Section A6.1.1 Acute Toxicity

Annex Point IIA6.1

Oral -rat

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted]., 1984. Acute oral LD50 study in rats using SY-83. Toxigenics Inc. Report nr. 410-1369	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Purac Biochem BV	
1.2.2	Companies with letter of access	No	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes: EPA/OPP Guidelines 1982	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	SY-83	
3.1.1	Lot/Batch number	Not presented	
3.1.2	Specification	Formulated from Purac HS pharmaceutical grade (USP XX) L(+) lactic acid (88%) by dilution to a concentration of 80% in water.	
3.1.2.1	**Description**	Liquid	
3.1.2.2	**Purity**	SY-83 is formulated from Purac HS pharmaceutical grade by dilution to a concentration of 80% with water: 83.5-76.5% lactic acid in water	
3.1.2.3	**Stability**	As given in section 2	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Albino	
3.2.3	Source	Charles River Breeding Laboratories, Inc., Wilmington, MA, USA	
3.2.4	Sex	Male and female	
3.2.5	Age/weight at study initiation	Young / 200 (m) and 219 (f)	X
3.2.6	Number of animals per group	Main study: 5 per sex per dose group Range-finding: 1 per sex per dose group	
3.2.7	Control animals	No	

Section A6.1.1 Acute Toxicity

Annex Point IIA6.1

Oral -rat

3.3	**Administration/ Exposure**	Oral	
3.3.1	Post exposure period	14 days	
		Oral	
3.3.2	Type	Gavage	
3.3.3	Concentration	Range-finding: 1000, 1585, 2512, 3981 and 6310 mg/kg	X
		Main study: 3162, 3548, 3981, 4467, 5012, 5623 and 6310 mg/kg	
3.3.4	Vehicle	Deionized water	
3.3.5	Concentration in vehicle	Range-finding: 0.1000, 0.1585, 0.2512, 0.3981 and 0.6310 mg/mL	
		Main study: 0.3162, 0.3548, 0.3981, 0.4467, 0.5012, 0.5623 and 0.6310 mg/mL	
3.3.6	Total volume applied	10 mL/kg bw	
3.3.7	Controls	No control group	
3.4	**Examinations**	Mortality, clinical observations, body weight and gross necropsy	
3.5	**Method of determination of LD_{50}**	Litchfield and Wilcoxon	
3.6	**Further remarks**	Not applicable	
		RESULTS AND DISCUSSION	
		See also the summary table below	
3.7	**Clinical signs**	Lethargy, ataxia, prostration, irregular breathing, piloerection, squinting, lacrimation, salivation, crusty muzzle, crusty eyes, lose stools, damp or yellow/brown stained fur in the perianal region and moribund animals were observed.	
3.8	**Pathology**	Effects on lungs, stomach, liver and kidneys were observed in the animals that died during the study. Necropsy of the 3 surviving animals of the 3.162 mg/kg female group revealed mottled lungs and thickened stomachs.	
3.9	**Other**	Not applicable.	
3.10	**LD_{50}**	An oral LD50 of 4936 mg/kg for males and 3543 mg/kg for females was determined.	
		4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	Study was performed according to EPA guidelines: EPA/OPP 1982	
4.2	**Results and discussion**	An oral LD50 of 4936 mg/kg for males and 3543 mg/kg for females was determined.	
4.3	**Conclusion**		
4.3.1	Reliability	1	
4.3.2	Deficiencies	No	

Section A6.1.1 Acute Toxicity

Annex Point IIA6.1

Oral -rat

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/06/05
Materials and Methods	Applicant's version is acceptable with the following amendments: 3.2.5 M: 208-243 g; F: 190-256 g 3.3.3 Main study: M: 4,467-5,012-5,623-6,310 mg/kg bw; F: 3,162-3,548-3,981-4,467-5,012-5,623-6,310
Results and discussion	Applicant's version is acceptable.
Conclusion	LD_{50}: 4936/3543 mg/kg bw (M/F, 80 % lactic acid)
Reliability	1
Acceptability	Acceptable without restrictions
Remarks	The study was conducted with 80 % L-(+)-lactic acid instead of 93 % (concentration of the active substance, the highest obtainable concentration). However, the LD_{50} of 3543 mg/kg bw is much higher than the limit dose for classification and is in the same range as the LD_{50} obtained in an older study with purified lactic acid (Smyth et al. 1941; LD_{50}: 3730 mg/kg bw). Thus, it seems to be justified to use the LD_{50} obtained in this study without concentration adjustment.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.1.1 Acute Toxicity

Annex Point IIA6.1

Oral -rat

Table A6_1-1. Table for Acute Toxicity (modify if necessary)

Dose [mg/kg]	*Number of dead / number of investigated*		*Time of death (range)*	*Observations*
	Males	*Females*		
3162	Not tested	1/5	Early morning of day 2	Lethargy, ataxia, prostration, irregular breathing, piloerection, squinting, lacrimation, salivation, crusty muzzle, crusty eyes, loose stools, damp or yellow/brown stained fur in the perianal region and moribund were abnormal clinical signs observed 0 to 1 hour after dosing until day 2. Necropsy showed effects on lungs, stomach, liver and kidneys in the animals that died during the study. Necropsy of the surviving animals of the 3.162 mg/kg female group revealed mottled lungs and thickened stomachs.
3548	Not tested	2/5	1-4 hours after dosing or in the early morning of the day following dosing (day 1)	
3981	Not tested	5/5		
4467	1/5	5/5		
5012	3/5	5/5		
5623	4/5	5/5		
6310	5/5	5/5		
LD_{50} value	4936 mg/kg for males and 3543 mg/kg for females			

Official use only

1 REFERENCE

1.1	**Reference**	[redacted] 1983. Acute dermal toxicity study in rabbits using SY-83 at a dose level of 2 grams per kilogram of body weight. Toxigenics Inc. Report nr. 410-1354.
1.2	**Data protection**	Yes
1.2.1	Data owner	Purac Biochem BV.
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its entry into Annex I

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	Yes: EPA/OPP Guidelines 1982
2.2	**GLP**	Yes
2.3	**Deviations**	No

3 MATERIALS AND METHODS

3.1	**Test material**	SY-83
3.1.1	Lot/Batch number	Not presented
3.1.2	Specification	Formulated from Purac HS pharmaceutical grade (USP XX) L(+) lactic acid (88%) by dilution to a concentration of 80% in water.
3.1.2.1	**Description**	Liquid
3.1.2.2	**Purity**	SY-83 is formulated from Purac HS pharmaceutical grade by dilution to a concentration of 80% with water: 83.5-76.5% lactic acid in water
3.1.2.3	**Stability**	As given in section 2
3.2	**Test Animals**	
3.2.1	Species	Rabbit
3.2.2	Strain	New Zealand White albino
3.2.3	Source	Langshaw Farms, Augusta, MI, USA
3.2.4	Sex	Male and female
3.2.5	Age/weight at study initiation	Young adult / mean weight of 2.97 kg (males) and 3.02 kg (females)
3.2.6	Number of animals per group	5 of each sex
3.2.7	Control animals	No
3.3	**Administration/ Exposure**	Dermal
3.3.1	Postexposure period	14 days

Dermal

3.3.2	Area covered	10 % of body surface	
3.3.3	Occlusion	Occlusive (impervious binder, consisting of a plastic wrap and adhesive tape)	
3.3.4	Vehicle	Not applicable, test article was applied neat	
3.3.5	Concentration in vehicle	Not applicable	
3.3.6	Total volume applied	25 milligrams of test article (2 gram / kg bw)	
3.3.7	Duration of exposure	24 hours	
3.3.8	Removal of test substance	Water	
3.3.9	Controls	Not applicable	
3.4	**Examinations**	Mortality, clinical observations, skin condition, body weight and gross necropsy	
3.5	**Method of determination of LD_{50}**	Limit test, statistics not applicable	
3.6	**Further remarks**	-	
		RESULTS AND DISCUSSION	
3.7	**Clinical signs**	No effects observed	
3.8	**Pathology**	No effects observed	
3.9	**Other**	Effects on skin were seen:	X
3.10	**LD_{50}**	No mortality was observed: LD50 > 2 g/kg bw	
		4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	The acute dermal toxicity test is performed according to EPA/OPP, 1982 guidelines. The test article was applied neat to the skin (clipped free of hair and abraded). After 24 hours the bandage (occlusive) was removed and the skin was cleaned with water.	
4.2	**Results and discussion**	All animals survived the 14-day observation period and gained body weight. No abnormal clinical signs were observed, however, skin effects were observed: severe erythema and severe edema were observed at the test sites of all animals after removal on day 1. Both decreased in severity in some animals by the end of the study. Other dermal reactions observed at the test site include blanching, eschar formation and desquamation. At necropsy brown crusted discolorations of the treated skin were found in 3 males and 3 females. Also multiple depressions (3 males / 1 female) and a dark red focus (1 male) were observed. No effects on mortality were observed and the LD50 is set at the limit test dose of > 2 g/kg bw.	
4.3	**Conclusion**		
4.3.1	Reliability	1	
4.3.2	Deficiencies	No	

Evaluation by Competent Authorities

	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/06/27
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is acceptable with the following amendment: 3.9 For details on local skin effects see CA-table 1.
Conclusion	LD_{50}: > 2,000 mg/kg bw
Reliability	1
Acceptability	Acceptable without restrictions
Remarks	The study was conducted with 80 % L-(+)-lactic acid instead of 93 % (concentration of the active substance, the highest obtainable concentration). However, the LD_{50} of > 2000 mg/kg bw with 80 % L-(+)-lactic acid without any mortality suggests an LD_{50} higher than the limit dose for classification for 93 % L-(+)-lactic acid, too.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table A6_1-1. Table for Acute Toxicity (modify if necessary)

Dose [unit]	*Number of dead / number of investigated*	*Time of death (range)*	*Observations*
2000 mg/kg	0 / 5 per sex	Not applicable	Skin irritation
LD_{50} value	No effects on mortality were observed and the dermal LD50 is set at the limit test dose of > 2 g/kg bw.		

CA-Table 1 Local Skin Effects

Effect	No. of animals	Duration
Erythema	10/10	day 1- day 14
Oedema	10/10	day 1- day 14
Blanching	10/10 6/10	day 1 day 1- day 4
Necrosis	10/10 7/10 4/10	day 1- day 2 day 1- day 6 day 1- day 11
Eschar formation	10/10 7/10	day 2- day 11 day 2- day 14
Atonia	8/10	day 3/4- day 11/14
Desquamation	10/10	day 10/11- day 14
Fissures	5/10	day 5- day 14
Denuded areas along abrasion lines	1/10	day 14

Section A6.1.3 Acute Toxicity

Annex Point IIA6.1

Inhalation - rat

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted]., 1987. Acute inhalation toxicity study of SY-83 in the rat Microbiological Associated Inc. Report nr. I-7083.112.	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Purac Biochem BV	
1.2.2	Companies with letter of access	No	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes: EPA, 1985 and OECD, 1981	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	SY-83	
3.1.1	Lot/Batch number	Not presented	X
3.1.2	Specification	Formulated from Purac HS pharmaceutical grade (USP XX) L(+) lactic acid (88%) by dilution to a concentration of 80% in water.	
3.1.2.1	**Description**	Liquid	X
3.1.2.2	**Purity**	SY-83 is formulated from Purac HS pharmaceutical grade by dilution to a concentration of 80% with water: 83.5-76.5% lactic acid in water	
3.1.2.3	**Stability**	As given in section 2	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Fischer 344	
3.2.3	Source	Charles River Breeding Laboratories, Raleigh, North Carolina, USA.	
3.2.4	Sex	Male and female	
3.2.5	Age/weight at study initiation	197.5 gram (male) and 139.9 gram (female)	
3.2.6	Number of animals per group	5 of each sex	
3.2.7	Control animals	Yes: sham-exposed control group to observe the biological effects of restraint. The animals were exposed for 4 hours to air alone.	

Section A6.1.3 Acute Toxicity

Annex Point IIA6.1

Inhalation - rat

3.3	**Administration/ Exposure**	Inhalation		
3.3.1	Post exposure period	14 days		
		Inhalation		
3.3.2	Concentrations	Nominal concentration	7.94 mg/L	X
		Analytical concentration	5 mg/L	X
3.3.3	Particle size	*Only for studies with aerosols*		
		MMAD (mass median aerodynamic diameter) 2.03 – 2.14 µm		
		The respirable concentrations (<15 microns) of SY-83 was 7.9 mg/L		
3.3.4	Type or preparation of particles	*For studies with particles:* Not applicable		
3.3.5	Type of exposure	Nose only		
3.3.6	Vehicle	Not applicable		
3.3.7	Concentration in vehicle	Not applicable		
3.3.8	Duration of exposure	4 hours		
3.3.9	Controls	sham exposure		
3.4	**Examinations**	Mortality, clinical observations, body weight and gross necropsy		
3.5	**Method of determination of LD_{50}**	Limit test, statistics not applicable		
3.6	**Further remarks**	Not applicable		
		RESULTS AND DISCUSSION		
3.7	**Clinical signs**	Rapid breathing and eye tearing were seen during and shortly after exposure. After 24 hours most animals appeared normal and no unusual behaviour or appearance was observed for the remainder of the test period. However, several treated female rats showed ruffled, ungroomed fur the first days after treatment and the treated female rats lost weight during the first week. At the end all surviving animals gained weight and no significant differences were observed in body weight between treated and control groups.		
3.8	**Pathology**	No gross lesions were observed at necropsy.		
3.9	**Other**	One female rat died on day 8 post-treatment, following labored breathing and gasping on day 7.		
3.10	**LD_{50}**	Based on the results of this study, the LC50 of SY-83 is greater than 7.94 mg/L.		

Section A6.1.3 Acute Toxicity

Annex Point IIA6.1

Inhalation - rat

		4 APPLICANT'S SUMMARY AND CONCLUSION
4.1	**Materials and methods**	Give concise description of method; give test guidelines no. and discuss relevant deviations from test guidelines The acute inhalation toxicity test is performed according to EPA/OPP, 1985 guidelines (Vol 50, no 188) and OECD guidelines (1981). The test article was applied by nose-only for four hours.
4.2	**Results and discussion**	Rapid breathing and eye tearing were seen during and shortly after exposure. After 24 hours most animals appeared normal and no unusual behaviour or appearance was observed for the remainder of the test period. Although one treated animal died, the LC50 of SY-83 is set as greater than 7.94 mg/L.
4.3	**Conclusion**	
4.3.1	Reliability	1
4.3.2	Deficiencies	No

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/06/27
Materials and Methods	Applicant's version is acceptable with the following amendments: 3.1.1 Lot number: AP6853 3.1.2.1 Description: colourless liquid 3.3.2 Nominal concentration: 5 mg/L (incorrect value given in the study report) Analytical concentration: 7.94 mg/L
Results and discussion	Applicant's version is acceptable.
Conclusion	LC_{50}: > 7.94 mg/L air x 4 h
Reliability	1
Acceptability	Acceptable without restrictions
Remarks	The study was conducted with 80 % L-(+)-lactic acid instead of 93 % (concentration of the active substance, the highest obtainable concentration). However, the LC_{50} of > 7.94 mg/L air x 4 h with 80 % L-(+)-lactic acid with only one mortality suggests an LC_{50} higher than the limit concentration for classification for 93 % L-(+)-lactic acid.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

Section A6.1.3 Acute Toxicity

Annex Point IIA6.1

Inhalation - rat

Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section 6.1.4 Acute Eye Irritation

Annex Point IIA6.1.4 Chicken enucleated eye test

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] 1996. Chicken Enucleated Eye Test with three samples of lactic acid; an alternative to the Draize eye irritation test with albino rabbits. TNO Report nr. V96.157	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Purac Biochem BV	
1.2.2	Companies with letter of access	No	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	CEET = Chicken Enucleated Eye Test is an alternative test system: in their latest updates of the guidelines on eye irritancy testing, both the EEC and the OECD allow for the use of alternative ex vivo/ in vitro test systems	
2.2	**GLP**	Yes	
2.3	**Deviations**	No	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Three different forms of lactic acid are tested: 1. Purac H60: powder 2. Purac HS88: liquid: an aqueous solution, as given in Section 2 3. Purac BF S36 Lactic acid B : liquid: a buffered solution	
3.1.1	Lot/Batch number	1. Purac H60: RB 374 EA 2. Purac HS88: AP 5074L 3. Purac BF S36 Lactic acid B : HM 960207	
3.1.2	Specification	1. Purac H60: L+ lactic acid solid adduct with Ca-lactate 2. Purac HS88: L+ lactic acid aqueous solution ; CAS 79-33-4, as given in Section 2 3. Purac BF S36 Lactic acid B : L+ lactic acid, sodium lactate: CAS 79-33-4 and CAS 867-56-1	
3.1.2.1	**Description**	1. Purac H60: creamy, yellow powder 2. Purac HS88: clear colourless liquid , as given in Section 2 3. Purac BF S36 Lactic acid B : clear colourless liquid	
3.1.2.2	**Purity**	1. Purac H60: 60% lactic acid and 40% Ca-lactate 2. Purac HS88: circa 88% lactic acid, as given in Section 2 3. Purac BF S36 Lactic acid B : 73 – 84 % lactic acid	

3.1.2.3	**Stability**	1. Purac H60: no information 2. Purac HS88: no information, as given in Section 2 3. Purac BF S36 Lactic acid B: no information
3.2	**Test Animals**	
3.2.1	Species	Chickens were used as eye donors
3.2.2	Strain	ROSS spring chickens
3.2.3	Source	Poultry slaughterhouse v.d. Bor, Nijkerkerveen, The Netherlands
3.2.4	Sex	Male and female
3.2.5	Age/weight at study initiation	7 weeks old / 2.5-3.0 kg
3.2.6	Number of animals per group	Not applicable for this test: the Chicken Enucleated Eye Test (CEET) is an 'ex vivo bioassay' and the eyes of the chicken were used
3.2.7	Control animals	Not applicable; however, control eyes were used.
3.3	**Administration/ Exposure**	
3.3.1	Preparation of test substance	Test substances were used undiluted
3.3.2	Amount of active substance instilled	The two liquid samples were each applied in an amount of 0.03 mL in such a way that the entire surface of the cornea was bathed with the test material. For the solid sample 0.03 gram powder was applied.
3.3.3	Exposure period	10 seconds
3.3.4	Postexposure period	After the 10 seconds exposure the corneal surface was rinsed with 20 ml of isotonic saline
3.4	**Examinations**	
3.4.1	Ophthalmoscopic examination	Not applicable
3.4.1.1	**Scoring system**	The scoring system for the CEET is included in the Annexes to the study report.
3.4.1.2	**Examination time points**	At 0, 30, 75, 120, 180 and 240 minutes after treatment
3.4.2	Other investigations	Not applicable
3.5	**Further remarks**	
		RESULTS AND DISCUSSION
3.6	**Clinical signs**	Not applicable
3.7	**Average score**	
3.7.1	Cornea	Not applicable
3.7.2	Iris	Not applicable

3.7.3 Conjunctiva	See under 3.9	
3.7.3.1 Redness	Not applicable	
3.7.3.2 Chemosis	Not applicable	
3.8 Reversibility	Not applicable	
3.9 Other	CEET:	
Swelling %	Maximum score and category for:	
	1. Purac H60: 17 %; category II	
	2. Purac HS88: 28 %; category III	
	3. Purac BF S36 Lactic acid B : 6 %; category II	
Opacity	Maximum score and category for:	
	1. Purac H60: 2.0; category III	
	2. Purac HS88: 4.0; category IV	
	3. Purac BF S36 Lactic acid B : 0.5; category I	
Fluorescein retention	Maximum score and category for:	
	1. Purac H60: 2.0; category III	
	2. Purac HS88: 3.0; category IV	
	3. Purac BF S36 Lactic acid B : 1.0; category II	
3.10 Overall result	The three lactic acid samples cause different corneal effects in the CEET:	X
	1. Purac H60: moderate corneal effects	
	2. Purac HS88: severe corneal effects	
	3. Purac BF S36 Lactic acid B : slight corneal effects	
	4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1 Materials and methods	Three different forms of lactic acid were tested for eye irritating/ corrosive potential in an *ex vivo* bioassay, namely the Enucleated Eye Test with chicken eyes (CEET). The eyes were collected from a slaughter-house for chickens (which were killed for human consumption).	
4.2 Results and discussion	On the basis of the results obtained with this in vitro (ex vivo) assay and according to the EU classification, the following was concluded:	
	1. Purac H60: irritating to the eyes (R36)	
	2. Purac HS88: severely irritating to the eyes (R41)	
	3. Purac BF S36 Lactic acid B : not irritating to the eyes	
4.3 Conclusion		X
4.3.1 Reliability	1	
4.3.2 Deficiencies	N	

Section 6.1.4 Acute Eye Irritation

Annex Point IIA6.1.4 Chicken enucleated eye test

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/05/08
Materials and Methods	Applicant's version is acceptable.
Results and discussion	3.9 See CA-Table 1
Conclusion	Purac HS88 (circa 88% lactic acid, pH 2): severely irritating to the eyes (R41)
Reliability	1
Acceptability	Acceptable without restrictions
Remarks	None
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Appendix

Table A6_1_4E-1. Results of eye irritation study

Use this table, if relevant effects occur.

