FOREWORD INTRODUCTION

GLUCONIC ACID AND ITS DERIVATIVES

CAS N°:
Gluconic Acid, 526-95-4
Glucono-Delta-Lactone, 90-80-2
Sodium Gluconate, 527-07-1
Calcium Gluconate, 299-28-5 /18016-24-5
Potassium Gluconate, 299-27-4

SIDS Initial Assessment Report

For

SIAM 18

Paris, France, 20-23 April 2004

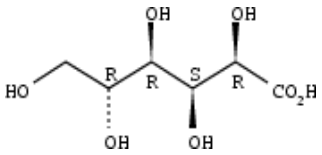
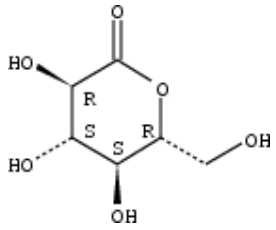
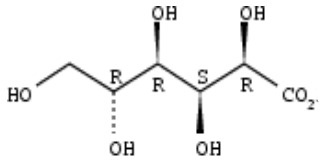
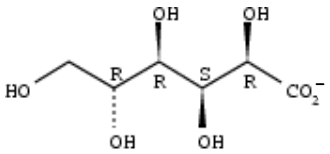
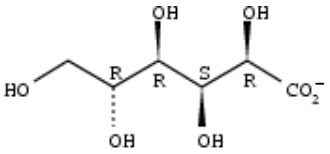
1.	**Chemical Name:**	The category of gluconic acid and its derivatives: gluconic acid, glucono-delta-lactone, sodium gluconate, calcium gluconate and potassium gluconate
2.	**CAS Number:**	526-95-4; 90-80-2; 527-07-1; 299-28-5 /18016-24-5 and 299-27-4
3.	**Sponsor Country:**	Belgium
4.	**Shared Partnership with:**	Japan
5.	**Roles/Responsibilities of the Partners:**	
•	Name of industry sponsor /consortium	Dr. T. Lakhanisky Institute of Public Health – Division Toxicology Rue J. Wytsman 16, B-1050 Brussels Tel. + 32 2 642 5104, Fax. + 32 2 642 5224,
•	Process used	
6.	**Sponsorship History**	
•	How was the chemical or category brought into the OECD HPV Chemicals Programme?	The initiative of this filing came from the industry who contacted Belgian Authorities for Sponsorship. One substance (sodium gluconate) of the category was already sponsored by the Japanese Government and in the process of being presented in 2004. This resulted to the co-sponsoring of the gluconic acid and its derivatives by Japan and Belgium. The industry consortium collected existing data and conducted literature search with the collaboration of the Belgian Authorities. IUCLID dossiers were prepared by the industry consortium as well as draft versions of the SIAR and SIAP. Belgian Authorities peer-reviewed the documents.

no testing (X)

testing ( )

7. **Review Process Prior to the SIAM:**
8. **Quality check process:**
9. **Date of Submission:**
10. **Date of last Update:**
11. **Comments:**

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	Chemical	Structural formula
526-95-4	D-Gluconic acid	
90-80-2	Glucono-delta-lactone	
527-07-1	Sodium D-gluconate	 • Na
299-28-5 18016-24-5	Calcium D-gluconate	 • 1/2 Ca
299-27-4	Potassium D-gluconate	 • K

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

Gluconate derivatives are presented as a category. Gluconic acid and its mineral salts freely dissociate to the gluconate anion and the respective cations. Glucono-delta-lactone (GDL), the 1,5-inner ester of gluconic acid, is formed from the free acid by the removal of water. On the basis of these spontaneous chemical rearrangements, glucono-delta-lactone, gluconic acid and its sodium, calcium and potassium salts can be considered as a category, with all members sharing the same representative moiety, the gluconate anion. Manufacturing and uses of the category members are also interlinked. The data summarized in this report are focused on the environmental and health effects from the gluconate anion and read-across to the lactone but do not deal with specific effects of the cations. Thus toxicological effects related to the cationic components are not part of the present report.

Human Health

Gluconic acid and its derivatives are naturally occurring substances. In mammalian organisms both D-gluconic acid and its 1,5-lactone are important intermediates in the carbohydrate metabolism. Gluconate is a metabolite of glucose oxidation. The daily production of gluconate from endogenous sources is about 450 mg/kg for a 60 kg person. A significant portion (60-85%) of parenterally administered gluconate is excreted unchanged in the urine.

The LD50 calculated after oral administration (gavage) of potassium gluconate on Wistar rats is 6060 mg/kg bw.

None of the repeated dose toxicity studies of any duration (4 weeks, 6 months, or 24 months) showed any significant toxicological effects of gluconates. Potential side effects were attributed to high doses of cation intake, evidenced by results from assays designed for the gluconate anion effect specifically. The NOAEL of sodium gluconate determined from the 28 days studies on rats was equal to 1000 mg/kg bw for males and 2000 mg/kg bw for females. These compounds are neither irritant to the eye or the skin nor show sensitizing properties.

The available in vitro and in vivo mutagenicity data with glucono-delta-lactone, sodium or calcium gluconate were negative. No carcinogenicity studies, and no inhalation toxicity data were available for any of the gluconates of the category.

SIDS testing requirements regarding reproductive toxicity were satisfied with histopathology of the reproductive organs in repeat dose studies on sodium gluconate and with developmental toxicity studies on glucono-delta-lactone. Indeed no changes were observed on the reproductive organs in 28 days oral studies with sodium gluconate (dosage up to 4400 mg/kg bw) and developmental toxicity studies on GDL on different species were all negative.

Environment

Gluconates are readily biodegradable both in aerobic and anaerobic conditions. As the sequestering tendency of gluconates decreases rapidly upon dilution or lowering pH, their chelated metal complexes are destroyed effectively and quickly by biological waste water treatment as well.

A closed bottle test for sodium D-gluconate showed that the Theoretical Oxygen Demand (ThOD) was 89% after 28 days which predicts 100% degradation; and an anaerobic study showed that 100% of sodium D-gluconate was degraded after 35 days.

Gluconic acid, its salts of sodium, potassium and calcium as well as glucono-delta-lactone are all characterised by a low vapour pressure (from 2.41e-009 hPa to 1.58e-022 hPa, estimated from the modified Grain Method), and a low octanol/water partition coefficient (estimated as -5.99 for the sodium salt, -7.51 for the calcium salt, -5.99 for the potassium salt, -1.87 for the free acid and -1.98 for GDL). The dissociation constant of gluconic acid is in the range of 3.5 to 3.8. Because of their good water solubility (from 30 g/L for calcium gluconate to 590 g/L for sodium gluconate) and low Log Ko/w, no bioaccumulation effects are to be expected, the substances were also shown to be readily metabolised.

Estimations from a level II/III fugacity model show that the main target compartments of gluconates are water (38.8 – 49.8 %) and soil (48.9-61.2%). The calculated Henry's law constants (1.38×10^{-4} $Pa.m^3$/mole for GDL, 4.74×10^{-8} $Pa.m^3$/mole for gluconic acid and 4.76×10^{-8} $Pa.m^3$/mole for sodium gluconate) indicate a low

potential for volatilization and the estimated indirect photodegradation in the atmosphere with OH radicals (AOP (v1.91) program) gives a $t_{1/2}$ between 1.7 and 4.0 hours. The good water solubility and low vapour pressure designate water to be a major target compartment for these substances.

Acute toxicity to aquatic organisms (fish, daphnia, algae) was tested on sodium gluconate. In the range of concentrations tested, sodium gluconate did not show toxicity to any of the aquatic species: fish (LC0-96 hrs > 100 mg/l), daphnids (NOEC 24-48 hrs > 1000 mg/l), algae ($NOEC_r$ (24-72 h): 560 mg/l - E_rC_{50} (24-72 h): > 1000 mg/l)) The data from these studies were used for the other members of the category.

No terrestrial toxicity data for gluconates are available.

Exposure

Gluconic acid and its derivatives presented in this category are naturally occurring substances. In mammalian organisms both D-gluconic acid and its 1,5-lactone are important intermediates in the carbohydrate metabolism.

Most of these compounds are listed as permitted food additives, which may be added to all foodstuffs, following the "quantum satis" principle, as long as no special regulations restrict their use.

The manufacturing of gluconic acid is based on a fermentation process. Estimation of the worldwide industrial production per year for all the members of the gluconate category is around 65000 - 100000 tonnes. There is no production site in Belgium.

The typical industrial applications for the category are both dispersive and non-dispersive. The main non-dispersive applications are industrial cleaning, metal surface treatment, textile bleach stabiliser and aluminium processing.

When gluconates are used in wide dispersive applications such as chelating agents in cement set retarding, institutional and household cleaning, personal care products, pharmaceuticals and foodstuffs, their use might result in exposure to the environment. However, when used as sequestering agents in the building industry (concrete and mortar), the gluconate ions react with calcium ions present in the cement to form an insoluble and impermeable layer of calcium gluconate. Therefore, the gluconate is bound within the microcrystalline fibres of cement and is not free to migrate to cause any environmental pollution. Food applications could potentially contribute to spreading gluconates and glucono-delta-lactone in the environment, as these products are added in their crystalline or powder forms to food components such as meat, milk or soma at levels below 5 %w/w. However, since the final food is meant for human consumption and mostly gets ingested, there is no real potential for environmental distribution of gluconates from this application either.

Human exposure by all routes (including inhalation) is possible. Workers exposure will mainly be by inhalation and by skin contact. Consumers' exposure may be from the oral and dermal routes. Individual exposure of consumers to gluconates is expected to be limited because gluconates are mostly used as additives in the different consumer products typically in low dosages. Furthermore, Consumer exposure in personal care products, pharmaceuticals and foodstuffs applications are subject to specific regulatory provisions requiring an authorization procedure where the evaluation of the hazardous properties as well as the actual exposure is taken into account.

RECOMMENDATION

The chemicals in this category are currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The chemicals in this category are currently of low priority for further work because of their low hazard potential.

FULL SIDS SUMMARY

Gluconic acid and derivatives Category

CAS Nos: 527-07-1, 90-80-2, 526-95-4, 299-28-5 and 18016-24-5, 299-27-4

Endpoint	Chemical	Species	Protocol	Result
Physical-Chemical				
2.1 Melting point	Sodium gluconate	N/A	No data	205-209°C (decomposition at ≥ 210°C)
	Glucono-delta-lactone	N/A	No data	153 °C (decomposition at ≥ 153°C)
	Gluconic acid	N/A	No data	131 °C
	Calcium gluconate	N/A	No data	120
	Potassium gluconate	N/A	No data	174-176 °C (decomposes at 180°C)
2.2 Boiling point	Sodium gluconate	N/A	Estimated with MPBPWIN (v1.41) program from US EPA (EPI v3.11)	613.1°C
	Glucono-delta-lactone	N/A		398.5°C
	Gluconic acid	N/A		417.1°C
	Calcium gluconate	N/A		731.1°C
	Potassium gluconate	N/A		613.1°C
2.3 Density at 20°C	Sodium gluconate	N/A	No data	1.789 g/cm³
	Glucono-delta-lactone	N/A	No data	1.68 (relative density)
	Gluconic acid	N/A	No data	1.23 g/cm³
	Calcium gluconate	N/A	No data	0.30-0.65 g/cm³ (bulk density)
	Potassium gluconate	N/A	No data	0.80 g/cm^3 (bulk density)
2.4 Vapour pressure	Sodium gluconate	N/A	Estimated with MPBPVP (v1.41) program from US EPA (EPI v3.11):- modified grain method):	4.53^{-17} hPa at 25°C
	Glucono-delta-lactone	N/A		2.41^{-9} hPa at 25°C
	Gluconic acid	N/A		10.87^{-10} hPa at 25°C
	Calcium gluconate	N/A		1.58^{-22} hPa at 25°C
	Potassium gluconate	N/A		11.89^{-17} hPa at 25°C
2.5 Partition coefficient (log Pow)	Sodium gluconate	N/A	Estimated with Kowwin (v1.67) Program from US EPA (EPI v3.11)	-5.99
	Glucono-delta-lactone	N/A		-1.98
	Gluconic acid	N/A		-1.87

Endpoint	Chemical	Species	Protocol	Result
	Calcium gluconate	N/A		-7.51
	Potassium gluconate	N/A		-5.99
2.6.1 Solubility in water	Sodium gluconate	N/A	No data	590 g/l at 25°C
	Glucono-delta-lactone	N/A	No data	590 g/l at 25°C
	Gluconic acid	N/A	Estimated with Water sol (v1.01) program from US EPA (EPI v3.11)	1000 g/l at 25°C
	Calcium gluconate	N/A	No data	35 g/l at 25°C
	Potassium gluconate	N/A	No data	450-1000 g/l at 20°C
2.12 Dissociation constant	Sodium gluconate	N/A	No data	KA at 25°C= 1.99 x 10^{-4} pKA = 3.70
	Glucono-delta-lactone	N/A	No data	
	Gluconic acid	N/A	No data	
	Calcium gluconate	N/A	No data	
	Potassium gluconate	N/A	No data	
Environmental Fate and Pathway				
3.1.1 Photodegradation	Sodium gluconate	N/A	Estimated with AOP (v1.91) program from US EPA (EPI v3.11)	$t_{1/2}$ = 3.366 Hrs
	Glucono-delta-lactone	N/A		$t_{1/2}$ = 3.96 Hrs
	Gluconic acid	N/A		$t_{1/2}$ = 3.033 Hrs
	Calcium gluconate	N/A		$t_{1/2}$ = 1.683 Hrs
	Potassium gluconate	N/A		$t_{1/2}$ = 3.366 Hrs
3.1.2. Stability in water	Sodium gluconate	N/A	No data	The dissociation in water expected to be complete as the pKa is 3.70
	Glucono-delta-lactone	N/A	No data	
	Gluconic acid	N/A	No data	
	Calcium gluconate	N/A	No data	
	Potassium gluconate	N/A	No data	
3.3.1.Transport between environmental compartments	Sodium gluconate	N/A	Estimated with the Level III Fugacity Model program	Air: 1.2 % Water: 49.8 % Soil: 48.9 % Sediment: 0.0743 %

Endpoint	Chemical	Species	Protocol	Result
	Glucono-delta-lactone	N/A	LEVEL3NT from US EPA (EPI v3.11)	Air: 0.8 % Water: 46.8 % Soil: 52.3 % Sediment: 0.0698%
	Gluconic acid	N/A		Air: 0.00821 % Water: 38.8 % Soil: 61.2 % Sediment: 0.0345 %
	Calcium gluconate	N/A		Air: 1.06^{-7} % Water: 38.8 % Soil: 61.2 % Sediment: 0.0345%
	Potassium gluconate	N/A		Air: 4.78^{-7} % Water: 42.8 % Soil: 57.1 % Sediment: 0.0638%
3.3.2. Distribution	Sodium gluconate	N/A	Henry's law constant estimated with HENRY (v3.10) program from US EPA (EPI v3.11)	K_H= 4.76^{-13} atm-m^3/mole at 25 °C
	Glucono-delta-lactone	N/A		K_H= 1.38^{-9} atm-m^3/mole at 25 °C
	Gluconic acid	N/A		K_H= 4.74^{-13} atm-m^3/mole at 25 °C
	Calcium gluconate	N/A		Not estimated
	Potassium gluconate	N/A		Not estimated
3.5. Biodegradation	Sodium gluconate	N/A	Aerobic : Directive 92/69/EEC, C.4-E	+/- 89 % of ThOD after 28 days
		N/A	Anaerobic: DIN EN ISO 11734	100 % after 35 days
	Glucono-delta-lactone			See sodium gluconate
	Gluconic acid			See sodium gluconate
	Calcium gluconate			See sodium gluconate
	Potassium gluconate			See sodium gluconate
Ecotoxicity				
4.1 Acute toxicity to fish	Sodium gluconate	*Oryzias latipes (Fish, fresh water)*	OECD Guideline 203	LC_0 (96 hrs) > 100 mg/l
	Glucono-delta-lactone			See sodium gluconate
	Gluconic acid			See sodium gluconate
	Calcium gluconate			See sodium gluconate

Endpoint	Chemical	Species	Protocol	Result
	Potassium gluconate			See sodium gluconate
4.2 Acute toxicity to aquatic invertebrates	Sodium gluconate	*Daphnia magna (Crustacea)*	OECD Guideline 202 (2 studies)	NOEC (24 hrs): > 1000 mg/l NOEC (48 hrs): > 1000 mg/l
	Glucono-delta-lactone			See sodium gluconate
	Gluconic acid			See sodium gluconate
	Calcium gluconate			See sodium gluconate
	Potassium gluconate			See sodium gluconate
4.3 Acute toxicity to aquatic plants	Sodium gluconate	*Selenastrum capricornutum (Algae)*	OECD Guideline 201	NOECb (0-72 h) = 560 mg/l EbC_{50} (72 h): > 1000 mg/l NOECr (24-72h) : 560 mg/l ErC_{50} (24-72 h): > 1000 mg/l
		Desmodesmus subspicatus	OECD Guideline 201	NOEC (72 hrs)> 100 mg/l cell growth inhibition (72 hrs): 70% inhibition at 1000 mg/l Average specific growth rate inhibition: (72 hrs): 42% inhibition at 1000 mg/l
	Glucono-delta-lactone			See sodium gluconate
	Gluconic acid			See sodium gluconate
	Calcium gluconate			See sodium gluconate
	Potassium gluconate			See sodium gluconate
4.4 Toxicity to microorganisms	Sodium gluconate	*Pseudomonas putida*	DIN 38 412 L8	EC_0 (16 hrs)> 5000 mg/l
	Glucono-delta-lactone	*Pseudomonas putida*	DIN 38 412 L8	EC_0 (16 hrs)> 500 mg/l (not reliable. See sodium gluconate)
	Gluconic acid			See sodium gluconate
	Calcium gluconate			See sodium gluconate
	Potassium gluconate			See sodium gluconate

Endpoint	Chemical	Species	Protocol	Result
Toxicity				
5.1.1 Acute oral toxicity	Sodium gluconate	*Rat Crj: CD(SD)*		LDL_0 > 2000 mg/kg bw
		Dog beagle		LDL_0 > 2000 mg/kg bw
	Glucono-delta-lactone			See sodium gluconate
	Gluconic acid			See sodium gluconate
	Calcium gluconate			See sodium gluconate
	Potassium gluconate	*Rat Wistar*		LD_{50} = 6060 mg/kg bw
5.2.1 Skin Irritation	Sodium gluconate			See gluconic acid
	Glucono-delta-lactone			See gluconic acid
	Gluconic acid	*Rabbit*	Directive 79/831/EEC, B.4. "Acute toxicity" (skin irritation)	Not irritant
	Calcium gluconate			See gluconic acid
	Potassium gluconate			See gluconic acid
5.2.2 Eye Irritation	Sodium gluconate			See gluconic acid
	Glucono-delta-lactone			See gluconic acid
	Gluconic acid	*Rabbit*	Draize Test	Not irritant
	Calcium gluconate			See gluconic acid
	Potassium gluconate			See gluconic acid
5.4 Repeated dose toxicity	Sodium gluconate	*Rat Crj: CD(SD)*		Sub-acute:(gavage- 28 days) NOAEL = 1000 mg/kg bw male NOAEL = 2000 mg/kg bw female
		Dog Beagle		Sub-acute (oral – 4 weeks) NOAEL= 500 mg/kg bw
	Glucono-delta-lactone	*Rat Sprague Dawley*		Chronic (oral – 6 months) NOAEL= not determined
		Rat Sprague Dawley		Chronic (oral – 24 months) NOAEL= not determined
	Gluconic acid			See sodium gluconate
	Calcium gluconate			See sodium gluconate

Endpoint	Chemical	Species	Protocol	Result
	Potassium gluconate			See sodium gluconate
5.5 Genetic toxicity in vitro	Sodium gluconate	*Saccharomyces Cerevisiae*	OECD Guideline 471	With and without metabolic activation: negative
		Salmonella typhimurium	OECD Guideline 471	With and without metabolic activation: negative
	Glucono-delta-lactone	*Saccharomyces Cerevisiae*	OECD Guideline 471	With and without metabolic activation: negative
		Salmonella typhimurium	OECD Guideline 471	With and without metabolic activation: negative
	Gluconic acid			See sodium gluconate
	Calcium gluconate	*Saccharomyces Cerevisiae*	OECD Guideline 471	With and without metabolic activation: negative
		Salmonella typhimurium	OECD Guideline 471	With and without metabolic activation: negative
	Potassium gluconate			See sodium gluconate
5.6 Genetic toxicity in vivo	Sodium gluconate	*Mouse C57BL*		Single dose: negative 4-day repeated dose: negative
	Glucono-delta-lactone	*Mouse C57BL*		Single dose: negative 4-day repeated dose: negative
	Gluconic acid			See sodium gluconate
	Calcium gluconate			See sodium gluconate
	Potassium gluconate			See sodium gluconate
5.8.2 Developmental toxicity/teratogenicity	Sodium gluconate			See glucono-delta-lactone
	Glucono-delta-lactone	*Rat wistar*		NOAEL maternal tox.: > 594 . mg/kg bw NOAEL teratogen.:> 594 . mg/kg bw
		Rat Sprague-Dawley		NOAEL maternal tox.: > 4000 . mg/kg bw NOAEL teratogen.:> 4000. mg/kg bw
		Mouse CD-1		NOAEL maternal tox.: > 695 . mg/kg bw NOAEL teratogen.:> 695. mg/kg bw
		Mouse ICR		NOAEL maternal tox.: > 4000 . mg/kg bw NOAEL teratogen.:> 4000. mg/kg bw

Endpoint	Chemical	Species	Protocol	Result
		Rabbit Dutch		NOAEL maternal tox.: > 780 . mg/kg bw NOAEL teratogen.:> 780. mg/kg bw
		Hamster		NOAEL maternal tox.: > 560 . mg/kg bw NOAEL teratogen.:> 560. mg/kg bw
	Gluconic acid			See glucono-delta-lactone
	Calcium gluconate			See glucono-delta-lactone
	Potassium gluconate			See glucono-delta-lactone

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

Category name:

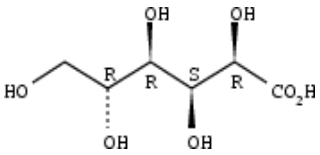
Gluconic acid and its derivatives

Acid: ($C_6H_{12}O_7$);

Lactone: ($C_6H_{12}O_7$) . (-H2O);

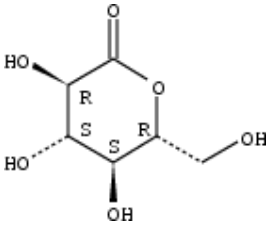
Salts: ($C_6H_{12}O_7$). (Na); or ($C_6H_{12}O_7$) . (1/2 Ca) or ($C_6H_{12}O_7$) .(K)

CAS Number: 526-95-4
IUPAC Name: D-Gluconic acid
Molecular Formula:
Structural Formula:



Molecular Weight: 196.16
Synonyms: EINECS Number 208-401-4

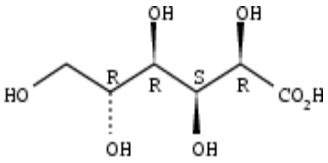
CAS Number: 90-80-2
IUPAC Name: Glucono-delta-lactone
Molecular Formula:
Structural Formula:



Molecular Weight: 178.14
Synonyms: EINECS Number 202-016-5

CAS Number: 527-07-1
IUPAC Name: Sodium D-gluconate
Molecular Formula:

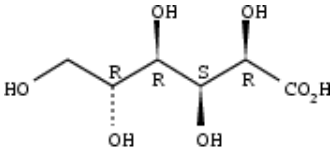
Structural Formula:



• IIa

Molecular Weight: 218.14
Synonyms: EINECS Number 208-407-7

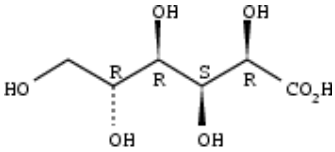
CAS Number: 299-28-5
18016-24-5
IUPAC Name: Calcium D-gluconate monohydrate
anhydrous
Molecular Formula:
Structural Formula:



• 1/2 Ca

Molecular Weight: 448.4
Synonyms: EINECS Number 206-075-8

CAS Number: 299-27-4
IUPAC Name: Potassium D-gluconate
Molecular Formula:
Structural Formula:



• K

Molecular Weight: 234.25
Synonyms: EINECS Number 206-074-2

Information below originates from the Gluconate Handbook, unless specified otherwise.

Anhydrous gluconic acid is a white, odorless, crystalline powder. (Ullman's Encyclopedia, 1999). It is a mild organic acid. The commercial form is a 50 % aqueous solution, which is a colorless to brownish liquid. Glucono-delta-lactone is also a white solid, which in aqueous solution slowly hydrolyses to gluconic acid until equilibrium is reached. The other members of the category are mineral salts of gluconic acid; i.e. sodium gluconate, potassium gluconate (anhydrous) and calcium gluconate (both anhydrous and the monohydrate).

Gluconic acid and its derivatives are naturally occurring substances. Besides being naturally present at a level up to 1% in wine, honey and other foods and drinks, sodium gluconate (E 576), potassium gluconate (E 577), calcium gluconate (E 578), gluconic acid (E 574) and glucono-delta-lactone (E 575) are all listed as permitted food additives, which may be added to all foodstuffs, following the "quantum satis" principle, as long as no special regulations restrict their use. (European Parliament and Council Directive 95/2/EC). The US Food and Drug Administration (FDA) assigned sodium gluconate, potassium gluconate, calcium gluconate and glucono-delta-lactone the "generally recognised as safe" (GRAS) status and permits their use in food without limitation other than good manufacturing practice.

The Select Committee on GRAS substances has also concluded that there is no evidence in the available information on potassium gluconate that demonstrates or suggests reasonable grounds to suspect a hazard to the public, should it be used as a food ingredient at levels now used for sodium gluconate, or that might be expected in the future.

1.2 Purity/Impurities/Additives

The purity of the marketed substances may vary depending on the intended uses, but it is generally above 97%. For food and/or medical applications the level of impurities complies with the restrictions laid down in the corresponding EU Directives.

Purity (%) of :

Gluconic acid 50% solution :	49-52%
Glucono-delta-lactone:	99-101%
Sodium gluconate:	98-102%
Calcium gluconate:	98-104%
Potassium gluconate:	97-103%

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Chemical	Physical state	Melting point	Boiling point	Relative Density (at 20°C)	Vapor pressure (at 20ºC)	Water Solubility	octanol /water partition coefficient (LogP)	pKa
Gluconic acid	White solid	131 °C	Estim. 417.1 °C	1.23 g/cm³	estim. 10.87e-010 hPa	Miscible Estim. 1000 g/l at 25°C	estim. -1.87 at 25°C	3.70
Glucono-delta-lactone	White solid	153 °C	Estim. 398.5 °C	1.68 (relative density)	estim. 2.41e-009 hPa	590 g/l at 25°C	estim. -1.98 at 25°C	3.70
Sodium gluconate	White/off white solid	205-209 °C (decomposes at ≥ 210 °C)	Estim. 613.1 °C	1.789/cm³	estim. 4.53e-017 hPa	590 g/l at 25°C	estim. -5.99 at 25°C	3.70
Calcium gluconate	White/off-white solid	120°C	Estim. 731.1 °C	0.3-0.65 g/cm³ (bulk density)	estim. 1.58e-022 hPa	35 g/l at 25°C	estim. -7.51 at 25°C	3.70
Potassium gluconate	White solid	174-176 °C (Decomposes at 180°C)	Estim. 613.1 °C	0.8 g/cm^3 (bulk density)	estim. 11.89e-017 hPa	450-1000 g/l at 20°C	estim. -5.99 at 25°C	3.70

1.4 Category Justification

In this report the above gluconate derivatives are presented for a preliminary assessment as a category. Gluconic acid, as well as its mineral salts freely dissociate to the gluconate anion and the respective cations. Glucono-delta-lactone (GDL), the 1,5-inner ester of gluconic acid, is formed from the free acid by the removal of water. (Gluconic acid also has another inner ester, the 1,4-lactone, which does not belong to this category because during manufacturing process, the 1,5-lactone is dominant and the 1,4-lactone is of no commercial interest.) On the basis of these spontaneous chemical rearrangements, glucono-delta-lactone, gluconic acid and its sodium, calcium and potassium salts can be considered as a category, with all members sharing the same representative moiety, the gluconate anion.

