviving animals (the number of the surviving animals was not reported) were sacrificed and histologically examined. Haematological and biochemical parameters were also measured but no details of the results are provided. A dose-dependent 13% decrease in body weight gain was observed in both sexes of the high-dose group (in the CLH report it was stated to be 880 mg/kg bw/day, but in the registration dossier 880 mg/kg bw/day in males and 930 mg/kg bw/day in females).

Overall, based on the summary of the chronic carcinogenicity study on calcium lactate, RAC concludes that the available data indicated neither toxic nor carcinogenic effects of the substance in F344 rats. As calcium lactate was administered in the diluted form, the study can partly be used for assessment of the carcinogenic potential of lactic acid and therefore RAC agrees with the conclusion in the CLH dossier, that **L-(+)-lactic acid should not be classified for carcinogenicity**.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Sexual function & fertility

According to the CLH dossier, no studies are available for this hazard class.

Effects on or via lactation

Also for this endpoint, no data are available.

Developmental toxicity

There is one study investigating potential developmental effects of lactic acid in Swiss albino mice (Colomina *et al.* 1992) and another one examining the effects on sex ratio in rats (D´Amour, 1934), but both studies lack details and only few reproductive or developmental endpoints were addressed. As no adverse effects were observed in dams, foetuses, or on the sex ratio, the DS concluded that L-(+)-lactic acid does not meet the criteria to be classified for developmental toxicity.

Comments received during public consultation

There were no comments provided in the public consultation regarding this hazard class.

Assessment and comparison with the classification criteria

The non-GLP oral gavage study by Colomina *et al*. (1992) was conducted to investigate the developmental toxicity of aluminium and the modifying influence of lactate on aluminium toxicokinetics. Aluminium is of no interest in this context, but in addition to a control group

(producing 13 litters), one group only received lactic acid (570 mg/kg bw/day during day 6-15 post mating) and the 12 litters produced by this group can thus provide some limited information on the potential developmental toxicity of lactic acid.

The treatment with lactic acid resulted in a decreased food consumption of 15% in the dams. It was assumed that the lactic acid treatment partly covered their daily energy requirement, and that the reduced food consumption therefore was not an adverse effect.

There was also a very slight (-4%) not statistically significant decrease in foetal weight and a statistically significant delayed ossification of parietal bones affecting 15% of the pups in contrast to 0% in the control pups (one-third of the foetuses of each group was examined for visceral anomalies). Although possibly being a substance-related effect, as indicated by the study authors, delayed ossification generally does not lead to classification.

The rat study by D´Amour was neither guideline- nor GLP-compliant. The dose levels administered (1250 mg/kg bw/day to 10 females and 2500 mg/kg bw/day to 28 females) by gavage from GD 0-22 did not show any effects of lactic acid on the sex ratio.

Although both studies lack details, RAC supports the DS´s opinion that based on the available data, **lactic acid does not warrant classification for developmental toxicology**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

The DS considered L-(+)-lactic acid as rapidly degradable, not bioaccumulative in the environment and not hazardous to the aquatic environment.

Stability

Hydrolysis

Experimentally derived data on hydrolysis in water are not available. From the structural formula of L-(+)-lactic acid it is clear that only one hydrolysable group is present: the acid group. For the hydrolysis of the acid group, the dissociation constant (pK) of 3.86 should be taken into account (ref. Doc IIIA7.1.1.1.1). As no further hydrolysable groups are available, a test on hydrolysis in aqueous solutions is scientifically not justified.

Photolysis

According to Holten (1971), the dissociation constant (pK) of the acid group (the only hydrolysable group) of L-(+)-lactic acid is 3.86 and light is absorbed in the wave-length range of 210 to 250 nm but not in the range of 290 to 800 nm by pure L-(+)-lactic acid. Therefore, no direct phototransformation is expected.

Biodegradation

Based on two Dutch guidelines (NEN 6633 and NEN 6634, the latter being comparable to OECD TG 301D), Biochemical Oxygen Demand (BOD) and Chemical Oxygen Demand (COD) were tested by Hanstveit and Pullens (1993) using the supernatant from settled activated sludge from an oxidation ditch which treats domestic sewage. In this study, the pass level for ready biodegradability (60% COD removal in 28 days) on L-(+)-lactic acid (purity 79.5-80%) was reached but since oxygen depletion was only measured on days 0, 5 and 20, it was not possible to determine the time-point at which 10% of the substance was degraded. The BOD (5 days)/COD

ratio at a concentration of 4 mg/L was 0.5 based on a BOD_5 value of 0.45 mg O_2/mg and a COD value of 0.90 mg O_2/mg.

In addition, the results of QSAR calculations (seven models) using the Biowin function of EPIWEP 4.1. indicate that L-(+)-lactic acid is readily biodegradable.

Bioaccumulation

By applying the experimentally derived log K_{OW} of -0.74 a BCF_{Fish} of 0.048 L/kg was calculated according to the TGD on Risk Assessment (part II, chapter 3, EC (2003)). Another indicator for a low bioaccumulation is the surface tension which is 70.7 mN/m of 93% L-(+)-lactic acid at 1 g/L in water.