	Cornea	Iris	Conjunctiva	
			redness	chemosis
score (average of animals investigated)	0 to 4	0 to 2	0 to 3	0 to4
60 min	Not applicable for CEET			
24 h				
48 h				
72 h				
Average 24h, 48h, 72h				
Area effected				
Maximum average score (including area affected, max 110)				

Reversibility*	
average time for reversion	
Give method of calculation maximum average score. * *c :* *completely reversible* *n c :* *not completely reversible* *n :* *not reversible*	

CA-Table 1:

[1] Classil
(R41)
Comm

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Rabbits

Official use only

	1 REFERENCE	
1.1	**Reference**	[redacted] (1995) Acute dermal irritation/corrosion study with a 10% aqueous solution of lactic acid in albino rabbits TNO report V95.387 GLP, unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Purac Biochem BV
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its entry into Annex I
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes, OECD 404 / EEC B4
2.2	**GLP**	Yes
2.3	**Deviations**	No
	3 MATERIALS AND METHODS	
3.1	**Test material**	10% aqueous solution of lactic acid
3.1.1	Lot/Batch number	JVR-NAL-21
3.1.2	Specification	
3.1.2.1	**Description**	Clear, colourless liquid
3.1.2.2	**Purity**	10%
3.1.2.3	**Stability**	Not mentioned (storage conditions: ambient)
3.2	**Test Animals**	
3.2.1	Species	Rabbit
3.2.2	Strain	SPF bred New Zealand White albino
3.2.3	Source	Broekman Institute, Someren, The Netherlands
3.2.4	Sex	Male
3.2.5	Age/weight at study initiation	Young adults (2000-2470 kg at start of the study))
3.2.6	Number of animals per group	3
3.2.7	Control animals	no
3.3	**Administration/ Exposure**	Dermal
3.3.1	Application	

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Rabbits

3.3.1.1	**Preparation of test substance**	Test substance was used as delivered.
3.3.1.2	**Test site and Preparation of Test Site**	Skin site in clipped back and flanks of the animal
3.3.2	Occlusion	Semi-occlusive
3.3.3	Vehicle	No vehicle, test substance was used as delivered.
3.3.4	Concentration in vehicle	Not applicable
3.3.5	Total volume applied	0.5 ml test material per patch per application site
3.3.6	Removal of test substance	Moistened tissue
3.3.7	Duration of exposure	4-hour exposure
3.3.8	Post exposure period	72 hours
3.3.9	Controls	No
3.4	**Examinations**	
3.4.1	Clinical signs	No
3.4.2	Dermal examination	Yes
3.4.2.1	**Scoring system**	Draize et al (J. Pharmacol. Exp. Ther. 82 (1944), pp 377-390)
3.4.2.2	**Examination time points**	1, 24, 48, 72 hours after treatment
	Other examinations	Not applicable
3.5	**Further remarks**	

RESULTS AND DISCUSSION

3.6	**Average score**	
3.6.1	Erythema	0
3.6.2	Edema	0
3.7	**Reversibility**	Not applicable
3.8	**Other examinations**	No
3.9	**Overall result**	A 10% aqueous solution of lactic acid, when buffered at pH 4.0, is not irritating for the skin of rabbits after a 4-hour dermal contact period..

4 APPLICANT'S SUMMARY AND CONCLUSION

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Rabbits

4.1	**Materials and methods**	Skin irritation was tested according to OECD 404 on three New Zealand White albino rabbits	
4.2	**Results and discussion**	No dermal irritation responses related to treatment with lactic acid were observed.	
4.3	**Conclusion**	Lactic acid is not irritating or corrosive to skin.	X
4.3.1	Reliability	1	
4.3.2	Deficiencies	No	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/12/18
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is acceptable.
Conclusion	A 10 % aqueous solution of lactic acid, when buffered at pH 4.0, is not irritating for the skin of rabbits after a 4-hour dermal contact period.
Reliability	1
Acceptability	Acceptable
Remarks	None
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Pigs

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted]. (1987). Acute dermal irritation/corrosion study with lactic acid (88%) in pigs. TNO report nr. V87/405/270419. GLP, unpublished.	
1.2	**Data protection**	Yes	
1.2.1	Data owner	Purac Biochem BV	
1.2.2	Companies with letter of access	No	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes, OECD 404 / EEC B4	
2.2	**GLP**	Yes	
2.3	**Deviations**	Pigs were used, as pigs are more appropriate test animals than rabbits (normally used for skin irritation tests). A detailed justification is included in the report.	
		3 MATERIALS AND METHODS	
		In some fields the values indicated in the EC or OECD test guidelines are given as default values. Adopt, change or delete these default values as appropriate.	
3.1	**Test material**	As given in section 2 (88% lactic acid)	
3.1.1	Lot/Batch number	USP, batch U198	
3.1.2	Specification	As given in section 2	
3.1.2.1	**Description**	Clear colourless liquid	
3.1.2.2	**Purity**	88 %	
3.1.2.3	**Stability**	As given in section 2	
3.2	**Test Animals**		
3.2.1	Species	Pigs	
3.2.2	Strain	Not applicable	
3.2.3	Source	F1 from Large White (GY) x Dutch Landrace (NL), born on 25-11-1986 and bred in the test laboratory	
3.2.4	Sex	Male	
3.2.5	Age/weight at study initiation	40-50 kg	
3.2.6	Number of animals per group	3	
3.2.7	Control animals	no	

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4 *Pigs*

3.3	**Administration/ Exposure**	Dermal
3.3.1	Application	
3.3.1.1	**Preparation of test substance**	Test substance was used as delivered.
3.3.1.2	**Test site and Preparation of Test Site**	Three separate areas of shaved dorsal skin
3.3.2	Occlusion	Occlusive patch
3.3.3	Vehicle	Not applicable
3.3.4	Concentration in vehicle	Not applicable
3.3.5	Total volume applied	0.5 ml test material per application site
3.3.6	Removal of test substance	Lukewarm water
3.3.7	Duration of exposure	Three exposure periods for different application sites: 3 minutes, 60 minutes and 4 hours
3.3.8	Post exposure period	21 days
3.3.9	Controls	No
3.4	**Examinations**	
3.4.1	Clinical signs	No
3.4.2	Dermal examination	Yes
3.4.2.1	**Scoring system**	Draize et al
3.4.2.2	**Examination time points**	1 day, 2, 3, 7, 14 and 21 days
	Other examinations	Not applicable
3.5	**Further remarks**	

RESULTS AND DISCUSSION

3.6	**Average score**	
3.6.1	Erythema	0
3.6.2	Edema	0
3.7	**Reversibility**	Not applicable

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Pigs

3.8	**Other examinations**	Some minor superficial wounds and one day later small crusts were observed at application site and non-treated skin areas in two pigs. This effect was not considered treatment related as it also occurred at non-treated skin. These minor injures were probably caused by shaving along the walls or floor of the stable.	
3.9	**Overall result**	No dermal irritation responses related to treatment with lactic acid were observed.	
		4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	Skin irritation was tested according to OECD 404 on three pigs	
4.2	**Results and discussion**	No dermal irritation responses related to treatment with lactic acid were observed.	
4.3	**Conclusion**	Lactic acid is not considered irritating or corrosive to skin.	X
4.3.1	Reliability	1	
4.3.2	Deficiencies	No	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/07/16
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is acceptable.
Conclusion	4.3 Under the conditions tested lactic acid was not irritant or corrosive to pig skin.
Reliability	1
Acceptability	Acceptable without restrictions
Remarks	L(+) lactic acid proved to be corrosive in *in vitro* and rabbit dermal irritation tests and irritating in human patch tests (York et al. 1996). The participant proposed classification as R38. Since this study does not support the classification with R38, it doesn't seem to be adequate to use this study as sole dermal irritation key study (as proposed by the participant) to provide information on the irritating properties of L(+) lactic acid.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Pigs

Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Human skin

			Official use only
		1 REFERENCE	
1.1	**Reference**	York, M., Griffiths, H.A., Whittle, E., Basketter, D.A. (1996) Evaluation of a human patch test for the identification and classification of skin irritation potential Contact Dermatitis, 34, pp 204-212	
		No GLP, published	X
1.2	**Data protection**	No	
1.2.1	Data owner	Not applicable	
1.2.2	Companies with letter of access	Not applicable	
1.2.3	Criteria for data protection	Not applicable	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not according to a guideline	
2.2	**GLP**	Yes	
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	88% lactic acid	
3.1.1	Lot/Batch number	Not mentioned	
3.1.2	Specification	Obtained from Sherman	
3.1.2.1	**Description**	Not specified	
3.1.2.2	**Purity**	88%	
3.1.2.3	**Stability**	Not mentioned	
3.2	**Test Animals**	Not applicable, tests performed *in vitro* with human skin (full thickness breast or abdomen tissue obtained from cosmetic surgery) and *in vivo* using human patch test on human volunteers (18-65 years old)	
3.2.1	Species	Not applicable	
3.2.2	Strain	Not applicable	
3.2.3	Source	Not applicable	
3.2.4	Sex	Not applicable	
3.2.5	Age/weight at study initiation	Not applicable	
3.2.6	Number of animals per group	Not applicable	
3.2.7	Control animals	Not applicable	

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Human skin

3.3	**Administration/ Exposure**	Dermal	
3.3.1	Application		
3.3.1.1	**Preparation of test substance**	Test substance was used undiluted	
3.3.1.2	**Test site and Preparation of Test Site**	*In vitro* corrosivity test: The skin, epidermal side uppermost, was sealed to polytetrafluoroethylene (PTFE) tubes, which was placed inside a separate plastic container containing electrolyte solution (154 mM MgSO4 in distilled water). The test substance was applied to the epidermis and removed using a jet of water after a 24-h application. The corrosive effect was determined by measuring the transcutaneous electrical resistance (TER). Human patch test: The sequential single patch test procedure was used. 0.2 mL (0.2 g for solid test materials) was applied onto a 25 mm Plain Hill Top Chamber containing a Webril pad (moistened for solid test materials). The test materials were applied progressively from 15 and 30 minutes through 1, 2,, 3, and 4 hours.The upper outer arm was used as the treatment site for all experiments. Treatment sites were assessed for the presence of irritation using a 4 point scale at 24, 48, and 72 h after patch removal.	
3.3.2	Occlusion	Not applicable	
3.3.3	Vehicle	Not applicable	
3.3.4	Concentration in vehicle	Not applicable	
3.3.5	Total volume applied	Not applicable	
3.3.6	Removal of test substance	Not applicable	
3.3.7	Duration of exposure	Not applicable	X
3.3.8	Post exposure period	Not applicable	
3.3.9	Controls	Not applicable	
3.4	**Examinations**		
3.4.1	Clinical signs	No	
3.4.2	Dermal examination	Yes	
3.4.2.1	**Scoring system**	Presence of irritation was scored on a 4 point scale: 0 – no reaction + – weakly positive reaction (usually characterized by mild erythema across most of the treatment site) ++ – moderately positive reaction (usually distinct erythema possibly spreading beyond the treatment site) +++ – strongly positive reaction (strong, often spreading erythema with oedema)	

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Human skin

3.4.2.2	**Examination time points**	24, 48, 72 hours after treatment	
	Other examinations	Not applicable	
3.5	**Further remarks**		
		RESULTS AND DISCUSSION	
3.6	**Average score**	Lactic acid was corrosive in the *in vitro* corrosivity test. In the human patch test, no positive reactions were observed at assessment at 24, 48, and 72 hours after treatment when volunteers were treated for 15 minutes, 30 minutes, or 1 hour. However, at 2, 3, and 4 hours, a total of 21 of the 26 volunteers who completed treatment had an irritant reaction to lactic acid.	X
3.6.1	Erythema	Not applicable	
3.6.2	Edema	Not applicable	
3.7	**Reversibility**	Not applicable	
3.8	**Other examinations**	No	
3.9	**Overall result**	88% lactic acid has corrosive properties and is irritating to the human skin.	
		4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	The corrosive and irritating properties of lactic acid on human skin were investigated using the *in vitrocorrosivity test and the in vivo* human patch test	
4.2	**Results and discussion**	Lactic acid was corrosive in the *in vitro* corrosivity test. In the human patch test, no positive reactions were observed at assessment at 24, 48, and 72 hours after treatment when volunteers were treated for 15 minutes, 30 minutes, or 1 hour. However, at 2, 3, and 4 hours, a total of 21 of the 26 volunteers who completed treatment had an irritant reaction to lactic acid.	
4.3	**Conclusion**	88% lactic acid has corrosive properties and is irritating to the human skin.	X
4.3.1	Reliability	2, study conducted with generally accepted scientific principles.	
4.3.2	Deficiencies	No	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/12/18
Materials and Methods	1.1 Work was conducted according to GLP Otherwise, the applicant's version is acceptable.

Section A6.1.4 Acute Dermal Irritation

Annex Point IIA6.4

Human skin

Results and discussion	The applicant's version is acceptable with the following amendment: 3.6 In the human patch test, no positive reactions were observed at assessment at 24, 48, and 72 hours after treatment when volunteers were treated for 15 minutes, 30 minutes, or 1 hour. After application times of 2, 3, and 4 hours, a total of 21 of the 26 volunteers who completed treatment had an irritant reaction to lactic acid at either 24, 48 or 72 h.
Conclusion	4.3 88% lactic acid has corrosive properties *in vitro* and is irritating to human skin *in vivo*.
Reliability	2
Acceptability	Acceptable
Remarks	None

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section 6.1.4 **Annex Point IIA6.4**	**Acute eye and dermal irritation**	
	JUSTIFICATION FOR CHOICE OF KEY STUDY	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [x]**	
Detailed justification:	***Statement*** **L(+) lactic acid as active substance in biocides: Doc. III-A** **Section 6.1.4 Skin and eye irritation** *Introduction: Lactic acid is widely occurring in nature as metabolic substance in all living cells. As such, it is a natural constituent of many foods, such as meat, dairy products and fruits. Since 1885, it has been manufactured for industrial purposes in Europe.* *Lactic acid is approved in the EU (E270) as food additive, and has a GRAS (Generally Recognized as Safe) status in the USA. It is used in many foodstuffs, cosmetics, pharmaceuticals, feed, and technical applications, such as in biocides.* *This statement has been written to evaluate the dermal irritation/corrosion properties of lactic acid in man. Several skin irritation tests were performed with lactic acid (88%) with different animals to establish the properties of lactic acid on the skin. I discuss below the preferred choice of the pig as animal model to predict the potential risks of lactic acid to human skin.* **Skin irritation** 1. Introduction Standard testing methods for skin irritation/corrosion properties are described in OECD guideline 404 (Acute Dermal Irritation/Corrosion). In the description of the testing strategy, evaluation of existing human studies or occupational reports should be considered first. Concerning the occupational experience with lactic acid, there is a long history of working with lactic acid and using lactic acid: there was no incidence reported with an irreversible adverse effect on the skin. Further in the testing strategy, concerning the physicochemical properties it is mentioned for substances exhibiting pH ≤ 2.0, as lactic acid, these can be considered corrosive, and then its acid reserve (or buffering capacity) may also be taken into consideration. If there is a buffering capacity, it may that a substance is not corrosive to the skin, then further testing should be undertaken to confirm this. We will show that lactic acid, as weak acid, is having a buffering capacity. The albino rabbit is described in OECD 404 as the preferred laboratory animal. Testing on other species is permitted, when a rationale for using	X

Section 6.1.4 Acute eye and dermal irritation

Annex Point IIA6.4

JUSTIFICATION FOR CHOICE OF KEY STUDY

Official use only

other species is provided. The reason why rabbit is mostly used as animal model for skin tolerance tests, is that it is more responsive than human skin and by this animal model, it is believed that very sensitive individuals or local reactions are taken into consideration.

Based on the dermal irritation studies with albino rabbits, one could suggest that lactic acid should be classified as severely irritating and corrosive. The rabbit however appeared to be extra sensitive to lactic acid.

Based on significant similarities between human and pig skin, the domestic pig was proposed as a valuable animal model for human skin (Bisset, 1985) and it has been suggested that the domestic pig offers the most appropriate model for all types of dermatological and surgical wound investigations (Vardaxis, 1997).

Therefore it was decided to use pigs in another dermal testing, because the emphasized anatomical similarities of pig skin to human skin, and the demonstrated similarity of skin penetration in pig and man.

2. Studies

Study 1 (TNO report V 87.405/270419): X

Summary of the study:

A sample of lactic acid (88%) was examined for acute dermal irritating/corrosive properties in an experiment with three pigs.
In each test animal, the test substance was brought into contact with three separate areas of shaved dorsal skin for 3 and 60 minutes and for 4 hours, respectively.

The test sample did not cause any skin irritation when it was brought into contact with the dorsal skin of pigs for 3 or 60 minutes or for 4 hours.