As presented in the different sections below, the manufacturing and uses of the category members are also interlinked. Gluconic acid is readily produced from glucose by mild oxidation. The oxidation can occur chemically, electrolytically or enzymatically, but the commercial production is mainly by fermentation. The salts are produced from the acid by neutralization with the corresponding alkaline hydroxide solution, while GDL is separated from the acid by crystallisation.

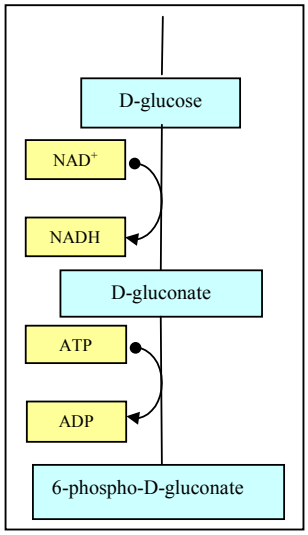
The data summarized in this report are focused on the environmental and health related characteristics of the gluconate anion and do not deal with specific effects of the cations. Evidence from the reviewed literature suggests that the eventual toxicity of the gluconate salts would be attributable to the cation rather than of the gluconate moity of these substances. Acute toxicity responses to the various gluconate salts are comparable with other salts of the same metals and long-term toxicities seem related to the tissue deposition of these metals. Because toxicological effects of these gluconates appear to be related to their cationic components, safe and acceptable levels in foods are limited only by the nature of the specific cations (Life Science Research Office, 1978). These effects, however, are not part of the present report, which focuses on the potential hazards associated with the gluconate anion.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Gluconates are natural substances. In mammalian organisms both D-gluconic acid and its 1,5-lactone are important intermediates in the carbohydrate metabolism.

Gluconate pathway



Gluconate is a metabolite of glucose oxidation. In the tissues, about 20 % of glucose may be metabolized through this route. A rough estimate of the daily production of gluconate in humans can be calculated by assuming that approximately 10 % of the glucose utilized by the body is metabolized through the phosphogluconate pathway. Therefore, an individual receiving 2800 kcal per day from an average diet, would oxidize about 275 g of glucose. Approximately 25 to 30 g of this amount would be oxidized through the phosphogluconate pathway to yield roughly the same amount of gluconate. Thus, the daily production of gluconate from endogenous sources is about 450 mg/kg for a 60 kg person (Life Science Research Office, 1978).

The manufacturing of gluconic acid is based on a fermentation process.

Glucono-delta-lactone (GDL), the inner ester of gluconic acid, is formed by the removal of water. Commercially it is produced by an aerobic fermentation process converting a carbohydrate source into gluconic acid. After fermentation gluconic acid is separated from GDL by crystallisation.

Sodium gluconate is the sodium salt of gluconic acid. It forms stable chelates with iron, aluminium, calcium, zinc and other heavy metals, especially in alkaline solution. It possesses good sequestering activity in cleaning baths and is highly stable, even in concentrated alkaline solutions.

The calcium and potassium salts are prepared from the acid. Calcium gluconate contains approximately 9% calcium in a form that is readily absorbed by plants and animals. The potassium salt is very soluble in water, which facilitates its use in pharmaceutical applications.

Estimation of the worldwide production per year for the members of the category:

gluconic acid (as 100% substance)	4000-6000 tonnes
glucono-delta-lactone	10000-20000 tonnes
sodium gluconate	50000-70000 tonnes
calcium gluconate	4000-6000 tonnes
potassium gluconate	1000-2000 tonnes

The primary applications of gluconic acid are based on its most important characteristic: it is a weak acid, capable of dissolving the oxides, hydroxides and carbonates of polyvalent cations, forming water-soluble complexes without attacking metallic or nonmetallic surfaces. These characteristics are exploited in the metal cleaning/finishing applications, aluminium and steel processing and detergent uses. Because of its additional physiological properties, D-gluconic acid is also used in food and pharmaceutical industries. Gluconic acid salts, like the free acid, form complexes with metal ions and the stability of these complexes increase considerably with increasing pH. In many applications, glucono-delta-lactone (GDL) is a convenient substitute of the free acid, especially where, due to the reversibility between the acid and its lactone form, a gradual change in the pH is preferred.

The typical applications for the category can be classified as dispersive or non-dispersive, depending on the potential for the gluconates spreading into the environment.

The main non- dispersive applications are industrial cleaning, metal surface treatment, textile bleach stabiliser and aluminium processing.

To the contrary, when gluconates are used in applications such as chelating agents in cement set retarding, institutional and household cleaning, personal care products, pharmaceuticals and foodstuffs, their use might result in exposure to the environment, hence, these uses will be considered as dispersive. However, as the following examples illustrate, the different uses of gluconates in food and pharmaceutical applications all result in the ingestion of the substances, and such do not contribute to their environmental exposure.

- as food additives and processing aids:

Gluconic acid and its salts have been used in various applications in the food industry. As a sequestrant, sodium gluconate finds broad application in cleaning solutions for the food industry. Also, sodium gluconate has been used in indirect application in washing solutions for eggs, denuding tripe, and for preventing the staining of the exteriors of canned goods by cooling and retort water. Sodium and calcium gluconate are used as nutritional supplements in sausage products and to increase the water binding properties of the products.

Over the past ten years, there has been considerable research conducted in Japan using sodium gluconate in order to complement sodium chloride in the proteins extraction from fish muscles. Sodium gluconate is used as a replacement for phosphates in the processing of Surimi (minced fish meat) to improve the whiteness and elasticity of the fish product.

A process to improve meat tenderness was developed by scientists at the US Meat Animal Research Center. The calcium activated Tenderization process uses post-mortem injected calcium to activate the calpain tenderizing enzymes. While the original work used calcium chloride, more recent tests showed that calcium gluconate is equally effective. (Gluconate Handbook)

Sodium and potassium gluconate have a unique impact on taste perception: debittering properties when used with artificial sweeteners, i.e. saccharine, cyclamates and aspartame.

Sodium gluconate is sometimes used as an ingredient in sugar replacement packets and diet beverages. The artificial sweetener, Aspartame, when used alone has a defect in that its sweetness is slightly delayed in onset and tends to remain longer on the tongue; its gustatory quality can be improved to be more sucrose-like by addition of sodium gluconate.

Potassium gluconate has been shown to suppress the sweetness of hydrolized lactose without producing bitterness or off-flavors. (Gluconate Handbook)

- in pharmaceutical applications:

Sodium, potassium and calcium gluconates are used as mineral supplements in pharmaceutical injection solutions at concentrations up to 55 g/l. (Drug Product Database (DPD))

2.2 Environmental Exposure and Fate

Environmental exposure during production is very limited. Material lost or spilled during manufacturing is collected and sent to the wastewater treatment plant.

The non-dispersive applications cover industrial uses, where subsequent wastewater treatment is practiced. As an example, in metal surface treatment, sodium gluconate is an effective sequestering agent in alkaline solutions where it forms chelates with earth metals such as calcium and magnesium. In this case, as well as in other industrial applications, the product finally flows into the wastewater treatment plant of the user's site. Also in industrial cleaning formulations, where gluconates are valuable complexing agents for di- or trivalent metal cations in alkaline solutions, they are washed out with clean water during the cleaning process. The washing water most likely flows into the wastewater treatment plant of the site. These applications, as shown by the figures in the table below represent about half of the estimated production volumes for sodium gluconate.

Non-dispersive consumption of sodium gluconate chelating agents in Western Europe and Japan in 1998 (tonnes)

	Western Europe	Japan
Metal surface treatment applications	5100	900
Industrial cleaners	5100	600
Cement set retardant	5100	7600
Other applications (ie, textile bleach stabiliser, aluminium processing)	1700	900
Total	17000	10000

(The Chemical Economics Handbook, 2000)

In wide-dispersive applications as well, however, the environmental impact is quite limited. When used as sequestering agents in the building industry (concrete and mortar), the gluconate ions react with calcium ions present in the cement to form an insoluble and impermeable layer of calcium gluconate. Therefore, the gluconate is bound within the microcrystalline fibers of cement and is not free to migrate to cause any environmental pollution.

Food applications could potentially contribute to spreading gluconates and glucono-delta-lactone in the environment, as these products are added in their crystalline or powder forms to food components such as meat, milk or soja at levels below 5 %w/w. However, since the final food is meant for human consumption and mostly gets ingested, there is no real potential for environmental distribution of gluconates from this application either.

If dispersed into the environment, the substances of the category will be found predominantly in the aquatic compartment. Indeed, on the basis of the fugacity Level II/III Fugacity Model from US EPA, the main target compartments of gluconates are water and soil but their good water solubility and low vapor pressure designate water as a major target compartment for these substances. For sodium gluconate the vapor pressure at 20°C is estimated (on the basis of the modified Grain Method) as 4.53e-017 hPa, which is negligible; the estimated values for the other members of the category are of the same order of magnitude (2.41e-009 hPa for glucono-delta-lactone, 10.87e-010 hPa for gluconic acid, 1.58e-022 hPa for calcium gluconate and 11.89e-017 hPa for potassium gluconate).

Gluconic acid is a weak acid; its dissociation in water is characterized by the pKa in the range of 3.5 to 3.8. Thus, dissociation of gluconates in water is expected to be complete (Ullman's Encyclopedia, 1999).

Glucono-delta-lactone slowly hydrolyses in aqueous solution until a balance is reached between gluconic acid and its lactone ester. Equilibrium of a 1 % glucono-delta-lactone solution is reached after 2 hours. At an initial concentration of 10 % glucono-delta-lactone, the equilibrium gluconate-lactone is 80/20.

The dilution and lowering of pH decrease the stability of metal complexes and the metal ions released during the complex degradation can be removed by precipitation or absorption by the sludge (Roquette Frères).

The octanol/water partition coefficient (Log K o/w) is estimated as -5.99 for the sodium salt, -7.51 for the calcium salt, - 5.99 for the potassium salt, -1.87 for the free acid and -1.98 for GDL. These partition data represent the good water solubility of gluconates and their very low solubility in organic solvents. The Henry constants (estimated with HENRY (v3.10) program from US EPA) and the calculated half-life of the substances by photodegradation (estimated with AOP (v1.91) program from US EPA) are summarized in the table below.

	Henrys Law Constant at 25 deg C estimated with HENRY (v3.10) program from US EPA (EPI v3.11	**Photodegradation Estimated with AOP (v1.91) program from US EPA (EPI v3.11) HALF-LIFE**
GDL	1.38e-009 atm-m3/mole	3.960 Hrs
Gluconic acid	4.74e-013 atm-m3/mole	3.033 Hrs
Calcium gluconate	Can neither be calculated with the bond estimation method nor with the group estimation method because of missing values for certain bonds/groups.	1.683 Hrs
Potassium gluconate	Can neither be calculated with the bond estimation method nor with the group estimation method because of missing values for certain bonds/groups.	3.366 Hrs
Sodium gluconate	4.76e-013 atm-m3/mole	3.36 Hrs

The tables further below present that, on the basis of a Level II/III Fugacity Model calculation from US EPA, the different gluconates are almost evenly distributed between the water and soil compartments, with virtually none being adsorbed to the sediment or volatilized to the air.

Sodium gluconate:

	Mass Amount (%)	**Half-Life (hr)**	**Emissions (kg/hr)**
Air	1.2	6.73	1000
Water	49.8	208	1000
Soil	48.9	208	1000
Sediment	0.0743	832	0

Gluconic acid:

	Mass Amount (%)	**Half-Life (hr)**	**Emissions (kg/hr)**
Air	0.00821	6.06	1000
Water	38.8	55.9	1000
Soil	61.2	55.9	1000
Sediment	0.0345	224	0

Glucono-delta-lactone:

	Mass Amount (%)	**Half-Life (hr)**	**Emissions (kg/hr)**
Air	0.8	7.92	1000
Water	46.8	208	1000
Soil	52.3	208	1000
Sediment	0.0698	832	0

Calcium gluconate:

	Mass Amount (%)	**Half-Life (hr)**	**Emissions (kg/hr)**
Air	1.06 e-007	3.37	1000
Water	38.8	55.9	1000
Soil	61.2	55.9	1000
Sediment	0.0345	224	0

Potassium gluconate

	Mass Amount (%)	Half-Life (hr)	Emissions (kg/hr)
Air	4.78e-007	6.73	1000
Water	42.8	208	1000
Soil	57.1	208	1000
Sediment	0.0638	832	0

All these data suggest that the gluconates have a very low potential for bioaccumulation.

The low potential for bioaccumulation is supported by metabolic in vivo studies showing that gluconate is readily catabolized or utilized for glucose synthesis (Life Science Research Office, 1980).

The biodegradability capacity of the category is represented by data acquired for sodium gluconate. In the aerobic Closed bottle test of sodium D-gluconate, (Hydrotox GmbH, 2001) the biodegradation was 89% expressed as the Theoretical Oxygen Demand after 28 days; while under anaerobic conditions (Hydrotox GmbH, 2001b), 100% of sodium D-gluconate was determined as degraded after 35 days. These data demonstrate that gluconates are readily biodegradable both under aerobic and anaerobic test conditions.

As the sequestering tendency of gluconates decreases rapidly upon dilution or lowering of pH, metal complexes of gluconates dissociate and are quickly and effectively destroyed by biological waste water treatment.

2.3 Human Exposure

Human exposure by all routes (including inhalation) is possible. However, due to the controlled manufacturing conditions in all countries of production and the intended uses, only very limited accidental human exposure is expected. For workers the potential routes of exposure will mainly be by inhalation and by skin contact, whereas for consumers the main routes of exposure are oral and dermal.

2.3.1 Occupational Exposure

Gluconic acid is produced by a fermentation process. After fermentation the product is separated from the rest of the broth by filtration, followed by demineralization and discoloration. After a concentration step the material is crystallized to obtain glucono-delta-lactone on one side and the run off on the other side. Separation happens in a centrifuge. All these operations are carried out in closed equipment in all countries of production. At this stage no human contact is possible other than during maintenance work or sample analysis in the laboratory. Maintenance operators who have to be in touch with the product wear the usual safety equipment: protective clothes, gloves and goggles. In the control laboratory operators wear the general safety equipment: gloves and goggles, so exposure is minimal.

Gluconic acid is a weak acid and while it only shows weak acidic characteristics, it has to be handled as an acid. Workers involved in preparing detergent formulations based on gluconic acid are required to take all the necessary measures when handling this type of material in order to avoid any skin or eye contact.

Sodium gluconate is manufactured from gluconic acid by neutralization with sodium hydroxide. It can be sold as an aqueous solution or a powder crystalline form.

The liquid aqueous solution is used mainly in concrete and mortar preparations. Liquid sodium gluconate manufacturers sell the material in large quantities to concrete producers. The material is shipped in bulk containers to their facilities, where it is unloaded into a storage tank. From there it is pumped into a mixer where other chemicals are also added. The mixture is filled into containers or drums in order to be supplied to concrete and mortar producers.

Workers are not in contact with sodium gluconate during the unloading and the mixing operations, since both operations are performed in closed systems.

Crystalline sodium gluconate is sold in bags. It has to be dissolved in water before further use. Some dust may be formed at this stage during the cracking of the paper bags or the emptying of the bags into the hopper before dissolution. Exposure by inhalation or skin contact could potentially occur at this stage. The product is mainly used in industrial detergent formulations and metal surface treatment preparations. In both cases it functions as a sequestering or chelating agent after blending with other chemicals like sodium peroxide. Companies making those preparations in large production units have already in place efficient safety procedures, including the use of protective clothes, gloves, masks and goggles by workers who could be in contact with the material.

Glucono-delta-lactone is the lactone form of gluconic acid. Because of its higher price it is mainly used in food applications. It is shipped and handled in bags.

2.3.2 Consumer Exposure

Exposure of consumers even in the dispersive uses of gluconates is expected to be limited because gluconates are mostly used as additives in the different consumer products typically in low dosages:

- in concrete: 0.1-0.2% based on cement weight
- in institutional and household cleaners: <5% based on formulation weight
- in personal care products: <1% based on formulation weight.
- in foodstuffs: <5% based on foodstuff weight

The daily exposure of consumers to gluconates through these uses is lower than the daily production of gluconate from endogenous sources; ie. 20-30 gr/day (Life Science Research, 1978).

Furthermore, gluconic acid, its salts and glucono-delta-lactone are also present naturally at a level up to 0.5% in wine, honey and other foods and drinks and can be ingested as additives or nutritional supplements in food.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Gluconic acid, the anion of potassium gluconate, is a normal metabolic product of glucose metabolism, 25-30 g being produced daily. For these reasons, and because potassium gluconate is widely used therapeutically as a source of potassium in cases of hypokalemia, conventional toxicological studies of potassium gluconate have not been regarded as necessary, explaining the lack of direct animal data on the compound. Orally administered gluconate is absorbed rapidly; a

major part is excreted in the urine and the remainder is metabolised (Life Science Research Office, 1980).

Gluconate is a metabolite of glucose oxidation in mammals. Its activity is greatest in the liver, adipose tissue, adrenal cortex, thyroid, erythrocyte, testis and the lactating mammary gland. In these organs as much as 20 % of the glucose can be metabolized; the daily production of gluconate from endogenous sources is about 450 mg/kg for a 60 kg person (Life Science Research, 1978).

A significant portion (60-85%) of parenterally administered gluconate is excreted unchanged in the urine (Life Science Research, 1980).

In an report evaluating the health aspects of gluconates, an in vivo excretion study is cited where it was established that a significant portion (60-85%) of parenterally administered gluconate is excreted unchanged in the urine (Life Science Research, 1980).

3.1.2 Acute Toxicity

Studies in Animals

Data on acute oral toxicity for sodium gluconate in rat (Mochizuki, M, Bozo Research Center 1995) (doses: 500, 1000, 2000 mg/kg) and dog (Okamoto M., 1995) (doses: 1000 and 2000 mg/kg) fed by gavage showed no death at any dose, hence the minimum lethal dose was estimated > 2000 mg/kg for both species.

Rats were fed by gavage 3000, 3600, 4320, 5190, 6210 mg/kg bw (30% (w/v) aqueous solution) potassium gluconate and were observed for signs of toxicity during a 14-day period. One animal died in the 5190 mg/kg bw group and four animals in the 6210 mg/kg bw group. Deaths occurred between 5 and 21 hours after treatment. Survivors recovered gradually. The LD_{50} was calculated (according to the method of Weil) to be 6060 mg/kg bw. However, the effects that were observed occurred at doses that exceed the accepted limit dose of 5000 mg/kg bw and the LD_{50} may be related to high dosing (TNO, 1978).

No relevant oral toxicity data were found in the literature for the other substances of the category.

Conclusion

Studies with sodium gluconate in the rat and dog report LD50 values > 2000 mg/kg bw for both species.

A gavage study with potassium gluconate and rats reported an LD50 of 6060 mg/kg bw.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Primary dermal irritation tests with 0.5 ml of the 50% solution of gluconic acid (pH: 1.8) in 12 albino rabbits demonstrated, that – as all the effects have cleared up after a 72 hours observation period – the test substance is not a dermal irritant (TNO, 1984).

No data were found on skin irritation for the other gluconates of the category

Eye Irritation

Studies in Animals

In-vitro and in-vivo eye irritation tests with 0.1 ml of the 50% solution of gluconic acid (pH: 1.8) in 9 albino rabbits demonstrated, that – as all the effects have cleared up after a 72 hours observation period – the test substance is not an eye irritant (TNO, 1984).

No data were found on eye irritation for the other gluconates of the category.

3.1.4 Sensitisation

No data are available.

3.1.5 Repeated Dose Toxicity

Studies in Animals

A 28-day study was conducted by feeding rats by gavage with sodium gluconate at doses of 0, 500, 1000, 2000 mg/kg bw in water at a volume of 1 ml/ 100g bw. No death or clinical signs of abnormality were observed in any of the groups. Histopathological examination showed a thickening of the limiting ridge of the stomach in 5 out of 12 males at 2000 mg/kg bw per day dose. No toxic changes associated with the test article were detected. As the limiting ridge is a tissue specific to rodents, this lesion is not toxicologically relevant for humans. Other lesions occurred incidentally and were not treatment -related.

The NOAEL was estimated to be 1000 mg/kg bw/day for males and 2000 mg/kg bw/day for female (Mochizuki, M, Bozo Research Center, 1995a).

Another 28-day toxicity study in rats fed with a diet containing up to 5% w/w sodium gluconate (max. 4100 mg/kg bw for males and 4400 mg/kg bw for females) was conducted using a control group receiving equivalent concentration of sodium in the form of NaCl in order to differentiate the potential effects of high doses of sodium intake. No deaths occurred during the study period. No revisions in the general condition, body weight, or food and water intake were observed in the animals over the study period. No changes were observed in the investigated ophthalmologic tests, urinalysis, hematology and blood chemistry over the study period. In addition, histopathological examination indicated no adverse effects as a result of the treatment regime. Statistically significant differences in some urinary parameters reported in animals receiving 2.5 or 5% sodium gluconate were comparable to those observed in the NaCl control group, and were interpreted as related to the high sodium concentration of the diet.

The authors concluded that the NOAEL was 5% (equal to 4100 mg/kg bw per day). However, The JECFA committee who evaluated this report has concluded that the study was not suitable for identifying a NOAEL because of the small group sizes and the positive findings in the qualitative analysis, even if they have acknowledged that the effects shown in the qualitative urine analyses were related to the high sodium intake (Mochizuki, M. Bozo Research Center, 1997).

Nonetheless, this study demonstrates the lack of effects of the gluconate anion even in large doses as the urinary effects were attributed to the high sodium intake and was therefore considered as critical for this endpoint.

Repeated toxicity studies were also performed on Beagle dogs with sodium gluconate administered orally for 4 weeks at 500, 1000, 2000 mg/kg bw. doses. None of the animals died during the period of treatment in any dose group and no significantly toxicologically changes were detected in the body weight, food intake, water intake, urinalysis, haematological test, blood chemistry analysis, ophthalmologic test, electrocardiography, autopsy and organ weight or in histopathological examination. However, increased frequency of vomiting and loose or watery stools were observed in the 1000 and 2000 mg/kg bw. dose groups, as compared to controls.

On the basis of these results, the non-toxic dose was estimated to be 500 mg/kg bw / day. However, the toxicological effects observed (vomiting, passage of loose or watery stools) were considered extremely slight since other tests did not show the same changes (Okamoto, M. Bozo Research Center, 1995a).

Oral chronic studies with glucono-delta lactone on rats:
Glucono-delta-lactone (250, 500, 1000, 2000 and 4000 mg/kgbw. for 6 months) was orally administered to Sprague-Dawley rats. In all dose groups, thickening of the stratified squamous epithelium was detected at the anterior stomach, particularly the transitional area continuous with the pyloric stomach; the frequency and severity of this thickening increased with the dose. In high dose groups, submucosal inflammatory cell infiltration was also detected, but this change was not statistically significant. No deaths or other abnormalities were detected (Fukuhara K, 1978).

In Wistar rats fed for 24 months with a diet containing 2.5% and 10% of glucono-delta-lactone (the total intake of the drug : 1240-1350 mg/kgbw. in 2.5% GDL group and 4920-5760 mg/kgbw. in the 10 % GDL group), no changes were observed in the general condition throughout the period of testing, but weight gain tended to be slightly reduced 2-3 months after the initiation of the test feeding in 10% GDL group. There was no statistically significant difference in the number and time of deaths between the treated and control groups. Histopathological changes accompanying aging were observed in all groups including the controls, but no specific changes likely to be associated with the test substance were detected (Fukuhara K, 1978a).
Repeated dose toxicity results on Sodium gluconate and Glucono-delta-lactone

Substance tested	Species	Exposure period/route of administration	Doses (mg/kg bw/day)	Results	References
Sodium gluconate	Rat - Sprague Dawley 12 males 12 females	4 weeks Gavage	0, 500, 1000, 2000	NOAEL $_{males}$= 1000 mg/kg bw/day NOAEL $_{females}$= 1000 mg/kg bw/day	Mochizuki, M, Bozo Research Center, 1995a
	Rat- Sprague Dawley 10 males 10 females	28-day oral feeding	0, 1000, 2000, 4100	NOAEL= 4100 mg/kg bw/day	Mochizuki, M. Bozo Research Center, (1997)
	Dog – Beagle 4 males 4 females	4 weeks oral unspecified	0, 500, 1000, 2000	NOAEL = 500 mg/kg bw/day	Okamoto, M. Bozo Research Center, (1995)
Glucono-delta-lactone	Rat - Sprague Dawley 10 males 10 females	6 months oral	250, 500, 1000-2000, 4000	NOAEL : not determined	Fukuhara K., (1978)
	Rat – Wistar 30 males 30 females	24 months oral	2.5% (1240-1350 mg/kg bw) and 10 % (4920-5760 mg/kg bw)	NOAEL : not determined	Fukuhara K., (1978a)

Conclusion

In summary, none of the repeated dose toxicity studies of any duration (4 weeks, 6 months or 24 months) showed significant toxicological effects of gluconates. Potential side effects were attributed to high doses of cation intake, evidenced by results from assays designed for the gluconate anion effect specifically. The NOAEL of sodium gluconate determined from the 28 days studies on rats was equal to 1000 mg/kg bw for males and 2000 mg/kg bw for females.

On the basis of these data and considering that gluconates are used as food additives permitted in the EU following the Quantum Satis principle (no maximum level specified), further chronic toxicity tests are considered unnecessary.

3.1.6 Mutagenicity

Studies in Animals

In vitro Studies

Sodium gluconate, glucono-delta-lactone and calcium gluconate were tested on saccharomyces cerevisiae and salmonella typhimurium with and without metabolic activation. OECD Guideline 471 was deviated for the number of strains tested and the choice of positive controls. The substances were tested on saccharomyces cerevisiae (strain D4) and salmonella typhimurium (3 strains) with and without metabolic activation. Only 3 concentrations were tested where OECD guideline recommends at least 5 concentrations. None of the test substances showed mutagenicity on the strains tested.

The doses, strains used and results are shown in the table below:

In vitro genetic toxicity results of sodium gluconate, calcium gluconate and glucono-delta-lactone

Substance tested	Strains	Concentrations (µg/ml)	Cytotoxic concentration (50% survival) (µg/ml)	Result	Reference
Sodium gluconate	Bacteria salmonella typhimurium TA1535 TA1537 TA1538	0.06 0.012 0.024	0.024	negative	Litton Bionetics, Inc. (1975)
	Yeast: saccharomyces cerevisiae strain D4	12.5, 25 and 50	50	negative	
Glucono-delta-lactone	Bacteria salmonella typhimurium TA1535 TA1537 TA1538	2.5, 5 (5µg/ml plate test)	10	negative	Litton Bionetics, Inc. (1974)
	Yeast: saccharomyces cerevisiae strain D4	12.5, 25	50	negative	
Calcium gluconate	Bacteria salmonella typhimurium TA1535 TA1537 TA1538	12.5, 25 and 50	50	negative	Litton Bionetics, Inc. (1975a)
	Yeast: saccharomyces cerevisiae strain D4	7.5, 15 and 30	30	negative	

In vivo Studies

Sodium gluconate and glucono-delta-lactone were tested for induction of chromosomal aberration in mouse bone marrow cells after an oral single and a 4 days repeated dose administration. At least 200 metaphase cells per mouse were scored (C57BL male mice) and were examined for the presence or absence of chromosomal aberrations (gaps, breaks, translocation, fragments, ring chromosomes and minutes chromosomes). None of the tested substances induced chromosomal aberration (Tatsuo Yamashita et al, Fujisawa Pharmaceutical Co., Ltd. 1974).