Aquatic toxicity

There are five acute toxicity studies in fish (*Oncorhynchus mykiss, Lepomis macrochirus, Danio rerio* and *Orechromis mossambicus*) with LC_{50} values between 130 mg a.s./L and 320 mg/L, three tests in aquatic invertebrates (*Daphnia magna*) with EC_{50} = 156-750 mg a.s./L and one study in algae (*Selenastrum capricornutum*) with E_rC_{50} = 3.9 g a.s./L. No long-term tests in fish and invertebrate are available but the algae test can be also considered as a chronic test.

The fish studies on *Oncorhynchus mykiss* and *Lepomis macrochirus* by Forbis *et al.* (1984a and 1984b) performed with the test substance SY-83 containing 76.5-83.5% L-(+)-lactic acid and on *Danio rerio* by Bowmer *et al*. (1998) are not considered reliable. This is because the pH value varied between treatments as a function of the L-(+)-lactic acid concentration and because there was no analytical monitoring of the test substance concentration. However, the results can be used as supporting information. In the fourth mentioned study, performed by Hooftman *et al.* (1992), the pH was also dependend on the L-(+)-lactic concentrations but the test concentrations were analytically verified and a concentration loss of approximately 70% was observed. The results of the semi-static bioassay by Saha *et al*. (2006), were comparable to the ones by Forbis. In this study, however, the medium was replaced every 24 hours.

In the *Daphnia magna* studies the same problem with the pH values occurred as in the fish studies. However, for fish as well as for invertebrates there are also QSAR analyses for L-(+)-lactic acid using the ECOSAR model 1.11 which support a low toxicity on fish (177 g a.s./L) and invertebrates (78.8 g/L). According to the ECOSAR model, algae can be considered as the most sensitive species for L-(+)-lactic acid with an effect concentration of E_rC_{50} = 21.3 g a.s./L.

Comments received during public consultation

No specific comments were received, but one MS indicated general agreement with the DS´s proposal not to classify L-(+)-lactic acid for the environment.

Assessment and comparison with the classification criteria

Degradation

A substance is classified to be rapidly degradable when it is demonstrated to be readily biodegradable in a 28-day test for ready biodegradability, while the pass level of the test (70% DOC removal or 60% theoretical oxygen demand) must be achieved within 10 days from the onset of biodegradation. If this is not possible, then the pass level should be evaluated within a 14 day time window if possible, or after the end of the test. Rapidly degradability is also indicated by a BOD(5 days)/COD ratio ≥0.5. Taking into account a mineralization of 67% within of 20 days in the screening test, and a BOD(5 days)/COD ratio of 0.5, the criteria mentioned above are fulfilled. The results of QSAR estimations further support that L-(+)-lactic acid can be classified as rapidly degradable in the environment.

RAC supports the DS´s conclusion that L-(+)-lactic can be considered as rapidly degradable in the environment.

Bioaccumulation

An experimentally derived BCF is not available and the log K_{OW} of -0.74 for L-(+)-lactic acid is far below the trigger value of log $K_{OW} \geq 4$ for classification as bioaccumulative. Hence, RAC agrees with the DS that L-(+)-lactic acid has to be considered to have a low bioaccumulative potential in the environment.

Aquatic toxicity

Short-term (acute) aquatic hazard

For L-(+)-lactic acid acute studies are available for fish, invertebrates and algae. For all three trophic levels the available effect values are $L(E)C_{50} > 100$ mg/L.

The criterion for classification as Aquatic Acute 1; H400 "Very toxic to aquatic life" is $LC_{50} \leq 1$ mg/L. Hence, L-(+)-lactic acid does not fulfil this criterion and no classification as Aquatic Acute 1 is necessary.

Long-term (chronic) aquatic hazard

For long-term aquatic toxicity, suitable chronic data is available only for algae. With a NOErC ≥ 1000 mg/L the effect value is far above the critical trigger value for rapidly degradable substances of NOEC ≤ 1 mg/L for classification.

Because there is not suitable chronic data available for all three trophic levels, according to CLP Annex I, figure 4.1.1 in a second step the surrogate approach has to be applied, in which data on the acute toxicity is combined with information on the fate in the environment. However, the trigger value for classification is a $L(E)_{50} \leq 100$ mg/L and as all acute effect values are $L(E)_{50} > 100$ mg/L no classification is needed.

None of the criteria for long-term (chronic) aquatic hazard classification is fulfilled and there is no need for long-term (chronic) aquatic hazard classification.

RAC agrees with the DS´s proposal that **no classification for environmental hazards *is warranted***.

Additional references

Alépée, N. et al., (2014) Sub-categorisation of skin corrosive chemicals by the EpiSkin reconstructed human epidermis skins corrosion test method according to UN GHS: Revision of OECD TG 431. Toxicology in Vitro 28(2):131-145.

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Guillot, J.P. et al., (1982) Safety evaluation of some humectants and moisturizers used in cosmetic formulations. International Journal of Cosmetic Science 4: 67-80.

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).