The test sample did not cause any skin irritation.
On the basis of the results obtained in the present study with pigs, it was concluded that, according to EEC standards, lactic acid (88%) is not irritating or corrosive to skin.

Study 2 (TNO Report V 87.406/270419).

Summary of the study:

A sample of lactic acid (50%) was examined for acute dermal irritating/corrosive properties in an experiment with three pigs.
In each test animal, the test substance was brought into contact with three separate areas of shaved dorsal skin for 3 and 60 minutes and for 4 hours, respectively.

The test sample did not cause any skin irritation when it was brought into contact with the dorsal skin of pigs for 3 or 60 minutes or for 4 hours.

On the basis of the results obtained in the present study with pigs, it was concluded that, according to EEC standards, lactic acid (50%) is not

Section 6.1.4 Acute eye and dermal irritation

Annex Point IIA6.4

JUSTIFICATION FOR CHOICE OF KEY STUDY

Official use only

irritating or corrosive to skin.

Study 3 (IRI report 235943 dated September 1986)

Summary of the study:

The corrosivity potential of a test material, Lactic Acid Q88, was investigated by means of a test in guinea pigs. The test was designed to assess irritancy and/or corrosivity by means of topical application of the test material to intact skin under semi occlusive conditions for various exposure times viz: 3 min, l h and 4 h. Two groups of 3 animals were used. In Group l exposures of 3 min and l h were investigated while 4 h exposures were investigated in Group 2.
No irritation or corrosion were noted in animals exposed to Lactic Acid Q88 for 3 min and l h. Responses in animals exposed to the test material for 4 h were limited to very slight erythema which was noted at patch removal and l h after patch removal only. Skin appeared normal at 24 h after patch removal.

Study 4 (PURAC report: Acid Reserve at pH 2, 21 August 2006)

In the Annex, the acid reserve at pH 2 and pH 4 is calculated for some weak acids and strong acids. The acid reserve is expressed as gram NaOH needed to raise the pH of 100 ml of the acid, to a pH of 2. Also the acid reserve, as gram NaOH, to raise the pH to pH 4, is calculated.

As expected, for strong acids, much NaOH is needed to raise the pH of < 2, to a pH 2. For weak acids, only small amounts are needed to raise to pH 2. For lactic acid only 0.6 g. This means that only a small amount of neutralizing agent is needed to raise the pH to pH of 2. The skin is having a neutralizing capacity to handle this.

Comparing the acid reserve at pH 2 with that of pH 4, it can be seen, that for the strong acids, there is practically no difference, while weak acids have their strongest buffering capacity close to pH 4. The skin is having a pH > 4, and when coming in contact with lactic acid, the local skin pH will decrease and skin fluids will start neutralizing, and as lactic acid is buffering strongly at pH 4, the local skin pH will not rapidly decrease to pH below 3.5 or to pH 2.

It can be concluded that the buffering capacity of lactic acid is making this substance not corrosive. X

3. Evaluation
Comparative evaluations studies are published of skin irritation in rabbits and humans, which have shown that rabbit skin is far more sensitive than human skin under similar testing conditions. A comparative study with several animal models (Motoyoshi, 1987) on the skin irritancy of twenty oils and twenty synthetic perfumes, indicates that the skin sensitivity decreases in the following order: rabbit, guinea pig, rat, man and miniature swine. The rabbit skin is more permeable than human skin, which may account for a significant part, for the

Section 6.1.4 Acute eye and dermal irritation

Annex Point IIA6.4

JUSTIFICATION FOR CHOICE OF KEY STUDY

Official use only

increased irritation observed in rabbits.

In this same study, 6 compounds that produced the least reaction in the human closed patch test, produced the most severe responses in the rabbit skin, and would be classified as severe irritants. Histologically, the skin of the miniature swine closely resembles that of human skin and was considered to be suitable for investigating skin irritancy.

Considerable inter-species variability's concerning the anatomy, physiology, and biochemistry of the skin are known. The structure of human skin consists of the epidermis (the superficial portion), and the dermis, which is the deeper, thicker portion of the skin that is composed of connective tissue, blood vessels, glands and nerves. Hair follicles and sweat glands are epidermal appendages. The human epidermis is composed of 5 strata (Klaassen, 2001), of which the stratum corneum acts as the absorption rate-limiting barrier of the skin. Human skin thickness ranges from 0.5 mm (eyelid) to 4.0 mm (palm and sole), over the various regions of the body.

In general, small mammals (rabbits, rats, mice, etc.) have a dense layer of body hair, and a thin epidermis and dermis, relative to the humans. The epidermis is only 2-4 cell layers in most mammals compared to 6-10 cell layers in the human and porcine epidermis (Vardaxis, 1997). The stratum corneum is also in general much thicker in humans than in animals, resulting in a lower percutaneous permeability in humans. Another major difference between most furry mammals and human skin is that these mammals lack eccrine sweat glands.

The use of the pig as animal model for human skin is based on the fact that porcine skin and human skin have several similar characteristics in contrast to small mammals. In the literature (Simon and Maibach, 2000) it is well-recognized that pig skin is an appropriate animal model for human skin, in terms of anatomy, physiology, biochemistry and absorption characteristics.

These similarities (Bissett, 1985) include hair density, skin surface structure, epidermal structure, sebum composition, epidermal turnover rate, epidermal lipid composition, and the use of fat for insulation (in contrast to fur in many small mammals).

A significant difference (Vardaxis, 1997) between porcine and human skin, is that the pig possesses apocrine glands instead of eccrine sweat glands present in human skin. However, it is unlikely that this difference in glands would have any impact on the predictive potential of a dermis irritation reaction in the pig.

For many chemicals, the skin permeability characteristics of pig skin resemble those of human skin, and the pig is a representative animal model for humans in skin permeation studies.

Remark: PURAC is producing lactic acid since 1936 at a high volume, during many years producing more than 100.000 ton per year. During all these years producing such high amounts of lactic acid, there was no incidence reported of operators in the factory, with an irreversible adverse effect on the skin, in the cases of direct dermal contact with lactic acid, after a spill / leakage incident.

Section 6.1.4 Acute eye and dermal irritation

Annex Point IIA6.4

JUSTIFICATION FOR CHOICE OF KEY STUDY

Official use only

4. Summary

The rabbit is more sensitive to skin irritants than other test species or humans. Although the rabbit is currently used as the most conservative animal in standard irritancy tests, the literature provides strong evidence that the pig is a more relevant animal model for human skin than the rabbit. Thus, in case of L(+) lactic acid for which there are irritancy/corrosion data in the guinea pig, domestic pig, and rabbit, greater emphasis should be given to findings in the guinea pig and pig irritancy tests, as these are more relevant models for predicting dermal effects in humans, than findings in the rabbit study.

Eye irritation

1. Introduction

Standard testing methods for eye irritation/corrosion properties are described in OECD guideline 405 (Acute eye Irritation/Corrosion). The rabbit is described in OECD 404 as the preferable laboratory animal. Testing on other species is permitted, provided that a rationale for using these other species is provided.

2. Studies

Study 1 (TNO report V96.157 dated March 1996)

Three different forms of **lactic acid,** i.e. a powder (sample code H60) and two liquids (sample code HS88 and sample code BF S36), were examined undiluted for eye irritating/corrosive potential in an ex vivo bioassay, namely the Enucleated Eye Test with chicken eyes (CEET) (The Chicken Enucleated Eye Test (CEET) is an alternative to the Draize eye irritation test with albino rabbits)

The eyes were collected as waste material from a slaughter-house for chickens, which were killed for human consumption.

The three lactic acid samples caused quite different corneal effects in the CEET. Generally, sample H60 induced moderate corneal effects, sample HS88 severe corneal effects and sample BF S36 slight corneal effects.

On the basis of the results obtained with this *in vitro (ex vivo)* assay and according to the

scheme for (EC-)classification applied, the following was concluded:

- the buffered lactic acid sample (BF S36) can be considered not irritating to eyes,

- the powder sample (H60) can be considered irritating to eyes (R36), and

- the lactic acid sample (HS88) can be considered severely irritating to eyes (R41)

Section 6.1.4 Acute eye and dermal irritation

Annex Point IIA6.4

JUSTIFICATION FOR CHOICE OF KEY STUDY

Official use only

Publication 1

Ocular tolerance studies were carried out with a group of humectants and moisturizers used in cosmetics (Guillot, 1982) including tests with lactic acid. Eyes of rabbits were examined after 1 and 24 h and after 2, 3, 4 and 7 days, with fluorescein staining. The ocular irritation index (OII) was determined and evaluated on a scale from 0 to 110. A compound does not provoke any significant injury to the eye mucous membrane when no opacity of the cornea and when OII is less than 15. Lactic acid instilled at 20% and 10% provoked a significant ocular irritation: OII was 39.5 resp. 31.2. Only for the 10% dilution, these lesions were reversible 7 days after instillation.

3. Evaluation

The results clearly demonstrate that Lactic Acid must be considered severely irritating to the eyes.

4. Summary:

L(+) lactic acid is severely irritating to the eyes

References:

Bissett, D.L.; McBride J.F. (1985) Use of domestic pig as animal model of human dry skin. Maibach H.I.; Lowe N.J. (Eds.) *Models in Dermatology Vol. 1: Dermatology. S. Karger; Basel, Switzerland & New York, pages 159-168.*

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.*

IRI (1986) Lactic acid Q88: a skin corrosivity test in Guinea Pigs. *Inveresk Research International,* Report 3625.

Klaassen, C.D. (ed.) (2001) *Casarett and Doull's Toxicology: the Basic Science of Poisons (6th ed.). McGraw-Hill Health Professionals Division; Chapter 5, pages 117-119 and Chapter 19, pages 657-658.*

Simon, G.A. and Maibach, H.I., (2000). The pig as an experimental model for percutaneous permeation in Man: Qualitative and Quantitative observations. An overview. *Skin Pharmacol. Appl. Skin Physiol.,* ***13****: 229-234.*

TNO (1987). Acute dermal irritation/corrosion study with lactic acid (88%) in pigs. L.van Beek, *TNO Report V 87.405 / 270419.*

TNO (1996). Chicken Enucleated Eye Test with three samples of lactic acid: an alternative to the Draize eye irritation test with Albino rabbits. M.K. Prinsen, *TNO Report V96.157.*

Vardaxis, N.J., et al., (1997). Confocal laser scanning microscopy of porcine skin: implications for human wound healing studies. *Journal Anat.,* ***190****(4): 601-611.*

Section 6.1.4 **Annex Point IIA6.4**	**Acute eye and dermal irritation**	
	JUSTIFICATION FOR CHOICE OF KEY STUDY Annex: PURAC (2006). Acid Reserve at pH 2. G. Nanninga. *Report 21 Aug. 2006.*	Official use only
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2008/07/16	
Evaluation of applicant's justification	Applicant's justification is acceptable with amendments: Relevant species: L(+) lactic acid proved to be corrosive in *in vitro* and in in *vivo* rabbit dermal irritation tests; and it was irritating in patch tests in humans (York et al. 1996). The participant proposed classification with R38. Since the studies with pigs do not support the classification with R38, it doesn't seem to be adequate to use these studies as sole dermal irritation key study (as proposed by the participant) to provide information on the irritating properties of L(+) lactic acid. From the human patch tests it is likely that dermal irritation studies in pigs underestimate the irritating potential of L(+) lactic acid for human skin while rabbit skin seems to be much more sensitive than human skin. Thus, the human patch test data should be used as key study (York et al. 1996) showing adequate results for classification and labelling. Acid reserve at pH2: L(+) lactic acid revealed skin corrosive properties in several studies (in vitro: Corrositex assay (Harbell 1994), TER assay (York et al. 1996), rabbit in vivo: Barnes 1983; [redacted] 1986). These studies show that the acid reserve of L(+) lactic acid at < pH 2 is high enough to display corrosive properties dependent on the test system used (e.g. the buffering capacity of the skin).	
Conclusion	Applicant's justification is acceptable with amendments (see Evaluation)	
Remarks	None	

Section 6.1.4 Annex Point IIA6.4	Acute eye and dermal irritation	
	JUSTIFICATION FOR CHOICE OF KEY STUDY	Official use only
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.1.5 Skin sensitisation

Annex Point IIA6.1.5 Buehler Test

		Official use only
	1 REFERENCE	
1.1 Reference	[redacted]., 1986. Dermal sensitization study in guinea pigs with SY-83. American Biogenics Corporation, Report nr. 480-2750	
1.2 Data protection	Yes	
1.2.1 Data owner	Purac Biochem BV	
1.2.2 Companies with letter of access	No	
1.2.3 Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing [a.s. / b.p.] for the purpose of its entry into Annex I	
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1 Guideline study	Yes: EPA, 1982 (modification of the Buehler closed patch technique)	X
2.2 GLP	Yes	
2.3 Deviations	Yes, during the induction phase (after the second induction application) the concentration of the test substance was reduced from 100% to 30% and a switch was made from the right flank to the left flank. This was done, because of the irritation observed at the 100% application on the right flank.	X
	3 MATERIALS AND METHODS	
3.1 Test material	SY-83	
3.1.1 Lot/Batch number	Not presented	
3.1.2 Specification	Formulated from Purac HS pharmaceutical grade (USP XX) L(+) lactic acid (88%) by dilution to a concentration of 80% in water.	
3.1.2.1 Description	Liquid	
3.1.2.2 Purity	SY-83 is formulated from Purac HS pharmaceutical grade by dilution to a concentration of 80% with water: 83.5-76.5% lactic acid in water	
3.1.2.3 Stability	As given in section 2	
3.1.2.4 Preparation of test substance for application	a) <u>For induction:</u> used as delivered (100% test substance), and also 3, 10 and 30% suspensions in deionized water. b) <u>For challenge:</u> used as delivered.	X
3.1.2.5 Pretest performed on irritant effects	Yes (range-finding test on 2 animals)	
3.2 Test Animals		
3.2.1 Species	Guinea pigs	
3.2.2 Strain	Hartley	
3.2.3 Source	Charles River Breeding laboratories Inc., Portage, MI facility, USA	
3.2.4 Sex	Female	

Section A6.1.5 Skin sensitisation

Annex Point IIA6.1.5 Buehler Test

3.2.5	Age/weight at study initiation	Young adult / 272 – 362 gram	
3.2.6	Number of animals per group	10	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	State study type: *Buehler Test*	
3.3.1	Induction schedule	3 times each week (Monday, Wednesday and Friday) until all 9 induction applications had been applied	
3.3.2	Way of Induction	Topical Occlusive	
3.3.3	Concentrations used for induction	100 % test substance, but after 2 induction applications the concentration was reduced to 30% and the test site was changed to the left flank (due to irritation effects seen at 100 % at the right flank)	
3.3.4	Concentration Freunds Complete Adjuvant (FCA)	*state concentration and vehicle (for GPMT only):* 10 % in water or physiological saline	X
3.3.5	Challenge schedule	Two weeks after the ninth induction; see table in appendix	X
3.3.6	Concentrations used for challenge	100 % test substance (usually maximum non-irritant concentration)	
3.3.7	Rechallenge	No	
3.3.8	Scoring schedule	24h, 48h after challenge	
3.3.9	Removal of the test substance	After 6 hours the binders and patches were removed / no information on rinsing	
3.3.10	Positive control substance	Dinitrochlorobenzene	
3.4	**Examinations**		
3.4.1	Pilot study	yes	
3.5	**Further remarks**	-	
		RESULTS AND DISCUSSION	
3.6	**Results of pilot studies**	0.5 mL of test article was applied at 3, 10, 30 and 100% concentration. The 100% test article concentration was selected for induction and challenge since dermal reactions were minimally irritation at this range-finding test site.	
3.7	**Results of test**		
3.7.1	24h after challenge	0/10	
3.7.2	48h after challenge	0/10	

Section A6.1.5 Skin sensitisation

Annex Point IIA6.1.5 Buehler Test

3.7.3 Other findings	Severe (grade 4 erythema and eschar formation) effects on the skin were observed both 24 and 48 hours after challenge (and also after induction); these reactions were considered irritation reactions, no sensitization reactions, as similar skin effects were observed in the control animals.	
3.8 Overall result	SY-83 was not considered to be a skin sensitizer	
	4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1 Materials and methods	The test is applied conform EPA, 1982 (modification of the Buehler Closed Patch technique).	
4.2 Results and discussion	Severe (grade 4 erythema and eschar formation) effects on the skin were observed both 24 and 48 hours after challenge (and also after induction); these reactions were considered irritation reactions, no sensitization reactions, as similar skin effects were observed in the control animals.	X
	SY-83 was not considered to be a skin sensitizer	X
4.3 Conclusion		X
4.3.1 Reliability	1	X
4.3.2 Deficiencies	No	X

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/07/16
Materials and Methods	The applicant's version is acceptable with the following changes: 2.1 Similar to OECD 406 2.3 80 % lactic acid (= 100 % SY-83, see remarks) was used for induction and challenge. This concentration proved to be highly irritating (grade 4) in naive as well as induction group animals. Only 10 animals were used in the treatment group instead of 20. 3.1.2.4 3, 10 and 30% suspensions were used only in the range-finding study (30 % in the main study for the last 7 out of 9 inductions). 3.3.4 No adjuvant used (Buehler test) 3.3.5 No corresponding table was included in the appendix.
Results and discussion	The applicant's version is acceptable with the following changes: 4.2 Severe effects (grade 4 erythema (pinpoint pitting, very little redness) and eschar formation) on the skin were observed both 24 and 48 hours after challenge (and also after induction). These reactions were considered irritation reactions, no sensitization reactions, as similar skin effects were observed in the control animals. SY-83 was not considered to be a skin sensitizer
Conclusion	4.3 L-(+)-lactic acid is not sensitising.
Reliability	2
Acceptability	Acceptable with restrictions (see remarks)

Section A6.1.5 Skin sensitisation

Annex Point IIA6.1.5

Buehler Test

Remarks	The concentrations of all dilutions (10 %, 30 %) in this study relate to 100 % SY-83 which yields 80 % L(+) lactic acid. The L-(+)-lactic acid concentration used for induction and challenge was 80 % and caused severe skin irritation. As stated in OECD guideline 406, "the concentration of test substance used for each induction should be the highest to cause mild irritation. The concentration used for the challenge should be the highest non-irritating dose." Since the quality of the observed skin effects (pitting of the skin, only little redness) differ from those caused by a skin sensitising substance the results of the study can be interpreted as skin irritation. Furthermore, L-(+)-lactic acid is a metabolic intermediate (~130 g/d in humans at rest). A sensitisation potential for endogenous substances which are formed in considerable amounts in the human (or animal) body is highly unlikely. Thus, a sensitisation study is considered not necessary.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.2 Metabolism

Annex Point IIA6.2

Official use only

1 REFERENCE

1.1	**Reference**	Sterenborg, I. (2007) Lactic acid as biocidal active substance, Statement to address requirements of Directive 98/8/EC ENVIRON Report, report nr. PU-LBD-20070039. Not GPL, Unpublished
1.2	**Data protection**	Yes
1.2.1	Data owner	Purac Biochem BV
1.2.2	Companies with letter of access	No
1.2.3	Criteria for data protection	Data on existing or new [a.s. / b.p.] to [maintain or vary a.s. Annex I/IA entry / vary conditions of a b.p.'s authorisation]

2 GUIDELINES AND QUALITY ASSURANCE

2.1	**Guideline study**	No, review report
2.2	**GLP**	No, review report
2.3	**Deviations**	Not applicable, review report

3 MATERIALS AND METHODS

Not applicable, review report

4 RESULTS AND DISCUSSION

Not applicable, review report

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Not applicable, review report
5.2	**Results and discussion**	The role of lactic acid in metabolism has kept researchers occupied for a long time. Many years, lactic acid was considered a dead-end waste product of the glycolysis, the conversion of glucose into pyruvate (producing a relatively small amount of ATP), in the absence of oxygen. The formation of lactic acid was thought to occur following exercise, as a result of muscle anoxia, and was thought to be the major cause of muscle fatigue (Gladden, 2004). Pyruvate serves as the starting point in the citric acid (or Krebs) cycle under aerobic conditions. It was thought that under anaerobic conditions, lactic acid is formed from pyruvate. The formation of lactic acid from glucose supplies the cell with limited amounts of energy. The main region for the formation of lactic acid in humans was believed to be the muscle, as it was hypothesized that, when muscles require energy for a short duration, for example during exercise, the citric acid cycle

cannot be entered due to the lack of oxygen. This means that pyruvate, which is formed during glycolysis, is further broken down to lactic acid. To prevent lactic acidosis, it was thought that lactic acid diffuses into the blood, is taken up by the liver, and converted back into pyruvate by the enzyme lactate dehydrogenase. Subsequently, gluceogenesis would convert pyruvate to glucose, which could be released into the blood to be used again for energy by the red blood cells and muscles. This reaction is energy consuming, as the gluceogenesis in the liver requires ATP (Holten, 1971, Stryer, 1995). This cycle is also known as the Cori cycle, and is depicted in Figure 1.