In vivo genetic toxicity results of sodium gluconate and glucono-delta-lactone

Substance	No animal tested/group	Doses	Chromosomes' aberration (%)	Conclusion
Sodium gluconate	3	control	0.5	negative
	3	2.5 g/kg	0.5	
Single dose	3	5 g/kg	all animals died	
	3	10 g/kg	all animals died	
Positive control (mitomycin C)	2	5 mg/kg (intraperitoneal)	20	
Sodium gluconate	2	control	0.5	negative
	2	1.25 g/kg	0.5 (1 animal died)	
repeated dose	3	2.5 g/kg	0.5 (1 animal died)	
Positive control (mitomycin C)	2	5 mg/kg (intraperitoneal)	30	
Glucono-delta-lactone	3	control	0.5	negative
	3	2 g/kg	0.5	
Single dose	3	4 g/kg	0.5	
	3	8 g/kg	all animals died	
Positive control (mitomycin C)	2	5 mg/kg (intraperitoneal)	20	
Glucono-delta-lactone	2	control	1	negative
	2	2 g/kg	1	
repeated dose	3	4 g/kg	1	
Positive control (mitomycin C)	2	5 mg/kg (intraperitoneal)	30	

Conclusion

Although in the in vitro assays the strains used, the concentration tested and positive controls differed from OECD guideline 471, none of the test substances showed mutagenic properties on the strains tested.

The available in vitro and in vivo mutagenicity data with glucono-delta-lactone, sodium or calcium gluconate were negative. Furthermore gluconates are naturally present in cells. Therefore there is no reason to evaluate the potential genotoxicity of these substances further and no genotoxic effects are expected.

3.1.7 Carcinogenicity

No carcinogenicity studies were available for any of the gluconates of the category.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

SIDS testing requirements regarding reproductive toxicity were satisfied with histopathology of the reproductive organs in repeat dose studies on sodium gluconate and with developmental toxicity studies on glucono-delta-lactone.

Developmental Toxicity

The only available studies reported on the developmental toxicity for the gluconates of the category are for glucono-delta-lactone. These studies (unpublished) investigated teratogenicity following oral daily dosing of glucono-delta-lactone in 4 species (Food & Drug Research Laboratories - Unpublished data (1973).

The species, doses and results of those studies are summarized in the table below:

Developmental toxicity results of glucono-delta-lactone in the rat, mouse, hamster and rabbit

Species	Duration of test	Exposure period	Doses	Result (maternal and teratogen)
Wistar rat	10 days	From day 6 to day 15 of gestation	0, 5.94, 27.6, 128.0, 594.0 mg/kg	NOAEL > 594 mg/kg bw
CD-1 mouse	10 days	From day 6 to day 15 of gestation	0, 6.95, 32.5, 150, 695 mg/kg	NOAEL > 695 mg/kg bw
Hamster	5 days	From day 6 to day 10 of gestation	0, 5.60, 6.0, 121, 560 mg/kg	NOAEL > 560 mg/kg bw
Dutch rabbit	13 days	From day 6 to day 18 of gestation	0, 7.80, 36.2, 168.5, 780.0 mg/kg	NOAEL > 780 mg/kg

Two other studies conducted in 1978 to assess the potential teratogenicity of GDL on rats (Fukuhara, K. 1978b) and mice (Fukuhara, K. 1978c) reported that GDL was not teratogenic when given orally at doses > 4000 mg/kgbw.

The species, doses and results of those studies are summarized in the table below:

Species	Duration of test	Exposure period	Doses	Result (maternal and teratogen)
Sprague-Dawley rat	10 days	From day 6 to day 15 of gestation	1000 and 4000 mg/kg	NOAEL > 4000 mg/kg bw
ICR mouse	10 days	From day 6 to day 15 of gestation	1000 and 4000 mg/kg	NOAEL > 4000 mg/kg bw

In the above experiments GDL was administered orally to female nulliparous rats and/or mice for 10 days and the fetuses were observed by laparotomy on pregnancy day 21 or 18, respectively. Several dams in each group were allowed to deliver spontaneously, and the offspring were observed until postnatal day 21. The report does not contain specific information on the method used.

During pregnancy, no abnormalities were observed in the general condition, body weight change or food consumption in any of the dose groups, nor were any death. In observation of dams after laparotomy, no abnormalities were detected in the number of implantations, dead foetuses, live offspring or mean body weight of offspring, nor was there any influence of the drug on the external appearance, organs, or skeletons of the foetuses. Observation of the dams allowed to deliver spontaneously, protraction of the duration of pregnancy or abnormalities at birth were not observed, nor any influence of the drug detected in the mortality rate, body weight gain, behavior, external appearance or visceral abnormalities of the offspring during the period of nursing.

In summary, these negative data on the teratogenicity of glucono-delta-lactone, together with the natural occurrence of gluconic acid in the human metabolism sufficiently support the lack of developmental toxicity for all the gluconates of the category.

3.2 Initial Assessment for Human Health

Gluconates of the category are naturally occurring substances. Most of these compounds are listed as permitted food additives, which may be added to all foodstuffs, following the "quantum satis" principle, as long as no special regulations restrict their use.

In mammalian organisms both D-gluconic acid and its 1,5-lactone are important intermediates in the carbohydrate metabolism. Gluconate anion is a metabolite of glucose oxidation. The daily production of gluconate from endogenous sources is about 450 mg/kg for a 60 kg person (Life Science Research Office, 1978).

A significant portion (60-85%) of parenterally administered gluconate is excreted unchanged in the urine (Life Science Research, 1980)

The LD50 for potassium gluconate (oral toxicity study, wistar rat) is 6060 mg/kg bw (TNO 1978).

None of the repeated dose toxicity studies of any duration (4 weeks, 6 months, or 4 months) showed significant toxicological effects of gluconates. Potential side effects were attributed to high doses of cation intake, evidenced by results from assays designed for the gluconate anion effect specifically. The NOAEL of sodium gluconate determined from the 28 days studies on rats was equal to 1000 mg/kg bw for males and 2000 mg/kg bw for females (Mochizuki, M. Bozo Research Center, 1995a). These compounds are neither irritant to the eye or the skin (TNO, 1984). No sensitization, acute or chronic inhalation toxicity data are available.

The available in vitro and in vivo mutagenicity data with glucono-delta-lactone (Litton Bionetics, Inc 1974), sodium (Litton Bionetics, Inc 1975) or calcium gluconate (Litton Bionetics, Inc 1975a) were negative. No carcinogenicity studies were available for any of the gluconates of the category.

No reproduction toxicity study was available for any of the gluconates of the category. However, negative results in the histopathology of the reproductive organs in repeat dose studies on sodium gluconate and negative data on the teratogenicity of glucono-delta-lactone (Food & Drug Laboratories, 1973) support the lack of reproductive toxicity for all the gluconates of the category.

On the basis of these data showing a lack of toxicity and considering that gluconates have been recognized direct food additives, no further tests are considered necessary.

Exposure:

The manufacturing of gluconic acid is based on a fermentation process. Estimation of the worldwide industrial production per year for all the members of the gluconate category is around 65000 - 100000 tonnes. There is no production site in Belgium.

Human exposure by all routes (including inhalation) is possible. Workers exposure will mainly be by inhalation and by skin contact. Controlled manufacturing conditions and use of safety equipments will limit the accidental occupational exposure. Consumer exposure may be from the oral and dermal routes.

Exposure of consumers to gluconates is expected to be limited because gluconates are mostly used as additives in the different consumer products typically in low dosages (< 5%). Furthermore, consumer exposure in personal care products, pharmaceuticals and foodstuffs applications are

subject to specific regulatory provisions requiring an authorization procedure where the evaluation of the hazardous properties as well as the actual exposure is taken into account.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute toxicity to fish

The acute toxicity to fish in the studies reported in the literature was tested for sodium gluconate and glucono-delta-lactone.

Sodium gluconate was tested on fish (*Oryzias laticeps*) during 96 hours exposure following the procedure of OECD guideline 203. No toxicological symptoms or death were observed at the limit test using 100 mg/l nominal concentration. The limit test concentration was determined following a range finding test. The measured concentration of the test substance was within +/- 20% of the nominal concentration. (Mitsubishi Chemical Safety Institute Ltd, 2002)

Results of unpublished acute toxicity studies on fish (species not reported), are available for sodium gluconate (LC_{50} > 10 000 mg/l) and glucono-delta-lactone (LC_{50} = 360 mg/l) (Rübelt C., 1992). Although poorly documented and performed, these results support the low toxicity profile of the chemicals to fish in test conditions that were not controlled/corrected for pH effects (a decrease to pH 4 was observed in the test medium).

In summary, when correctly interpreted, these studies demonstrate that gluconates do not have any toxic effect on fish within the concentration ranges that are environmentally relevant.

Acute toxicity to aquatic invertebrates

The details of the studies on the acute toxicity of sodium gluconate, when tested on *Daphnia magna* are summarized in the table below:

Test substance: Sodium gluconate

Exposure period	Biomass loading	Concentration tested	Result	Method	Reference
24-48 hours	20 daphnias/concentration	0-1000 mg/l (nominal)*	24 hours: EC_{50}: > 1000 mg/l NOEC: > 1000 mg/l EC_{100}: > 1000 mg/l 48 hours: EC_{50}: > 1000 mg/l NOEC: > 1000 mg/l EC_{100}: > 1000 mg/l	OECD guideline 202	Mitsubishi Chemical Safety Institute Ltd, (2002a)
24-48 hours	20 daphnias/concentration	0-1000 mg/l	EC_0: > 1000 mg/l	OECD guideline 202	Hydrotox GmbH, (2001c)

*Measured concentrations of the test substance in the test solution were within +/- 20 % of the nominal concentration. Results were based on the nominal concentrations.

In summary, the tests suggest that gluconates (represented by sodium gluconate) do not have any toxic effects on daphnia.

Acute toxicity to aquatic plants (algae)

The details of the studies on the acute toxicity of sodium gluconate when tested on algae are summarized in the table below:

Test substance: Sodium gluconate

Species	Endpoint/ Exposure period/ Biomass loading	Concentration	Result	Method	Reference
Selenastrum capricornutum	Biomass and growth rate 72 hours/ 1 x 10^4 cells/ml	0, 100, 180, 320, 560, 1000 mg/l (nominal)*	E_bC_{50} (0-72 h): > 1000 mg/l $NOEC_b$ (0-72 h): 560 mg/l E_r C_{50} (24-48 h): > 1000 mg/l E_r C_{50} (24-72 h): > 1000 mg/l $NOEC_r$ (24-48h): 560 mg/l $NOEC_r$ (24-72h) : 560 mg/l	OECD guideline 201	Mitsubishi Chemical Safety Institue Ltd. (2002b)
Desmodesmus subspicatus CHODAT	Biomass and growth rate/ 72 hours/ 10 x 10^4 cells/ml	100-1000 mg/l	Cell growth inhibition : no inhibition at 100 mg/l 70% inhibition at 1000 mg/l Average specific growth rate inhibition: no inhibition at 100 mg/l 42% inhibition at 1000 mg/l	OECD guideline 201	Hydrotox GmbH (2001d)

*Measured concentrations of the test substance in the test solution were within +/- 20 % of the nominal concentration. Results were based on the nominal concentrations.

On the basis of these data sodium gluconate can be considered non toxic for algae.

Acute toxicity to micro-organisms (bacteria)

Results of a study on toxicity to bacteria (*Pseudomonas putida MIGULA*) following the German standard DIN 38 412 L8 are available for sodium gluconate (EC_0 > 5000 mg/l) and glucono-delta-lactone (EC_0 > 500 mg/l) (Rübelt C., 1992). Although not properly designed and performed, these results support that gluconates do not have any inhibiting capacity on the growth of bacteria.

4.2 Terrestrial Effects

No data are available for any of the gluconate of the category, however while the fugacity modeling reveals water and soil as the main target compartments for the substances, no direct exposure is expected to occur at any stage of the life-cycle of gluconates. Moreover, the demonstrated biodegradability and the low intrinsic toxicity of gluconates that was observed for aquatic organisms, the available animal toxicokinetic and metabolism data (cfr. human toxicology) and their role in mammalian carbohydrate metabolism may predict also a low effect on terrestrial organisms. Therefore, no terrestrial toxicity studies would be required.

4.3 Other Environmental Effects

4.4 Initial Assessment for the Environment

Gluconic acid, its salts of sodium, potassium and calcium as well as glucono-delta-lactone are all characterised by a low vapour pressure and a low octanol/water partition coefficient. The dissociation constant of gluconic acid is in the range of 3.5 to 3.8. Because of their good water solubility and low Log Kow, no bioaccumulation effects are to be expected and the substances were also shown to be readily metabolised.

Gluconates are readily biodegradable in aerobic and anaerobic conditions (Hydrotox GmbH, 2001 and 2001b). There is no potential of direct exposure of any environmental compartment.

Estimations from a Level II/III Fugacity Model from US EPA, show that the main target compartments of gluconates are water and soil. The calculated Henrys' law constants indicate a low potential for volatilization and the estimated photodegradation (AOP (v1.91) program) gives a $t_{1/2}$ between 1.7 to 4.0 hours. The good water solubility and low vapour pressure designate water to be a major target compartment for these substances.

Acute toxicity to aquatic organisms (fish, daphnia, algae) and bacteria were performed on sodium gluconate. In the range of concentrations tested, exceeding largely any expected environmental exposure; sodium gluconate did not show toxicity to any of the aquatic species. Because gluconates freely dissociate in water to the gluconate anion and their respective cation, data on sodium gluconate are acceptable for the other members of the category.

No terrestrial toxicity data for gluconates are available. However, the demonstrated biodegradability and the low intrinsic toxicity of gluconates that was observed for aquatic organisms, data on animal toxicokinetic and metabolism (cfr. human toxicology) and their role in mammalian carbohydrate metabolism may predict also a low effect on terrestrial organisms. Therefore, no terrestrial toxicity studies would be required.

Based on the physical-chemical properties of these substances, their low toxicity profile and their natural presence in living organisms, no toxic effect would be expected to the environment from the gluconate anion. Release of large amounts of gluconate salts in the environment leads also to the release of the sodium, calcium and potassium cations, which in certain circumstances may add to the overall cation load locally affecting the ecosystem. As these effects would be largely due to the presence of counter ions, these scenarios are not considered within the present SIAR document. While the lowering of the pH can be observed locally upon the release of gluconates in the aquatic environment, this change is adapted readily upon the control of the waste water stream, hence no significant impact on the pH of the aquatic environment can be expected in the long term. Further, as the sequestering tendency of gluconates decreases rapidly upon dilution or lowering the pH, they are destroyed effectively and quickly by biological waste water treatment.

Environmental exposure from non-dispersive uses is supposed to be limited as waste-water treatment is commonplace in such applications.

In wide dispersive applications, the chelating agents uses in building industry would not result in environmental exposure as the gluconate is bound within the microcrystalline fibers of cement and is not free to migrate to cause any environmental pollution.

Food applications could potentially contribute to spreading gluconates and glucono-delta-lactone in the environment, as these products are added in their crystalline or powder forms to food components such as meat, milk or soma at levels below 5 %w/w. However, since the final food is

meant for human consumption and mostly gets ingested, there is no real potential for environmental distribution of gluconates from this application either.

The only potential exposure to the environment would result from the release of counter-ions at high discharge concentration of gluconate salts.

5 RECOMMENDATIONS

The chemicals in this category are currently of low priority for further work because of their low hazard profile.

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I U C L I D

D a t a S e t

Existing Chemical	ID: 526-95-4
CAS No.	526-95-4
EINECS Name	D-gluconic acid
EC No.	208-401-4
Molecular Formula	C6H12O7
Producer Related Part	
Company:	Keller and Heckman LLP
Creation date:	02-APR-2003
Substance Related Part	
Company:	Keller and Heckman LLP
Creation date:	02-APR-2003
Memo:	OECD HPV Chemicals Programme, SIDS Dossier, approved at SIAM 18 (20-23 April 2004)
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Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

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Remark: Sponsor Country for this Category: Belgium; Co-sponsor country: Japan.
12-DEC-2005

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03-AUG-2004

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

Remark: Glucono-delta-lactone, gluconic acid and its sodium, calcium and potassium salts have been proposed in a category, as the salts of gluconic acid freely dissociate to the gluconate anion and the respective cation.

Glucono-delta-lactone (GDL) is the inner ester of gluconic acid formed by the removal of water.

When glucono-delta-lactone is used in aqueous solution, it is slowly hydrolysed until an equilibrium is reached between gluconic acid and its delta-lactone.

12-AUG-2004

1.1.0 Substance Identification

IUPAC Name: D-gluconic acid
Smiles Code: O=C (O) C (O) C (O) C (O) C (O) CO
Mol. Formula: C6H12O7
Mol. Weight: 196.16

07-JUN-2003

1.1.1 General Substance Information

Purity type: typical for marketed substance
Substance type: organic
Physical status: solid
Purity: ca. 49 - 52 % w/w
Colour: clear, yellow to brownish (for the aqueous solution)
Odour: characteristic

Remark: Gluconic acid is a mild organic acid, neither caustic nor corrosive and with excellent complexing ability. Gluconic acid is prepared by fermentation of pure dextrose, whereby the physiological d-form is produced.
The substance referred in this dossier is the aqueous solution (ca. 50%). Purity of the marketed substance in aqueous solution is 49-52%.

Anhydrous gluconic acid is a white, odorless, crystalline powder.
14-NOV-2005 (11)

1.1.2 Spectra

1.2 Synonyms and Tradenames

D(-)-pentahydroxy caproic acid

05-JUN-2003

dextronic acid

12-AUG-2004

glycogenic acid

12-AUG-2004

glyconic acid

12-AUG-2004

maltonic acid

12-AUG-2004

Pentahydroxy hexanoic acid

25-JUN-2003

1.3 Impurities

Purity type: typical for marketed substance

Remark: For food and/or medical applications the level of impurities complies with the restrictions laid down in the corresponding EU Directives.
15-JAN-2004

1.4 Additives

Remark: For all the chemicals of the category: no additives used
10-NOV-2005

1.5 Total Quantity

Quantity: ca. 4000 - 6000 tonnes produced in 2000

Remark: Estimation of the worldwide market per year (as 100% gluconic acid). There is no production in Belgium.

Flag: confidential
20-OCT-2003

1.6.1 Labelling

Remark: For all the chemicals in the category: proposal of Industry: no labelling required
10-NOV-2005

1.6.2 Classification

Classified: other, as in legislation

Remark: For all chemicals of the category: proposal of Industry: no classification required
10-NOV-2005

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Non dispersive use

Remark: Data for the category: see sodium gluconate
14-AUG-2003

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

Source of exposure: other

Remark: Data for the category: see sodium gluconate
14-AUG-2003

1.11 Additional Remarks

Remark: Gluconic acid is readily produced from glucose by mild oxidation. The oxidation may be accomplished chemically, electrolytically or enzymatically. Gluconic acid is used in industry and medicine largely for its ability to form readily soluble salts or complexes with various metals. This solubilizing function facilitates the absorption of cations from the intestine. In the tissues, the gluconates readily dissociate, liberating the metallic ion.
14-NOV-2005 (12)

Memo: Regulatory status

Remark: In the European Parliament and Council Directive 95/2/EC gluconic acid is listed as a generally permitted food additive (E 574) and may be added to all foodstuffs, following the "quantum satis" principle, as long as no special regulations restrict the use.
14-AUG-2003

1.12 Last Literature Search

1.13 Reviews

2.1 Melting Point

Value: = 131 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
10-AUG-2004 (22)

Value: ca. 120 - 131 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: The spread in melting point values is due to the formation of intramolecular anhydrides whose presence lowers the melting point
Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
09-AUG-2004 (23)

2.2 Boiling Point

Value: = 417.1 degree C

Method: other: calculated
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with MPBPVP (v1.41) program from US EPA (EPI v3.11)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2004

Value: = 102 degree C

Remark: Aqueous solution (approximately 50%)
25-JUN-2003 (10)

2.3 Density

Type: density
Value: = 1.23 g/cm³ at 20 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
09-AUG-2004 (23)

Type: density
Value: = 1.24 g/cm³ at 20 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used
Flag: Critical study for SIDS endpoint
09-AUG-2004 (5)

Type: density
Value: = 1.25 g/cm³

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used
Flag: Critical study for SIDS endpoint
09-AUG-2004 (20)

Type: density
Value: = 1.23 - 1.25 g/cm³ at 20 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used
Flag: Critical study for SIDS endpoint
09-AUG-2004 (11)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = .00000000109 hPa at 25 degree C

Method: other (calculated)
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with MPBPVP (v1.41) program from US EPA (EPI v3.11):

Vapor Pressure Estimations (25 deg C):
(Using BP: 417.09 deg C (estimated))

(Using MP: 131.00 deg C (exp database))
VP: 6.94E-011 mm Hg (Antoine Method)
VP: 8.17E-010 mm Hg (Modified Grain Method)
VP: 5.9E-007 mm Hg (Mackay Method)

Selected VP: 8.17E-010 mm Hg = 10.87E-010 hPa (Modified Grain Method)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2004

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: = -1.87 at 25 degree C

Method: other (calculated)
GLP: no

Remark: Estimated with Kowwin (v1.67) program from US EPA (EPI v3.11)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2004

2.6.1 Solubility in different media

Solubility in: Water
pKa: 3.7 at 25 degree C
Descr.: miscible

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
12-AUG-2004 (23)

Solubility in: Water
Value: > 999999 mg/l at 25 degree C

Method: other: calculated
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with Water sol (v1.01) program from US EPA (EPI v3.11) :

Log Water Sol (moles/L) at 25 dec C = 0.7074

Water Solubility (mg/L) at 25 dec C = 1e+006
Reliability: (2) valid with restrictions

Accepted calculation method
Flag: Critical study for SIDS endpoint
12-AUG-2004

Solubility in: Water
Descr.: other: freely soluble

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data.
Flag: Critical study for SIDS endpoint
12-AUG-2004 (22)

Solubility in: Water
Value: at 25 degree C
pH value: = 1.8
Conc.: 50 vol% degree C
Descr.: miscible

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used
Flag: Critical study for SIDS endpoint
12-AUG-2004 (11)

Solubility in: Water
pKa: 3.7 at 25 degree C
Descr.: miscible

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used
Flag: Critical study for SIDS endpoint
12-AUG-2004 (20)

Solubility in: other: ethanol
Descr.: slightly soluble (0.1-100 mg/L)

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data.
Flag: Critical study for SIDS endpoint
12-AUG-2004 (23)

Solubility in: other: nonpolar solvents

Descr.: insoluble (< 0.1 mg/L)

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data.
Flag: Critical study for SIDS endpoint
12-AUG-2004 (23)

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

2.9 Flammability

2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Dissociation Constant

Acid-base Const.: KA at 25°C= 1.99 x 10 exp-4, pKA = 3.70

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data.
Flag: Critical study for SIDS endpoint
09-AUG-2004 (23)

Acid-base Const.: K at 25°C = 2.5 x 10e-4

Method: other: no data specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data.
Flag: Critical study for SIDS endpoint
12-AUG-2004 (22)

2.13 Viscosity

2.14 Additional Remarks

Remark: Hydrogenation of gluconic acid in aqueous solution over a platinum oxide catalyst results in a modest yield of D-glucose, whereas the 1,5-lactone undergoes this reaction in high yield.

The 6 functional groups of gluconic acid can, in principle, react with a variety of reagents, such as alcohols, acids, etc. Nevertheless, the resulting derivatives tend to be stable only if reaction is complete. Partial reaction leads to nonuniform mixtures that are sensitive to hydrolysis; such reactions have little significance.

In contrast, considerable interest exists in the ability of gluconic acid and its alkali salts to form complexes with polyvalent cations. Some of these complexes are very stable.

07-JUN-2003 (23)

3.1.1 Photodegradation

Type: other

Method: other (calculated): Estimated with AOP (v1.91) program from US EPA (EPI v3.11)
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with AOP (v1.91) program from US EPA (EPI v3.11)

OVERALL OH Rate Constant = 42.3224 E-12 cm3/molecule-sec

HALF-LIFE = 0.253 Days (12-hr day; 1.5E6 OH/cm3)

HALF-LIFE = 3.033 Hrs
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
12-AUG-2004

3.1.2 Stability in Water

Type: abiotic

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: The dissociation in water is expected to be complete as the pKa is 3.70
Flag: Critical study for SIDS endpoint
14-NOV-2005 (23)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III
Media: other
Method: other: calculated

Remark: Estimated with the Level III Fugacity Model program LEVEL3NT from US EPA (EPI v3.11)

Chem Name : D-Gluconic acid
Molecular Wt: 196.16
Henry's LC : 4.74e-013 atm-m3/mole (Henrywin program)
Vapor Press : 8.17e-010 mm Hg (Mpbpwin program)

```
Liquid VP   : 9.13e-009 mm Hg  (super-cooled)
Melting Pt  : 131 deg C (user-entered)
Log Kow     : -1.87  (Kowwin program)
Soil Koc    : 0.00553  (calc by model)

         Mass Amount       Half-Life        Emissions
           (percent)            (hr)       (kg/hr)
-------------------------------------------------------
Air        0.00821             6.06       1000
Water       38.8               55.9       1000
Soil        61.2               55.9       1000
Sediment   0.0345               224         0
_______________________________________________________


          Fugacity  Reaction   Advection   Reaction  Advection
          (atm)     (kg/hr)    (kg/hr)     (%)       (%)
-------------------------------------------------------------
Air     2.41e-016    2.2       0.193      0.0734   0.00642
Water    1.1e-018  1.13e+003     91         37.6    3.03
Soil    6.42e-017  1.78e+003      0         59.3      0
Sediment 4.89e-019  0.251      0.00162    0.00837  5.4e-005

Persistence Time: 78.2 hr
Reaction Time:    80.7 hr
Advection Time:   2.57e+003 hr
Percent Reacted:  97
Percent Advected: 3.04

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air:      6.065
Water:    55.92
Soil:     55.92
Sediment: 223.7
Biowin estimate: 3.930  (days)

Advection Times (hr):
Air:      100
Water:    1000
Sediment: 5e+004
Reliability:      (2)  valid with restrictions
                  Accepted calculation method

Flag:             Critical study for SIDS endpoint
25-JAN-2006
```

3.3.2 Distribution

```
Media:            air - biota - sediment(s) - soil - water
Method:           other (calculation)

Remark:           Henry's law constant estimated with HENRY (v3.10) program
                  from US EPA (EPI v3.11)

                  HENRYs LAW CONSTANT at 25 deg C = 4.74E-013 atm-m3/mole
                  ------------------------------------------------------------
```

Soil Adsorption Coefficient estimated with PCKOC (v1.66)
program from US EPA (EPI v3.11)

First Order Molecular Connectivity Index : 5.913
Non-Corrected Log Koc : 3.7674
Fragment Correction(s):
* Organic Acid (-CO-OH) : -1.7512
2 Aliphatic Alcohol (-C-OH) : -3.0386

Corrected Log Koc : -1.0224
Over Correction Adjustment to Lower Limit Log Koc : 1.0000

Estimated Koc: 10
NOTE: The Koc of this structure may be sensitive to pH!
The estimated Koc represents a best-fit to the majority of
experimental values; however, the Koc may vary
significantly with pH.

Reliability: (2) valid with restrictions
Accepted calculation method

Flag: Critical study for SIDS endpoint

09-AUG-2004

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type:	aerobic
Inoculum:	other: secondary effluent of a municipal sewage plant (Breisgauer Bucht, 500000 population equivalent), 0.4 ml/l
Concentration:	3 mg/l related to Test substance
Contact time:	28 day(s)
Degradation:	= 89 % after 28 day(s)
Result:	readily biodegradable
Kinetic:	3 day(s) = 61.13 %
	7 day(s) = 74.35 %
	14 day(s) = 66.09 %
	21 day(s) = 71.94 %
	28 day(s) = 88.88 %
Control Subst.:	Acetic acid, sodium salt
Kinetic:	3 day(s) = 67.15 %
	28 day(s) = 80.93 %
Deg. product:	not measured
Method:	Directive 92/69/EEC, C.4-E
Year:	2001
GLP:	yes
Test substance:	other TS

Remark: The 89% degradation indicated here relates to the
Theoritical Oxygen Demand (ThOD).
Data for the category: see details of study under sodium
gluconate SIDS dossier.