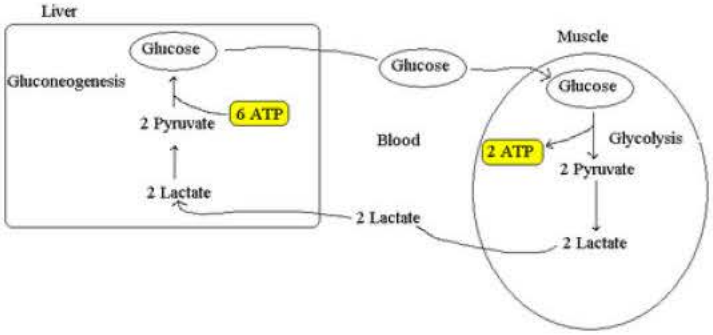

Figure 1: The Cori cycle

Based on this cycle, it has long been thought that during physical exercise, the working muscle needs energy more rapidly than oxidative metabolism can supply, which means the anaerobic conversion of pyruvate to lactic acid will occur. Consequently, lactic acid and pyruvic acid are released into the blood circulation, which was believed to result in lactic acidosis and oxygen debt (Holten, 1971).

Recently, the role of lactic acid in metabolism is reconsidered, and L-lactate is considered as a functional metabolite and mammalian fuel. Recent studies show that during hard exercise, glycolysis in muscles involves the formation of L-lactate regardless of the state of oxygenation. Furthermore, several studies support a carrier-mediated process for lactic acid transport in and out of skeletal muscle (Philp *et al.*, 2005). The concept "lactate-shuttle", which was introduced by Brooks (1998, 1999), basically means that lactate is able to transfer from its site of production (cytosol) to neighbouring cells and other organs, as well as intracellular, where its oxidation or continued metabolism can occur. The discovery of an entire family of monocarboxylate transport (MCT) proteins, which facilitate lactate transport into and out of the cell, supports this concept (Philp *et al.*, 2005).

The lactate shuttle results in the distribution of lactic acid to other cells, where it is directly oxidised, re-converted back to pyruvate or glucose, allowing the process of glycolysis to restart and ATP provision maintained. The processes involved in the lactate shuttle are depicted in Figure 2 (taken from Philp *et al*, 2005).

Section A6.2 Metabolism

Annex Point IIA6.2

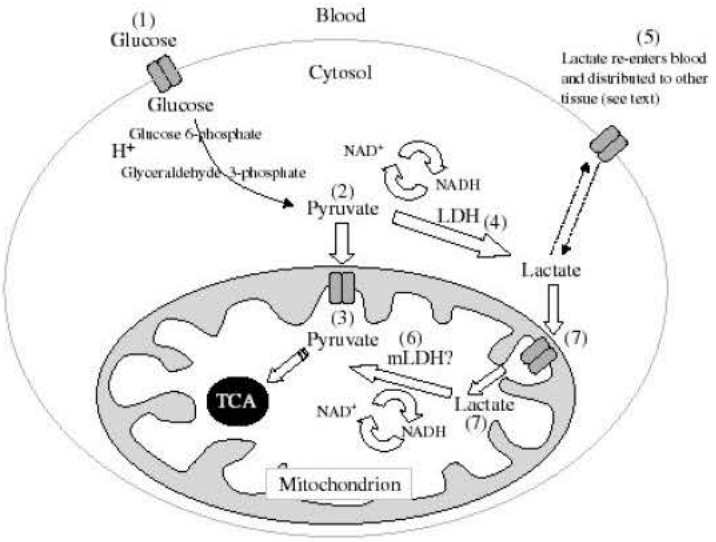

Figure 2: The processes involved in the lactate shuttle hypothesis (Brooks, 1986). The pathway proposes that (1) glucose enters the cell, where it is sequentially broken down to pyruvate (2). Pyruvate enters the mitochondrion, allowing respiration to continue in the tricarboxylic acid (TCA) cycle (3). Lactate is subsequently formed via the lactate dehydrogenase (LDH) reaction (4) and is then exported from the cytosolic compartment via monocarboxylate transporter (MCT) transport (5), where it is redistributed to a variety of functional sites. Note the suggested presence of mitochondrial lactate dehydrogenase (mLDH) (6), which forms the construct of the intracellular shuttle system (7). (taken from Philp *et al*., 2005)

X

In light of the newly discovered role of lactic acid in metabolism, its role in muscle fatigue is questioned. Several investigations indicate that the classical theory of exercise-induced fatigue due to anaerobic conversion of pyruvate into lactic acid is superseded; an increase of inorganic phosphate produced during contraction is suggested as the major cause of muscle fatigue. Lactic acid may even delay the onset of fatigue by maintaining the excitability of muscles during extremely intensive exercise. However, the exact mechanism remains unclear (Philp *et al.*, 2005).

X

The effect of artificially elevated lactate concentrations was investigated in human subjects in a study by Miller et al. (2002). The authors concluded that when lactate is provided by intravenous infusion, blood glucose is spared and glucose production decreased. The processes underlying these effects are depicted in Figure 3 (taken from Philp *et al.*, 2005).

X

Section A6.2 Metabolism

Annex Point IIA6.2

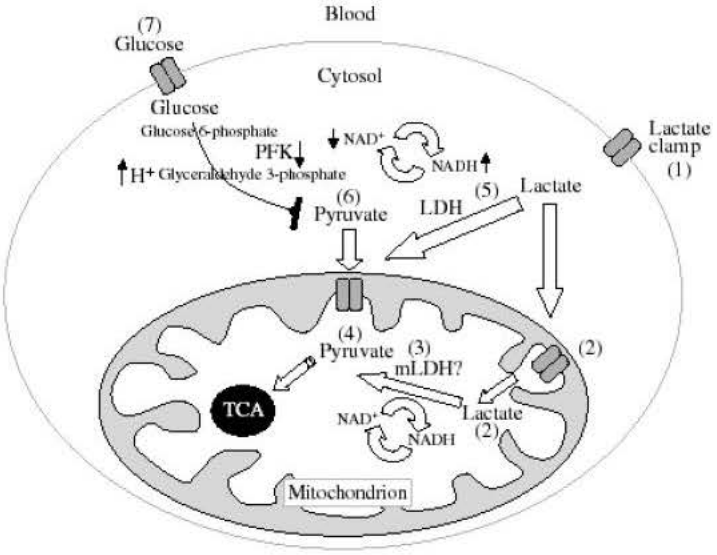

Figure 3: The effect of artificially elevated lactate concentrations (lactate clamp) on metabolic processes. Increased circulatory lactate concentrations (1) result in lactate entering the cytosol, where it then enters the mitochondrion via MCT1 (2). Within the mitochondrion, lactate is converted to pyruvate via mLDH (3), which then progresses into the tricarboxylic acid (TCA) cycle (4). However, artificially raised cytosolic lactate concentrations (5) lead to suppression in glycolysis. Therefore, a resulting increase in H+ and NADH occurs, and acidosis inhibits phosphofructokinase (PFK) activity (6). This suppression finally results in reduced glycolytic activation and a reduction, or sparing, of glycogenolysis. (taken from Philp *et al.*, 2005)

X
X
X

After the discovery of the lactate shuttle, the exact role of lactic acid *in vivo* remains still to be investigated. It is suggested that lactic acid plays a role as metabolic signal at the whole-organism level, due to its ability to be transported and regulate the cellular redox state in cells. Several investigations indicate that lactate plays a role in wound-healing, which may be associated with the signalling function (Philp *et al.*, 2005, Gladden, 2004).

5.3 Conclusion

It may be concluded that, based on the discovery of the lactate shuttle, lactic acid can no longer be considered as a "dead-end" waste product, but should instead be seen as a central player in cellular, regional, and whole body metabolism.

5.3.1 Reliability: 1

5.3.2 Deficiencies: Not applicable, review report

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/05/21

Section A6.2 Metabolism

Annex Point IIA6.2

Materials and Methods	Not applicable (see remarks).
Results and discussion	Applicant's version adopted with minor correction: Figures 2 and 3: NADH is not consumed during conversion of lactate to pyruvate by mLDH as the direction of the arrows in figures 2 and 3 suggest, but is generated from NAD^+. Philp et al. (2005) concluded that "elevated lactate helps reduce glucose usage and glycogenolysis, minimising depletion of these stores as escalating acidosis reduces PKC (phophofructokinase) function." Furthermore, gluconeogenesis was increased under artificially elevated lactate levels during moderate exercise.
Conclusion	Other conclusions: Lactate is an integral part of normal mammalian metabolism. Physiological plasma levels in man range between 1 mM at rest and 10 mM during exercise. Monocarboxylate transport proteins facilitate the distribution of lactate between organs, cells and subcellular organelles. Cytosolic and mitochondrial lactate dehydrogenases convert lactate into pyruvate, producing NADH. Pyruvate can be transformed to oxaloacetate, which is utilised for gluconeogenesis via production of phosphoenolpyruvate by decarboxylation and phosphorylation. Alternatively, metabolites of pyruvate (oxaloacetate and acetyl-CoA) are consumed in the tricarboxylic (citric) acid cycle generating NADH and ATP, or pyruvate may be transaminated to the amino acid L-alanine. Increased cellular levels of lactate influence pathways of cellular metabolism, resulting in reduction of glycolysis and glycogenolysis (reducing the generation of pyruvate from other sources such as glucose) and in enhancement of gluconeogenesis.
Reliability	2
Acceptability	Acceptable with restrictions (see remarks)
Remarks	Review, no original data

	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.2 Metabolism

Annex Point IIA6.2

			Official use only
		1 REFERENCE	
1.1	**Reference**	Andersen, F.A. (1998). Report of the cosmetic ingredient review expert panel. Mutagenicity: Lactic acid. International Journal of Toxicology, volume 17. Supplement 1, p 124. Not GLP, published	X
1.2	**Data protection**	No	
1.2.1	Data owner	Not applicable	
1.2.2	Companies with letter of access	Not applicable	
1.2.3	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No, review article	
2.2	**GLP**	No, review article	
2.3	**Deviations**	Not applicable, review article	
		3 MATERIALS AND METHODS	
		Not applicable, review article	
		4 RESULTS AND DISCUSSION	
		Not applicable, review article	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Not applicable, review article	X
5.2	**Results and discussion**	In this review by the cosmetic ingredient review expert panel, the dermal absorption of lactic acid was discussed, as lactic acid is an ingredient in many topical applications. The *in vitro* dermal absorption of 5% lactic acid in 2% PEG-100 stearate and 1% laureth-4 was examined in human abdominal skin at pH 3 and 7. The total absorption was highest at lowest pH: 30.4% and 9.73% at pH 3 and 7, respectively. To determine the effect of vehicle and pH on the *in vitro* dermal absorption, several emulsions of lactic acid (w/o, o/w, and w/o/w) were applied to porcine skin. The absorption was highest in o/w emulsions, and lowest in w/o emulsions. When pH was decreased, the absorption was higher, up to 100% in 6 hr from the o/w emulsion. Finally, the percutaneous absorption of topically applied lactic acid (5%	X

Section A6.2 Metabolism

Annex Point IIA6.2

		in an oil-in-water cream) in rats was 50% after 3 days.	
5.3	**Conclusion**	The dermal absorption of lactic acid is highest in oily formulations, and at low pH. As a worst-case, a dermal absorption of 100% is used in the risk assessment.	X
5.3.1	Reliability	1, review prepared by the cosmetic ingredient review (CIR) expert panel	X
5.3.2	Deficiencies	Not applicable, review article	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/05/21
Materials and Methods	Studies on the dermal absorption of lactic acid formulations in human and pig skin ex vivo and rats in vivo were reviewed. No information on the technical product was provided.
Results and discussion	Applicant's version adopted with following amendments: Lactic acid is also known as mild exfoliant and used as skin peeling agent. This may further affect dermal absorption after repeated exposure. 5.2 From the original publication of Sah et al. (1998) it becomes clear that a dermal absorption of 100 % was not observed but a > 100 % increase of dermal absorption from ~7 % to ~32 %.
Conclusion	The dermal absorption of lactic acid is highest in oily formulations, and at low pH. Since dermal absorption values from 7 % to 50 % were observed dependent on formulation, a dermal absorption of 100 % is used in the risk assessment as a worst-case assumption.
Reliability	2
Acceptability	Acceptable with restrictions (see remarks)
Remarks	Review, no original data 1.1 Reference: According to the manuscript, page numbers are 1-241 (the mutagenicity part, p. 124, is not relevant for this section). <u>Other results:</u> 42 % conversion into CO2 following gavage application of 2 g/kg bw DL-lactic acid to male Fisher 344 rats within 6 hours. Volume of distribution of ~0.5 L/kg bw, turnover 2.3 g/kg bw/d and 88 % conversion into CO_2 following i.v. application of L(+) lactic acid in humans. 100 % oral absorption of sodium DL-lactate in dogs.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*

Section A6.2 Metabolism

Annex Point IIA6.2

Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.2 Metabolism

Annex Point IIA6.2

			Official use only
		1 REFERENCE	
1.1	**Reference**	Sah, A. Mukherjee, S. Wickett, R.R (1998) An in vitro study of the effects of formulation variables and product structure on percutaneous absorption of lactic acid. J. Cosmet. Sci. 49, 257-273 Not GPL, Published	
1.2	**Data protection**	No	
1.2.1	Data owner	Purac Biochem BV	X
1.2.2	Companies with letter of access	No	X
1.2.3	Criteria for data protection	Data on existing or new [a.s. / b.p.] to [maintain or vary a.s. Annex I/IA entry / vary conditions of a b.p.'s authorisation]	X
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No, Publication	
2.2	**GLP**	No, *Publication*	
2.3	**Deviations**	Not applicable, *Publication*	
		3 MATERIALS AND METHODS	
		L+[14C(u))] lactic acid, 150 mCi/mmol Synperonic PE/F127 Hpermer A60 Lactic acid Paraffin oil Propylene glycol Dermal penetration was studied on 3-4-week old female porcine dorsal skin, without adipose tissue and hair, thinned to 510 µm. 13 mm disks were mounted in flow-through cells. Viability was determined by transepidermal water loss measurements. Lactic acid was dissolved in oil-in-water, water-in-oil, and water-in-oil-in-wtaer emulsions, using appropriate surfactants and emulsification procedures. All test emulsions had a concentration of 8% lactic acid w/w. Emulsions were applied at two dose levels, viz. 2 µL / 0.64 cm^2 and 75 µL / 0.64 cm^2. Uptake of lactic acid into the skin layers and the receptor fluid (phosphate-buffered saline, pH 7.4, flow rate 5 mL/h) was studied for 6 hour penetration periods, for neat emulsions at pH 3.8 and 7, as well as emulsions at pH 3.8, with addition of 5% propylene glycol.	
		4 RESULTS AND DISCUSSION	
		Uptake from 2 µL o/w emulsion after 6 h pH 7: ca 7% in skin; 0.2% in receptor fluid.	