Test substance: Sodium gluconate: 99.0-101.0%

Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid
test,quality assurance and GLP certificates

Flag: Critical study for SIDS endpoint
14-NOV-2005 (8)

Type: anaerobic
Inoculum: other: Digesting sludge of a municipal sewage plant (Breisgauer Bucht, 500000 population equivalent), 2.9 g total solids/l
Concentration: 303 mg/l related to Test substance
Contact time: 35 day(s)
Degradation: = 100 % after 35 day(s)
Result: readily biodegradable
Kinetic: 1 day(s) = 8 %
8 day(s) = 51 %
15 day(s) = 57 %
22 day(s) = 61 %
35 day(s) = 100 %
Control Subst.: Benzoic acid, sodium salt
Kinetic: 8 day(s) = 6 %
35 day(s) = 100 %
Deg. product: not measured

Method: other: DIN EN ISO 11734
Year: 2001
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
14-NOV-2005 (9)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: semistatic
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: > 100 -
LC0: > 100 -
Limit Test: yes

Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 2002
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate : 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
14-NOV-2005 (14)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: > 1000 -
EC100: > 1000 -
Limit Test: yes

Method: OECD Guide-line 202
Year: 2002
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate : 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
14-NOV-2005 (15)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: yes

NOEC: = 560 -
EC50: > 1000 -
Limit Test: yes

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 2002
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate : 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
14-NOV-2005 (16)

4.4 Toxicity to Microorganisms e.g. Bacteria

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

Species: other

Remark: No data available but exposure in sediment expected to be extremely limited according to the Level III Fugacity Model program LEVEL3NT from US EPA (EPI v3.11).
09-AUG-2004

4.6.2 Toxicity to Terrestrial Plants

Method: other

Remark: No data available
14-AUG-2003

4.6.3 Toxicity to Soil Dwelling Organisms

Type: other

Method: other

Remark: no data available but due to the low intrinsic toxicity in aquatic organisms, it is reasonable to expect a similar low toxic impact on terrestrial organisms
19-JAN-2004

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type:	LDLo
Species:	rat
Strain:	Crj: CD(SD)
Sex:	male/female
No. of Animals:	10
Vehicle:	no data
Doses:	500, 1000, 2000 mg/kg
Value:	> 2000 mg/kg bw
Method:	other: no data
Year:	1995
GLP:	no data
Test substance:	other TS
Remark:	Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance:	sodium gluconate
Reliability:	(2) valid with restrictions Short abstract not well documented but key study for initial assessment.
Flag:	Critical study for SIDS endpoint

14-NOV-2005 (18)

5.1.2 Acute Inhalation Toxicity

5.1.3 Acute Dermal Toxicity

5.1.4 Acute Toxicity, other Routes

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species:	rabbit
Concentration:	50 %
Exposure:	Occlusive
Exposure Time:	24 hour(s)
No. of Animals:	12
Vehicle:	water
Result:	not irritating
EC classificat.:	not irritating
Method:	other: Directive 79/831/EEC, B.4. "Acute toxicity" (skin irritation)
Year:	1984
GLP:	no data

Test substance: as prescribed by 1.1 - 1.4

Method: Primary irritation of the skin was measured by a patch-test technique on the abraded and intact skin of albino rabbits.

24 hours prior to applying the materials, the hair is removed from the backs of the animals with an electric clipper in such a way to avoid abrasions.

An amount of 0.5 ml (or 0.5g in case of solids or semi solids) of the test substance is brought on the intact or abraded skin under a surgical patch measuring 1 inch x 1 inch. The patches are fixed on the application site by means of adhesive tape and the entire trunk of the rabbits is wrapped with an impervious material to maintain the patches in position and to retard evaporation of volatile substances. 6 rabbits are treated on the intact skin, the other 6 on the abraded skin (abrasions are minor icisions through the stratum corneum but not deep enough to disturb the derma or to produce bleeding).

The exposure period was 4 hours and skin effects were examined at the end of the exposure period and then after 24, 48 and 72 hours.

The resulting skin reactions are evaluated by the method of Draize and CIVO-grading system.

Result: The test material caused very slight erythema in the 3 out of 6 rabbits. After 72 hours, these effects had cleared up completely.

Individual and average skin irritation scores of gluconic acid (50% in water)

Rabbit no	Hours after patch removal 1	24	48	72
(A=erythema) (B=oedema)	A-B	A-B	A-B	A-B
2059	1-0	0-0	0-0	0-0
2060	1-0	1-0	1-0	0-0
2061	1-0	0-0	0-0	0-0
2062	0-0	0-0	0-0	0-0
2063	0-0	0-0	0-0	0-0
2064	0-0	0-0	0-0	0-0
Average	0.5	0.2	0.2	0.0

Test substance: gluconic acid, 50% solution in water (pH of the test material: 1.8)
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-NOV-2005 (19)

5.2.2 Eye Irritation

Species: rabbit
Concentration: 50 %
Dose: .1 ml
Exposure Time: 4 hour(s)
No. of Animals: 9
Vehicle: water
Result: not irritating
EC classificat.: not irritating

Method: Draize Test
Year: 1984
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: For the in vivo eye irritation test, 9 New Zealand white albinos rabbits were used.

The eyes of the animals are examined before testing and only those animals without observable eye defects are used. 0.1 ml of the test substance is allowed to fall on the everted lower lid of one eye of each rabbit; the upper and lower eye lid are then carefully closed and subsequently held together for at least one second before releasing. The other eye, untreated, serves as a control.

Their eyes of 3 rabbits were not washed out after the instillation of the test substance. The eyes of the other 6 animals are washed out with 20 ml lukewarm water after 2 seconds (3 animals) or after 4 seconds (3 animals). The eyes are examined at 1, 24, 48, 72 hours and 7 days after instillation of the test material or until the eye effects have cleared up completely. Ocular reactions are scored with the Draize Method.

The in vitro assessment of eye irritating properties of the test material was made in enucleated rabbit eyes, placed in superfusion chambers at 32°C. The test material was applied to 4 eyes and the effects were observed with a Haag-Streit slit lamp biomicroscope, over a period of 4 hours following the application.

Result: Eye irritation (in vivo)

The test material generally caused slight redness and slight swelling of the conjuctivae. After 72 hours, these effects had cleared up.

Individual scores awarded to the ocular lesions elicited by gluconic acid (50% in water)

After one hour:

Rabbit Number	cornea opacity	Iris area	Conjunctivae redness	Conjunctivae chemosis	Discharge	Total score
2044	0	0	0	2	1	6

```
2100   / 0      0   / 1  / 1          1    /   1    /  11
2101   / 0      0   / 0  / 1          1    /   0    /  4
**********************************************************

After 24 hours:

_______________

Rabbit /cornea      /Iris /Conjunctivae     /Discharge/ Total
Number /opacity area/    /redness - chemosis/         / score
-------/------------/----/------------------/--------/-------
2044   / 0       0  / 0  / 1          1     /   0    /    4
2100   / 0       0  / 0  / 1          1     /   0    /    4
2101   / 0       0  / 0  / 1          0     /   0    /    2
**********************************************************

After 48 hours:

_______________

Rabbit /cornea      /Iris /Conjunctivae     /Discharge/ Total
Number /opacity area/    /redness - chemosis/         / score
-------/------------/----/------------------/--------/-------
2044   / 0       0  / 0  / 1          1     /   0    /    4
2100   / 0       0  / 0  / 1          1     /   0    /    4
2101   / 0       0  / 0  / 1          0     /   0    /    2
**********************************************************

After 72 hours:

_______________

Rabbit /cornea      /Iris /Conjunctivae     /Discharge/ Total
Number /opacity area/    /redness - chemosis/         / score
-------/------------/----/------------------/--------/-------
2044   / 0       0  / 0  / 0          0     /   0    /    0
2100   / 0       0  / 0  / 0          0     /   0    /    0
2101   / 0       0  / 0  / 0          0     /   0    /    0


Eye irritation (in vitro)
-------------------------
During the course of the 4 hours after treatment cornea
swelling was 4% and slight permeability of the superficial
epithelial cell layers of the cornea was observed.  These
effects were not considered to be of any toxicological
significance.
Test substance:   gluconic acid, 50% solution in water (pH of the test
                  material: 1.8)
Reliability:      (1)  valid without restriction
Flag:             Critical study for SIDS endpoint
25-JAN-2006                                                    (19)


5.3 Sensitization


5.4 Repeated Dose Toxicity

Type:                   Sub-acute
Species:                rat                          Sex: male/female
```

```
Strain:                  Crj: CD(SD)
Route of administration: gavage
Exposure period:         4 weeks
Frequency of treatment:  daily
Doses:                   0, 500, 1000, 2000 mg/kg bw
Control Group:           yes, concurrent no treatment
NOAEL:                   = 1000 mg/kg bw
NOAEL females :          = 2000 mg/kg bw

Method:           other: no data
  Year:           1995
   GLP:           no data
Test substance:   other TS

Remark:           Data for the category: see details of study under sodium
                  gluconate SIDS dossier
Test substance:   sodium gluconate
Reliability:      (2)  valid with restrictions
                  Secondary litterature but described in sufficient detail ina
                  recognised WHO report.  Acceptable for initial assessment.
Flag:             Critical study for SIDS endpoint
14-NOV-2005                                                              (17)


Type:                    Sub-acute
Species:                 rat                                Sex:
Strain:                  no data
Route of administration: oral feed
Exposure period:         10 days
Frequency of treatment:  daily
Doses:                   400 mg/kg/day
Control Group:           no data specified

Method:           other: no data specified
  Year:           1942
   GLP:           no data
Test substance:   as prescribed by 1.1 - 1.4

Result:           No effect on the metabolic rate.  Also, sodium and magnesium
                  gluconate were fed at a level of 450 mg/kg/day and the
                  metabolic rate reduced.  However, the rate returned to
                  normal when the gluconate feeding was discontinued. These
                  results suggest that the observed effects were produced by
                  the cations and not by the gluconate portion of the
                  molecule.
Test substance:   gluconic acid
Reliability:      (3)  invalid
                  secondary litterature
14-NOV-2005                                                               (1)

Type:                    Sub-acute
Species:                 human                              Sex: no data
Route of administration: oral unspecified
Exposure period:         3-6 days
Frequency of treatment:  no data
Doses:                   5-10 g/day
Control Group:           no data specified
```

Method: other: no data specified
Year: 1941
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: Oral administration of gluconic acid at doses of 5-10 g/day for periods varying from 3 to 6 days to five volunteers induced no renal changes, i.e. no blood, protein, casts, or sugar was observed in the urine.
Test substance: gluconic acid
Reliability: (3) invalid
old study
14-NOV-2005 (2)

Type: Sub-acute
Species: other: cats and dogs Sex: no data
Strain: no data
Route of administration: gavage
Exposure period: 14 days
Frequency of treatment: daily
Doses: 1 g gluconic acid (10% solution)
Control Group: no data specified

Method: other: not specified
Year: 1941
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: 5 cats and 3 dogs received a daily dose of 1 g gluconic acid (10% solution) by stomach intubation for 14 days.
Result: No changes were observed in general appearance or in the urine of either species. Several incidences of vomiting and diarrhoea were reported in 3 of the cats. Gross examination of the lungs, heart, liver, kidneys, gastrointestinal tract, urinary bladder, ureter, and spleen of treated animals showed that they were normal. No histological abnormalities were observed in the livers, lungs, or kidneys. The blood pressure of cats given intravenous injections of gluconic acid and ammonium gluconate (500 mg/kg) fell temporarily but returned to normal within 5 minutes.
Test substance: gluconic acid
Reliability: (3) invalid
14-NOV-2005 (2)

5.5 Genetic Toxicity 'in Vitro'

Type: other: Saccharomyces Cerevisiae and Salmonella typhimurium reverse mutation assay
System of testing: bacterial and non bacterial
Concentration: bacteria: 0.006%, 0.0012 %, 0.0024 % and yeast: 1.25%, 2.50% and 5.00%
Cytotoxic Concentration: 50% survival in bacteria calculated was at 0.0024 % test substance and 5% for yeast
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
Year: 1975
GLP: no data
Test substance: other TS

Remark: This study was conducted using 3 bacteria strains (salmonella typhimurium) and one yeast strain (saccharomyces cervisiae) rather than a fourth bacteria strain as indicators for this in vitro microbial assay with and without metabolic activation. Therefore, the results of this report on bacteria and yeast are included in the same entry.

Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate
Reliability: (2) valid with restrictions
OECD guideline No. 471 followed except that the study was made on one yeast strain : saccharomyces cerevisiae, strain D4 and 3 bacteria strains: S. typhimurium TA1535, TA1537 and TA 1538.

Positive controls different from the ones described in the OECD guideline No 471.

The study was made only on 3 test concentrations.
Flag: Critical study for SIDS endpoint
14-NOV-2005 (13)

5.6 Genetic Toxicity 'in Vivo'

Type: other: in vivo chromosomal aberration test with mouse bone marrow cells
Species: mouse Sex: male
Strain: C57BL
Route of admin.: oral feed
Exposure period: single dose and 4 days
Doses: single dose administration : 2.5, 5 and 10 g/kg.
4 day repeated dose: 1.25 and 2.5 g/kg
Result: negative

Method: other: no data specified
Year: 1974
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate
Reliability: (2) valid with restrictions
translation of a report not fully documented but acceptable for initial assessment
Flag: Critical study for SIDS endpoint
14-NOV-2005 (21)

5.7 Carcinogenicity

5.8.1 Toxicity to Fertility

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat Sex: female
Strain: Wistar
Route of administration: gavage
Exposure period: from day 6 to day 15 of gestation
Frequency of treatment: daily
Duration of test: 10 days
Doses: 0, 5.94, 27.6, 128.0, 594.0 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 594 mg/kg bw
NOAEL Teratogenicity: > 594 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-NOV-2005 (4)

Species: mouse Sex: female
Strain: CD-1
Route of administration: gavage
Exposure period: from day 6 to day 15 of gestation
Frequency of treatment: daily
Duration of test: 10 days
Doses: 0, 6.95, 32.5, 150, 695 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 695 mg/kg bw
NOAEL Teratogenicity: > 695 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-NOV-2005 (4)

Species: rabbit Sex: female

Strain: Dutch
Route of administration: gavage
Exposure period: from day 6 to 18 of gestation
Frequency of treatment: daily
Duration of test: 13 days
Doses: 0, 7.80, 36.2, 168.5, 780.0 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 780 mg/kg bw
NOAEL Teratogenicity: > 780 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-NOV-2005 (4)

Species: hamster Sex: female
Route of administration: gavage
Exposure period: from day 6 to day 10 of gestation
Frequency of treatment: daily
Duration of test: 5 days
Doses: 0, 5.60, 26.0, 121, 560 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 560 mg/kg bw
NOAEL Teratogenicity: > 560 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-NOV-2005 (3)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: oral unspecified
Exposure period: from day 6 to day 15 of gestation
Frequency of treatment: daily
Duration of test: 10 days
Doses: 1000 and 4000 mg/kg
Control Group: no data specified
NOAEL Maternal Toxity: > 4000 mg/kg bw
NOAEL Teratogenicity: > 4000 mg/kg bw

Result: non teratogen

Method: other: no data specified
Year: 1978
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (2) valid with restrictions
short abstract but acceptable for initial assessment
Flag: Critical study for SIDS endpoint
14-NOV-2005 (6)

Species: mouse Sex: female
Strain: ICR
Route of administration: oral unspecified
Exposure period: from day 6 to day 15 of gestation
Frequency of treatment: daily
Duration of test: 10 days
Doses: 1000 and 4000 mg/kg
Control Group: no data specified
NOAEL Maternal Toxity: > 4000 mg/kg bw
NOAEL Teratogenicity: > 4000 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1978
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (2) valid with restrictions
short abstract but acceptable for initial assessment
Flag: Critical study for SIDS endpoint
14-NOV-2005 (7)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

5.11 Additional Remarks

Type: Excretion

Remark: Effect of gluconic acid on the urine of human subjects:

Oral administration of gluconic acid at doses of 5-10 g/day for periods varying from 3 to 6 days to five volunteers

induced no renal changes, i.e. no blood, protein, casts, or sugar was observed in the urine. The results show that gluconic acid produces no signs of renal injury, judged in this way.

Oral administrations of 10-30 g gluconic acid showed that the excretion varies from 7.7 to 15 % of the dose in the 24 hours, the major part of the excretion taking place within the first few hours. The concentration in urine at 10-30 g doses was extremely variable, ranging fro 0.03 to .4 %, usually, however, less than 0.5 %

Effect of gluconic acid on the pH of the urine:

10 - 50 g doses gluconic acid were given at one time to 10 persons, 5 with and 5 without a urinary infection and marked variation of the average pH of the urine examined. In normal urine, the pH usually decined. In infected urine, a decline rarely occurred and the usual response was a rise of the pH. A similar resistance of infected urine to acidification by intravenous injections of gluconic acid in human beings was reported by Bodon. (1936)

Reliability: (3) invalid
Secondary litterature. Old study, not well documented

14-NOV-2005 (2)

Type: Metabolism

Remark: D-gluconic acid and its 1,5-lactone are important intermediates in carbohydrate metabolism. These compounds serve two important functions:

(1) they contribute to the synthesis of reduced nicotinamide-adenine dinucleotide phosphate (NADPH), which is required in the biosynthesis of fatty acids and steroids, and

(2) they lead to the formation of ribose-5-phosphate, which is used in nucleic acid synthesis.

Reliability: (2) valid with restrictions
Data from Handbook or collection of data.

14-NOV-2005 (23)

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I U C L I D

D a t a S e t

Existing Chemical	ID: 90-80-2
CAS No.	90-80-2
EINECS Name	D-glucono-1,5-lactone
EC No.	202-016-5
Molecular Formula	C6H10O6
Producer Related Part	
Company:	Keller and Heckman LLP
Creation date:	02-APR-2003
Substance Related Part	
Company:	Keller and Heckman LLP
Creation date:	02-APR-2003
Memo:	OECD HPV Chemicals Programme, SIDS Dossier, approved at SIAM 18 (20-23 April 2004)
Printing date:	25 JAN-2006
Revision date:	
Date of last Update:	25-JAN-2006
Number of Pages:	49
Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

Type: lead organisation
Name: The Gluconic acid and its sodium, potassium and calcium salts and glucono-delta-lactone consortium
Contact Person: Jean-Philippe Montfort Date: 02-APR-2003
Street: Rue Blanche 25
Town: 1060 Brussels
Country: Belgium
Phone: +32 2 541 05 70
Telefax: + 32 2 541 05 80
Email: montfort@khlaw.be

Remark: Sponsor Country for this Category: Belgium; Co-sponsor country: Japan.
12-DEC-2005

Type: manufacturer
Name: FUSO Chemical Co. Ltd
Contact Person: Ph.D. Shinichi Sugita Date:
Street: Iwamoto-cho Toyo Building, 1-2 Iwamoto-cho 3-chome, Chiyoda-ku
Town: 101 0032 Tokyo
Country: Japan
Phone: +81 3 5820 1611
Telefax: +81 3 5820 1634
Email: Shinichi.Sugita@fusokk.co.jp

03-AUG-2004

Type: manufacturer
Name: Jungbunzlauer International AG
Contact Person: Raphaël Singer Date: 17-APR-2003
Street: St. Alban-Vorstadt 90
Town: 4002 Basel
Country: Switzerland
Phone: +41 61 295 51 25
Telefax: +41 61 295 52 66
Email: raphael.singer@jungbunzlauer.ch

17-OCT-2003

Type: manufacturer
Name: Roquette Freres
Contact Person: Johnny Pallot Date:
Town: 62080 Lestrem Cedex
Country: France
Phone: +33 3 21 63 37 40
Telefax: +33 3 21 63 38 50
Email: JOHNNY.PALLOT@roquette.com

31-JUL-2003

Type: manufacturer
Name: PURAC
Contact Person: Ton van Dongen Date:
Street: PO BOX 21
Town: 4200 AA Gorinchem

Country: Netherlands
Phone: +31 183 695 730
Telefax: +31 183 695 603
Email: t.van.dongen@purac.com

03-AUG-2004

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

Remark: Glucono-delta-lactone, gluconic acid and its sodium, calcium and potassium salts have been proposed in a category, as the salts of gluconic acid freely dissociate to the gluconate anion and the respective cation.

Glucono-delta-lactone (GDL) is the inner ester of gluconic acid formed by the removal of water.

When glucono-delta-lactone is used in aqueous solution, it is slowly hydrolysed until an equilibrium is reached between gluconic acid and its delta-lactone.

12-AUG-2004

1.1.0 Substance Identification

IUPAC Name: D-gluconic acid, .delta. -lactone
Smiles Code: O=C (OC (C (O) C1O) CO) C1O
Mol. Formula: C6H10O6
Mol. Weight: 178.14

10-AUG-2004

1.1.1 General Substance Information

Purity type: typical for marketed substance
Substance type: organic
Physical status: solid
Purity: ca. 99 - 101 % w/w
Colour: white
Odour: neutral

Remark: Glucono-delta-lactone (GDL) is the inner ester of gluconic acid formed by the removal of water. GDL is commercially produced by an aerobic oxidising fermentation process to convert a carbohydrate source into gluconic acid. After fermentation a blend of gluconic acid and GDL is separated by crystallisation.

oxidation crystallisation

```
                Glucose -----------> gluconic acid <================> GDL

                        1/2 O2                          -H2O
                C6H12O6 -----------> C6H12O7     <================> C6H10O6
                                                        +H2O
10-NOV-2005                                                                 (21)
```

1.1.2 Spectra

1.2 Synonyms and Tradenames

D(-)-Pentahydroxycaproic acid-1,5-lactone

25-JUN-2003

Glucono-1,5-lactone

25-JUN-2003

glucono-delta-lactone

25-JUN-2003

pentahydroxycaproic acid 1,5-lactone

25-JUN-2003

1.3 Impurities

Purity type: typical for marketed substance

Remark: For food applications the level of impurities complies with the restrictions laid down in the corresponding EU Directives.
19-JAN-2004

1.4 Additives

Remark: For all the chemicals of the category: no additives used
10-NOV-2005

1.5 Total Quantity

Quantity: ca. 10000 - 20000 tonnes produced in 2000

Remark: Estimation of the worldwide market.
Flag: confidential
10-AUG-2004

Quantity: > 1000 tonnes produced in 1999

Remark: Estimated production capacity for glucono-delta-lactone in

Western Europe.
Flag: confidential
10-NOV-2005 (29)

1.6.1 Labelling

Remark: For all the chemicals in the category: proposal of Industry: no labelling required
10-NOV-2005

1.6.2 Classification

Classified: other, as in legislation

Remark: For all chemicals of the category: proposal of Industry: no classification required
10-NOV-2005

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Wide dispersive use

Remark: Data for the category: see sodium gluconate
14-AUG-2003

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

Source of exposure: other

Remark: Data for the category: see sodium gluconate
14-AUG-2003

1.11 Additional Remarks

Remark: In the European Parliament and Council Directive 95/2/EC glucono-delta-lactone is listed as a generally permitted food additive (E 575) and may be added to all foodstuffs, following the "quantum satis" principle, as long as no special regulations restrict the use.

The US Food and Drug Administration (FDA) assigned glucono-delta-lactone the "generally recognised as safe" (GRAS) status and permitted its use in food without limitation other than good manufacturing practice (21 CFR, §184.1318).
10-AUG-2004

1.12 Last Literature Search

12-AUG-2004

1.13 Reviews

2.1 Melting Point

Decomposition: yes at = 153 degree C

Method: other: no data specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data.
Flag: Critical study for SIDS endpoint
12-AUG-2004 (30)

Decomposition: yes at = 153 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
12-AUG-2004 (4)

Value: ca. 153 degree C

Method: other: no data specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
12-AUG-2004 (22)

Value: ca. 153 degree C
Decomposition: yes at > 180 degree C

Method: other: no data specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
12-AUG-2004 (13)

2.2 Boiling Point

Value: = 398.5 degree C

Method: other: calculated
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with MPBPWIN (v1.41) program from US EPA (EPI v3.11)

Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
10-AUG-2004

2.3 Density

Type: relative density
Value: = 1.68

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
10-AUG-2004 (4)

Type: bulk density
Value: = 800 kg/m3

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
10-AUG-2004 (13)

Type: bulk density
Value: ca. 800 kg/m3

Method: other: no data
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
10-AUG-2004 (22)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = .00000000241 hPa

Method: other (calculated)
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with MPBPVP (v1.41) program from US EPA (EPI v3.11):

```
                  Vapor Pressure Estimations (25 deg C):
                    (Using BP: 398.51 deg C (estimated))
                    (Using MP: 153.00 deg C (user entered))
                      VP:  2.5E-010 mm Hg (Antoine Method)
                      VP:  1.81E-009 mm Hg (Modified Grain Method)
                      VP:  1E-006 mm Hg (Mackay Method)
                    Selected VP:  1.81E-009 mm Hg = 2.41E-009 hPa (Modified
                  Grain Method)
Result:           Selected VP:  1.81E-009 mm Hg = 2.41E-009 hPa (Modified
                  Grain Method)
Reliability:      (2)  valid with restrictions
                  Accepted calculation method
Flag:             Critical study for SIDS endpoint
10-AUG-2004


2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow:          = -1.98

Method:           other (calculated)
   GLP:           no

Remark:           Estimated with Kowwin  (v1.67) program from US EPA (EPI
                  v3.11)
Reliability:      (2)  valid with restrictions
                  Accepted calculation method
Flag:             Critical study for SIDS endpoint
10-AUG-2004


2.6.1 Solubility in different media

Solubility in:    Water
Value:            = 590 g/l at 25 degree C

Method:           other: no data
   GLP:           no data
Test substance:   as prescribed by 1.1 - 1.4

Reliability:      (2)  valid with restrictions
                  Data from Handbook or collection of data
Flag:             Critical study for SIDS endpoint
10-AUG-2004                                                          (30)

Solubility in:    other: alcohol
Value:            ca. 10 g/l at 25 degree C

Method:           other: no data specified
   GLP:           no data
Test substance:   as prescribed by 1.1 - 1.4

Reliability:      (2)  valid with restrictions
                  Data from Handbook or collection of data.
Flag:             Critical study for SIDS endpoint
12-AUG-2004                                                          (30)
```

Solubility in: Water
Value: ca. 500 g/l at 20 degree C
pH value: = 4
Conc.: 1 vol% degree C

Remark: pH = 2.6 after 2 hours (equilibrium with gluconic acid of the 1% solution is reached after 2 hours)
Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
10-AUG-2004 (13)

Solubility in: Water
Value: ca. 500 g/l at 20 degree C
pH value: ca. 4
Conc.: 1 vol% degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: pH: approximately 4 at 1%, approximately 2.6 after 2 hours
Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
10-AUG-2004 (22)

Solubility in: Water
Value: = 590 g/l

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
10-AUG-2004 (4)

Solubility in: Water
Value: ca. 900 g/l at 20 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
12-AUG-2004 (32)

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

2.9 Flammability

2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Dissociation Constant

Acid-base Const.: pKA = 3.70

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
10-AUG-2004 (32)

2.13 Viscosity

2.14 Additional Remarks

3.1.1 Photodegradation

Type: air
Deg. products: not measured

Method: other (calculated): Estimated with AOP (v1.91) program from US EPA (EPI v3.11)
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with AOP (v1.91) program from US EPA (EPI v3.11)

OVERALL OH Rate Constant = 32.4111 E-12 cm3/molecule-sec

HALF-LIFE = 0.330 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 3.960 Hrs
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
12-AUG-2004

3.1.2 Stability in Water

Type: abiotic

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: When glucono-delta-lactone is used in aqueous solution, it is slowly hydrolysed until a balance is reached between gluconic acid and its delta-lactone. (see attached document).

At an initial concentration of 10% glucono-delta-lactone, the equilibrium gluconate-lactone is 80/20.

At 25°C, glucono-delta-lactone in solution in water at a concentration of w/w 0.75% has an equilibrium pH of 2.5-2.7.

When an alkaline product is added, the equilibrium is upset and all the lactone is converted into acid.
Attached doc.: hydrolysis rate of GDL at pH 6 and 7 (see attached document)
Reliability: (4) not assignable
Data from commercial brochures. No data on method used.
Flag: Critical study for SIDS endpoint
25-JAN-2006 (5) (23)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III
Media: other
Method: other: calculated

Remark: Estimated with the Level III Fugacity Model program LEVEL3NT from US EPA (EPI v3.11)

Chem Name : D-Gluconic acid, .delta.-lactone
Molecular Wt: 178.14
Henry's LC : 1.38e-009 atm-m3/mole (Henrywin program)
Vapor Press : 1.81e-009 mm Hg (Mpbpwin program)
Liquid VP : 3.34e-008 mm Hg (super-cooled)
Melting Pt : 153 deg C (user-entered)
Log Kow : -1.98 (Kowwin program)
Soil Koc : 0.00429 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.8	7.92	1000
Water	46.8	208	1000
Soil	52.3	208	1000
Sediment	0.0698	832	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	2.59e-013	461	52.7	15.4	1.76
Water	1.19e-014	1.03e+003	308	34.2	10.3
Soil	4.95e-013	1.15e+003	0	38.3	0
Sediment	8.91e-015	0.383	0.0092	0.0128	0.000307

Persistence Time: 220 hr
Reaction Time: 250 hr
Advection Time: 1.83e+003 hr
Percent Reacted: 88
Percent Advected: 12
Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 7.92
Water: 208.1
Soil: 208.1
Sediment: 832.3
Biowin estimate: 3.586 (days-weeks)

Advection Times (hr):

```
                  Air:      100
                  Water:    1000
                  Sediment: 5e+004
Reliability:      (2)  valid with restrictions
                  Accepted calculation method
Flag:             Critical study for SIDS endpoint
10-AUG-2004
```

3.3.2 Distribution

```
Media:            air - biota - sediment(s) - soil - water
Method:           other (calculation)

Result:           Henry's law constant estimated with HENRY (v3.10) program
                  from US EPA (EPI v3.11)

                  HENRYs LAW CONSTANT at 25 deg C = 1.38E-009 atm-m3/mole

                  ------------------------------------------------------------
                  Soil Adsorption Coefficient estimated with PCKOC (v1.66)
                  program from US EPA (EPI v3.11)

                  First Order Molecular Connectivity Index   :  5.575
                  Non-Corrected Log Koc   :  3.5876
                  Fragment Correction(s):
                  2   Aliphatic Alcohol  (-C-OH)   : -3.0386
                  1   Ester  (-C-CO-O-C-) or (HCO-O-C)  : -1.3089
                  Corrected Log Koc  : -0.7599
                  Over Correction Adjustment to Lower Limit Log Koc :  1.0000

                  Estimated Koc:  10
Reliability:      (2)  valid with restrictions
                  Accepted calculation method
Flag:             Critical study for SIDS endpoint
10-AUG-2004
```

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

```
Type:             aerobic
Inoculum:         other: secondary effluent of a municipal sewage plant
                  (Breisgauer Bucht, 500000 population equivalent), 0.4 ml/l
Concentration:    3 mg/l related to Test substance
Contact time:     28 day(s)
Degradation:      = 89 % after 28 day(s)
Result:           readily biodegradable
Kinetic:              3 day(s)    = 61.13 %
                      7 day(s)    = 74.35 %
                     14 day(s)    = 66.09 %
                     21 day(s)    = 71.94 %
                     28 day(s)    = 88.88 %
Control Subst.:   Acetic acid, sodium salt
Kinetic:               3 day(s)    = 67.15 %
                      28 day(s)    = 80.93 %
Deg. product:     not measured
```

Method: Directive 92/69/EEC, C.4-E
Year: 2001
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
The 89% degradation indicated here relates to the Theoritical Oxygen Demand (ThOD)
Test substance: Sodium gluconate: 99.0-101.0%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
10-NOV-2005 (11)

Type: anaerobic
Inoculum: other: Digesting sludge of a municipal sewage plant (Breisgauer Bucht, 500000 population equivalent), 2.9 g total solids/l
Concentration: 303 mg/l related to Test substance
Contact time: 35 day(s)
Degradation: = 100 % after 35 day(s)
Result: readily biodegradable
Kinetic: 1 day(s) = 8 %
8 day(s) = 51 %
15 day(s) = 57 %
22 day(s) = 61 %
35 day(s) = 100 %
Control Subst.: Benzoic acid, sodium salt
Kinetic: 8 day(s) = 6 %
35 day(s) = 100 %
Deg. product: not measured

Method: other: DIN EN ISO 11734
Year: 2001
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: Sodium gluconate
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
10-NOV-2005 (12)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: semistatic
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: > 100 -
LC0: > 100 -
Limit Test: yes

Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 2002
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate : 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
10-NOV-2005 (16)

Type: other
Species: other: no data
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: no data
LC0: = 250 -
LC50: = 360 -
LC100: = 400 -
Limit Test: no

Method: other: DIN 38 412 L15
Year: 1992
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: Due to the hydrolysis of the glucono-delta-lactone to gluconic acid, the pH was reduced and therefore the LC50 and LC100 observed are not related to the toxicity of the substance but rather due to the non physiologic conditions (pH= 4).
Test substance: Glucono-delta-lactone
Reliability: (3) invalid
short abstract, no data on species, unphysiologic conditions, no OECD guidelines
10-NOV-2005 (26)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)

Unit: mg/l Analytical monitoring: yes
NOEC: > 1000 -
EC100: > 1000 -
Limit Test: yes

Method: OECD Guide-line 202
Year: 2002
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate : 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
10-NOV-2005 (17)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: = 305 -
Limit Test: no

Method: other: DIN 38 412 -L 30
Year: 1997
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: At 200 mg/l, all daphnia kept their swimming capabilities.
At 250 mg/l, 7 daphnia kept their swimming capabilities.
At 333 mg/l, none of the daphnia kept their swimming capabilities.

The EC calculated for glucono-delta-lactone was 305 mg/l.

The report also refers to the GD value = dilution level where minimum 90% of the daphnia survived

= > Due to the GD value = 5 (at 200 mg/l 100% daphnia survived); glucono-delta-lactone was considered to be weak toxic.
Test condition: Species: daphnia magna
Biomass loading: 2 groups of 5 daphnias
Test concentration : 1 g/l
T°: 20°C
PH: 3.17
Test substance: glucono-delta-lactone

Reliability: (3) invalid
short abstract, no OECD guidelines
10-NOV-2005 (27)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: = 560 -
EC50: > 1000 -
Limit Test: yes

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 2002
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: Sodium gluconate: 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
10-NOV-2005 (18)

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: no data
EC50: > 1000 -
Limit Test: no

Method: other: DIN 38412 - L33
Year: 1997
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: GA = smallest dilution where inhibition of biomass production is reduced by 20% = > GA= 2

Dilution	Measured value	pH	% inhibition
1	11.3	6.02	30
2	13.4	6.46	-15*
3	13.3		-36.7*

* negative value = increase of the biomass production
Test condition: Incubation: 72 h
T°: 23°C.
Measurement of chlorophylle fluorescence: lambda = 450- 685 nm
Concentration of test: 1 g/l
pH= 3.09
Test substance: Glucono-delta-lactone
Reliability: (3) invalid
short abstract, no OECD guidelines
10-NOV-2005 (24)

4.4 Toxicity to Microorganisms e.g. Bacteria

Species: Pseudomonas putida (Bacteria)

Exposure period: 16 hour(s)
Unit: mg/l Analytical monitoring: no data
EC0: > 500 -

Method: other: DIN 38 412 L8
Year: 1992
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: 0-500 mg/l: stimulation of growth
> 500 mg/l: inhibition of growth due to the high concentration of glucono-delta-lactone that hydrolyses into the acid and reduces the pH (3.2-3.3).
Test condition: Exposure period: 16 h (+/- 1 h incubation)
Temperature: 21°C
Limit test: yes
2 range of concentration tested:
0-500 mg/l
> 500 mg/l
The pH was corrected to reach a value between 6 and 8.
Test substance: Glucono-delta-lactone
Reliability: (3) invalid
short abstract, no OECD guidelines
10-NOV-2005 (25)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

Species: other

Remark: No data available but exposure in sediment expected to be extremely limited according to the Level III Fugacity Model program LEVEL3NT from US EPA (EPI v3.11).
10-AUG-2004

4.6.2 Toxicity to Terrestrial Plants

Method: other

Remark: no data available
14-AUG-2003

4.6.3 Toxicity to Soil Dwelling Organisms

Method: other

Remark: no data available but due to the low intrinsic toxicity in aquatic organisms, it is reasonable to expect a similar low toxic impact on terrestrial organisms.
10-AUG-2004

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

In Vitro/in vivo:	In vivo
Type:	Absorption
Species:	rat

Method:	other: no data specified
Year:	1979
GLP:	no
Test substance:	as prescribed by 1.1 - 1.4
Method:	Radioactivity was measured in the blood of normal and alloxan diabetic rats, after oral administration of [U-14C]gluconate and [U-14C]glucono-delta-lactone (0.8 g/kg), respectively. Radioactivity was also measured in the intestinal contents and feces 5 h after ingestion of the radioactive materials.
Result:	glucono-delta-lactone is absorbed more rapidly from the intestine than sodium gluconate. A higher retention in tissues and a greater loss in urine was also observed after administration of the lactone. Incorporation into liver glycogen is also higher from the lactone than from the gluconate, particularly in diabetic animals. Initial oxidation occurred after 7 h with the gluconate and 4 h for the lactone. The oxidative turnover of lactone and gluconate was significantly enhanced in diabetic animals. The better utilisation in diabetic metabolism is in part explainable by a rise of glycolitic intermediates in the liver, which are decreased in starvation and diabetes.
Test substance:	glucono-delta-lactone
Reliability:	(4) not assignable Secondary literature

14-NOV-2005 (28)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type:	LDLo
Species:	rat
Strain:	Crj: CD(SD)
Sex:	male/female
No. of Animals:	10
Vehicle:	no data
Doses:	500, 1000, 2000 mg/kg
Value:	> 2000 mg/kg bw

Method:	other: no data
Year:	1995
GLP:	no data
Test substance:	other TS

Test substance: Sodium gluconate
Reliability: (2) valid with restrictions
Short abstract not well documented but key study for initial assessment.
Flag: Critical study for SIDS endpoint
14-NOV-2005 (19)

Type: LD50
Species: rat
Strain: no data
Sex: no data
Vehicle: no data
Doses: no data
Value: = 5940 mg/kg bw

Method: other: no data specified
Year: 1973
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Test substance: glucono-delta-lactone
Reliability: (4) not assignable
These are only results reported in another review paper. No other data are available
Flag: Critical study for SIDS endpoint
14-NOV-2005 (33)

Type: LD50
Species: mouse
Strain: no data
Sex: no data
Vehicle: no data
Doses: no data
Value: = 6800 mg/kg bw

Method: other: no data specified
Year: 1973
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Test substance: glucono-delta-lactone
Reliability: (4) not assignable
These are only results reported in another review paper. No other data are available.
Flag: Critical study for SIDS endpoint
14-NOV-2005 (33)

Type: LD50
Species: rabbit
Strain: no data
Sex: no data
Vehicle: no data
Doses: no data
Value: = 7850 mg/kg bw

Method: other: no data specified
Year: 1973
GLP: no data

Test substance: as prescribed by 1.1 - 1.4

Test substance: glucono-delta-lactone
Reliability: (4) not assignable
These are only results reported in another review paper. No other data are available.
Flag: Critical study for SIDS endpoint
14-NOV-2005 (33)

Type: LD50
Species: hamster
Strain: no data
Sex: no data
Vehicle: no data
Doses: no data
Value: = 5600 mg/kg bw

Method: other: no data specified
Year: 1973
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Test substance: glucono-delta-lactone
Reliability: (4) not assignable
These are only results reported in another review paper. No other data are available.
Flag: Critical study for SIDS endpoint
14-NOV-2005 (33)

5.1.2 Acute Inhalation Toxicity

5.1.3 Acute Dermal Toxicity

5.1.4 Acute Toxicity, other Routes

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: other: no data on glucono-delta-lactone. See gluconic acid

10-AUG-2004

5.2.2 Eye Irritation

Species: other: no data on glucono-delta-lactone. See gluconic acid

10-AUG-2004

5.3 Sensitization

5.4 Repeated Dose Toxicity

Type: Sub-acute
Species: rat Sex: male/female
Strain: Crj: CD(SD)
Route of administration: gavage
Exposure period: 4 weeks
Frequency of treatment: daily
Doses: 0, 500, 1000, 2000 mg/kg bw
Control Group: yes, concurrent no treatment
NOAEL: = 1000 mg/kg bw
NOAEL : = 2000 mg/kg bw

Method: other: no data
Year: 1995
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: Sodium gluconate
Reliability: (2) valid with restrictions
Secondary litterature but described in sufficient detail in a recognised International Organisation report. Acceptable for assessment.
Flag: Critical study for SIDS endpoint
14-NOV-2005 (20)

Type: Chronic
Species: rat Sex: male/female
Strain: Sprague-Dawley
Route of administration: oral unspecified
Exposure period: 6 months
Frequency of treatment: no data
Doses: 250, 500, 1000, 2000 and 4000 mg/kg
Control Group: no data specified

Method: other: no data specified
Year: 1978
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: In all dose groups, thickening of the stratified squamous epithelium was detected at the anterior stomach, particularly the transitional area continuous with the pyloric stomach, and the frequency and severity of this thickening increased with dose. In high dose groups, submucosal inflammatory cell infiltration was also detected, but this change was not statistically significant. The above changes seemed to represent irritation due to the drug.

No other abnormalities likely to be associated with the drug were detected, and there was no death.
Test condition: 10 males and 10 females tested.

During the period of treatment, observation of the general condition, measurement of body weight and food consumption and urinalysis were carried out.

At the end of treatment, animals were sacrificed, and blood specimen were collected for hematological and chemical analyses.

Major organs were observed grossly, weighed and examined histopathologically.

Test substance: glucono-delta-lactone
Reliability: (2) valid with restrictions
only abstract, no data on control group, GLP, method, frequency of exposure
Flag: Critical study for SIDS endpoint
14-NOV-2005 (7)

Type: Chronic
Species: rat Sex: male/female
Strain: Wistar
Route of administration: oral feed
Exposure period: 24 months
Frequency of treatment: no data
Doses: 2.5 % (1240-1350 mg/kg bw) and 10% (4920-5760 mg/kg) doses (30 males and 30 females tested)
Control Group: no data specified

Method: other: no data
Year: 1978
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: In test diet groups, no abnormalities were observed in the general condition throughout the period of testing, but weight gain tended to be slightly reduced since 2-3 months after the initiation of the test feeding in 10% GDL group. There was no statistically siginificant difference in the number of deaths
and the time to death between the test diet and the control groups.

Histopathological examination showed changes accompanying ageing were observed in all groups including the control, but no specific changes likely to be associated with the test diet were detected. Tumor development occurred considerably frequently, but tumor induction by the drug was not detected.

Test condition: The rats were fed with pellets containing 2.5% and 10 % concentration of glucono-delta-lactone. The total intake of the drug during testing was 1240-1350 mg/kg bw for the group receiving 2.5% GDL and 4920-5760 mg/kg bw for the group receiving 10 % in the pellets.

Test substance: glucono-delta-lactone
Reliability: (2) valid with restrictions
only abstract, no data on control group, GLP, frequency of exposure
Flag: Critical study for SIDS endpoint

14-NOV-2005 (6)

Type: Chronic
Species: rat Sex: male/female
Strain: no data
Route of administration: other: diet
Exposure period: 26 weeks
Doses: 0 and 500 mg/kg bw
Control Group: no data specified
NOAEL: > 500 mg/kg bw

Method: other: no data specified
Year: 1962
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: No reported adverse effects and no histopathological findings.
Test substance: glucono-delta-lactone
Reliability: (3) invalid
only secondary litterature + old study

14-NOV-2005 (2)

Type: Sub-acute
Species: human Sex: no data
Strain: no data
Route of administration: oral feed
Exposure period: 3-6 days
Frequency of treatment: daily
Doses: 80-170mg/kg/day
Control Group: no data specified

Method: other: no data specified
Year: 1941
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: Oral doses of GDL (80-170mg/kg/day) were administered to 5 healthy human subjects for 3-6 days.
Result: There was no sign of renal injury as judged by examining urine for protein, casts, blood cells, pus cells and sugar.
Test substance: glucono-delta-lactone
Reliability: (3) invalid
old study

14-NOV-2005 (1)

5.5 Genetic Toxicity 'in Vitro'

Type: other: Saccharomyces Cerevisiae and Salmonella typhimurium
System of testing: bacterial and non bacterial
Concentration: bacteria: 0.25%, (2.5 µg/ml) and 0.50% (5 µg/ml) (0.50% plate test) and yeast: 1.25% (12.5 µg/ml) and 2.50% (25 µg/ml)
Cytotoxic Concentration: 50% survival in bacteria calculated was at 1% (10 µg/ml) test substance and 5% (50 µg/ml) for yeast
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
Year: 1974
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: A. Toxicity:

The solubility, toxicity and doses for all chemicals were determined prior to screening.

Each chemical was tested for survival against strains TA-1537 and D4 over a range of doses to determine the 50% survival dose. Bacteria were tested in phosphate buffer, pH 7.4 for one hour at 37°c on a shaker.

Yeasts were tested in phosphate buffer, pH 7.4 for 4 hours at 30°c on a shaker. The 50% survival curve and the 1/4 and 1/2 50% doses calculated. If no toxicity was obtained for a chemical with a given strain, a maximum dose of 5% (w/v) was used.

The doses calculated for the tests in buffer were applied to the activation tests. The solubility of the test substance under treatment conditions was measured and GDL is soluble in 0.067 M phosphate buffer, pH 7.4 (solvent used for this compound)

B. Plate tests

Approximately 10 exp9 cells from a log phase culture of each strain were spread over the surface of a minimal plate, and a measured amount of the test chemical was placed in the center of the test plate.

In activation tests, the test chemical was added to the cells, and an aliquot of the mixture was spread on the surface o fhte test plate. The reaction mixture (0.1 ml) plus tissue extract was then spotted on hte surface of the plate.

The plates were incubated for 4 days at 37°C, and scored. Positive and
solvent controls were run with each assay.

C. Suspension tests

1. Nonactivation

Log phase bacteria and stationary phase yeast cultures were grown in complete broth, washed and resuspended in 0.9% saline to densities of 1 x 10 exp9 cells/ml and 5 x 10 exp7 cells/ml respectively. Tests were conducted in plastic tissue culture plates. Cells plus chemicals were added to the wells to give a final volume of 2 ml. The solvent

replaced the test chemical in the negative controls.

Treatment was at 30°C for 4 hours for yeast tests and at 37°c for one hour for bacterial tests. All flasks were shaken during treatment. After treatments, the plates were set on ice. Aliquots of cells were removed, diluted in sterile saline (4°c) and plated on the appropriate complete media. Undiluted samples from flasks containing the bacteria were plated on minimal selective medium in reversion experiments. Samples from a 1/10 dilution of treated cells were plated on the selected media for enumeration of gene conversion with strain D4.

Bacterial plates were scored after incubation for 48 hours at 37°C. The yeast plates were incubated at 30°C for 3-5 days before scoring.

2. Activation

Bacteria and yeast cells were grown and prepared as described in the nonactivation tests except that the cell densities were increased approximately 5 x for working stock suspensions. Measured amounts of the test and control chemicals plus 0.25 ml of the stock cell suspension were added to a 30 ml plastic tissue homogenate. All flasks were incubated at 37°C with shaking.

Remark: This study was conducted using 3 bacteria strains (salmonella typhimurium) and one yeast strain (saccharomyces cervisiae) rather than a fourth bacteria strain as indicators for this in vitro microbial assay with and without metabolic activation. Therefore, the results of this report on bacteria and yeast are included in the same entry.

Result: Glucono-delta-lactone was not genetically active, either directly or in the presence of organ homogenates, in any of the in vitro assays employed in this evaluation.

Test condition:

Strains tested:

Yeast: Saccharomyces Cerevisiae, Strain D4

Bacteria: Salmonella typhimurium, strains: TA1535, TA1537, TA1538

Reaction mixture:

Component:	Final concentration/ml
TNP (sodium salt)	6 µM
Isocitric acid	49 µM
Tris buffer, pH 7.4	28 µM
MgCl2	1.7 µM
Isocitric dehydrogenase	6.3 units

Tissue homogenate or cell fraction

Tissue homogenates and supernatants:

The tissue homogenates and supernatants (9000 g) were prepared from tissues of mouse (ICR random bred adult males); rat (Sprague-Dawnley adult males) and monkey (Macaca mulatta adult males)

Positive controls in direct and activation assays:

Non activation:

Chemical	Solvent	Probable mutagenic specificity
Ethyl methanesulfonate (EMS)	water or saline	base-pair substitution
2-nitrofluorene (NF)	dimethylsulfoxide	frameshift
Quinacrine or quinacrinemustard (QM)	water or saline	frameshift

****

Activation:

Chemical	Solvent	Probable mutagenic specificity
Dimethylnitrosamine (DMN)	water or saline	base-pair substitution
2-acetylaminofluorene (AAF)	dimethylsulfoxide	frameshift

Concentration of positive controls:

Non activation:
TA-1535 EMS 0.05ml/plate
TA-1537 QM 0.25mg/plate
TA-1538 NF 0.25 mg/plate

Activation:
TA-1535 DMN 25 µM/plate
TA-1537 AAF 1.25 mg/plate
TA-1538 AAF 1.25 µg

Test substance: glucono-delta-lactone

Reliability: (2) valid with restrictions
OECD guideline 471 requires that 5 strains of bacteria at least are tested: 4 strains of S. typhimurium (TA1535,TA1537 or TA97 or TA97a, TA98, TA100) and E. Coli WP2 uvrAor E. Coli WP2uvrA (pKM101) or S.typhirmurium TA102.
The study was made on one yeast strain : saccharomyces cerevisiae, strain D4 and 3 bacteria strains: S. typhimuriumTA1535, TA1537 and TA 1538

Positive controls are different from the controls described in OECD guideline 471.

At least 5 concentrations should be tested, the substance was only tested on 3 concentrations.

Flag: Critical study for SIDS endpoint

25-JAN-2006 (14)

5.6 Genetic Toxicity 'in Vivo'

Type:	other: in vivo chromosomal aberration test with mouse bone marrow cells
Species:	mouse Sex: male
Strain:	C57BL
Route of admin.:	oral feed
Exposure period:	single dose and 4 days
Doses:	single dose administration : 2, 4 and 8 g/kg 4 day repeated dose: 2 and 4 g/kg
Result:	negative
Method:	other: no data specified
Year:	1974
GLP:	no data
Test substance:	as prescribed by 1.1 - 1.4

Method: After receiving the single dose and the repeated dose test substance, the animals were sacrified at 24 hours (single dose) and 27 hours after last administration (4-days repeated dose). 0.3 ml of 500 µg/ml colchicine was intraperitoneally injected to each mouse at one hour before sacrifice so that the metaphase cells could be observed.

After the bone marrow cells were washed, treated and fixed with a fixing solution (1:3 acetic acid:ethanol solution), the cells were suspended and dripped on a slide glass and stained with Giemsa solution and examined.

Examination:

At least 200 metaphase cells per mouse were examined for the presence or absence of chromosomal aberrations (gaps, breaks, translocation, fragments, ring chromosomes and minutes chromosomes)

Result: Single dose administration:

At 8 g/kg, all mice died.

MMC induced chromosomal aberrations in at least 20% of bone marrow cells.

GDL induced chromosomal aberrations in the cells at a frequency of about 0.5% comparable to the control.

4-day repeated dose administration:

MMC induced chromosomal aberrations at about 30% cells.

The frequency of cells with chromosomal aberrations was 1 % or less in the test groups which is comparable to the control group.

Induction of chromosomal aberration by GDL was

not detected after in vivo single and repeated dose treatment.

Test condition: Animals:

Male C57BL/6 mice aged 12 or 13 weeks

Materials:

Test substance: GDL dissolved with 0.9% physiological saline solution and orally administered at a dose of 1ml/mouse

Positive control: MMC (mitomycin C) dissolved with 0.9% physiological saline solution and administered intraperitoneally at a dose of 0.5 ml/mouse

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Single dose administration :

Control (physiological solution) :
group 1 - 3 animals

MMC:
group 1 - 2 animals - 5 mg/kg (intraperitoneal)

GDL :
group 1 - 3 animals - 8 g/kg
group 2 - 3 animals - 4 g/kg
group 3 - 3 animals - 2 g/kg

4-day repeated dose administration :

Control (physiological solution) :
group 1 - 2 animals

MMC:
group 1 - 2 animals - 5 mg/kg (single dose intraperitoneal)

GDL :
group 1 - 3 animals - 4 g/kg
group 2 - 2 animals - 2 g/kg

Test substance: glucono-delta-lactone

Reliability: (2) valid with restrictions
Translation of a report. No data on GLP, guidelines, conditions, mitotic index, but sufficient for initial assessment.

Flag: Critical study for SIDS endpoint

14-NOV-2005 (15)

5.7 Carcinogenicity

5.8.1 Toxicity to Fertility

5.8.2 Developmental Toxicity/Teratogenicity

Species:	rat	Sex: female
Strain:	Wistar	
Route of administration:	gavage	
Exposure period:	from day 6 to day 15 of gestation	
Frequency of treatment:	daily	
Duration of test:	10 days	
Doses:	0, 5.94, 27.6, 128.0, 594.0 mg/kg	
Control Group:	yes, concurrent vehicle	
NOAEL Maternal Toxity:	> 594 mg/kg bw	
NOAEL Teratogenicity:	> 594 mg/kg bw	
Result:	non teratogen	

Method: other: no data specified
Year: 1973
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: The administration of up to 594 mg/kg bw of GDL to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

Test condition: Positive control: 250 mg/kg Aspirin

Body weights were recorded on days 0, 6, 11, 15 and 20 of gestation. On day 20, all dams were subjected to caesarean section and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded.Body weights of the live pups were also recorded.The urogenital tract of each dam was examined in detail for anatomical normality. All the fetuses were examined grossly for the presence of external congenital abnormalities. 1/3 of the fetuses of each litter underwent detailed visceral examinations employing the Wilson technique. The remaining 2/3 were cleared in KOH, stained with alizarin red S dye and examined for skeletal defects.
Test substance: glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-NOV-2005 (3)

Species:	mouse	Sex: female
Strain:	CD-1	
Route of administration:	gavage	
Exposure period:	from day 6 to day 15 of gestation	
Frequency of treatment:	daily	
Duration of test:	10 days	
Doses:	0, 6.95, 32.5, 150, 695 mg/kg	
Control Group:	yes, concurrent vehicle	

NOAEL Maternal Toxity: > 695 mg/kg bw
NOAEL Teratogenicity: > 695 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: The administration of up to 695 mg/kg bw of GDL to pregnant mice for 10 consecutive days had no clearly discernibleeffect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.
Test condition: Positive control: 150 mg/kg Aspirin

Body weights were recorded on days 0, 6, 11, 15 and 17 ofgestation.On day 17, all dams were subjected to caesarean section and the numbers of implantation sites, resorption sites, andlive and dead fetuses were recorded.Body weights of the live pups were also recorded.The urogenital tract of each dam was examined in detail foranatomical normality.All the fetuses were examined grossly for the presence ofexternal congenital abnormalities.1/3 of the fetuses of each litter underwent detailedvisceral examinations employing the Wilson technique.The remaining 2/3 were cleared in KOH, stained with alizarinred S dye and examined for skeletal defects.
Test substance: glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-NOV-2005 (3)

Species: rabbit Sex: female
Strain: Dutch
Route of administration: gavage
Exposure period: from day 6 to 18 of gestation
Frequency of treatment: daily
Duration of test: 13 days
Doses: 0, 7.80, 36.2, 168.5, 780.0 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 780 mg/kg bw
NOAEL Teratogenicity: > 780 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: The administration of up to 780 mg/kg bw of GDL to pregnant rabbits for 13 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. Thenumber of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

Test condition: Positive control: 2.5 mg/kg 6-aminonicotinamide dosed on day 9.