Section A6.2 Metabolism

Annex Point IIA6.2

		pH 3.8: ca. 25% in skin; 0.3% in receptor fluid. Uptake from 75 µL o/w emulsion after 6 h pH 7: ca 0.6%; 0.01% in receptor fluid. pH 3.8: ca. 0.95%; 0.01% in receptor fluid. Uptake from 2 µL o/w emulsion with 5% PG after 6 h pH 3.8: ca. 30% in skin; 0.7% in receptor fluid. Uptake from 75 µL o/w emulsion with 5% PG after 6 h pH 3.8: ca. 1.6%; 0.2% in receptor fluid. Penetration from water-in-oil and water-in-oil-in-water emulsions (2 µL, pH 3.8) is lower than from an oil-in-water emulsion.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Materials and methods appear appropriate for determining the dermal uptake of lactic acid from low concentration emulsions, as are encountered in cosmetics containing lactic acid as a relevant component.	
5.2	**Results and discussion**	It is clear that at low amounts of available lactic acid, the 6 hour potential dermal uptake from low concentration emulsions does not exceed 31%, at pH 3.8. Under these conditions propylene glycol enhances the uptake slightly. At higher doses, no significant effect of propylene glycol on dermal uptake percentage is observed. As such, it can be concluded that dermal uptake from large (‚infinite') amounts of lactic acid at high concentrations in aqueous solutions will not be higher than 31%.	
5.3	**Conclusion**	A worst case upper limit of the dermal uptake of lactic acid can be set at 31%	X
5.3.1	Reliability	1	X
5.3.2	Deficiencies	None	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/12/18
Materials and Methods	The applicant's version is acceptable with the following amendments: 1.2.1 Not applicable, publication 1.2.2 Not applicable, publication 1.2.3 Not applicable, publication
Results and discussion	Applicant's version is acceptable.
Conclusion	5.3 A worst case upper limit of the dermal uptake of lactic acid can be set at 32 % in pig skin.
Reliability	2 (reliable with restrictions, see remarks)
Acceptability	Acceptable

Section A6.2 Metabolism

Annex Point IIA6.2

Remarks	No guideline, non-GLP data, in part results are only reported in diagrams (exact values missing).
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6 Annex Point A6.3	Short-term repeated-dose toxicity	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	According to the 'Technical Guidance Document on data requirements' these test are used as a range-finding test and are not required when an adequate sub-chronic toxicity is available in a rodent. For lactic acid, a 13-week oral sub-chronic toxicity study was performed in rats. Furthermore, a chronic toxicity/carcinogenicity study was performed in rats. Lactic acid is a naturally occurring substance in the human body and in human food, and is also authorized to be used as a food additive. As the exposure due to the use of biocidal products will not substantially contribute to the total systemic exposure, no further repeated-dose studies are deemed necessary. An expert statement on the role of lactic acid in the human body, as well as its presence in food (both naturally and as a food additive) is presented in A6.2-01.	X
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2008/07/08	
Evaluation of applicant's justification	The 13-week oral sub-chronic toxicity study and the chronic toxicity /carcinogenicity study were performed using calcium lactate and lack some detail (published literature). Furthermore, it is not clear from the data which effects are due to high calcium uptake and which might be due to lactic acid. Thus, the data are of low reliability and are only in part relevant for lactic acid. Nonetheless, in light of the low toxicity of lactic acid and the high endogenous exposure the applicant's justification is acceptable.	
Conclusion	Applicant's justification is acceptable.	
Remarks	None	

Section A6	Short-term repeated-dose toxicity
Annex Point A6.3	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.4 Repeated dose toxicity

Annex Point
IIA6.3 / 6.4 / 6.5

13 weeks - rat

			Official use only
		1 REFERENCE	
1.1	**Reference**	Matsushima, Y., Onodera, H., Nagaoka, T., Todate, A., Shibutani, M., Maekawa, A., Kurokawa, Y., Hayashi, Y., 1989. Subchronic Oral Toxicity study of Calcium lactate in F344 Rats Bulletin of the National Institute of Hygienic Sciences, Tokyo (Eisei Shikenjo Hokuku) Vol. 107: pp 78-83.	
1.2	**Data protection**	No	
1.2.1	Data owner	Literature publication	
1.2.2	Companies with letter of access	No	
1.2.3	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not applicable, literature publication	
2.2	**GLP**	Not applicable, literature publication	
2.3	**Deviations**	Not applicable, literature publication	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Calcium lactate pentahydrate ($C_6H_{10}CaO_6 \cdot 5H_2O$ 308.30) In the current study calcium lactate dissolved in water was tested. As it is administered dissolved in water, the results of this study can be used for lactic acid.	
3.1.1	Lot/Batch number	Sample obtained from Musashino Chemical Inst. Ltd (Tokyo, Japan)	
3.1.2	Specification	Deviating from specification given in section 2 as follows Product contains calcium lactate at 97.0% to 101% when calculated as a dried product. Product was colourless and clear, pH 6.0-8.0; heavy metals (Pb) 20 µg/g maximum; alkaline metals and magnesium 1% maximum, arsenic < 4 µg/g maximum.	
3.1.2.1	**Description**	Odourless white powder or granules	
3.1.2.2	**Purity**	97.0 – 101.0 % when calculated as dried product	
3.1.2.3	**Stability**	Not reported	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	Male rats: SPF Female rats: F344/DuCrj	X
3.2.3	Source	Charles River Laboratories Japan, Inc.	

Section A6.4 Repeated dose toxicity

Annex Point IIA6.3 / 6.4 / 6.5

13 weeks - rat

3.2.4	Sex	Male and female	
3.2.5	Age/weight at study initiation	Five weeks old	X
3.2.6	Number of animals per group	Experiment I: 5 males and 5 females/group Experiment II: 5 male and 5 females/group Experiment III: 10 male/group	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Oral	
3.3.1	Duration of treatment	Experiment I: 13 weeks Experiment II: 20 weeks Experiment III: 8 weeks	
3.3.2	Frequency of exposure	Daily, ad libitum	
3.3.3	Postexposure period	No post-exposure period	
3.3.4	**Oral**		
3.3.4.1	**Type**	Experiment I: in drinking water Experiment II: in food Experiment III: no lactate, comparison of CRF-1 solid diet (used in experiment I) and B-blend power diet (used in experiment II) (both supplied by Oriental Yeast Co., Ltd.)	
3.3.4.2	**Concentration**	Experiment I: 0, 0.3, 0.6, 1.25, 2.5, and 5 % Experiment II: 0, 5, 10, 20, 30 % Experiment III: no lactate, comparison of diets	
3.3.4.3	**Vehicle**	Experiment I: Ion-exchanged water Experiment II: in standard blend of purified diet (B-blend powder diet, Oriental Yeast Co., Ltd.) Experiment III: no lactate, comparison of diets	
3.3.4.4	**Concentration in vehicle**	Experiment I: 0, 0.3, 0.6, 1.25, 2.5, and 5 % Experiment II: 0, 5, 10, 20, 30 % Experiment III: no lactate, comparison of diets	
3.3.4.5	**Total volume applied**	Ad libitum	
3.3.4.6	**Controls**	vehicle	
3.4	**Examinations**		
3.4.1	Observations	Weekly	
3.4.1.1	**Clinical signs**	Yes	

Section A6.4 Repeated dose toxicity

Annex Point IIA6.3 / 6.4 / 6.5

13 weeks - rat

3.4.1.2	**Mortality**	Yes
3.4.2	Body weight	Yes, weekly
3.4.3	Food consumption	Yes
3.4.4	Water consumption	Yes
3.4.5	Ophthalmoscopic examination	No
3.4.6	Haematology	Yes, number of animals: surviving animals time points: end of study Parameters: erythrocyte, leucocyte, haemoglobin, haematocrit, MCV.
3.4.7	Clinical Chemisty	Yes, number of animals: surviving animals time points: end of study Parameters: GOT, GPT, LDH, AIP, TTT, total billirubin., total cholesterol, TG, β-Lipo-protease, total protein, A/G, BUN, Creatinine, Uric acid, ZTT, γ-GTP, calcium,
3.4.8	Urinalysis	Yes, in experiment II number of animals: not specified time points: in the 18th week of administration Parameters: volume, calcium
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	Yes, organs (only reported when significant changes were observed): heart, brain.
3.5.2	Gross and histopathology	Yes, all dose groups/ high dose group and controls, other dose groups only if effects organs(only reported when abnormalities were observed): lymph nodes, Harderian gland, lungs, heart, grandular stomach, liver, spleen, kidney, testis, prostate gland, bone marrow.
3.5.3	Other examinations	Calcium deposit on the urinary tubule
3.5.4	Statistics	Not reported
3.6	**Further remarks**	Not applicable

4 RESULTS AND DISCUSSION

4.1	**Observations**	
4.1.1	Clinical signs	Experiment I: no abnormalities Experiment II: no abnormalities reported Experiment III: no abnormalities reported
4.1.2	Mortality	No mortality observed in all three experiments

Section A6.4 Repeated dose toxicity

Annex Point IIA6.3 / 6.4 / 6.5

13 weeks - rat

4.2	**Body weight gain**	Experiment I: Male rats in the 1.25 and 5% groups showed slight inhibition of weight gain, but this inhibition stayed within 10% of the control group. No significant difference was seen in the female rats between groups. Experiment II: Significant inhibition of body weight gain in both males and females in the highest dose group (30%), and in the males of the 20% group. Experiment III: Not reported	
4.3	**Food consumption and compound intake**	Experiment I: Average intake of drinking water was 75% of the control group in the highest dose (5%) and 88% in the 2.5% group. Total intake of test substance was calculated from the intake of drinking water. Experiment II: Not reported Experiment III: Not reported	X
4.4	**Ophtalmoscopic examination**	Not applicable	
4.5	**Blood analysis**		
4.5.1	Haematology	Experiment I: Variations observed in male rats could not be correlated with doses Experiment II: No correlation with doses was found Experiment III: Not reported	
4.5.2	Clinical chemistry	Experiment I: Slight increases in BUN and creatinine levels were observed in female rats in the 0.6, 1.25, 2.5, and 5% groups. Increases in LDH levels were observed in the 0.6, 1.25, 2.5, and 5% groups, and increases in GOT levels in the 1.25, 2.5, and 5% groups. In the females from all of those groups, slight correlation with doses was noted. Experiment II: Not reported Experiment III: Not reported	X
4.5.3	Urinalysis	Experiment I: Not reported. Experiment II: The urinary output of male rats was approximately 6 mL in two highest dose groups (20 en 30%), which was twice the amount of the control group (3 mL). In females, the urinary output was almost 5 mL in all groups. Calcium concentrations significantly increased with higher doses in both males and females, and correlated with the doses. Experiment III: Not reported	
4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	Heart weight was significantly lower in the 5% group of male rats, compared to the control group. Based on the body weight ratios, the brain weight was significantly lower in the 1.25% group of males.	

Section A6.4 Repeated dose toxicity

Annex Point IIA6.3 / 6.4 / 6.5

13 weeks - rat

4.6.2	Gross and histopathology	Experiment I: No severe toxicological findings were observed in any of the treated groups. Experiment II: Nephrocalcinosis was observed in all groups, including the control group, and an inverse dose-effect relation was observed with regard to the degree of its development. Experiment III: Nephrocalcinosis was found only in the group fed B-blend power diet (used in experiment II)	
4.7	**Other**	Not reported	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Experiment I: Six groups of rats (5 males and 5 females) were exposed to calcium lactate dissolved in the drinking water (ad libitum) at concentrations of 0, 0.3, 0.6, 1.25, 2.5, and 5% for 13 weeks. Experiment II: Five groups of rats (5 males and 5 females) were exposed to calcium lactate in the diet (ad libitum) at concentrations of 0, 5, 10, 20, or 30% calcium lactate. Experiment III: Two groups of ten male rats were each given a different diet, one group the diet used in experiment I (CRF-1 solid diet), and the other group the diet used in experiment II (β-blend powder diet).	
5.2	**Results and discussion**	Experiment I: No mortality was observed. Hematological and hematobiochemical studies showed slight increases in BUN, creatinine, LDH, and GOT in females, which could be correlated with the doses. However, pathohistologically, there were no findings supporting possible nephrotoxicity and/or hepatotoxicity.	X
		Experiment II: No mortality was observed. In the highest dose group, body weight gain was strongly reduced compared to the control group. Histological examination revealed nephrocalcinosis in all groups, including the control group, and an inverse dose-effect relation was observed with regard to the degree of its development.	
		Experiment III: Nephrocalcinosis was observed only in the group fed the diet used in experiment II (β-blend powder diet). It was concluded that the β-blend powder diet causes nephrocalcinosis due to a low Ca/P ratio. Exposure to calcium lactate in experiment II causes increases in the Ca/P ratio, resulting in increased nephrocalcinosis. In experiment I, the CRF-I diet was given, which contains a high Ca/P ratio, which explains why in experiment I no nephrocalcinosis was found. Nephrocalcinosis can therefore not be attributed to the exposure to calcium lactate.	X
5.3	**Conclusion**		
5.3.1	LO(A)EL	Not reported. Based on increased creatinine levels in blood, the LOAEL can be set at 0.6%. As no exact doses are mentioned in the publication, no exact LOAEL (mg/kg) can be set.	X
5.3.2	NO(A)EL	Not reported. Based on increased creatinine levels in blood, the NOAEL can be set at 0.3%. As no exact doses are mentioned in the publication, no exact NOAEL (mg/kg) can be set.	X

Section A6.4 Repeated dose toxicity

Annex Point IIA6.3 / 6.4 / 6.5

13 weeks - rat

5.3.3	Other	This study was used to determine the optimal dose for a long-term toxicity/carcinogenicity study. Based on the values obtained from Experiment I, 5 and 2.5% were used in this study (see A6.5-01 and A6.7-01)	
5.3.4	Reliability	2	
5.3.5	Deficiencies	Yes, study is not performed according to current guidelines. As it is a literature publication, the reporting is concise and raw data are missing. However, the study has been performed well and can be used for the purpose of this dossier. As calcium lactate was used, effects of calcium should also be taken into account.	X

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/06/30
Materials and Methods	3.2.2 F344/DuCrj (both sexes) 3.2.5 6 weeks at study begin
Results and discussion	The applicant's version is acceptable with the following amendment: 4.3 Experiment II: Food consumption in the high dose group was 65 % and 57 % of the food intake of control group for males and females, respectively. 4.5.2 The increases in clinical chemistry parameters were slight and not dose-dependent, except for LDH (see CA-table 1). 5.2 Hematological and hematobiochemical studies showed slight increases in BUN, creatinine, LDH, and GOT in females, which could not be correlated with the doses except for LDH. Experiment III: Exposure to calcium lactate in experiment II causes increases in the Ca/P ratio, resulting in decreased nephrocalcinosis.
Conclusion	LO(A)EL: 30 % lactic acid in food, ~12 g/kg bw/d NO(A)EL: 20 % lactic acid in food, ~ 8.5 g/kg bw/d
Reliability	2
Acceptability	Acceptable with restrictions
Remarks	The results of this study can used as a very rough approximation for a NOAEL for L(+) lactic acid because the effects observed (decrease in food consumption and body weight gain) might be due to high calcium intake, palatability problems and/or malabsorption due to local gastrointestinal irritation (provoked by calcium or lactate). Thus, in the view of the RMS, the study seems to be inadequate to use the obtained NOAEL for derivation of reference values.
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*

Section A6.4 Repeated dose toxicity

Annex Point IIA6.3 / 6.4 / 6.5

13 weeks - rat

Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Table 1. Serum biochemistry and hematology results (Exptl. I, male)

Dose (%)	Control	0.3	0.6	1.25	2.5	5
Effective No.	10	10	10	10	10	10
GOT(KU)	94.2±8.9	87.4±10.6	85.6±11.2	167.2±58.3*	83.4±6.7	96.2±4.6
GPT(KU)	28.8±4.3	31.2±2.6	28.6±3.0	27.4±2.9	30.0±3.8	26.2±3.6
LDH(WU)	102±313	512±349*	684±445	847±623	496±211*	1121±166
AlP(KAU)	12.1±0.9	12.1±0.8	12.8±0.6	12.7±0.8	12.6±0.7	13.1±0.5
TTT(SHU)	0.58±0.23	0.64±0.15	0.82±0.21	0.70±0.35	0.84±0.23	0.90±0.27
Total-bil.(mg/dl)	0.44±0.11	0.50±0.15	0.42±0.17	0.48±0.14	0.42±0.14	0.42±0.17
Total-cho.(mg/dl)	56.2±2.2	55.6±3.1	54.8±2.2	58.6±2.1	55.0±4.4	56.0±4.4
TG(mg/dl)	164±29	167±19	156±16	196±29	154±54	169±23
β-Lipo-pro.(mg/dl)	132±24	137±19	124±15	161±29	114±43	137±23
Total-pro.(g/dl)	7.20±0.14	7.30±0.07	7.08±0.08	7.12±0.13	6.96±0.23	6.92±0.13
A/G	1.54±0.05	1.50±0.07	1.54±0.11	1.50±0.07	1.58±0.08	1.58±0.10
BUN(mg/dl)	19.0±1.2	19.2±0.8	19.0±1.0	16.4±2.7	20.0±1.2	21.4±0.9*
Creat.(mg/dl)	0.58±0.05	0.54±0.05	0.48±0.04*	0.56±0.05	0.54±0.05	0.56±0.05
Uric acid(mg/dl)	1.76±0.59	1.54±0.15*	1.52±0.16*	1.72±0.17*	1.84±0.88	1.94±0.25
ZTT(KU)	0.56±0.08	0.50±0	0.56±0.05	0.66±0.11	0.50±0.10	0.64±0.05
γ-GTP(mu/ml)	1.60±0.54	1.60±0.54	1.60±0.54	1.40±0.54	1.40±0.54	2.40±0.89
Ca(mg/dl)	9.90±0.97	11.06±0.37*	10.80±0.07	11.16±0.82	11.54±0.52*	10.74±0.49
Erythrocyte($\times10^4$/mm^3)	951±31	975±19	951±31	942±14	943±59	910±76
Leucocyte($\times10^3$/mm^3)	95±12	74±15*	47±12**	51±7**	58±5**	60±3**
Hb.(g/dl)	175±3	175±7	164±5**	166±4**	178±9	198±38
Ht.(%)	52.0±1.0	50.8±0.4*	50.6±0.5*	50.8±0.4*	51.3±1.3	52.7±1.3
MCV(μ^3)	496±7	496±8	470±18*	478±9*	484±21	481±31

* : $p<0.05$ ** : $p<0.01$ Mean±SD

Table 2. Serum biochemistry and hematology results (Exptl. I, female)

Dose (%)	Control	0.3	0.6	1.25	2.5	5
Effective No.	10	10	10	10	10	10
GOT(KU)	74.0±6.7	77.0±7.9	74.4±3.4	85.0±8.3*	88.4±6.2**	90.0±6.0**
GPT(KU)	17.8±2.7	21.6±5.0	21.2±2.6	18.6±5.2	23.4±4.7	24.0±2.9**
LDH(WU)	267±179	473±227	586±221*	880±271**	889±403*	712±232**
AlP(KAU)	8.0±0.8	9.1±1.0	8.0±1.0	8.5±1.4	8.0±0.6	8.3±0.4
TTT(SHU)	0.74±0.13	0.88±0.42*	0.90±0.12	0.86±0.32	0.82±0.23	1.12±0.23*
Total-bil.(mg/dl)	0.58±0.08	0.46±0.18	0.54±0.19	0.62±0.14	0.42±0.13*	0.62±0.15
Total-cho.(mg/dl)	94.4±6.1	92.6±3.8	92.8±4.7	88.4±4.0	90.2±8.0	86.2±4.7*
TG(mg/dl)	114±18	120±35	116±33	110±24	119±14	147±29
β-Lipo-pro.(mg/dl)	96±20	105±36	95±32	91±23	108±20	131±31
Total-pro.(g/dl)	7.02±0.10	7.04±0.16	6.96±0.16	7.16±0.23	7.10±0.12	7.08±0.26
A/G	1.66±0.05	1.64±0.08	1.64±0.08	1.60±0.10	1.62±0.13	1.54±0.23*
BUN(mg/dl)	18.2±0.8	18.6±0.9	18.6±2.1	21.2±1.5**	22.0±1.4**	21.0±4.0
Creat.(mg/dl)	0.46±0.05	0.50±0.10	0.54±0.05*	0.54±0.05*	0.56±0.05*	0.66±0.05**
Uric acid(mg/dl)	1.96±0.15	1.96±0.28	2.16±0.19	2.16±0.08*	2.26±0.40	2.34±0.20*
ZTT(KU)	0.58±0.13	0.64±0.11	0.74±0.18	0.68±0.10	0.70±0.24	0.88±0.13**
γ-GTP(mu/ml)	1.60±0.54	2.20±0.44	2.00±0.70	2.20±0.44	1.80±0.44	2.00±0.70
Ca(mg/dl)	10.48±0.76	10.38±0.81	10.88±0.66	10.66±0.52	10.06±0.50	10.24±0.23*
Erythrocyte($\times10^4$/mm^3)	912±24	894±33	907±17	905±12	897±18	916±46
Leukocyte($\times10^3$/mm^3)	50±8	58±8	41±6	59±9	49±9	74±10**
Hb.(g/dl)	154±5	161±9	162±4	164±3	161±4	164±11
Ht.(%)	53.6±0.5	54.0±0.7	53.6±0.5	53.6±0.5	53.8±0.5	53.6±0.5
MCV(μ^3)	488±12	482±16	486±8	485±7	482±9	491±24