On day 0, each doe was given an injection of 0.4 ml of human chorionic gonadotropin (400 IU) via the marginal ear vein. 3 hours later, each doe was inseminated artificially with 0.3 ml of diluted semen using approximately 20 x 10exp6 motile sperm. Beginning on day 6 until day 18, the females were dosed by oral intubation. Body weights were recorded on days 0, 6, 12, 18 and 29 of gestation. On day 29, all does were subjected to caesarean section andthe numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. Body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality.All the fetuses were examined grossly for the presence of external congenital abnormalities.The live fetuses of each litter were placed in an incubator for 4 hours for evaluation of neonatal survival. All surviving pups were sacrificed and examined for visceral abnormalities. All fetuses were then cleared in KOH, stained with alizarin red S dye and examined for skeletal defects.

Test substance: glucono-delta-lactone
Reliability: (1) valid without restriction

Flag: Critical study for SIDS endpoint
14-NOV-2005 (3)

Species: hamster Sex: female
Strain: no data
Route of administration: gavage
Exposure period: from day 6 to day 10 of gestation
Frequency of treatment: daily
Duration of test: 5 days
Doses: 0, 5.60, 26.0, 121, 560 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 560 mg/kg bw
NOAEL Teratogenicity: > 560 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: The administration of up to 560 mg/kg bw of GDL to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.
Test condition: Positive control: 50 mg/kg Aspirin

Body weights were recorded on days 0, 6, 8, 10 and 14 of gestation. On day 14, all animals were subjected to caesarean section and the numbers of implantation sites,

resorption sites, and live and dead fetuses were recorded.Body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality. All the fetuses were examined grossly for the presence of external congenital defects. 1/3 of the fetuses of each litter underwent detailed visceral examinations employing the Wilson technique. The remaining 2/3 were cleared in KOH, stained with alizarin red S dye and examined for skeletal defects.
Test substance: glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-NOV-2005 (3)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: oral unspecified
Exposure period: from day 6 to day 15 of gestation
Frequency of treatment: daily
Duration of test: 10 days
Doses: 1000 and 4000 mg/kg
Control Group: no data specified
NOAEL Maternal Toxity: > 4000 mg/kg bw
NOAEL Teratogenicity: > 4000 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1978
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: During pregnancy, no abnormalities were observed in the general condition, body weight change or food consumption in any of the dose groups, nor were the deaths. In observation of dams after laparotomy, no abnormalities were detected in the number of implantations, dead fetuses, live offspring or mean body weight of offspring, nor was there any influence of the drug on the external appearance, organs, or skeletons of the fetuses. Observation of the dams allowed to deliver spontaneously, protraction of the duration of pregnancy or abnormalities at birth were not observed, nor any influence of the drug detected in the mortality rate, body weight gain, behavior,external appearance or visceral abnormalities of the offspring during the period of nursing.
Test condition: GDL was administered orally to female nulliparous rats for 10 days and the fetuses were observed by laparotomy on pregnancy day 21. Several dams in each group were allowed to deliver spontaneously, and the offspring were observed until postnatal day 21.
Test substance: glucono-delta-lactone
Reliability: (2) valid with restrictions
Short abstract but acceptable for initial assessment
Flag: Critical study for SIDS endpoint
14-NOV-2005 (9)

Species: mouse Sex: female
Strain: ICR
Route of administration: oral unspecified
Exposure period: from day 6 to day 15 of gestation
Frequency of treatment: daily
Duration of test: 10 days
Doses: 1000 and 4000 mg/kg
Control Group: no data specified
NOAEL Maternal Toxity: > 4000 mg/kg bw
NOAEL Teratogenicity: > 4000 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1978
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: During pregnancy, no abnormalities were observed in the general condition, body weight change or food consumption in any of the dose groups, nor were the deaths. In observation of dams after laparotomy, no abnormalities were detected in the number of implantations, dead fetuses, live offspring or mean body weight of offspring, nor was there any influence of the drug on the external appearance,organs, or skeletons of the fetuses. Observation of the dams allowed to deliver spontaneously, protraction of the duration of pregnancy or abnormalities atbirth were not observed, nor any influence of the drug detected in the mortality rate, body weight gain, behavior,external appearance or visceral abnormalities of the offspring during the period of nursing.
Test condition: GDL was administered orally to female nulliparous mice for10 days and the fetuses were observed by laparotomy on damson pregnancy day 18. Several dams in each group wereallowed to deliver spontaneously, and the offspring wereobserved until postnatal day 21.
Test substance: glucono-delta-lactone
Reliability: (2) valid with restrictions
Short abstract but acceptable for initial assessment
Flag: Critical study for SIDS endpoint
14-NOV-2005 (8)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

5.11 Additional Remarks

Type: Biochemical or cellular interactions

Remark: GDL was reported to inhibit competitively mannosidase and glucosidase isolated from rat epididymis and limpet tissue

(Levvy et al. 1964). These findings were confirmed using acid alpha-glucosidase from rabbits (Palmer, 1971).

GDL is a non-competitive inhibitor of polysaccharide phosphorylase in in vitro assays (Tu et al., 1971)

Reliability: (3) invalid
only secondary litterature

07-JUN-2003 (31)

Type: Excretion

Remark: 16 persons (7 with urologic conditions) received doses of 5 g glucono-delta-lactone every 2 hours up to total doses of 15-25g daily for 2 days usually followed by a 2-day control period, then 10-25 g doses every 2 hours up to total doses of 20-50 g for an additional day.

No consistent changes in the pH of the urine were detectable. However, diarrhea was observed in 11 of the 16 patients. No other adverse effects were reported.

Reliability: (3) invalid
Secondary litterature

14-NOV-2005 (10)

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I U C L I D

D a t a S e t

Existing Chemical	ID: 527-07-1
CAS No.	527-07-1
EINECS Name	sodium gluconate
EC No.	208-407-7
Molecular Formula	C6H12O7.Na

Producer Related Part	
Company:	Keller and Heckman LLP
Creation date:	02-APR-2003
Substance Related Part	
Company:	Keller and Heckman LLP
Creation date:	02-APR-2003
Memo:	OECD HPV Chemicals Programme, SIDS Dossier, approved at SIAM 18 (20-23 April 2004)

Printing date:	25-JAN-2006
Revision date:	
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Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

Type: lead organisation
Name: The Gluconic acid and its sodium, potassium and calcium salts and glucono-delta-lactone consortium
Contact Person: Jean-Philippe Montfort Date: 02-APR-2003
Street: Rue Blanche 25
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Email: montfort@khlaw.be

Remark: Sponsor Country for this Category: Belgium; Co-sponsor country: Japan.
12-DEC-2005

Type: manufacturer
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Contact Person: Ph.D. Shinichi Sugita Date:
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03-AUG-2004

Type: manufacturer
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Contact Person: Raphaël Singer Date: 17-APR-2003
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Town: 4002 Basel
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Email: raphael.singer@jungbunzlauer.ch

17-OCT-2003

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Contact Person: Johnny Pallot Date:
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31-JUL-2003

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Email: t.van.dongen@purac.com

03-AUG-2004

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

Remark: Glucono-delta-lactone, gluconic acid and its sodium, calcium and potassium salts have been proposed in a category, as the salts of gluconic acid freely dissociate to the gluconate anion and the respective cation.

Glucono-delta-lactone (GDL) is the inner ester of gluconic acid formed by the removal of water.

When glucono-delta-lactone is used in aqueous solution, it is slowly hydrolysed until an equilibrium is reached between gluconic acid and its delta-lactone.

12-AUG-2004

1.1.0 Substance Identification

IUPAC Name: sodium gluconate
Smiles Code: [Na]OC (=O) C (O) C (O) C (O) C(O) CO
Mol. Formula: C6H11NaO7
Mol. Weight: 218.14
Petrol Class: other: N/A

Attached doc.: sodium gluconate.bmp
03-AUG-2004

1.1.1 General Substance Information

Purity type: typical for marketed substance
Substance type: organic
Physical status: solid
Purity: ca. 98 - 102 % w/w
Colour: white/ off white
Odour: none

Remark: Sodium gluconate is the sodium salt of gluconic acid. It forms stable chelates with iron, aluminium, calcium, zinc and other heavy metals, especially in alkaline solution. It possesses good sequestering activity in cleaning baths and is highly stable, even in concentrated alkaline solutions.

03-AUG-2004

1.1.2 Spectra

1.2 Synonyms and Tradenames

D-Gluconic acid, monosodium salt

02-MAY-2003

sodium pentahydroxy-capronate

17-APR-2003

1.3 Impurities

Purity type: typical for marketed substance

Remark: For food applications the level of impurities complies with the restrictions laid down in the corresponding EU Directives.
19-JAN-2004

1.4 Additives

Remark: For all the chemicals of the category: no additives used
10-NOV-2005

1.5 Total Quantity

Quantity: ca. 50000 - 70000 tonnes produced in 2000

Remark: Estimation of the worldwide market per year. There is no production in Belgium.
Flag: confidential
03-AUG-2004

Quantity: > 32000 tonnes produced in 1999

Remark: Estimated production capacities for gluconates in Western Europe.
10-NOV-2005 (40)

Quantity: = - 5500 tonnes produced in 1998

Remark: Japanese production of gluconic acid and salts (sodium salt basis)
10-NOV-2005 (39)

1.6.1 Labelling

Remark: For all the chemicals in the category: proposal of Industry:

no labelling required
10-NOV-2005

1.6.2 Classification

Classified: other, as in legislation

Remark: For all chemicals of the category: proposal of Industry: no classification required
10-NOV-2005

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Non dispersive use

Remark: The listed uses cover all the members of the category.

The main non dispersive applications are industrial cleaning, metal surface treatment, textile bleach stabiliser and aluminium processing.For potential volumes, see under 1.10 Source of exposure.
03-AUG-2004

Type: type
Category: Wide dispersive use

Remark: The wide dispersive applications are chelating agents in cement set retarding, institutional and household cleaning, personal care, pharmaceuticals and foodstuffs. For potential volumes, see under 1.10 Source of exposure
03-AUG-2004

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

Source of exposure: Human: exposure by production
Exposure to the: Substance

Remark: Gluconic acid is produced by a fermentation process using dextrose as a raw material. After the fermentation process the product is separated from the rest of the broth by filtration, followed by demineralization and discoloration. After a concentration step the material is then crystallized to obtain glucono-delta-lactone on one side and the run off on the other side. Separation happens in a centrifuge. The run off material is gluconic acid. It can be sold as such or transformed into sodium gluconate by neutralization with sodium hydroxide.

All these operations are carried out in closed equipment. At this stage no human contact is possible but in case of some maintenance work or sample analysis done in the laboratory. Maintenance operators who have to be in touch with the product wear the usual safety equipment: protective clothes, gloves and goggles. In the control laboratory operators wear the general safety equipment: gloves and goggles.
Source: Roquette Frères
Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
05-AUG-2004

Source of exposure: Human: exposure of the operator by intended use
Exposure to the: Substance

Remark: Sodium gluconate is sold as a liquid aqueous solution as well as in a powder crystalline form.

The liquid aqueous solution is being used mainly in concrete and mortar admixtures. Liquid sodium gluconate manufacturers sell the material in large quantities to concrete admixture producers. The material is shipped in bulk containers to their facilities, where it is unloaded into a storage tank. From there it is pumped into a mixer where other chemicals are also added. The mixture is filed into containers or drums in order to be supplied to concrete and mortar producers.

Workers are not in contact with sodium gluconate during the unloading and the mixing operations, since both operations are done in completely closed systems. Companies involved in the production of this type of mixtures are aware of the risks related to chemicals and their handling. Therefore workers as well as laboratory operators have to wear safety equipment in order to avoid skin or eye contact: protective clothes, gloves and goggles.

Crystalline sodium gluconate is sold in bags or big bags. It has to be dissolved into water before further use. Some dust may be formed at this stage during the cracking of the paper bags or the emptying of the big bags into the hopper before dissolution. The product is mainly used in industrial detergent formulations and metal surface treatment preparations. In both cases it functions as a sequestering or chelating agent after blending with other chemicals . Companies making those preparations in large production units are used to use chemicals and therefore have already in place efficient safety procedures, including the use of protective clothes, gloves, masks and goggles by workers and laboratory operators who could be in contact with the material.

Gluconic acid is also used in detergent formulations. Since it shows an acidic function although weak, it has to be handled as an acid. Companies involved in preparing detergent formulations are aware of the risks linked with handling this type of material. Therefore all the necessary measures are taken in order to avoid any skin or eye contact, as described in the previous paragraph.

Glucono-delta-lactone also called GDL is the lactone form of the gluconic acid. Because of its higher price it is mainly used in food applications as a slowly released acid. It is shipped and handled in bags or big bags. Because it is only converted into acid by a very slow hydrolysis process, it does not show as such any acidic function. It can be handled by using the usual safety measures taken on any food-manufacturing site: hygienic clothes and gloves. Western European and Japanese consumption of sodium gluconate chelating agents in metal surface treatment applications in 1998 (tonnes/year):

EU: 5100
JP: 900

Western European and Japanese consumption of sodium gluconate chelating agents as industrial cleaners in 1998 (tonnes/year):

EU : 5100
JP : 600

Western european and Japanese consumption of sodium gluconate chelating agents in other applications in 1998 (ie, textile bleach stabiliser, aluminium processing)

(tonnes/year):

EU: 1700
JP: 900

Western European and Japanese consumption of sodium gluconate chelating agents as cement set retarder (tonnes/year):

EU : 5100
JP : 7600

Source: Roquette Frères
Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
05-AUG-2004

Source of exposure: Human: exposure of the consumer/bystander
Exposure to the: Substance

Remark: Exposure of consumers in the dispersive uses of gluconates is expected to be extremely limited because gluconates are most of the time only additives, not main ingredients in the products where they are used.

Typical dosages:

-sodium gluconate in concrete: 0.1-0.2% based on cement weight
-sodium gluconate in institutional and household cleaners: <5% based on formulation weight
-sodium gluconate in personal care products: <1% based on formulation weight.

- glucono-delta-lactone in foodstuffs: <3% in dairy and bakery products,
<1% in meat and seafood products and other food applications

The daily exposure of consumers to gluconates is lower than the daily production of gluconate from endogenous sources.

Furthermore, gluconic acid and glucono-delta-lactone are also present naturally at a level up to 1% in wine, honey and other foods and drinks like kombucha.
Source: Jungbunzlauer International AG
Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
05-AUG-2004

Source of exposure: other: human
Exposure to the: Substance

Remark: Gluconate is a metabolite of glucose oxidation in mammals. The activity is greatest in the liver, adipose tissue, adrenal cortex, thyroid, erythrocyte, testis and the lactating mammary gland.

In these tissues, as much as 20 % of the glucose may be

metabolized through this route. In contrast, the phosphogluconate pathway is little utilised in muscle tissue. Gluconate formation increases during active lipogenesis and carbohydrate intake and decreases during starvation or periods of inanition.

A rough estimate of the daily production of gluconate can be calculated by assuming approximately 10 % of the glucose utilized by the body to be metabolized through this alternative pathway: An individual receiving 2800 kcal per day from an average diet, would oxidize about 275 g of glucose. Approximately 25 to 30 g of this amount would be oxidized through the phosphogluconate pathway to yield roughly the same amount of gluconate. Thus, the daily production of gluconate from endogenous sources is about 450 mg/kg for a 60 kg person. The body can easily cope with this load since only a small amount of 6-phosphogluconate is found in the liver (approximately 10 mg/kg). This reflects the efficiency of the liver in the conversion of gluconate.

Reliability: (2) valid with restrictions
Secondary literature. Abstract of a report from a recognised institution
Flag: Critical study for SIDS endpoint
10-NOV-2005 (19)

Source of exposure: Environment: exposure from production
Exposure to the: Substance

Remark: Environmental exposure during production is very limited. Material lost or spilled during manufacturing is collected and sent to the wastewater treatment plant, where it is completely degraded.
Source: Roquette Frères
Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
05-AUG-2004

Source of exposure: Environment: exposure from intended use
Exposure to the: Substance

Remark: In the application as a sequestering agent in the building industry (concrete and mortar), the gluconate ion reacts with calcium ions present in the cement to form an insoluble and impermeable layer of calcium gluconate. Therefore, the gluconate is bound within the microcrystalline fibers of cement and is not free for any environmental pollution.

When used in detergent formulations, sodium gluconate or gluconic acid are valuable as complexing agent for di- or trivalent metal cations in alkaline industrial cleaning solutions. Since they are washed out with clean water during the cleaning process, they necessarily flow into the wastewater treatment plant of the site, where the bacteria will transform the easily biodegradable gluconate ion.

In metal surface treatment sodium gluconate is an effective sequestering agent in alkaline solutions where it chelates earth metal such as calcium and magnesium ions. In this case

as in the detergent application the product finally flows into the wastewater treatment plant of the user's site for further biotransformation.

In food applications glucono-delta-lactone is added in a crystalline or powder form to the other food components such as meet or milk or soja at levels below 5 %w/w. There is no need for an environmental evaluation in this case since the final food is anyway ingested.

Source: Roquette Frères
Reliability: (4) not assignable
Flag: Critical study for SIDS endpoint
05-AUG-2004

1.11 Additional Remarks

Memo: Regulatory status

Remark: In the European Parliament and Council Directive 95/2/EC sodium gluconate is listed as a generally permitted food additive (E 576) and may be added to all foodstuffs, following the "quantum satis" principle, as long as no special regulations restrict the use.

The US Food and Drug Administration (FDA) assigned sodium gluconate the "generally recognised as safe" (GRAS) status and permitted its use in food as a sequestrant without limitation other than good manufacturing practice (21 CFR, §182.6757).
14-AUG-2003

1.12 Last Literature Search

1.13 Reviews

2.1 Melting Point

Value: = 205 - 209 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
05-AUG-2004 (11)

Value: ca. 170 - 175 degree C
Decomposition: yes at ca. 196 - 198 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
05-AUG-2004 (17)

Decomposition: yes at >= 210 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Decomposes before melting
Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
05-AUG-2004 (8)

2.2 Boiling Point

Value: = 613.1 degree C

Method: other: calculated
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with MPBPWIN (v1.41) program from US EPA (EPI v3.11)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2004

2.3 Density

Type: density
Value: = 1.789 g/cm³

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
05-AUG-2004 (8)

Type: bulk density
Value: ca. 850 kg/m3

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
05-AUG-2004 (32)

Type: bulk density
Value: ca. 850 kg/m3

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
05-AUG-2004 (17)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = 0 hPa at 25 degree C

Method: other (calculated)
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with MPBPVP (v1.41) program from US EPA (EPI v3.11):

Vapour pressure estimations (25°C, using estimated boiling point: 613.05°C and entered melting point = 210.00°C)

VP: 1.18E-022 mm Hg (Antoine Method)
VP: 3.4E-017 mm Hg (Modified Grain Method)
VP: 1.05E-012 mm Hg (Mackay Method)
Result: Selected VP: 3.4E-017 mm Hg =4.53e-017 hPa (Modified Grain Method)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint

03-AUG-2004

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: = -5.99

Method: other (calculated)
GLP: no

Remark: Estimated with Kowwin (v1.67) Program from US EPA (EPI v3.11)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
03-AUG-2004

2.6.1 Solubility in different media

Solubility in: Water
Value: = 590000 mg/l at 25 degree C
pH value: = 6.5 - 7.5
Conc.: 10 vol% at 25 degree C
Descr.: very soluble (> 10000 mg/L)

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4
Stable: yes

Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
12-AUG-2004 (41)

Solubility in: Water
Value: = 590 g/l at 25 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
05-AUG-2004 (8)

Solubility in: Water
Value: = 600 g/l at 20 degree C
pH value: = 6.5 - 7.5
Conc.: 10 vol% degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4
Stable: yes

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
05-AUG-2004 (17)

Solubility in: Water
Value: ca. 600 g/l at 25 degree C
pH value: = 6.5 - 7.5
Conc.: 10 vol% degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4
Stable: yes

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
05-AUG-2004 (32)

Solubility in: other: alcohol
Value: < .1 mg/l at 20 degree C
Descr.: insoluble (< 0.1 mg/L)

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
05-AUG-2004 (18)

Solubility in: other: ether
Value: < .1 mg/l
Descr.: insoluble (< 0.1 mg/L)

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
05-AUG-2004 (9)

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

Value: > 200 degree C

Remark: ROQUETTE MSDS : 400 °C (GG - CLOUD)
Source: Jungbunzlauer International AG MSDS
Reliability: (3) invalid
02-MAY-2003

2.9 Flammability

2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Dissociation Constant

Acid-base Const.: pKa= 3.70

Method: other: no data
GLP: no data
Test substance: other TS

Remark: The dissociation in water is expected to be complete as the pKa values of gluconic acid found in literature range from 3.5 to 3.8.
Test substance: gluconic acid
Reliability: (2) valid with restrictions
Data from Handbook or collection of data.

Flag: Critical study for SIDS endpoint
12-AUG-2004 (42)

2.13 Viscosity

2.14 Additional Remarks

3.1.1 Photodegradation

Type: air

Method: other (calculated): Estimated with AOP (v1.91) program from US EPA (EPI v3.11)
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with AOP (v1.91) program from US EPA (EPI v3.11)

OVERALL OH Rate Constant = 38.1277 E-12 cm3/molecule-sec

HALF-LIFE = 0.281 Days (12-hr day; 1.5E6 OH/cm3)

HALF-LIFE = 3.366 Hrs
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
12-AUG-2004

3.1.2 Stability in Water

Type: abiotic

Method: other: no data
GLP: no data
Test substance: other TS

Remark: The dissociation in water is expected to be complete as the pKa values of gluconic acid found in literature range from 3.5 to 3.8
Test substance: gluconic acid
Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
10-NOV-2005 (42)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III
Media: other
Method: other: calculated

Remark: Estimated with the Level III Fugacity Model program LEVEL3NT from US EPA (EPI v3.11)

```
                    Mass Amount (%)   Half-Life (hr)    Emissions (kg/hr)
                    ---------------------------------------------------
                    Air   1.2         6.73        1000
                    Water 49.8        208         1000
                    Soil  48.9        208         1000
                    Sediment0.0743          832         0
                    ___________________________________________________

                    Fugacity  Reaction   Advection      Reaction Advection
                    (atm)   (kg/hr)     (kg/hr)    (%)      (%)
                    ---------------------------------------------------
                    Air   2e-020        720         70  24    2.33
                    Water 3.17e-018   968         291   32.3  9.69
                    Soil  1.15e-016   951         0           31.7  0
                    Sed.  2.36e-018   0.361       0.00867     0.012 0.000289
                    ___________________________________________________

                    Persistence Time: 195 hr
                    Reaction Time: 221 hr
                    Advection Time: 1.62e+003 hr
                    % Reacted: 88
                    % Advected: 12

                    Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
                    Air: 6.732
                    Water: 208.1
                    Soil: 208.1
                    Sediment: 832.3
                    Biowin estimate: 3.517 (days-weeks)

                    Advection Times (hr):
                    Air: 100
                    Water: 1000
                    Sediment: 5e+004
Reliability:        (2)  valid with restrictions
                    Accepted calculation method
Flag:               Critical study for SIDS endpoint
12-AUG-2004


3.3.2 Distribution

Media:              air - biota - sediment(s) - soil - water
Method:             other (calculation)

Remark:             Henry's law constant estimated with HENRY (v3.10) program
                    from US EPA (EPI v3.11)

                    HENRYs LAW CONSTANT at 25 deg C = 4.76E-013 atm-m3/mole
                    ---------------------------------------------------
                    Soil Adsorption Coefficient estimated with PCKOC (v1.66)
                    program from US EPA (EPI v3.11)

                    NOTE: THE METAL (Na, Li or K) HAS BEEN REMOVED TO ALLOW
                    ESTIMATION!
                    First Order Molecular Connectivity Index : 5.913
```

Non-Corrected Log Koc : 3.7674
Fragment Correction(s):
* Organic Acid (-CO-OH) : -1.7512
2 Aliphatic Alcohol (-C-OH) : -3.0386
Corrected Log Koc : -1.0224
Over Correction Adjustment to Lower Limit Log Koc: 1.0000

Estimated Koc: 10

NOTE:
The Koc of this structure may be sensitive to pH! The estimated Koc represents a best-fit to the majority of experimental values; however, the Koc may vary significantly with pH.

Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
05-AUG-2004

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type:	aerobic
Inoculum:	other: secondary effluent of a municipal sewage plant (Breisgauer Bucht, 500000 population equivalent), 0.4 ml/l
Concentration:	3 mg/l related to Test substance
Contact time:	28 day(s)
Degradation:	= 89 % after 28 day(s)
Result:	readily biodegradable
Kinetic:	3 day(s) = 61.13 %
	7 day(s) = 74.35 %
	14 day(s) = 66.09 %
	21 day(s) = 71.94 %
	28 day(s) = 88.88 %
Control Subst.:	Acetic acid, sodium salt
Kinetic:	3 day(s) = 67.15 %
	28 day(s) = 80.93 %
Deg. product:	not measured
Method:	Directive 92/69/EEC, C.4-E
Year:	2001
GLP:	yes
Test substance:	as prescribed by 1.1 - 1.4

Method: The bottles were kept in the dark for 28 days.

T° remained between 20-20.5°C.

On days 3, 7, 10, 14, 21 and 28, at least duplicate bottles were removed for determination of dissolved oxygen and pH. If the oxygen concentration of duplicate bottles differed more than 0.4 mg/l, a third bottle was measured to make sure.

At the end of test, dissolved oxygen concentration in all

remaining bottles was measured.
Remark: The 89% degradation indicated here relates to the Theoritical Oxygen Demand (ThOD)
Result: Blanks:

Maximum deviation between parallels = 8.9%
Oxygen consumption after 28 days = 0.79-1.18 mg/l.
pH : 7.2 at the beginning and 6.7 at the end of the test.

Sodium gluconate:

Maximum deviation between parallels = 4.6% at day 3.
Biological degradation : 61% of ThOD after 3 days and maximum degradation = 89% of the ThOD at day 28.
pH : 7.2 at the beginning and 6.7 at the end of the test.
Oxygen concentration during test never felt below 5.9 mg/l

Reference item (sodium acetate):

Maximum deviation between parallels = 3.8% at day 14.
Biological degradation : 67% after 3 days
pH : 7.2 at the beginning and 6.7 at the end of the test.
Test condition: Verification of identity:

TOC of the test item was compared to TOC of sodium D-gluconate from Aldrich (Cat N° 18,633-3, lot 50824 50323012). The results matched.

Inoculum: the inoculum was used on the day of collection.

Stock solutions: according to OECD 301D

Mineral medium: 20 ml of each stock solutions A-D were added to 10 litres deionised water and made up to 20 litres. The medium was areated for 30 minutes and held in darkness for 24 h (t° 20°C-20.5°C).

Test item : 16 test bottles (concentration = 3 mg/l.) with 0.4 ml/l inoculum were filled bubble-free and incubated in the dark at 20°C.

Reference item: reference item bottles containing sodium acetate stock solution (concentration= 4 mg/l) with 0.4 ml/l inoculum were also filled and incubated in the dark at 20°C.

A blank was also prepared without any stock solution.
Test substance: Sodium gluconate: 99.0-101.0%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test, quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
10-NOV-2005 (13)

Type: anaerobic
Inoculum: other: Digesting sludge of a municipal sewage plant (Breisgauer Bucht, 500000 population equivalent), 2.9 g total

solids/l
Concentration: 303 mg/l related to Test substance
Contact time: 35 day(s)
Degradation: = 100 % after 35 day(s)
Result: readily biodegradable
Kinetic: 1 day(s) = 8 %
8 day(s) = 51 %
15 day(s) = 57 %
22 day(s) = 61 %
35 day(s) = 100 %
Control Subst.: Benzoic acid, sodium salt
Kinetic: 8 day(s) = 6 %
35 day(s) = 100 %
Deg. product: not measured

Method: other: DIN EN ISO 11734
Year: 2001
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: Washed digested sludge containing very low amounts of inorganic carbon (IC), is diluted to 1-3 g/l total solids concentration and incubated in the absence of oxygen at 35 +/- 2 °C in sealed vessels with the test item at a concentration of 20-200 mg/l total organic carbon (TOC) for 35 days.

The increase in headspace pressure in the test vessels resulting from the production of carbon dioxide and methane is measured.

A considerable amount of CO2 will be dissolved in water or transformed to hydrogen carbonate or carbonate under the conditions of the test. This IC is measured at the end of the test. The amount of microbiologically produced biogas carbon is calculated from the net biogas production and the net DIC formation in excess over blank values.
Remark: At day 35, the average degradation percentage is 66% but the value shown includes the dissolved inorganic carbon (DIC).
Result: Test item:
The percentage biodegradation is calculated from the total carbon transformed to biogas and DIC and the measured or calculated amount of carbon added as test item.

The test item was degraded to 50% by day 8 and to 66% by day 35. The summing up of the net-mass carbon in the liquor shows that the test item is completely anaerobically degraded after 35 days.
The pH at the end of the test was 6.8 in every bottle.

Bottles with blanks showed a pH of 7.1-7.2.

Reference (sodium benzoate)
The degradation of the reference item took some time to get started. Between days 18 and 22 this lag-phase was over and the curve reached 67% by day 35. After considering the DIC in the liquor, the reference item was also anaerobically

degraded completely in 35 days.

The pH at the end of the test was 6.8 in every bottle.

Test condition: T° range: 34.7°C-35.4°C

The inoculum was kept for 24 h at 35°C before use.

Test item: 0.121 g/400ml

Reference item: sodium benzoate (0.069 g/400 ml)

Blanks: 3 additional test bottles were prepared with 10 ml deionised water.

Test substance: sodium gluconate

Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test, quality assurance and GLP certificates

Flag: Critical study for SIDS endpoint

10-NOV-2005 (14)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type:	semistatic
Species:	Oryzias latipes (Fish, fresh water)
Exposure period:	96 hour(s)
Unit:	mg/l Analytical monitoring: yes
NOEC:	> 100 -
LC0:	> 100 -
Limit Test:	yes
Method:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year:	2002
GLP:	yes
Test substance:	as prescribed by 1.1 - 1.4

Result: Measured concentrations of the test substance were within +/- 20% of the nominal concentrations. Results were based on the nominal concentrations.

No toxicological symptoms nor any death were observed at 100 mg/l (limit test).

Test condition: A range finding test (5 fish/vessel/concentration) was conducted before the definitive test (only 2 concentrations were set based on toxicological data) and determined the concentration range in the definitive test: 0 and 100 mg/l (limit test)

Biomass loading: 10 fish/concentration

T°: 24 +/- 1°C

Dissolved oxygen concentrations were over 60% of the saturation value (8.25 mg/l/24.0°C)

pH : min: 7.1 - max : 7.6

Light: fluorescent light. 16 hours light/8 hours dark

Analytical method: HPLC

Test substance: sodium gluconate : 99.6%

Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test, quality assurance and GLP certificates

Flag: Critical study for SIDS endpoint

10-NOV-2005 (22)

Type:	other: no data
Species:	other: no data
Exposure period:	48 hour(s)
Unit:	mg/l Analytical monitoring:
LC0:	= 10000 -
LC50:	> 10000 -
LC100:	= 50000 -
Method:	other: DIN 38 412 L15
Year:	1992

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: The potential toxicity observed here (LC100 = 50 000) is due to the high concentration of the substance that changed the test conditions.
Reliability: (3) invalid
Report not complete. No data on species. Unphysiological conditions and not conform to OECD guidelines
10-NOV-2005 (33)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: > 1000 -
EC100: > 1000 -
Limit Test: yes

Method: OECD Guide-line 202
Year: 2002
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: Measured concentrations of the test substance in the test solution were within +/- 20% of the nominal concentration in all concentrations. Results were based on the nominal concentrations:

EC(50) 0-24 hours: > 1000 mg/l
NOEC 0-24 hours: > 1000 mg/l
EC100 0-24 hours: > 1000 mg/l

EC(50) 0-48 hours: > 1000 mg/l
NOEC 0-48 hours: > 1000 mg/l
EC100 0-48 hours: > 1000 mg/l
Test condition: Species:

Daphnia magna from the National Institute for Environmental Studies, Japan.

Growth step: female juvenile (less than 24 hours)

Biomass loading: 20 daphnids/concentration (5 daphnids/vessel)

T°: 20 +/- 1°C

Light: fluorescent light, 16 hours light (below 800 lux)/8 hours dark

Analytical method: HPLC

Dissolved oxygen concentration: >= 60% of the saturation

Dilution water (Elendt M4) recommended by OECD guidelines for testing of chemicals No. 211 was used.

A range-finding test (2 vessels/concentration, 10 daphnids/concentration) was conducted before the definitive test and enabled the nominal concentrations of the definitive test : 0 and 1000 mg/l (limit test)

Test substance: sodium gluconate : 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test, quality assurance and GLP certificates
Flag: confidential, Critical study for SIDS endpoint
10-NOV-2005 (23)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: yes
EC0: > 1000 -
Limit Test: yes

Method: OECD Guide-line 202
Year: 2001
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: study conducted in accordance to OECD guideline 202.

A limit test with 1000 mg/l was conducted: a solution of 100.5 mg in 100 ml or 1005 mg/l was prepared and distributed to 4 beakers. pH and
oxygen concentration were measured and 5 daphnia were put into each beaker.

Controls: 4 beakers with 20 ml dilution water + 5 daphnia each.

The vessels were held for 48 h in an incubator at 20°C in complete darkness.

After 24 and 48 h, the swimming capability of the daphnia was observed. An animal not swimming within 15 seconds after gently moving the beaker was considered immobile. After 48 h, the oxygen concentration and the pH was measured.

The stability of the investigated concentration of sodium D-gluconate during testing was also examined via enzymatic analysis. The test concentration did not decrease during the test period.

Result:
At 1000 mg/l, all daphnia kept their swimming capability.

EC0 (24 h) > 1000 mg/l
EC0 (48 h) > 1000 mg
Test condition: Test organisms:
Daphnia magna Straus origin from a clone breeding of the

German Federal Environmental Agency, department V 3.2.

Quality Assurance takes place in regular intervals using a concentration range of Potassium dichromate. Last quality check was January 2001 and EC50 was between 1.16and 2.32 mg/l (required: 0.6-2.4 mg/l).

For testing, daphnia of the age of 2-23 h were used. Before using, the new young Daphnia were held at 20°C for 2 hours to ensure that none of them was younger than 2 h.

Verification of identity : TOC of the test item was compared to TOC of sodium D-gluconate from Aldrich (Cat N° 18,633-3, Lot 50824 50323012). The results matched.

pH difference between beginning and end of test = 0.2 units.

Oxygen concentration was 95% of the start concentration.

T° in the incubator was stable at 20°C during the test period.

Test substance: sodium gluconate: 99.0-101.0%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test, quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
10-NOV-2005 (15)

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l Analytical monitoring: no data
EC0: > 1000 -

Method: other: DIN 38 412 -L 30
Year: 1997
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: At 1000 mg/l, all daphnia kept their swimming capability.

EC0 (24 h) > 1000 mg/l
Test condition: Species: daphnia magna
Biomass loading: 2 groups of 5 daphnias
Test concentration: 1 gr/l
T°: 20°C
pH: 6.54
Reliability: (3) invalid
Abstract, no data on purity of substance, test conditions. not compliant with OECD guidelines.
10-NOV-2005 (36)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)

Unit: mg/l Analytical monitoring: yes
NOEC: = 560 -
EC50: > 1000 -
Limit Test: yes

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 2002
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Result: Results were based on the nominal concentrations (measured concentrations were +/-20% of the nominal concentrations)

Cell growth inhibition at 1000 mg/l = 25.4 %

Growth rate inhibition (24-48 h) at 1000 mg/l = 7.6%

Growth rate inhibition (24-72 h) at 1000 mg/l = 9.0 %

50% growth inhibition concentration by comparison of areas under the growth curves:

EbC50 (O-72 h): > 1000 mg/l
NOECb (0-72 h): 560 mg/l

50% growth inhibition concentration by comparison of growth rates:

ErC50 (24-48 h): > 1000 mg/l.
ErC50 (24-72 h): > 1000 mg/l.
NOECr (24-72h) : 560 mg/l
NOECr (24-48h) : 560 mg/l

Color of the test solutions were observed with naked eye and the cell shapes of algae were observed through the microscope. The test solutions were green at 24 hours after the start of exposure. Afterwards, the color of the test solutions showed a tendency to get more greenish with the passage of time.

No unusual cell shapes of algae and no agglutination were observed at the end of exposure and the algae looked normal compared to the control.

Test condition: Test concentrations (nominal): control, 100, 180, 320, 560, 1000 mg/l.

A range-finding test was conducted before the definitive test to enable the above-mentioned concentration range in the definitive test.

Measured concentrations of the test substance in the test solutions at the beginning of exposure were +/-20 % of the nominal concentrations.

Biomass loading: 1 x 10 Exp4 cells/ml

T° range: 23+/- 2°C

Illumination: 4000 lux - continuous(+/- 20% at the surface of the test solutions)

Exposure procedure: static

Analytical method: HPLC
Test substance: sodium gluconate: 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test, quality assurance and GLP certificates.
Flag: Critical study for SIDS endpoint
10-NOV-2005 (24)

Species: other algae: Desmodesmus subspicatus CHODAT (strain No 86.81 SAG)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: = 100 -
EC50: > 100 -
Limit Test: yes

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 2001
GLP: yes
Test substance: as prescribed by 1.1 - 1.4

Method: Study conducted in accordance to OECD guideline 201.

However, for test 2, the procedure has been modified by covering the test vessels with glass petri dishes to prevent contamination by micro-organisms.

The flasks were incubated in a water bath for 3 days and illuminated with 4 parallel set universal white fluorescent tubes of approximately 65 cm above the level of the tested media.

Min/max t° was recorded on a daily basis.

After 24, 48 and 72 hours, cell concentration was determined using a microscope with a counter chamber (8 fields counted).

The stability of the investigated concentration of sodium D-gluconate during testing was also examined via enzymatic analysis. A decrease of the test concentration in test 1 was observed.
Result: test 1 : 1000 mg/l
not valid - a decrease of the test item concentration was observed and therefore the test could not meet the stability

requirements.

Cell growth inhibition : 85%
Average specific growth rate inhibition: 55%
---

test 2 : 100 mg/l and 1000 mg/l

Cell growth inhibition : no inhibition at 100 mg/l
70% inhibition at 1000 mg/l

Average specific growth rate inhibition: no inhibition at 100 mg/l
42% inhibition at 1000 mg/l

Cell concentration increase in controls: factor 65.9 after 72 h

Test condition: T° range:

Test 1: 22.7-24.8°C
test 2: 23.4-27.9°C

Illumination: 8900-9300 lux.

pH maximal difference between 0 and 72 hours: 0.3

Sample preparation: stock solution in redistilled water.

Verification of identity : TOC of the test item was compared to TOC of sodium D-gluconate from Aldrich (Cat N° 18,633-3, Lot 50824 50323012). the results matched.

3 days before starting the tests, algae samples were transferred to Erlenmeyer flasks under sterile conditions. The stock solutions were also sterilised.

Inoculum concentration: 10 x 10E4 algae/ml

Test 1 = limit test:

1000 mg/l (pH of stock solution = 7)
3 flasks with test item and 6 flasks without test item were prepared.

Test 2

All the media used were sterilised. Flasks, graduated cylinders and pipettes were also sterilised before using.

2 concentrations test: 100 mg/l and 1000 mg/l (pH of stock solution = 7)
3 flasks with 100 mg/l, 3 flasks with 1000 mg/l and 6 flasks without test item.

Test substance: Sodium gluconate: 99.0-101.0%

Reliability: (1) valid without restriction
The substance has only been tested at 100 and 1000 mg/l because this test has been made on the basis of an older test according to a German norm. The inhibition level was thus expectable and the test concentrations limited to 100 and 1000 mg/l.
Flag: Critical study for SIDS endpoint
10-NOV-2005 (16)

Species: Scenedesmus subspicatus (Algae)
Endpoint: biomass
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: no data
EC10: > 1000 -

Method: other: DIN 38412 - L33
Year: 1997
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: GA = smallest dilution where inhibition of biomass production is reduced by 20% = > GA= 1

Dilution	Measured value	% inhibition
1	16.1	3.0
2	17.4	-4.8*
3	19.3	-16.3*

* negative value = increase of the biomass production
Test condition: Incubation: 72 h
T°: 23°C.
Measurement of chlorophylle fluorescence: lambda= 450- 685 nm
Concentration of test: 1 g/l
PH= 5.84
Reliability: (3) invalid
Abstract, not compliant with OECD guidelines
10-NOV-2005 (34)

4.4 Toxicity to Microorganisms e.g. Bacteria

Species: Pseudomonas putida (Bacteria)
Exposure period: 16 hour(s)
Unit: mg/l Analytical monitoring: no data
EC0: > 5000 -

Method: other: DIN 38 412 L8
Year: 1992
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: 0-40 mg/l: no effect
80-5000 mg/l: stimulation of growth
> 5000 mg/l: no stimulation of growth but not toxic
Test condition: Exposure period: 16 h (+/- 1 h incubation)
Temperature: 21°C
Limit test: yes

3 range of concentration tested:
0-40 mg/l
80-5000 mg/l
> 5000 mg/l
Test substance: sodium gluconate
Reliability: (3) invalid

Abstract, not compliant with OECD guidelines
10-NOV-2005 (35)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

Species: other

Remark: No data available but exposure in sediment expected to be extremely limited according to the Level III Fugacity Model program LEVEL3NT from US EPA (EPI v3.11)
31-JUL-2003

4.6.2 Toxicity to Terrestrial Plants

Method: other

Remark: No data available.
14-AUG-2003

4.6.3 Toxicity to Soil Dwelling Organisms

Method: other

Remark: no data available but due to the low intrinsic toxicity in aquatic organisms, it is reasonable to expect a similar low toxic impact on terrestrial organisms
19-JAN-2004

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

In Vitro/in vivo:	In vivo
Type:	Absorption
Species:	rat
Doses, males:	no data
Doses, females:	no data
Vehicle:	no data
Route of administration:	oral unspecified
Exposure time:	5 hour(s)

Test substance: as prescribed by 1.1 - 1.4

Method: Radioactivity was measured in the blood of normal and alloxan diabetic rats, after oral administration of [U-14C]gluconate and [U-14C]glucono-delta-lactone, respectively.

Radioactivity was also measured in the intestinal contents and feces 5 h after ingestion of the radioactive materials.

Result: glucono-delta-lactone is absorbed more rapidly from the intestine than sodium gluconate. A higher retention in tissues and a greater loss in urine was also observed after administration of the lactone. Incorporation into liver glycogen is also higher from the lactone than from the gluconate, particularly in diabetic animals.

Initial oxidation occurred after 7 h with the gluconate and 4 h for the lactone. The oxidative turnover of lactone and gluconate was significantly enhanced in diabetic animals. The better utilisation in diabetic metabolism is in part explainable by a rise of glycolitic intermediates in the liver, which are decreased in starvation and diabetes.

Test substance: sodium gluconate
Reliability: (4) not assignable
Secondary litterature
10-NOV-2005 (38)

In Vitro/in vivo:	In vivo
Type:	Excretion
Species:	other: no data
Doses, males:	no data
Doses, females:	no data
Vehicle:	no data
Route of administration:	i.p.

Method: other: no data
Year: 1962
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: A significant portion (60-85%) of parenterally administered gluconate is excreted unchanged in the urine. However, gluconate is readly catabolized (Wang et al., 1962) or

utilized for glucose synthesis, mainly from CO2 derived from carbon 1 and from glucogenic compounds derived from carbons 2 through 6 of the gluconate (Stetten and stetten, 1950; Stetten and Topper, 1953). Renal excretion of gluconate appears to be by tubular secretion (Herken et al., 1975)
Reliability: (3) invalid
Short abstract, secondary litterature, no data on test conditions, species, method used.
10-NOV-2005 (20)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LDLo
Species: rat
Strain: Crj: CD(SD)
Sex: male/female
No. of Animals: 10
Vehicle: no data
Doses: 500, 1000, 2000 mg/kg
Value: > 2000 mg/kg bw

Method: other: no data
Year: 1995
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: No death in males or females in any of the dose groups, minimum lethal dose estimated > 2000 mg/kg

One female passed loose stools in 1000 mg/kg dose group, and all males and females passed loose or diarrheal in 2000 mg/g dose group but all animals recovered on the next day.

Body weight:
All males and females in all dose groups showed similar time-course changes in body weight.

Autopsy:
no abnormalities detected
Test substance: sodium gluconate
Reliability: (2) valid with restrictions
Short abstract not well documented but key study for initial assessment
Flag: Critical study for SIDS endpoint
10-NOV-2005 (25)

Type: LDLo
Species: dog
Strain: Beagle
Sex: male/female
No. of Animals: 2
Vehicle: no data
Doses: 1000 and 2000 mg/kg
Value: > 2000 mg/kg bw

Method: other: no data
Year: 1995
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: No deaths were observed in 1000 or 2000 mg/kg dose groups.

No changes likely to be associated with the test article were detected in observation of the general condition, body weight, food intake, hematological test, blood chemistry analysis, autopsy or weighing of organs.

No toxicity was shown at the single dose of 2000 mg/kg (maximum dose that could be administered by gavage to beagle dogs)
Test substance: sodium gluconate
Reliability: (2) valid with restrictions
Short abstract not well documented but can be a key study for initial assessment.
Flag: Critical study for SIDS endpoint
10-NOV-2005 (30)

5.1.2 Acute Inhalation Toxicity

5.1.3 Acute Dermal Toxicity

5.1.4 Acute Toxicity, other Routes

Type: LDLo
Species: rabbit
Strain: no data
Sex: no data
No. of Animals: 1
Vehicle: water
Doses: 3270, 4360, 6540, 7194, 7630, 7848, 8720
Route of admin.: i.v.
Value: = 7630 mg/kg bw

Method: no data
Year: 1939
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Result: At the non lethal doses, no particular symptoms are observed except a reduction of the temperature of 2.5°C at the end of injection (3270 m/kg bw) and at higher non lethal doses can reach 3°C.

Diffuse shaking and slight muscular contractions were also observed at the non lethal doses which stopped when the injection is interrupted.

At the highest non lethal dose (7194 mg/kg bw), a growing weakness of the animal was observed (difficulty to stand on

its legs) during injection and it disappeared progressively after the injection.

At the lethal doses, no serious observed cardiological effects were detected. A high reduction of the body t° was noted (up to 5.8°C), a higher number of the respiratory acts (not for dose 7848 mg/kg bw). Muscular contraction and high weakness.

Respiration and heart rythms progressively slowered and death occurred at 15 to 24 hours after injection.

Autopsy and histological examinations only revealed slight congestion in all organs. The author explains that death is probably related to the depresive effect of the test substance on the activity of central nervous system.

Test substance: sodium gluconate
Reliability: (4) not assignable
Short abstract, secondary litterature, old study.
10-NOV-2005 (10)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: other: no data on sodium gluconate. See gluconic acid

06-AUG-2004

5.2.2 Eye Irritation

Species: other: no data for sodium gluconate. See gluconic acid

06-AUG-2004

5.3 Sensitization

5.4 Repeated Dose Toxicity

Type: Sub-acute
Species: rat Sex: male/female
Strain: Crj: CD(SD)
Route of administration: gavage
Exposure period: 4 weeks
Frequency of treatment: daily
Doses: 0, 500, 1000, 2000 mg/kg bw
Control Group: yes, concurrent no treatment
NOAEL: = 1000 mg/kg bw
NOAEL females : = 2000 mg/kg bw

Method: other: no data
Year: 1995

GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result:

No death or clinical signs of abnormality were observed in any of the groups.

Histopathological examination showed a thickening of the limiting of the border of the stomach in 5/12 males at 2000 mg/kg bw per day. No toxic changes associated with the test article were detected.

As the limiting ridge is a tissue specific to rodents, this lesion is not toxicologically significant for humans. Other lesions occurred incidentally and were not related to treatment.

The qualitative urinary analysis showed increased prevalences of urinary ketone bodies, urobilogen and phosphate sedimentation and increased urinary protein concentrations in all treated animals justified by interference in the assay.

The non-toxic dose was estimated to be 1000 mg/kg/day for males and 2000 mg/kg/day for femal

Test condition:

Animals : 12 males and 12 females - 6 weeks of age

Route : gavage of sodium gluconate in water at a volume of 1ml/100g bw

Satellite groups of 4 rats of each sex were included to determine the plasma concentration of sodium gluconate.

Body weights and food consumption were measured on day 1 and every third or fourth day of the study.

Ophthalmological examinations were performed on all animals at the start of the study and on 6 rats of each sex per group at week 4.

Haematological and clinical chemical parameters were measured at the end of treatment on blood collected from fasted surviving rats on all animals at necropsy.

Qualitative and quantitative urinary examinations (urinary pH, protein, ketones and glucose content) were performed on 6 rats of each sex from each group at the end of treatment and water intake was measured over 24 hours.

The weights of the brain, pituitary, thyroids, salivary glands, thymus, heart, lungs, liver, spleen, kidneys, adrenals, testes, prostate, seminal vesicles, ovaries, and uterus were recorded.

Detailed histopathological examinations were performed on cerebrum, heart, lung, cecum, liver, kidney, testis, epididymis, prostate and eye on all control animals and

those receiving 2000 mg/kg bw per day and on all gross lesion
Test substance: sodium gluconate
Reliability: (2) valid with restrictions
Secondary litterature but described in sufficient detail in a recognised WHO report. Acceptable for assessment.
Flag: Critical study for SIDS endpoint
10-NOV-2005 (26)

Type: Sub-acute
Species: rat Sex: male/female
Strain: Crj: CD(SD)
Route of administration: oral feed
Exposure period: 28 days
Frequency of treatment: daily
Doses: 0, 1000, 2000, 4100 mg/kg bw for males (and 0, 1000, 2000, 4400 mg/kg bw females)
Control Group: other: 1.35% w/w NaCl (equivalent to the sodium concentration of the group receiving 5% sodium gluconate)
NOAEL: = 4100 mg/kg bw

Method: other: no data
Year: 1997
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: The JECFA committee (Joint FAO/WHO Expert Committee on Food Additives) who has evaluated this report concluded that this study is not suitable for identifying a NOAEL because of the small group sizes and the positive findings in the qualitative analysis.
Result: No death occurred during the study period. No changes in the general condition, body weight or food and water intake, were observed in the animals over the study period. No revisions were observed in the investigated ophthalmologic tests, urinalysis, heamatology and blood chemistry over the study period. In addition, histopathological examination indicated no adverse effects as a result of the treatment regime.

Statistically significant differences in some urinary parameters (no specific data in the report) were reported in animals receiving 2.5 or 5% sodium gluconate when compared with those on basal diet; however, these differences were comparable to those observed in the NaCl control group and appeared to be related to the high sodium concentration of the sodium gluconate.

Qualitative measurements of urinary protein showed significantly increased concentrations in females at 2.5 and 5% sodium gluconate when compared with those on basal diet. Males at 5% showed a tendency for increased urinary protein concentrations, while the concentrations in males at 2.5% were not affected. The author reported that the increases in urinary protein were due to assay interference, however, the report does not provide detailed information.

Qualitative measurements of urinary ketone bodies also showed increases in males at 2.5% sodium gluconate.

The authors concluded that the NOAEL was 5% (equal to 4100 mg/kg bw per day). The JECFA committee who evaluated this report has considered that effects shown in the qualitative urine analyses are related to the high sodium intake arising from the sodium gluconate.

Source: Glucono-delta-Lactone and the Calcium, Magnesium, Potassium and Sodium Salts of Gluconic acid, in Safety Evaluation of Certain Food Additives, WHO Food Additives Series 42, prepared by the 51st meeting of the Joint FAO/WHO Expert Committee on Food Additives, World Health Organisation, Geneva, 1999 (absorption, distribution and excretion, acute toxicity, short-term toxicity, long-term toxicity, reproductive and developmental toxicity, genotoxicity, observations in humans, 24 references).

Test condition: Animals : Sprague-Dawley SPF rats [Crj:CD (SD)] in groups of 10 males and 10 females

Oral feed: 0, 1.25, 2.5, 5 % w/w or 0, 1000, 2000, 4100 mg/kg bw for males (and 0, 1000, 2000, 4400 mg/kg bw females) sodium gluconate and 1.35 %w/w sodium chloride (equivalent to the sodium content of diet containing 5% sodium gluconate) in order to differentiate the potential effects of high doses of sodium intake.

Body weights and food consumption were measured on day 1 and every third or fourth day of the study. food-efficiency was calculated from the body-weight gain and food consumption. Ophthalmological examinations were performed on all animals at the start of the study and on 6 rats of each sex per group at week 4.

Haematological and clinical chemical examinations were performed on all animals at necropsy.

Qualitative and quantitative urinary examinations (urinary pH, protein, ketones and glucose content) were performed at the end of treatment and water intake was measured over 24 h. The weights of the brain, pituitary, thyroids, salivary glands, thymus, heart, lungs, liver, spleen, kidneys, adrenals, testes, prostate, seminal vesicles, ovaries, and uterus were recorded. Detailed histopathological examinations were performed on cerebrum, heart, lung, cecum, liver, kidney, testis, epididymis, prostate and eye from all animals at 0% and 5 % sodium gluconate and the NaCl control group and on all gross lesions.

Test substance: sodium gluconate

Reliability: (2) valid with restrictions
Secondary litterature but described in sufficient detail in a recognised WHO report. Acceptable for assessment.

Flag: Critical study for SIDS endpoint

10-NOV-2005 (27)

Type: Sub-acute

Species: dog Sex: male/female
Strain: Beagle
Route of administration: oral unspecified
Exposure period: 4 weeks
Frequency of treatment: no data
Doses: 0, 500, 1000, 2000 mg/kg
Control Group: yes
NOAEL: = 500 mg/kg

Method: other: no data
Year: 1995
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: None of the animals died during the period of treatment in any dose group.

Statistically significant increased frequency of vomiting and passage of loose or watery stools in 1000 and 2000 mg/kg dose groups was observed, as compared to controls.

No significantly toxicologically changes were detected in the body weight, food intake, water intake, urinalysis, hematologic test, blood chemistry analysis, ophthalmologic test, electrocardiography, autopsy and organ weight or in histopathological examination.

The non-toxic dose under the conditions of this testing was therefore estimated to be 500 mg/kg/day. However, the toxicological effects observed (vomiting, passage of loose or watery stools) were considered extremely slight since other tests didn't show the same changes.

Test condition:
Animals : groups of 4 males and 4 females
Route : oral unspecified

Observation on the general conditions of the animals was noted daily before and after dosing during treatment.

Ophthalmological examinations were performed on all animals 1 week before dosing and at the third week of the study.

Qualitative and quantitative urinary examinations (urinary pH, protein and glucose) were performed on weeks 2 and 1 before dosing and on weeks 2 and 4 during the study.