* : $p<0.05$ ** : $p<0.01$ Mean±SD

Section A6 Annex Point A6.4	Subchronic toxicity	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	According to the 'Technical Guidance Document on data requirements' subchronic toxicity should be available in a rodent and a non-rodent. For lactic acid, a 13-week oral sub-chronic toxicity study was performed in rats. Furthermore, a chronic toxicity/carcinogenicity study was performed in rats. Lactic acid is a naturally occurring substance in the human body and in human food, and is also authorized to be used as a food additive. As the exposure due to the use of biocidal products will not substantially contribute to the total systemic exposure, no further repeated-dose studies are deemed necessary. An expert statement on the role of lactic acid in the human body, as well as its presence in food (both naturally and as a food additive) is presented in A6.2-01.	X
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2008/07/09	
Evaluation of applicant's justification	The 13-week oral sub-chronic toxicity study and the chronic toxicity /carcinogenicity study were performed using calcium lactate and lack some detail (published literature). Furthermore, it is not clear from the data which effects are due to high calcium uptake and which might be due to lactic acid. Thus, the data are of low reliability and are only in part relevant for lactic acid. Nonetheless, in light of the low toxicity of lactic acid and the high endogenous exposure, the applicant's justification is acceptable.	
Conclusion	Applicant's justification is acceptable.	
Remarks	None	

Section A6 Annex Point A6.4	Subchronic toxicity
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.5 Repeated dose toxicity

Annex Point IIA6.3 / 6.4 / 6.5

Long-term toxicity, oral, rat

			Official use only
		1 REFERENCE	
1.1	**Reference**	Maekawa, A., Matsushima, H., Onodera, H., Shibutani, M., Yoshida, J., Kodama, Y., Kurokawa, Y., Hayashi, Y., 1991. Long-term carcinogenicity/carcinogenicity study of calcium lactate in F344 rats Food and Chemical Toxicology, Vol. 29, No. 9: pp 589-594.	
1.2	**Data protection**	No	
1.2.1	Data owner	Published literature	
1.2.2	Companies with letter of access	-	
1.2.3	Criteria for data protection	Not applicable.	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not applicable	
2.2	**GLP**	Not applicable	
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Calcium lactate (CAS 814-80-2)	
		In the current study calcium lactate dissolved in water was tested. As it is administered dissolved in water, the results of this study can be used for lactic acid.	X
3.1.1	Lot/Batch number	Commercial sample obtained from Musashino Chemical Inst. Ltd (Tokyo, Japan)	
3.1.2	Specification	Deviating from specification given in section 2 as follows	
		Calcium lactate was dissolved in distilled water	
		Clarity and colour of solution: colourless and clear, pH 6.0-8.0; heavy metals (Pb) < 20 µg/g; alkaline metals and magnesium < 1%, arsenic < 4 µg/g; volatile fatty acids: no odour of fatty acids; loss on drying 25.0 – 30.0%.	
3.1.2.1	**Description**	Odourless white powder	
3.1.2.2	**Purity**	97.0 – 101.0 %	
3.1.2.3	**Stability**	Not reported	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	SPF Fischer (F344)	
3.2.3	Source	Charles River Japan Inc., Kanagawa, Japan	
3.2.4	Sex	Male and female	

Section A6.5 Repeated dose toxicity

Annex Point IIA6.3 / 6.4 / 6.5

Long-term toxicity, oral, rat

3.2.5	Age/weight at study initiation	6 weeks / 90 to 120 grams
3.2.6	Number of animals per group	50 males and 50 females / group
3.2.7	Control animals	Yes
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of treatment	104 weeks
3.3.2	Frequency of exposure	Daily
3.3.3	Postexposure period	9 weeks recovery period
3.3.4	**Oral**	
3.3.4.1	**Type**	In drinking water
3.3.4.2	**Concentration**	0, 2.5 or 5% in drinking water (distilled water)
3.3.4.3	**Vehicle**	Drinking water
3.3.4.4	**Concentration in vehicle**	0, 2.5 or 5% in drinking water
3.3.4.5	**Total volume applied**	Not applicable
3.3.4.6	**Controls**	Drinking water without test substance
3.4	**Examinations**	
3.4.1	Observations	Daily
3.4.1.1	**Clinical signs**	Yes, daily
3.4.1.2	**Mortality**	Yes, daily
3.4.2	Body weight	Yes, once a week for the first 13 weeks, and every 4 weeks thereafter
3.4.3	Food consumption	Not reported
3.4.4	Water consumption	Yes, three times a week
3.4.5	Ophthalmoscopic examination	Not reported
3.4.6	Haematology	Yes on all surviving rats at week 113
		No details reported
3.4.7	Clinical Chemisty	Yes, on all surviving rats at week 113
		No details reported

Section A6.5 Repeated dose toxicity

Annex Point IIA6.3 / 6.4 / 6.5

Long-term toxicity, oral, rat

3.4.8	Urinalysis	Not reported
3.5	**Sacrifice and pathology**	
3.5.1	Organ Weights	Yes on all surviving rats at week 113 Including kidney, brain
3.5.2	Gross and histopathology	Yes on all surviving rats at week 113 Including pituitary gland, thyroid gland, adrenal gland, pancreas, haematopoetic organs, testis, prostate, mammary gland, uterus, vagina, ovary, lung, heart, tongue, forestomach, large instestine, liver, kidney, urinary bladder, skin/subcutis, preputial/chtoral gland, brain, thoracic cavity and., abdominal cavity
3.5.3	Other examinations	Carcinogenicity: see under A6.7
3.5.4	Statistics	Statistical analyses were performed using Fisher's exact probability test and/or the chi-square test. Also the age-adjusted statistical test recommended by Peto et al (1980) was used.
3.6	**Further remarks**	None

4 RESULTS AND DISCUSSION

4.1	**Observations**	
4.1.1	Clinical signs	Results not reported.
4.1.2	Mortality	First mortalities occurred after 56 weeks. For females the mortality rate in the highest dose group (5%) was slightly higher than those in the other two groups; not statistically significant.
4.2	**Body weight gain**	A dose-dependent inhibitory effect on the growth of rats was observed. Compared with the controls a 13% decrease in body-weight gain was observed in both male and female rats of the high-dose group (5%).
4.3	**Food consumption and compound intake**	Not reported
4.4	**Ophtalmoscopic examination**	Not reported
4.5	**Blood analysis**	
4.5.1	Haematology	No specific dose related changes were observed
4.5.2	Clinical chemistry	No specific dose related changes were observed
4.5.3	Urinalysis	Not reported

Section A6.5 Repeated dose toxicity

Annex Point IIA6.3 / 6.4 / 6.5

Long-term toxicity, oral, rat

4.6	**Sacrifice and pathology**		
4.6.1	Organ weights	Females in the high dose group exhibited slightly but significantly higher kidney weights compared with controls. However, histologically there was no difference in the severity of chronic nephropaty between different groups. No toxic lesions were observed in the kidney. A significant dose-dependent increase in relative brain weights was observed for both male and female rats, although no histological change was detected.	
4.6.2	Gross and histopathology	A number of non-neoplastic lesions (e.g. myocardial fibrosis, bile-duct proliferation, hepatic microgranulomas and chronic nephropathy) were observed in all groups.	
4.7	**Other**	None	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Published article on a long term carcinogenicity study performed by the National Institute of Hygiene Sciences in Tokyo, Japan. No reference is made to a specific test guideline (i.e. OECD), but study resembles OECD guidelines 453. However, no intermediate examinations are reported. It is not clear if these have been performed. All reported endpoints were examined at termination of the study.	
5.2	**Results and discussion**	No clear toxic lesion could be attributed to long-term exposure to calcium lactate. No significant dose-related increase was found in the incidences of tumours in any organ or tissue.	
5.3	**Conclusion**	The results indicate that calcium lactate had neither toxic nor carcinogenic activity in F344 rats.	
5.3.1	LO(A)EL	Not applicable	
5.3.2	NO(A)EL	No adverse effects were observed at the highest dose level. Therefore the NOAEL is > 5% (in drinking water).	X
		In the article the mean total calcium lactate intake (in grams/rat) is calculated. The 5% dose corresponds with 6254 g/ rat for male rats and 4121 g/rat for female rats. (over 104 weeks? Thus per day: 8.6 g/day (male) or 5.6 g/day (female)	X
5.3.3	Other		
5.3.4	Reliability	2	
5.3.5	Deficiencies	Yes, study is not performed according to current guidelines. As it is a literature publication, the reporting is concise and raw data are missing. However, the study has been performed well and can be used for the purpose of this dossier. As calcium lactate was used, effects of calcium should also be taken into account.	

Evaluation by Competent Authorities
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
EVALUATION BY RAPPORTEUR MEMBER STATE

Section A6.5 Repeated dose toxicity

Annex Point IIA6.3 / 6.4 / 6.5

Long-term toxicity, oral, rat

Date	2008/07/16
Materials and Methods	3.1 The applicant's version is acceptable with the following amendment: As calcium lactate is administered dissolved in water, the results of this study can partly be used for lactic acid considering also calcium effects.
Results and discussion	Applicant's version is acceptable.
Conclusion	LO(A)EL: 5 % calcium lactate in drinking water, based on 13 % decreased decrease in body weight gain NO(A)EL: 2.5 % calcium lactate in drinking water In the article the mean total calcium lactate intake (in grams/rat) is calculated. The 5 % dose corresponds with 625.4 g/ rat for male rats and 412.1 g/rat for female rats. This is per day approx. 880 mg/kg bw/d (male) or approx. 930 mg/kg bw/d (female). 2.5 % intake is estimated to be approx. 464 mg/kg bw/d (male) or 535 mg/kg bw/d (female).
Reliability	2
Acceptability	Acceptable with restrictions
Remarks	The results of this study can only be used as a very rough approximation for a NOAEL for L(+) lactic acid because the effects observed (decrease in food consumption and body weight gain) might be due to high calcium intake, low water/food intake (no data presented in the publication) and/or malabsorption due to local gastrointestinal irritation (provoked by calcium or lactate). Thus, in the view of the RMS, the study seems to be inadequate to use the obtained NOAEL for derivation of reference values.

	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6 Annex Point A6.5	Chronic toxicity	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	According to the 'Technical Guidance Document on data requirements' chronic toxicity should be available in a rodent and one other mammalian species. For lactic acid, a chronic toxicity/carcinogenicity study was performed in rats. Lactic acid is a naturally occurring substance in the human body and in human food, and is also authorized to be used as a food additive. As the exposure due to the use of biocidal products will not substantially contribute to the total systemic exposure, no further repeated-dose studies are deemed necessary. An expert statement on the role of lactic acid in the human body, as well as its presence in food (both naturally and as a food additive) is presented in A6.2-01.	X
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2008/07/09	
Evaluation of applicant's justification	The chronic toxicity /carcinogenicity study was performed using calcium lactate and lacks some detail (published literature). Furthermore, it is not clear from the data which effects are due to high calcium uptake and which might be due to lactic acid. Thus, the data are of low reliability and are only in part relevant for lactic acid. Nonetheless, in the light of the low toxicity of lactic acid and the high endogenous exposure the applicant's justification is acceptable.	
Conclusion	Applicant's justification is acceptable.	
Remarks	None	

Section A6 Annex Point A6.5	Chronic toxicity
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.6.1/6.6.2/ 6.6.3

Genotoxicity in vitro

Ames test

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3

			Official use only
		1 REFERENCE	
1.1	**Reference**	Al-Ani, F.Y., Al-Lami, S.K. (1988) Absence of mutagenic activity of acidity regulators in the Ames Salmonella/microsome test Mutation Research, 206, p. 467-470 Not GLP, published	
1.2	**Data protection**	No	
1.2.1	Data owner	Not applicable	
1.2.2	Companies with letter of access	Not applicable	
1.2.3	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No, method comparable to OECD guidelines (Standard plate incorporation assay (Maron and Ames, 1983))	X
2.2	**GLP**	No, not common to report in literature	
2.3	**Deviations**	Not applicable	X
		3 MATERIALS AND METHODS	
3.1	**Test material**	Lactic acid and 3 other acidity regulators (andryhous citric acid, phosphoric acid, and malic acid)	
3.1.1	Lot/Batch number	Not reported	
3.1.2	Specification	Lactic acid obtained from BDH	
3.1.2.1	**Description**	Not reported	
3.1.2.2	**Purity**	Not reported	
3.1.2.3	**Stability**	Not reported	
3.2	**Study Type**	Standard plate incorporation assay (Maron and Ames, 1983)	
3.2.1	Organism/cell type	*Salmonella typhimurium* strains TA97, TA98, TA100, and TA104.	
3.2.2	Deficiencies / Proficiencies	Not applicable	
3.2.3	Metabolic activation system	S9 mix (rat liver homogenate S9 fraction prepared as in Ames et al. (1975)	
3.2.4	Positive control	2-aminoanthracene (2-AA)	

Section A6.6.1/6.6.2/ 6.6.3	Genotoxicity in vitro *Ames test*
Annex Point IIA6.6.1 / 6.6.2 / 6.6.3	

3.3	**Administration / Exposure; Application of test substance**		
3.3.1	Concentrations	0, 0.5, 1.0, 2.0 µL/plate (all concentrations were tested in triplicate)	
3.3.2	Way of application	According to Maron and Ames (1983)	
3.3.3	Pre-incubation time	According to Maron and Ames (1983)	
3.3.4	Other modifications	Not mentioned	
3.4	**Examinations**	Mutagenic activity (His^+ revertants)	
3.4.1	Number of cells evaluated	Not applicable	
		RESULTS AND DISCUSSION	
3.5	**Genotoxicity**		
3.5.1	without metabolic activation	No	
3.5.2	with metabolic activation	No	
3.6	**Cytotoxicity**	No	
		4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	Standard plate incorporation assay (Maron and Ames, 1983)	
4.2	**Results and discussion**	No genotoxicity detected	
4.3	**Conclusion**	Lactic acid does not have genotoxic properties	X
4.3.1	Reliability	2, study conducted in compliance with generally accepted scientific principles	
4.3.2	Deficiencies	No	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/01/22

Section A6.6.1/6.6.2/ 6.6.3 — Genotoxicity in vitro

Ames test

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3

Materials and Methods	2.1 Similar to OECD test guideline 471 2.3 Deviations from OECD test guideline 471: selection of strains (TA1535 missing, TA104 instead of TA102 or E. coli WP2); 2-Aminoanthracene as sole positive control
Results and discussion	Applicant's version is acceptable. For results see CA-Table 1
Conclusion	Lactic acid revealed no genotoxic properties in the Ames test under the conditions tested.
Reliability	2
Acceptability	Acceptable
Remarks	Deviations from current OECD test guideline 471 do not affect the overall integrity of the test.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

CA-table 1:

Lactic acid concentration (µl/plate)	*S. typhimurium* strain							
	TA97		TA98		TA100		TA104	
	+S9	−S9	+S9	−S9	+S9	−S9	+S9	−S9
0	47.0 ± 1.73	27.0 ± 1.73	56.3 ± 1.15	44.0 ± 2.64	167.6 ± 2.51	139.3 ± 1.52	449.3 ± 8.14	379.3 ± 9.29
0.5	50.3 ± 1.52	25.6 ± 1.15	57.6 ± 2.51	46.6 ± 2.08	168.0 ± 5.29	149.3 ± 2.51	491.6 ± 7.63	448.3 ± 3.51
1.00	49.0 ± 1.00	29.3 ± 0.57	53.0 ± 2.64	49.3 ± 0.57	160.0 ± 2.00	143.3 ± 2.88	509.3 ± 9.01	454.3 ± 5.13
2.00	50.3 ± 0.57	25.6 ± 2.08	51.3 ± 1.15	49.3 ± 2.51	143.0 ± 2.64	122.0 ± 1.00	478.3 ± 10.40	426.0 ± 7.63
2-AA (10 µg/plate)	442.6 ± 2.30	32.0 ± 2.00	499.3 ± 6.11	53.3 ± 1.15	557.3 ± 6.42	154.3 ± 0.57	992.3 ± 4.93	688.0 ± 7.21

Data represent means of 3 plates.

Section A6.6.1/6.6.2/ 6.6.3

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3

Genotoxicity in vitro

Ames test and chromosomal aberration test

			Official use only
		1 REFERENCE	
1.1	**Reference**	Ishidate, M. Jr., Sofuni, T., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., Matsuoka, A. (1984) Primary mutagenicity screening of food additivies currently used in Japan Fd Chem. Toxic., Vol. 22, No. 8, pp. 623-636 Not GLP, published	
1.2	**Data protection**	No	
1.2.1	Data owner	Not applicable	
1.2.2	Companies with letter of access	Not applicable	
1.2.3	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No	X
2.2	**GLP**	No, not common to report in literature	
2.3	**Deviations**	Not applicable	X
		3 MATERIALS AND METHODS	
3.1	**Test material**	Lactic acid and 241 other food additives	
3.1.1	Lot/Batch number	Not reported	
3.1.2	Specification	Not reported	
3.1.2.1	**Description**	Not reported	
3.1.2.2	**Purity**	90.5%	
3.1.2.3	**Stability**	Not reported	
3.2	**Study Type**	Standard plate incorporation assay (Maron and Ames, 1983) and chromosomal aberration tests in vitro	
3.2.1	Organism/cell type	Ames test: *Salmonella typhimurium* strains TA92, TA1535, TA100, and TA1537, TA94, and TA98. Chromosomal aberration test: Chinese hamster fibroblast cell line	
3.2.2	Deficiencies / Proficiencies	Not applicable	
3.2.3	Metabolic activation system	Ames test:: S9 mix (rat liver microsome fraction) Chromosomal aberration test: no metabolic activation system applied	
3.2.4	Positive control	No	

Section A6.6.1/6.6.2/ 6.6.3

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3

Genotoxicity in vitro

Ames test and chromosomal aberration test

3.3	**Administration / Exposure; Application of test substance**		
3.3.1	Concentrations	Ames test: maximum dose: 10 mg/plate Chromosomal aberration test: maximum dose: 1.0 mg/mL	
3.3.2	Way of application	Ames test: dissolved in phosphate buffer Chromosomal aberration test: dissolved in physiological saline	
3.3.3	Pre-incubation time	Ames test: pre-incubation with both the test sample and the S-9 mix for 20 min at 37°C before plating Chromosomal aberration test: no pre-incubation	
3.3.4	Other modifications	Not applicable	
3.4	**Examinations**	Ames test: mutagenic activity (His^+ revertants) Chromosomal aberration test: incidence of polyploidy cells and cells with structural chromosomal aberrations (chromatid or chromosome gaps, breaks, exchanges, ring formations, fragmentations and others)	
3.4.1	Number of cells evaluated	Ames test: not applicable Chromosomal aberration test: a hundred well-spread metaphases	
		RESULTS AND DISCUSSION	
3.5	**Genotoxicity**		
3.5.1	without metabolic activation	No	
3.5.2	with metabolic activation	No	
3.6	**Cytotoxicity**	No	
		4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	Standard plate incorporation assay (Maron and Ames, 1983) and chromosomal aberration tests in vitro	
4.2	**Results and discussion**	No genotoxicity detected	
4.3	**Conclusion**	Lactic acid does not have genotoxic properties	X
4.3.1	Reliability	2, study conducted in compliance with generally accepted scientific principles	
4.3.2	Deficiencies	No	

Section A6.6.1/6.6.2/ 6.6.3

Annex Point IIA6.6.1 / 6.6.2 / 6.6.3

Genotoxicity in vitro

Ames test and chromosomal aberration test

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2009/01/22
Materials and Methods	Applicant's version is acceptable.
Results and discussion	Applicant's version is acceptable.
Conclusion	Lactic acid revealed no genotoxic properties in the Ames test and a chromosomal aberration assay under the conditions tested.
Reliability	2
Acceptability	Acceptable
Remarks	No detailed data (e.g. no. of revertants) are reported.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.7 Carcinogenicity

Annex Point IIA6.7

Oral, rat

			Official use only
		1 REFERENCE	
1.1	**Reference**	Maekawa, A., Matsushima, H., Onodera, H., Shibutani, M., Yoshida, J., Kodama, Y., Kurokawa, Y., Hayashi, Y., 1991. Long-term carcinogenicity/carcinogenicity study of calcium lactate in F344 rats. Food and Chemical Toxicology, Vol. 29, No. 9: pp 589-594	
1.2	**Data protection**	No	
1.2.1	Data owner	Published literature	
1.2.2	Companies with letter of access	-	
1.2.3	Criteria for data protection	Not applicable	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Not applicable	
2.2	**GLP**	Not applicable	
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Calcium lactate (CAS 814-80-2), In the current study calcium lactate dissolved in water was tested. As it is administered dissolved in water, the results of this study can be used for lactic acid.	X
3.1.1	Lot/Batch number	Commercial sample obtained from Musashino Chemical Inst. Ltd (Tokyo, Japan)	
3.1.2	Specification	*Deviating from specification given in section 2 as follows* Calcium lactate was dissolved in distilled water Clarity and colour of solution: colourless and clear, pH 6.0-8.0; heavy metals (Pb) < 20 µg/g; alkaline metals and magnesium < 1%, arsenic < 4 µg/g; volatile fatty acids: no odour of fatty acids; loss on drying 25.0 – 30.0%.	
3.1.2.1	**Description**	Odourless white powder	
3.1.2.2	**Purity**	97.0 – 101.0 %	
3.1.2.3	**Stability**	Not reported	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	SPF Fischer (F344)	
3.2.3	Source	Charles River Japan Inc., Kanagawa, Japan	
3.2.4	Sex	Male and female	

Section A6.7 Carcinogenicity

Annex Point IIA6.7

Oral, rat

3.2.5	Age/weight at study initiation	6 weeks / 90 to 120 grams	
3.2.6	Number of animals per group	50 males and 50 females / group	
3.2.6.1	**at interim sacrifice**	No scheduled sacrifice, autopsy was immediately performed on rats that died during the study	
3.2.6.2	**at terminal sacrifice**	Autopsy on all animals by the end of the study	
3.2.7	Control animals	Yes	
3.3	**Administration/ Exposure**	Oral	
3.3.1	Duration of treatment	104 weeks	
3.3.2	Interim sacrifice(s)	No scheduled sacrifices	
3.3.3	Final sacrifice	At week 113	
3.3.4	Freqency of exposure	daily	
3.3.5	Postexposure period	9 weeks recovery period	
		Oral	
3.3.6	Type	In drinking water	
3.3.7	Concentration	0, 2.5 or 5% in drinking water (distilled water)	
3.3.8	Vehicle	Drinking water	
3.3.9	Concentration in vehicle	0, 2.5 or 5% in drinking water	
3.3.10	Total volume applied	*Ad libitum*	
3.3.11	Controls	Drinking water only	
3.4	**Examinations**		
3.4.1	Body weight	Yes, once a week for the first 13 weeks, and every 4 weeks thereafter	
3.4.2	Food consumption	Not reported	
3.4.3	Water consumption	Yes, three times a week	
3.4.4	Clinical signs	Yes, daily	
3.4.5	Makroskopic investigations	Yes	
3.4.6	Ophthalmoscopic examination	Not reported	
3.4.7	Haematology	Yes/No	Yes
		Number of animals:	All animals
		Time points:	End of study

Section A6.7 Carcinogenicity

Annex Point IIA6.7 *Oral, rat*

		Parameters:	No details reported
		Other:	-
3.4.8	Clinical Chemistry		Yes
		Number of animals:	All animals
		Time points:	End of study
		Parameters:	No details reported
		Other	-
3.4.9	Urinalysis	Yes/No	Not reported
		Number of animals:	-
		Time points:	-
		Parameters:	-
		Other	-
3.4.10	Pathology	Yes	
3.4.10.1	**Organ Weights**	Yes/No	Yes
		from:	All surviving animals, at terminal sacrifice
		Organs:	Including kidney, brain
			Other
3.4.11	Histopathology	Yes/No	Yes
		from:	All dose groups
		from:	All surviving animals
		Organs:	Including pituitary gland, thyroid gland, adrenal gland, pancreas, haematopoetic organs, testis, prostate, mammary gland, uterus, vagina, ovary, lung, heart, tongue, forestomach, large instestine, liver, kidney, urinary bladder, skin/subcutis, preputial/chtoral gland, brain, thoracic cavity and., abdominal cavity
			Other
3.4.12	Other examinations	Not applicable.	
3.5	**Statistics**	Statistical analyses were performed using Fisher's exact probability test and/or the chi-square test.	
		Also the age-adjusted statistical test recommended by Peto et al (1980) was used.	
3.6	**Further remarks**	None	

RESULTS AND DISCUSSION

3.7 Body weight

A dose-dependent inhibitory effect on the growth of rats was observed. Compared with the controls a 13% decrease in body-weight gain was observed in both male and female rats of the high-dose group (5%).

Section A6.7 Carcinogenicity

Annex Point IIA6.7

Oral, rat

3.8	**Food consumption**	Not reported	
3.9	**Water consumption**	Daily water consumption was almost constant in all groups of both sexes.	
3.10	**Clinical signs**	Results not reported (but daily observations were made)	
3.11	**Macroscopic investigations**	No effects reported	
3.12	**Ophthalmoscopic examination**	Not reported	
3.13	**Haematology**	No specific dose related changes were observed	
3.14	**Clinical Chemistry**	No specific dose related changes were observed	
3.15	**Urinalysis**	Not reported	
3.16	**Pathology**	No effects reported	
3.17	**Organ Weights**	Females in the high dose group exhibited slightly but significantly higher kidney weights compare with controls. However, histologically there was no difference in the severity of chronic nephropaty between different groups. No toxic lesions were observed in the kidney. A significant dose-dependent increase in relative brain weights was observed for both male and female rats, although no histological change was detected.	
3.18	**Histopathology**	Histologically, all the tumours observed in this experiment were similar to those know to occur spontaneously in F34 rats. None of the experimental groups showed a significant increase in the incidence of any specific tumour	
3.19	**Other examinations**	Not applicable	
3.20	**Time to tumours**	Not applicable, exposure by drinking water	
3.21	**Other**	Not applicable	
		4 APPLICANT'S SUMMARY AND CONCLUSION	
4.1	**Materials and methods**	Published article on a long term carcinogenicity study performed by the National Institute of Hygiene Sciences in Tokyo, Japan. No reference is made to a specific test guideline (i.e. OECD), but study resembles OECD guideline 453. No intermediate examinations are reported, all reported endpoints were examined at termination of the study.	
4.2	**Results and discussion**	No clear toxic lesion was specifically caused by long-term exposure to calcium lactate. No significant dose-related increase was found in the incidences of tumours in any organ or tissue..	
4.3	**Conclusion**	The results indicated that calcium lactate had neither toxic nor carcinogenic activity in F344 rats	X
4.3.1	Reliability	2	
4.3.2	Deficiencies	Yes, study is not performed according to current guidelines. As it is a literature publication, the reporting is concise and raw data are missing. However, the study has been performed well and can be used for the purpose of this dossier. As calcium lactate was used, effects of calcium should also be taken into account.	

Section A6.7 Carcinogenicity

Annex Point IIA6.7 *Oral, rat*

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/07/16
Materials and Methods	3.1 The applicant's version is acceptable with the following amendment: As calcium lactate is administered dissolved in water, the results of this study can partly be used for lactic acid considering also calcium effects.
Results and discussion	Applicant's version is acceptable.
Conclusion	Carcinogenic LO(A)EL: > 5 % calcium lactate in drinking water, Carcinogenic NO(A)EL: 5 % calcium lactate in drinking water (highest dose tested) In the article the mean total calcium lactate intake (in grams/rat) is calculated. The 5 % dose corresponds with 625.4 g/ rat for male rats and 412.1 g/rat for female rats for 104 weeks. This are per day ~880 mg/kg bw/d (male) or ~ 930 mg/kg bw/d (female).
Reliability	2
Acceptability	Acceptable with restrictions
Remarks	None
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6 Annex Point A6.7	Carcinogenicity	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	According to the 'Technical Guidance Document on data requirements' carcinogenicity should be available in a rodent and one other mammalian species. For lactic acid, a chronic toxicity/carcinogenicity study was performed in rats. Lactic acid is a naturally occurring substance in the human body and in human food, and is also authorized to be used as a food additive. As the exposure due to the use of biocidal products will not substantially contribute to the total systemic exposure, no further carcinogenicity studies are deemed necessary. An expert statement on the role of lactic acid in the human body, as well as its presence in food (both naturally and as a food additive) is presented in A6.2-01.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2008/07/08	
Evaluation of applicant's justification	The chronic toxicity /carcinogenicity study were performed using calcium lactate and lack some detail (published literature). Furthermore, it is not clear from the data which effects are due to high calcium uptake and which might be due to lactic acid. Thus, the data are of low reliability and are only in part relevant for lactic acid. Nonetheless, in the light of the low toxicity of lactic acid and the high endogenous exposure the applicant's justification for the missing study in a second species is acceptable.	
Conclusion	Applicant's justification is acceptable.	
Remarks	None	

Section A6 Annex Point A6.7	Carcinogenicity
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.8.1 Teratogenicity Study

Annex Point IIA6.8.1 *Developmental toxicity in the mouse*

			Official use only
		1 REFERENCE	
1.1	**Reference**	*Colomina, M.T, Gomez, M., Domingo, J.L., Llobet, J.M., Corbella, J. (1992)* *Concurrent ingestion of lactate and aluminium can result in developmental toxicity in mice* *Res. Commun. Chem. Pathol. Pharmacol. Vol. 77, No 1, pp. 95-108* *Not GLP, Published*	
1.2	**Data protection**	No	
1.2.1	Data owner	*Purac Biochem*	X
1.2.2	Companies with letter of access	*Not applicable*	
1.2.3	Criteria for data protection	No data protection claimed	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No	
2.2	**GLP**	No, not common to report in literature	
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	*Aluminium hydroxide ($Al(OH)_3$) ; lactic acid; aluminium lactate.*	
3.1.1	Lot/Batch number	*Not available. Suppliers were Merck (Darmstadt) and Riedel-de Haën (Seelze).*	
3.1.2	Specification	*Not given*	
3.1.2.1	Description	*Not applicable*	
3.1.2.2	Purity	*Not given*	
3.1.2.3	Stability	*No remarks.*	
3.2	**Test Animals**		
3.2.1	Species	Mouse	
3.2.2	Strain	Swiss albino (CD-1)	
3.2.3	Source	Interfauna Iberica	
3.2.4	Sex	Females (dams) exposed, sires only used for producing offspring, not exposed; offspring of both sexes.	
3.2.5	Age/weight at study initiation	28-32 g	
3.2.6	Number of animals per group	*Control: 13* *$Al(OH)_3$: 11* *$Al(OH)_3$ + lactic acid: 13* *Aluminium lactate: 10* *Lactic acid: 12*	

Section A6.8.1 Teratogenicity Study

Annex Point IIA6.8.1 *Developmental toxicity in the mouse*

3.2.7	Control animals	Yes	
3.2.8	Mating period	Not specified (until gestation).	
3.3	**Administration/ Exposure**	Oral, by gavage	
3.3.1	Duration of exposure		
		mouse: day 6-15 post mating	
3.3.2	Postexposure period	3 days (dams were killed on gestational day 18).	
		Oral	
3.3.3	Type	Gavage	
3.3.4	Concentration	Gavage 57.5..... mg aluminium/kg bw	
		$Al(OH)_3$: 166 mg/kg bw Al lactate: 627 mg/kg bw $Al(OH)_3$ + lactic acid: 166 mg/kg bw + 570 mg/kg bw Lactic acid: 570 mg/kg bw	
3.3.5	Vehicle	Not mentioned. Probably water, since control group was administered distilled water.	
3.3.6	Concentration in vehicle	Not available.	
3.3.7	Total volume applied	Not available.	
3.3.8	Controls	Distilled water.	
3.4	**Examinations**		
3.4.1	Body weight	Yes	
3.4.2	Food consumption	Yes	
3.4.3	Clinical signs	Yes (liver and kidney weights)	
3.4.4	Examination of uterine content	Gravid uterine weight	
		Number of implantations,	
3.4.5	Examination of foetuses		
3.4.5.1	General	live fetuses, resorptions, dead fetuses, post-implatation loss, sex ratio, fetal body weight	
3.4.5.2	Skelet	Yes	
3.4.5.3	Soft tissue	No (except for fetal aluminium content)	X
3.5	**Further remarks**	Note that this study was not intended to investigate the developmental toxicity of lactic acid, but of aluminium, with or without organic acid complexing agent. The effect of lactic acid on the (developmental) toxicity of aluminium is enhanced absorption of Al in the GI tract – this effect has been described for a number of carboxylic acids, including but not limited to citric acid, lactic acid and ascorbic acid.	

Section A6.8.1

Annex Point IIA6.8.1

Teratogenicity Study

Developmental toxicity in the mouse

		4 RESULTS AND DISCUSSION	
		We will only discuss the effects of lactic acid per se here.	
4.1	**Maternal toxic Effects**	*No effects except for a slight decrease in relative liver weight. Slight reduction in food consumption during treatment was accompanied by a larger reduction in food consumption pre-treatment, and as such is concluded not to be treatment related.*	X
4.2	**Teratogenic / embryotoxic effects**	*The only effect observed for lactic acid was a delay in parietal ossification.*	X
4.3	**Other effects**	*Decrease in aluminium content of the dam brain (possibly through complexation of native aluminium).*	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	*Study was not performed to any (given) guideline, but appears to have been well conceived and carried out.*	
5.2	**Results and discussion**	*Study was conceived to investigate the developmental toxicity of aluminium and the modifying influence of lactate on aluminium toxicokinetics – apparently spurred by concern of the use of aluminium-containing antacids in combination with complexing acids (citric acid, ascorbic acid, lactic acid) by pregnant women. While it can be concluded that lactic acid enhances the uptake of aluminium and thereby 'increases' the developmental toxicity potential of aluminium, lactic acid itself is not a developmental toxicant.*	
5.3	**Conclusion**	*Not teratogenic.*	
5.3.1	LO(A)EL maternal toxic effects	*Minor, non-relevant effects observed; dose was 570 mg/kg bw*	X
5.3.2	NO(A)EL maternal toxic effects		X
5.3.3	LO(A)EL embryotoxic / teratogenic effects	*No relevant embryotoxic or teratogenic effects*	X
5.3.4	NO(A)EL embryotoxic / teratogenic effects	*570 mg/kg bw*	
5.3.5	Reliability	*1*	X
5.3.6	Deficiencies	*No*	

Section A6.8.1 Teratogenicity Study

Annex Point IIA6.8.1 *Developmental toxicity in the mouse*

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/12/19
Materials and Methods	1.2.1 Not applicable , publication 3.4.5.3 One-third of the fetuses of each group was examined for visceral anomalies.
Results and discussion	4.1 There was a statistically significant treatment-related decrease in food consumption of 15 % during treatment (see CA-table 1). Since no compensation (higher food consumption than control animals) was observed during the post-treatment period and no statistically significant decrease in weight gain it can be assumed that the lactic acid given by gavage partly covered the daily energy requirement of the dams. Thus, this finding was not considered adverse. 4.2 The delay in parietal ossification (CA-Table 3) in combination with a slightly decreased foetal weight (CA-Table 2) was not considered to represent a specific substance-related effect.
Conclusion	5.3.1. LOAEL maternal effects: > 570 mg/kg bw/d 5.3.2 NOAEL maternal effects: 570 mg/kg bw/d (only dose tested) 5.3.3 LOAEL embryotoxic / teratogenic effects: > 570 mg/kg bw/d 5.3.4 NOAEL embryotoxic / teratogenic effects: 570 mg/kg bw/d (only dose tested) Lactic acid does not exhibit a teratogenic potential under the conditions tested.
Reliability	2 (reliable with restrictions, see remarks)
Acceptability	Acceptable
Remarks	Non-guideline, non-GLP, reporting lacks some detail
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.8.1 Teratogenicity Study

Annex Point IIA6.8.1 *Developmental toxicity in the mouse*

Table A6_8-1. Table for Teratogenic effects (separate data for all dosage groups)

Maternal effects

Modify if necessary and give historical data if available

Parameter	**control data**		**low dose**	**medium dose**	**high dose**	**dose-response + / -**
	historical	study				
Number of dams examined						
Clinical findings during application of test substance						
Mortality of dams *state %*						
Abortions						
Body weight gain *day 0-x, day 0-y, day x-y, day 0-end of test,*						
Food consumption						
Water consumption *if test substance is applied with drinking water*						
Pregnancies *pregnancy rate or %*						
Necropsy findings in dams dead before end of test						

Section A6.8.1 Teratogenicity Study

Annex Point IIA6.8.1 *Developmental toxicity in the mouse*

Table A6_8-2. Table for Teratogenic effects (separate data for all dosage groups)

Litter response (Caesarean section data)

Modify if necessary and give historical data if available

Parameter	**control data**		**low dose**	**medium dose**	**high dose**	**dose-response + / -**
	historical	study				
Corpora lutea *state total/number of dams*						
Implantations *state total/number of dams*						
Resorptions *state total/number of dams*						
total number of fetuses						
pre-implantation loss *state %*						
post-implantation loss *state %*						
total number of litters						
fetuses / litter						
live fetuses / litter *state ratio*						
dead fetuses / litter *state ratio*						
fetus weight (mean) *[g]*						
placenta weight (mean) *[g]*						
crown-rump length (mean) *[mm]*						
Fetal sex ratio *[state ratio m/f]*						

Section A6.8.1 Teratogenicity Study

Annex Point IIA6.8.1 *Developmental toxicity in the mouse*

Table A6_8-3. Table for Teratogenic effects (separate data for all dosage groups)

Examination of the fetuses

Modify if necessary and give historical data if available

Parameter	control data		low dose	medium dose	high dose	dose-response + / -
	historical	study				
External malformations* *[%]*						
External anomalies* *[%]*						
Skeletal malformations* *[%]*						
Skeletal anomalies* *[%]*						
Skeletal variants* *[%]*						
Visceral malformations* *[%]*						
Visceral anomalies* *[%]*						
Variants visceral* *[%]*						

CA-Table 1

TABLE 1. Body weight change and food consumption data of mice given $Al(OH)_3$, $Al(OH)_3$ and lactic acid, aluminum lactate, or lactic acid on gestation days 6-15

	Control	$Al(OH)_3$	$Al(OH)_3$ + lactic acid	Aluminum lactate	Lactic acid
Number of dams	13	11	13	10	12
Gestational body weight change (g) on days:					
0-6 (pretreatment)	3.14±1.27	3.90±1.75	4.00±1.08	4.50±1.35	3.01±1.85
6-9	2.50±1.49	1.72±1.48	1.61±1.19	0.20±1.85***	1.25±1.71
6-12	7.92±3.83	7.18±4.44	4.92±3.68*	3.51±1.50**	6.33±2.42
6-15 (treatment)	18.79±5.88	14.18±6.74	10.77±7.21**	8.00±3.49	14.25±3.01
15-18 (posttreatment)	9.00±3.82	8.00±4.56	8.76±4.56	6.51±2.87	9.83±3.81
0-18 (gestation)	30.93±6.66	26.08±10.18	23.53±5.01*	19.01±5.78***	27.08±3.04
Food consumption (g/dam) on days:					
0-6 (pretreatment)	38.23±3.92	35.33±2.58	38.00±1.73	40.00±3.74	38.60±4.78
6-9	20.73±4.03	22.00±1.54	19.56±2.92	13.55±2.11***	16.10±2.55*
6-12	40.23±3.68	41.67±1.03	37.89±3.75	28.90±2.16***	27.00±7.14**
6-15 (treatment)	58.03±4.06	60.33±1.03	57.56±4.27	48.27±4.85*	48.60±8.73
15-18 (posttreatment)	21.83±2.03	23.33±3.06	22.33±5.02	15.91±1.97*	20.90±2.02*
0-18 (gestation)	118.09±3.97	118.99±1.54	117.89±10.41	104.18±6.23**	108.10±12.55

Results are presented as means ± SD. Asterisks indicate significantly different from controls: *$P<0.05$, **$P<0.01$, ***$P<0.001$, respectively.

CA-Table 2 Reproductive and fetal data of mice given oral $Al(OH)_3$, $Al(OH)_3$ and lactic acid, aluminum lactate, or lactic acid on gestation days 6-15

	Control	$Al(OH)_3$	$Al(OH)_3$ + lactic acid	Aluminum lactate	Lactic acid
No. of litters	13	11	13	10	12
No. of implantation sites/ litter	14.83±3.01	12.70±4.27	12.15±4.46	14.70±2.16	13.92±1.67
No. of live fetuses	14.17±3.29	11.90±4.90	10.85±4.37	13.80±2.34	13.00±1.88
No. of resorptions	0.66±0.77	0.80±1.03	1.23±1.73	0.70±0.66	0.76±1.01
No. of dead fetuses	0.00±0.00	0.00±0.00	0.07±0.27	0.20±0.63	0.16±0.38
Postimplantation loss/ litter (%)	4.45±6.53	6.29±7.92	10.69±12.91	6.12±7.24	6.61±8.13
No. of litters with dead fetuses	0	0	1	1	2
Sex ratio (M/F)	0.88±0.24	0.93±0.46	0.86±0.19	0.89±0.37	0.82±0.30
Fetal body weight/ litter (g)	1.24±0.14	1.26±0.11	1.27±0.15	1.04±0.18**	1.19±0.12

Asterisks indicate significantly differents from control, **P < 0.01.

CA-Table 3 Summary incidence of malformations and variations in fetuses from dams given oral doses of $Al(OH)_3$, $Al(OH)_3$ and lactic acid, aluminum lactate, or lactic acid on gestation days 6-15

	Control	$Al(OH)_3$	$Al(OH)_3$ + lactic acid	Aluminum lactate	Lactic acid
Internal examination					
No. of fetuses (litters) examined	54 (13)	40 (11)	50 (13)	53 (10)	47 (12)
Cleft palate	0 (0)	0 (0)	0 (0)	7 (4)*	0 (0)
Skeletal examination					
No. of fetuses (litters) examined	74 (13)	55 (11)	53 (13)	52 (10)	66 (12)
Assymetrical sternebrae	3 (2)	4 (3)	9 (6)	5 (3)	8 (5)
Dorsal hyperkiphosis	0 (0)	0 (0)	0 (0)	7 (4)*	1 (1)
Parietal, delayed ossification	0 (0)	0 (0)	0 (0)	8 (5)**	10 (4)*
Sternebrae, reduced ossification	0 (0)	0 (0)	0 (0)	7 (3)	3 (1)
Total skeletal defects	3 (2)	4 (3)	9 (6)	11 (5)	17 (6)

Asterisks indicate significantly different from control: *P < 0.05, **P < 0.01, respectively. The litter was the statistical unit of comparison.

Section A6 Annex Point A6.9	Neurotoxicity	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [x] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	According to the 'Technical Guidance Document on data requirements' this is an additional data requirement and under IIIA6.9 the following is cited: "Neurotoxicity study [Ann. IIIA, VI. 1.] - This data may be relevant on the basis of the toxicological properties of a substance - Neurotoxicity studies detect functional changes and/or structural and biochemical changes in the central and peripheral nervous systems. These changes can be morphological, physiological (e.g. electroencephalographic changes), or behavioural nature, or can be changes in biochemical parameters (e.g. neurotransmitter levels). - If there are any indications that the active substance may have neurotoxic properties then specific neurotoxicity studies are required. Indications of neurotoxicity can be acquired from the standard systemic toxicity studies. Further investigation is possible using standard repeated dose toxicity tests with incorporation of specific neurotoxicity measures, like sensory activity, grip strength, and motor activity assessment (e.g. EC method B7 or the corresponding OECD guideline 407) and/or acute neurotoxicity testing using the OECD method 424. Expert judgement is required to decide whether a repeated dose neurotoxicity study is needed (see Chapter 1.2, point 4). - These studies have to be performed for substances of similar or related structures to those capable of inducing delayed neurotoxicity. If anticholinesterase activity is detected a test for response to reactivating agent may be required." Lactic acid is not expected to cause delayed neurotoxicity, as it does not have a similar or related structure of those capable of inducing delayed neurotoxicity. Furthermore, lactic acid is a naturally occurring substance in the human body and in human food, and is also authorized to be used as a food additive. As the exposure due to the use of biocidal products will not substantially contribute to the total systemic exposure, no studies on neurotoxicity are deemed necessary. An expert statement on the role of lactic acid in the human body, as well as its presence in food (both naturally and as a food additive) is presented in A6.2-01.	
Undertaking of intended data submission [ ]	Not applicable	

Section A6 Annex Point A6.9	Neurotoxicity
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	2008/07/08
Evaluation of applicant's justification	Applicant's justification is acceptable.
Conclusion	Applicant's justification is acceptable.
Remarks	None
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6 Annex Point A6.10	Mechanistic studies	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	According to the 'Technical Guidance Document on data requirements' this is an additional data requirement and under IIIA 6.10 the following is cited: "Mechanistic study - any studies necessary to clarify effects reported in toxicity studies [Ann.IIIA, VI. 7.] · This data may be relevant on the basis of the toxicological properties of a substance. · Studies of the mechanisms of toxicity may be necessary when there are indications that active substance may have e.g. a non-genotoxic mechanism for carcinogenicity, species specific effects, adverse effects on reproduction, immunotoxicity or hormone related effects. · Scientific judgement is required to decide whether any supplementary studies are needed (see Chapter 1.2, point 4)." L(+) Lactic acid does not have specific effects as meant under this section. Lactic acid is a naturally occurring substance in the human body and in human food, and is also authorized to be used as a food additive. As the exposure due to the use of biocidal products will not substantially contribute to the total systemic exposure, no further studies on specific effects are deemed necessary. An expert statement on the role of lactic acid in the human body, as well as its presence in food (both naturally and as a food additive) is presented in A6.2-01.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2008/07/09	
Evaluation of applicant's justification	Applicant's justification is acceptable.	
Conclusion	Applicant's justification is acceptable.	
Remarks	None	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	

Section A6	**Mechanistic studies**
Annex Point A6.10	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6 Annex Point A6.11	Studies on other routes of administration	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	According to the 'Technical Guidance Document on data requirements' this is an additional data requirement and under IIIA 6.11 the following is cited: "· For existing substances, data (if already existing) by alternative routes should be submitted by the applicant. · New studies will be required only in exceptional cases. · Studies on parenteral routes may supplement the information received from toxicokinetic studies and give valuable information e.g. in cases when the gastrointestinal absorption of the chemical in question is poor. · E.g. acute toxicity studies on intraperitoneal, intravenous subcutaneous and intramuscular routes, where conducted, should be submitted. · A scientific judgement is required to decide whether any supplementary studies are needed (see Chapter 1.2, point 4)." The dossier contains studies on respiratory, dermal, and oral exposure.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2008/07/09	
Evaluation of applicant's justification	Applicant's version is acceptable.	
Conclusion	Applicant's version is acceptable.	
Remarks	None	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6 Annex Point A6.12	Medical data in anonymous form	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	This statement covers 6.12.1 to 6.12.8 ! According to the 'Technical Guidance Document on data requirements' under IIIA 6.12 the following is cited: "Medical data in anonymous form *[Ann IIA, VI. 6.9.]* • Data and information on the effects of human exposure, if available, may provide valuable information for confirming the validity of extrapolations made and conclusions reached from animal data and for identifying unexpected adverse effects which are specific to humans. • Data and information following accidental or occupational exposure have to be submitted where available and of adequate quality. Practical data and information relevant to the recognition of the symptoms of poisoning, on the effectiveness of first aid and therapeutic measures must be included. • It is usually not possible to require this data for new active substances." Thus, the information under 6.12 should be provided if available; if no information is available, there is no need to justify this further. Lactic acid is a naturally occurring substance in the human body and in human food, and is also authorized to be used as a food additive. As the exposure due to the use of biocidal products will not substantially contribute to the total systemic exposure, no medical data are deemed necessary. An expert statement on the role of lactic acid in the human body, as well as its presence in food (both naturally and as a food additive) is presented in A6.2-01.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
Date	**EVALUATION BY RAPPORTEUR MEMBER STATE** 2008-06-30	

Section A6 **Annex Point A6.12**	**Medical data in anonymous form**
Evaluation of applicant's justification	Justification is acceptable with restriction (see remarks) There is a publication on a fatal lactic acid poisoning available. This publication was introduced by the RMS (Führer, 1934; cf CA-Table 1 for details). Since the participant has a long history and experience in the production, packaging and shipping of L(+) lactic acid it can be assumed that there are medical records available of the workers working in the plants of the participant. These data have to be included in the dossier. There are also data on skin irritation in humans available (York et al. 1996) which should be used as a key study in the skin irritation/corrosion part.
Conclusion	Applicant's version is acceptable (see remarks). Lactic acid is a physiological part of human metabolism and occurs in food. The applicant's justification is acceptable with the following amendment: A publication on a fatal lactic acid poisoning is available (cf CA- Table 1 for details). Since the participant has a long history and experience in the production, packaging and shipping of L(+) lactic acid, so it can be assumed that there are medical records of the workers working in the plants of the participant are available. These data have to be included in the dossier.
Remarks	As exposure to lactic acid during the manufacturing process could differ in route and amount from background levels, medical surveillance data on personnel working in the applicant's plant should be provided for reason of completeness.
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

CA-Table 1:

Kind of study (e.g. case reports)	Examination methods, number of individuals examined	Results	References
Case report, fatal poisoning (accidental exposure to ca. 33 g lactic acid by stomach tube)	Clinical observation, (histo-)pathology, tissue distribution of lactic acid; 1 F	Pain, vomitting, gastrointestinal necrosis, haemorrhages and bleeding, death within 12 h, 4 d p.m.: from analysis of lactic acid content in different organs an estimate of 17 g lactic acid is given, mainly in the gastrointestinal tract and brain	Führer H 1932, Arch Toxicol 3(1):71-74

Section A6 Annex Point A6.13	Toxic effects on livestock and pets	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	According to the 'Technical Guidance Document on data requirements' this is an additional data requirement and under IIIA 6.13 the following is cited: "An estimation on toxic effects and exposure via different exposure routes (e.g. inhalation, licking, skin contact and ingestion of poisoned bait) and in relevant, but exceptional cases, toxicity testing in livestock and pets is required. Toxic effects for livestock and pets should to be estimated or studied if the substance is to be used in spaces in which animals are housed, kept or transported or exposure is possible via drinking water or feedingstuffs. Information on lethal doses for different species, symptoms of poisoning, details of the time courses in case of poisoning and antidotes should also be submitted, if available. · This data may be relevant e.g. for product type 3 (substances used for veterinary hygiene purposes), product type 4 (disinfection of surfaces and equipment), product type 5 (drinking water) product types 8 and 10 (treated materials in areas in which animals are housed, kept or transported), product types 14, 15 and 23 (ingestion of baits), product types 16 and 17 (contaminated drinking water), product types 18 and 19 (repellents to be used for veterinary hygiene purposes). An expert judgement is required to decide whether any studies are needed (see Chapter 1.2, point 4). · This data is usually not required for the product types 1, 2, 6, 7, 9, 11, 12, 13, 20, 21 and 22." Lactic acid is a naturally occurring substance in all living organisms, which also occurs in food. As the exposure due to the use of biocidal products will not substantially contribute to the total systemic exposure, no toxic effects on livestock and pets are expected. An expert statement on the role of lactic acid in mammals, as well as its presence in food is presented in A6.2-01.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2008/11/10	

Section A6 **Annex Point A6.13**	**Toxic effects on livestock and pets**
Evaluation of applicant's justification	Applicant's justification is acceptable.
Conclusion	Applicant's justification is acceptable.
Remarks	None
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6 Annex Point A6.14	Other test(s) related to the exposure of humans	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	According to the 'Technical Guidance Document on data requirements' this is an additional data requirement and under IIIA 6.14 the following is cited: "· Toxicity of degradation products, by-products and reaction products related to human exposure. · Information is required on the toxic effects of substances generated from an active substance, other than mammalian metabolites, in normal use of biocidal product. · The decision as to the need for this data should be made on case-by-case basis by expert judgement (see Chapter 1.2, point 4). Where human exposure is significant, toxicity testing may be needed. · This data may be relevant for many product types. As examples, product types 1 and 2 (reaction products with water when the substance is used for human hygiene purposes or reaction products with water or other materials released in water or air when the substance is used for the treatment of bathing waters), product type 5 (substances produced in a reaction with drinking water), product types 6, 7, 9 and 10 (residuals in treated materials), product type 8 (irritating and sensitising effects of chemical compounds, such as metal salts, developed on the surface of the treated wood) and product type 18 (products, which may produce harmful substances with water during gassing)." Lactic acid is a naturally occurring substance in the human body and in human food, and is also authorized to be used as a food additive. As the exposure due to the use of biocidal products will not substantially contribute to the total systemic exposure, no tests related to the exposure of humans are deemed necessary. An expert statement on the role of lactic acid in the human body, as well as its presence in food (both naturally and as a food additive) is presented in A6.2-01.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2008/07/09	
Evaluation of applicant's justification	Applicant's justification is acceptable.	
Conclusion	Applicant's justification is acceptable.	

Section A6 **Annex Point A6.14**	**Other test(s) related to the exposure of humans**
Remarks	None
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6 Annex Point A6.15	Food and feedingstuffs	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	This point covers 6.15.1 to 6.15.6 ! According to the 'Technical Guidance Document on data requirements' this is an additional data requirement and under IIIA 6.15 the following is cited: "If the active substance is to be used in preparations for use where food for human consumption is prepared, consumed or stored, or where feedingstuff for livestock is prepared, consumed or stored, the tests and results in accordance with paragraphs A6.15.1-6.15.5. shall be required." Lactic acid is a naturally occurring substance in the human body and in human food, and is also authorized to be used as a food additive. As the exposure due to the use of biocidal products will not substantially contribute to the total systemic exposure, no data on food and feedingstuffs are deemed necessary. An expert statement on the role of lactic acid in the human body, as well as its presence in food (both naturally and as a food additive) is presented in A6.2-01.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2014/05/05	
Evaluation of applicant's justification	As the active substance of the representative (dummy) biocidal product, lactic acid is intended to be used as a disinfecting liquid handsoap that is rinsed off the hands after a short contact time. No contact with food or drinking water occurs.	
Conclusion	Submission of data on food and feedingstuffs is not required.	
Remarks	None	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	

Section A6	Food and feedingstuffs
Annex Point A6.15	
Remarks	

Section A6 Annex Point A6.16	Any other test data on exposure	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	According to the 'Technical Guidance Document on data requirements' this is an additional data requirement and under IIIA 6.16 the following is cited: "Any other tests related to the exposure of the active substance to humans, in its proposed biocidal products, that are considered necessary may be required. *[Ann. IIIA, VI.3.5 and XI. 2]*. • An expert judgement for suitable tests and reasoned case is needed as to decision that such additional studies are required (see Chapter 1.2, point 4). " It is clear that the dossier contains all data relevant for an appropriate risk assessment for lactic acid used in disinfectants. Lactic acid is a naturally occurring substance in the human body and in human food, and is also authorized to be used as a food additive. As the exposure due to the use of biocidal products will not substantially contribute to the total systemic exposure, no further studies on exposure are deemed necessary. An expert statement on the role of lactic acid in the human body, as well as its presence in food (both naturally and as a food additive) is presented in A6.2-01.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2008/09/12	
Evaluation of applicant's justification	Applicant's version is accepted.	
Conclusion	Dossier contains all information for an appropriate risk assessment.	
Remarks	None	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	

Section A6	**Any other test data on exposure**
Annex Point A6.16	
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6 Annex Point A6.17	Metabolites in plants	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ]** **Scientifically unjustified [x]** **Other justification [ ]**	
Detailed justification:	According to the 'Technical Guidance Document on data requirements' this is an additional data requirement and under IIIA 6.17 the following is cited: "If the active substance is to be used in products for action against plants then tests to assess toxic effects of metabolites from treated plants, if any, where different from those identified in animals shall be required *[Ann. IIIA, VI.6]*. • Ann. IIIA VI.6. is action against plants, and therefore seen as covered sufficiently by directive 91/414/EC 867." It is clear that from the proposed uses of lactic acid as disinfectant, no exposure of plants will occur. The product is not meant to be used against plants or on plants.	
Undertaking of intended data submission [ ]	Not applicable	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	2008/08/28	
Evaluation of applicant's justification	Applicant's justification is acceptable.	
Conclusion	The submission of data on metabolites in plants is not required.	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		