Haematological and clinical chemical parameters were measured at the end of treatment on blood collected from fasted surviving rats on all animals at necropsy.

The weights of the brain, pituitary, thyroids, salivary glands, thymus, heart, lungs, liver, spleen, kidneys, adrenals, testes, prostate, seminal vesicles, ovaries, and uterus were recorded.

Detailed histopathological examinations were performed on

the cerebrum, cerebellum, medulla oblongata, spinal cord, sciatic nerve, aorta,heart, larynx, trachea, lung, tongue, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, submandibular gland, sublingual gland, parotid gland, liver, gallbladder, pancreas, pituitary, thyroid, parathyroid, adrenal, thymus, spleen, submandibular lymph node, mesenteric lymph node, kidney, urinary bladder, testis, epididymis, prostate, mammary gland, skin, eye, optic nerve, lacrimal gland, bone marrow of sternum and femur and femoral muscl

Test substance: sodium gluconate

Reliability: (2) valid with restrictions
Abstract not sufficiently detailed but could be acceptable for an initial assessment.

Flag: Critical study for SIDS endpoint

10-NOV-2005 (29)

Type: Sub-acute
Species: dog Sex: no data
Strain: Beagle
Route of administration: oral feed
Exposure period: 1 week
Frequency of treatment: daily
Doses: 1500 mg/kg
Control Group: yes

Method: other: no data
Year: 1997
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: Sodium gluconate was administered to beagle dogs (3 animals per group) in dosage
of 0 and 1500 mg/kg as an additive to food or in capsules for 1 week.

Vomiting and fecal properties were compared between two methods of administration and confirmed.

As a reference article, 405 mg/kg of sodium chloride (NaCl) was administered likewise.

Result: None of the animals died during the period of observation in any dose group.

Passage of loose stools only was detected in the sodium gluconate diet group,and vomiting and loose stools were detected in the capsule group. Only vomiting was detected in the NaCl containing diet group and the capsule group. The above findings suggested that vomiting was caused by physical stimulation by massive administration of the test article in capsules or caused by sodium chloride in the test substance. Loose stools seemed to be related to homeostatic adjustment to increased osmolarity following administration of a solution of the test article.

Test substance: sodium gluconate

Reliability: (3) invalid
Short abstract on a comparison of 2 methods of administration of sodium gluconate.

10-NOV-2005 (28)

Type: Sub-acute
Species: rat Sex: no data
Strain: no data
Route of administration: oral feed
Exposure period: 10 days
Frequency of treatment: daily
Doses: 450 mg/kg/day
Control Group: no data specified

Method: other: no data
Year: 1942
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Result: metabolic rate reduced. However, the rate returned to normal when the gluconate feeding was discontinued. Also, gluconic acid fed at approximately 400 mg/kg per day had no effect on the metabolic rate. These results suggest that the observed effects were produced by the cations and not by the gluconate portion of the molecule.
Source: Evaluation of the Health Aspects of Sodium, Potassium, Magnesium and Zinc Gluconates as Food Ingredients, SCOGS-78, prepared for Bureau of Foods, Food and Drug Administration, Department of Health, Education, and Welfare, Washington D.C., Contract No. FDA 233-75-2004, Life Science Research Office, Federation of American Societies for Experimental Biology, 9650 Rockville Pike Bethesda, Maryland, 1978 (absorption and methabolism, acute toxicity, short-term studies, teratogenicity, mutagenicity, 26 references).
Test substance: sodium gluconate
Reliability: (4) not assignable
Short abstract, secondary litterature, old study, no data on sample size
10-NOV-2005 (1)

5.5 Genetic Toxicity 'in Vitro'

Type: other: Saccharomyces Cerevisiae and Salmonella typhimurium reverse mutation assay
System of testing: bacterial and non bacterial
Concentration: bacteria: 0.006%, 0.0012 %, 0.0024 % and yeast: 1.25%, 2.50% and 5.00%
Cytotoxic Concentration: 50% survival in bacteria calculated was at 0.0024 % test substance and 5% for yeast
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
Year: 1975
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: A. Toxicity:

The solubility, toxicity and doses for all chemicals were determined prior to screening.

Each chemical was tested on the strains over a range of doses (10, 1.0, 0.1, 0.01, 0.001 %) to determine the concentration that lead to 50% survival. Bacteria were tested in phosphate buffer, pH 7.4 for one hour at 37°c on a shaker. Yeasts were tested in phosphate buffer, pH 7.4 for 4 hours at 30°c on a shaker. The 50% survival curve and the 1/4 and 1/2 50% doses calculated. If no toxicity was obtained for a chemical with a given strain, a maximum dose of 5% (w/v) was used.

The doses calculated for the tests in buffer were applied to the activation tests. The solubility of the test substance under treatment conditions was measured and sodium gluconate is insoluble in dimethylsulfoxide (DMSO)

B. Plate tests (overlay method)

Approximately 10 exp9 cells from a log phase culture of each strain were added to test tubes containing 2.0 ml of molten agar supplemented with biotin and a trace of histidine. For nonactivation tests, the 3 dose levels of the test compound were added to the tubes and poured over the surfaces of selective agar plates.

In activation tests, the 9000 x g tissue supernatant and required cofactors (core reaction mixture) were added to the overlay tubes. 3 dose levels of the test chemical were added to the tubes, which were mixed and content poured over the surface of a minimal agar (selective medium) plate and allowed to solidify.

The plates were incubated for 48 to 72 hours at 37°C, and scored for colonies growing on each plate. Positive and solvent controls were run with each assay.

C. Suspension tests

1. Nonactivation

Log phase bacteria and stationary phase yeast cultures were grown in complete broth, washed and resuspended in 0.9% saline to densities of 1 x 10 exp9 cells/ml and 5 x 10 exp7 cells/ml respectively. Tests were conducted in plastic tissue culture plates. Cells plus chemicals were added to the wells to give a final volume of 1.5 ml. The solvent replaced the test chemical in the negative controls. Treatment was at 30°C for 4 hours for yeast tests and at 37°c for one hour for bacterial tests. All flasks were shaken during treatment. After treatments, the plates were set on ice. Aliquots of cells were removed, diluted in sterile saline (4°c) and plated on the appropriate complete media. Undiluted samples from flasks containing the bacteria were plated on minimal selective medium in reversion experiments. Samples from a 1/10 dilution of treated cells were plated on the selected media for

enumeration of gene conversion with strain D4.

Bacterial plates were scored after incubation for 48 hours at 37°C. The yeast plates were incubated at 30°C for 3-5 days before scoring.

2. Activation

Bacteria and yeast cells were grown and prepared as described in the nonactivation tests. Measured amounts of the test and control chemicals plus 0.25 ml of the stock-cell suspension were added to wells of the Linbro plate containing the appropriate tissue fraction and reaction mixture. All flasks (bacteria and yeast) were incubated at 37°c in an oxygen atmosphere with shaking. The treatment times, dilutions, plating procedure and scoring of the plates were the same as described for non activation tests.

Remark: This study was conducted using 3 bacteria strains (salmonella typhimurium) and one yeast strain (saccharomyces cervisiae) rather than a fourth bacteria strain as indicators for this in vitro microbial assay with and without metabolic activation. Therefore, the results of this report on bacteria and yeast are included in the same entry.

Result: A. Salmonella typhimurium:

1. Plate tests: negative

2. Nonactivation suspension tests: negative

3. Activation suspension tests: negative (the 0.0024% dose with TA-1538 using mouse lung tissue fraction and the doses with TA-1537 usring rat lung tissue fraction were repeated because of low population counts.

B. Saccharomyces cerevisiae

1. Non-activation suspension tests: negative (the 2.50% dose was repeated because of a low mutant plate count.

2. Activation suspension tests: negative

Conclusion:

The test compound sodium gluconate did not exhibit genetic activity in any of the assays employed in study.

Test condition: Strains tested:

Yeast: Saccharomyces Cerevisiae, Strain D4

Bacteria: Salmonella typhimurium, strains: TA1535, TA1537, TA1538

Reaction mixture:

Component:	Final concentration/ml
TNP (sodium salt)	6 µM
Isocitric acid	49 µM
Tris buffer, pH 7.4	28 µM
MgCl2	1.7 µM
Homogenate fraction equivalent to 25 mg of wet tissue	

Tissue homogenates and supernatants:

The tissue homogenates and supernatants (9000 g) were prepared from tissues of mouse (ICR random bred adult males); rat (Sprague-Dawnley adult males) and monkey (Macaca mulatta adult males)

Positive controls in direct and activation assays:

Non activation:

Chemical	Solvent	Probable mutagenic specificity
Ethyl methanesulfonate (EMS)	water or saline	base-pair substitution
2-nitrofluorene (NF)	dimethylsulfoxide	frameshift
Quinacrine mustard (QM)	water or saline	frameshift

****

Activation:

Chemical	Solvent	Probable mutagenic specificity
Dimethylnitrosamine (DMN)	water or saline	base-pair substitution
2-acetylaminofluorene (AAF)	dimethylsulfoxide	frameshift
8-Aminoquinoline (AMQ)	dimethylsulfoxide	frameshift

Concentration of positive controls:

Non activation:
TA-1535 EMS 10µl/plate
TA-1537 QM 20 µg/plate
TA-1538 NF 100 µg/plate

Activation:
TA-1535 ANTH (DMN ?) 100 µM/plate
TA-1537 AMQ 100 µg/plate
TA-1538 AAF 100 µg/plate

No information is reported on the positive control origin and criteria used for determining the positive result.

Test substance: sodium gluconate: no data on purity of substance

Reliability: (2) valid with restrictions
OECD guideline No. 471 followed except that the study was made on one yeast strain : saccharomyces

cerevisiae, strain D4 and 3 bacteria strains: S. typhimurium TA1535, TA1537 and TA 1538

Positive controls different from the ones described in the OECD guideline No 471

The study was made only on 3 test concentrations.
Flag: Critical study for SIDS endpoint
25-JAN-2006 (21)

5.6 Genetic Toxicity 'in Vivo'

Type: other: in vivo chromosomal aberration test with mouse bone marrow cells
Species: mouse Sex: male
Strain: C57BL
Route of admin.: oral feed
Exposure period: single dose and 4 days
Doses: single dose administration : 2.5, 5 and 10 g/kg
4 day repeated dose: 1.25 and 2.5 g/kg
Result: negative

Method: other: no data specified
Year: 1974
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: After receiving the single dose and the repeated dose test substance, the animals were sacrified at 24 hours (single dose) and 27 hours after last administration (4-days repeated dose). 0.3 ml of 500 µg/ml colchicine was intraperitoneally injected to each mouse at one hour before sacrifice so that the metaphase cells could be observed.

After the bone marrow cells were washed, treated and fixed with a fixing solution (1:3 acetic acid:ethanol solution), the cells were suspended and dripped on a slide glass and stained with Giemsa solution and examined.

Examination:

At least 200 metaphase cells per mouse were examined for the presence or absence of chromosomal aberrations (gaps, breaks, translocation, fragments, ring chromosomes and minutes chromosome)
Result: Single dose administration:

At 10 and 5 g/kg, all mice died.

At 2.5 g/kg, observation could be made only on 2 animals(preparation of the chromosome specimen failed).

MMC induced chromosomal aberrations in at least 20% of bone marrow cells.

Sodium gluconate induced chromosomal aberrations in the cells at a frequency of about 0.5% is comparable to the control. (1 gap and 1 minute chromosome for 283 cells).

****
4-day repeated dose administration:

At 1.25 and 2.5 g/kg, one mouse died in each group.

MMC induced chromosomal aberrations at about 30% cells.

The frequency of cells with chromosomal aberrations was 0.5% in the test groups which is comparable to the control group.

Conclusion: Induction of chromosomal aberration by sodium gluconate was not detected after in vivo single and repeated dose
treatment.

Test condition: Animals:

Male C57BL/6 mice aged 12 or 13 weeks

Materials:

Test substance: sodium gluconate dissolved with 0.9% physiological saline solution and orally administered at a dose of 1ml/mouse

Positive control: MMC (mitomycin C) dissolved with 0.9% physiological saline solution and administered intraperitoneally at a dose of 0.5 ml/mouse

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Single dose administration :

Control (physiological solution) :
group 1 - 3 animals

MMC:
group 1 - 2 animals - 5 mg/kg (intraperitoneal)

Sodium gluconate :
group 1 - 3 animals - 10 g/kg
group 2 - 3 animals - 5 g/kg
group 3 - 3 animals - 2.5 g/kg

4-day repeated dose administration :

Control (physiological solution) :
group 1 - 2 animals

MMC:
group 1 - 2 animals - 5 mg/kg (single dose intraperitoneal)

Sodium gluconate :
group 1 - 3 animals - 2.5 g/kg
group 2 - 2 animals - 1.25 g/kg

Test substance: sodium gluconate: no data on purity of the substance
Reliability: (2) valid with restrictions
Translation of a report not fully documented but sufficient for initial assessment

Flag: Critical study for SIDS endpoint
10-NOV-2005 (37)

5.7 Carcinogenicity

5.8.1 Toxicity to Fertility

5.8.2 Developmental Toxicity/Teratogenicity

Species:	rat	Sex: female
Strain:	Wistar	
Route of administration:	gavage	
Exposure period:	from day 6 to day 15 of gestation	
Frequency of treatment:	daily	
Duration of test:	10 days	
Doses:	0, 5.94, 27.6, 128.0, 594.0 mg/kg	
Control Group:	yes, concurrent vehicle	
NOAEL Maternal Toxity:	> 594 mg/kg bw	
NOAEL Teratogenicity:	> 594 mg/kg bw	
Result:	non teratogen	

Method: other: no data specified
Year: 1973
GLP: no
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
10-NOV-2005 (4)

Species:	mouse	Sex: female
Strain:	CD-1	
Route of administration:	gavage	
Exposure period:	from day 6 to day 15 of gestation	
Frequency of treatment:	daily	
Duration of test:	10 days	
Doses:	0, 6.95, 32.5, 150, 695 mg/kg	
Control Group:	yes, concurrent vehicle	
NOAEL Maternal Toxity:	> 695 mg/kg bw	
NOAEL Teratogenicity:	> 695 mg/kg bw	
Result:	non teratogen	

Method: other: no data specified
Year: 1973
GLP: no
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
10-NOV-2005 (4)

Species: rabbit Sex: female
Strain: Dutch
Route of administration: gavage
Exposure period: from day 6 to 18 of gestation
Frequency of treatment: daily
Duration of test: 13 days
Doses: 0, 7.80, 36.2, 168.5, 780.0 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 780 mg/kg bw
NOAEL Teratogenicity: > 780 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
10-NOV-2005 (5)

Species: hamster Sex: female
Route of administration: gavage
Exposure period: from day 6 to day 10 of gestation
Frequency of treatment: Daily
Duration of test: 5 days
Doses: 0, 5.60, 26.0, 121, 560 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 560 mg/kg bw
NOAEL Teratogenicity: > 560 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
10-NOV-2005 (4)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: oral unspecified

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Exposure period:           from day 6 to day 15 of gestation
Frequency of treatment:    daily
Duration of test:          10 days
Doses:                     1000 and 4000 mg/kg
Control Group:             no data specified
NOAEL Maternal Toxity:     > 4000 mg/kg bw
NOAEL Teratogenicity:      > 4000 mg/kg bw
Result:                    Non teratogen

Method:           other: No data specified
  Year:           1978
   GLP:           no data
Test substance:   other TS

Remark:           Data for the category: see details of study under
                  glucono-delta-lactone SIDS dossier.
Test substance:   Glucono-delta-lactone
Reliability:      (2)  valid with restrictions
                  short abstract but acceptable for initial assessment
Flag:             Critical study for SIDS endpoint
10-NOV-2005                                                          (6)

Species:                   mouse                          Sex: female
Strain:                    ICR
Route of administration:   oral unspecified
Exposure period:           from day 6 to day 15 of gestation
Frequency of treatment:    daily
Duration of test:          10 days
Doses:                     1000 and 4000 mg/kg
Control Group:             no data specified
NOAEL Maternal Toxity:     > 4000 mg/kg bw
NOAEL Teratogenicity:      > 4000 mg/kg bw
Result:                    non teratogen

Method:           other: no data specified
  Year:           1978
   GLP:           no data
Test substance:   other TS

Remark:           Data for the category: see details of study under
                  glucono-delta-lactone SIDS dossier.
Test substance:   Glucono-delta-lactone
Reliability:      (2)  valid with restrictions
                  short abstract but acceptable for initial assessment
Flag:             Critical study for SIDS endpoint
10-NOV-2005                                                          (7)
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5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Type of experience: Human - Exposure through Food

Remark: On the basis of a re-evaluation of data previously considered by JECFA and new data on the short-term toxicity of sodium gluconate, the Committee extended the previous ADI
'not specified' for glucono-delta-lactone to a group ADI for
glucono-delta-lactone and the calcium, magnesium, potassium,
and sodium salts of gluconic acid.

01-AUG-2003 (43)

Type of experience: Human - Exposure through Food

Remark: Gluconic acid and its salts have been used in various applications in the food industry. As a sequestrant, sodium
gluconate finds broad application in cleaning solutions for the food industry. Also, sodium gluconate has been used in indirect application in washing solutions for eggs, denuding
tripe, and for preventing the staining of the exteriors of canned goods by cooling and retort water. Sodium and calcium gluconate have been utilized as a partial replacement for sodium chloride in sausage products. The emulsifying and water binding properties of the sausage as well as the nutritional properties were improved.

Over the past ten years, there has been considerable research conducted in Japan using sodium gluconate to complement sodium chloride in the extraction of proteins from fish muscle. Surimi, which had excellent whiteness and
good elasticity, was produced by replacing the phosphates in
the process with sodium gluconate.

A process to improve meat tenderness was developed by scientists at the US Meat Animal Research Center. The calcium activated Tenderization process uses post-mortem injected calcium to activate the calpain tenderizing enzymes. While the original work used calcium chloride, more recent tests showed a calcium gluconate compound equally effective.

Sodium and potassium gluconate have a unique impact on taste
perception. The gluconates perform a debitterant function when used with artificial sweeteners, i.e. saccharine, cyclamates and aspartame.

Sodium gluconate is sometimes used as an ingredient in sugar
replacement packets and diet beverages. The artificial sweetener, Aspartame, when used alone has a defect in that its sweeteness is slightly delayed in onset and tends to remain longer on the tongue. The gustatory quality of aspartame is improved to be more like sucrose with the addition of sodium gluconate.

Potassium gluconate has been shown to suppress the sweeteness of hydrolized lactose without producing bitterness or off-flavors.

Fujisawa Pharmaceutical Company, has conducted research on the reduction of sodium in foods. Fujisawa scientists have developed a "low sodium" type product that combines sodium chloride with potassium gluconate. Extensive tests have shown its functionality in various food products.

14-AUG-2003 (12)

Type of experience: Human - Medical Data

Remark: Sodium gluconate is also used in pharmaceutical injection solutions in concentrations up to 55 g/l.

Company	Product	Sodium gluconate Content
Abbott Laboratories	Normosol R Inj	5.02 g/l
	Normosol R W 5% dextrose Inj	5.02 g/l
Baxter	Plasmalyte 148	5.02 g/l
	Plasmalyte 148 in 5% dextrose inj	5.02 g/l
B. Braun Medical	Isolyte S	5.00 g/l
	Isolyte S with 5% dextrose inj	5.00 g/l
	Isolyte S pH 7.4	5.00 g/l
	Hyperlyte	43.6 g/l
Pharmaceutical Partners of Canada	Lypholyte - Liq IV	55 g/l

http://www.hc-sc.gc.ca/hpb/drugs-dpd/

10-NOV-2005 (2)

5.11 Additional Remarks

Type: other

Remark: Opinion of the SCF in Reports of the Scientific Committee for Food, Twenty-fifth series (1991), First series of food additives of various technological functions (opinion expressed on 18 May 1990)

Gluconate and glucono-delta-lactone:

Consideration of these substances may be based on the metabolic evidence as intermediates of normal glucose metabolism in mammalian species. There is considerable experience with gluconates in man and animals. A single long-term test at one dose level showed no evidence of carcinogenicity for the lactone. Teratogenic tests have

shown no abnormalities in 4 species. In view of their role in the glucose metabolism in mammals the Committee agrees with the group ADI not specified established by JECFA

10-NOV-2005 (31)

Type: other

Remark: Opinion of the Select Committee on GRAS substances:

Gluconates are useful as nutritional supplements since their high solubility allows relatively rapid absorption of the cations. Evidence suggests that any possible toxicity is a function of the cation rather than of the gluconate portion of these substances. Thus, the acute toxic responses to the various gluconate salts are comparable with other salts of the same metals and long-term toxicities seem related to the tissue deposition of these metals. These observations could have been anticipated because gluconic acid is a normal metabolic product of glucose. The amount of gluconic acid produced endogenously is many times greater than the largest amounts likely to be consumed from food. Because the toxicological activities of these gluconates appear to be a function of their cationic components, safe and acceptable levels in foods are limited only by the nature of the specific cations. Based on the foregoing, the Select Committee concludes that there is no evidence in the available information on sodium gluconate, potassium gluconate, magnesium gluconate and zinc gluconate that demonstrates or suggests reasonable grounds to suspect a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future.

17-OCT-2003 (3)

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I U C L I D

D a t a S e t

Existing Chemical	ID: 299-28-5
CAS No.	299-28-5
EINECS Name	calcium gluconate
EC No.	206-075-8
Molecular Formula	C6H12O7.1/2Ca

Producer Related Part	
Company:	Keller and Heckman LLP
Creation date:	02-APR-2003
Substance Related Part	
Company:	Keller and Heckman LLP
Creation date:	02-APR-2003
Memo:	OECD HPV Chemicals Programme, SIDS Dossier, approved at SIAM 18 (20-23 April 2004)

Printing date:	25-JAN-2006
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Number of Pages:	39

Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

Type: lead organisation
Name: The Gluconic acid and its sodium, potassium and calcium salts and glucono-delta-lactone consortium
Contact Person: Jean-Philippe Montfort Date: 02-APR-2003
Street: Rue Blanche 25
Town: 1060 Brussels
Country: Belgium
Phone: +32 2 541 05 70
Telefax: + 32 2 541 05 80
Email: montfort@khlaw.be

Remark: Sponsor Country for this Category: Belgium; Co-sponsor country: Japan.
12-DEC-2005

Type: manufacturer
Name: FUSO Chemical Co. Ltd
Contact Person: Ph.D. Shinichi Sugita Date:
Street: Iwamoto-cho Toyo Building, 1-2 Iwamoto-cho 3-chome, Chiyoda-ku
Town: 101 0032 Tokyo
Country: Japan
Phone: +81 3 5820 1611
Telefax: +81 3 5820 1634
Email: Shinichi.Sugita@fusokk.co.jp

03-AUG-2004

Type: manufacturer
Name: Jungbunzlauer International AG
Contact Person: Raphaël Singer Date: 17-APR-2003
Street: St. Alban-Vorstadt 90
Town: 4002 Basel
Country: Switzerland
Phone: +41 61 295 51 25
Telefax: +41 61 295 52 66
Email: raphael.singer@jungbunzlauer.ch

17-OCT-2003

Type: manufacturer
Name: Roquette Freres
Contact Person: Johnny Pallot Date:
Town: 62080 Lestrem Cedex
Country: France
Phone: +33 3 21 63 37 40
Telefax: +33 3 21 63 38 50
Email: JOHNNY.PALLOT@roquette.com

31-JUL-2003

Type: manufacturer
Name: PURAC
Contact Person: Ton van Dongen Date:
Street: PO BOX 21
Town: 4200 AA Gorinchem
Country: Netherlands

Phone: +31 183 695 730
Telefax: +31 183 695 603
Email: t.van.dongen@purac.com

03-AUG-2004

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

Remark: Glucono-delta-lactone, gluconic acid and its sodium, calcium and potassium salts have been proposed in a category, as the salts of gluconic acid freely dissociate to the gluconate anion and the respective cation.

Glucono-delta-lactone (GDL) is the inner ester of gluconic acid formed by the removal of water.

When glucono-delta-lactone is used in aqueous solution, it is slowly hydrolysed until an equilibrium is reached between gluconic acid and its delta-lactone.

12-AUG-2004

1.1.0 Substance Identification

IUPAC Name: calcium-di- 2,3,4,5,6 - pentahydroxy hexanoate anhydrous
Smiles Code: [Ca](OC(=O)C(O)C(O)C(O)C(O)CO)OC(=O)C(O)C(O)C(O)C(O)CO
Mol. Formula: C12H22O14Ca
Mol. Weight: 430.4

20-OCT-2003

IUPAC Name: calcium-di- 2,3,4,5,6 - pentahydroxy hexanoate monohydrate
Mol. Formula: C12H22O14Ca.H2O
Mol. Weight: 448.4

Remark: CAS No for calcium gluconate monhydrate is 18016-24-5.
12-AUG-2004

1.1.1 General Substance Information

Purity type: typical for marketed substance
Substance type: organic
Physical status: solid
Purity: ca. 98 - 104 % w/w
Colour: white/off-white
Odour: none

Remark: Calcium gluconate is the calcium salt of gluconic acid, which is obtained from glucose (dextrose) by fermentation.

Gluconic acid is produced naturally as a main metabolism product via the decomposition of glucose in foods such as wine or honey.

09-AUG-2004

1.1.2 Spectra

1.2 Synonyms and Tradenames

calcium gluconate

11-JUN-2003

mono calcium di-D(-)-pentahydroxycapronate

11-JUN-2003

1.3 Impurities

Purity type: typical for marketed substance

Remark: For food and/or medical applications the level of impurities complies with the restrictions laid down in the corresponding EU Directives.

15-JAN-2004

1.4 Additives

Remark: For all the chemicals of the category: no additives used

10-NOV-2005

1.5 Total Quantity

Quantity: ca. 4000 - 6000 tonnes produced in 2000

09-AUG-2004

1.6.1 Labelling

Remark: For all the chemicals in the category: proposal of Industry: no labelling required

10-NOV-2005

1.6.2 Classification

Classified: other, as in legislation

Remark: For all chemicals of the category: proposal of Industry: no classification required

10-NOV-2005

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Wide dispersive use

Remark: Data for the category: see sodium gluconate
14-AUG-2003

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

Source of exposure: other

Remark: Data for the category: see sodium gluconate
14-AUG-2003

1.11 Additional Remarks

Memo: Regulatory status

Remark: In the European Parliament and Council Directive 95/2/EC, calcium gluconate is listed as a generally permitted food additive (E578) and may be added to all foodstuffs, following the "quantum satis" principle, as long as no special regulations restrict the use.

the US Food and Drug Administration (FDA) assigned calcium gluconate the "generally recognised as safe" (GRAS) status and permitted its use in food without limitation other than good manufacturing practice.

14-AUG-2003

1.12 Last Literature Search

1.13 Reviews

2.1 Melting Point

Value: = 120 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Test substance: Calcium gluconate monohydrate: -H2O
Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
09-AUG-2004 (2)

2.2 Boiling Point

Value: = 731.1 degree C

Method: other: calculated
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with MPBPVP (v1.41) program from US EPA (EPI v3.11)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2004

2.3 Density

Type: bulk density
Value: ca. 300 - 650 kg/m3

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used
Flag: Critical study for SIDS endpoint
09-AUG-2004 (9)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = 0 hPa at 25 degree C

Method: other (calculated)
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with MPBPVP (v1.41) program from US EPA (EPI

```
                  v3.11):

                  Vapor Pressure Estimations (25 deg C):
                    (Using BP: 731.14 deg C (estimated))
                    (Using MP: 320.57 deg C (estimated))
                      VP:  8.69E-034 mm Hg (Antoine Method)
                      VP:  1.19E-022 mm Hg (Modified Grain Method)
                      VP:  5.84E-017 mm Hg (Mackay Method)
Result:           Selected VP:  1.19E-022 mm Hg or 1.58E-022 hPa (Modified
                  Grain Method)
Reliability:      (2)  valid with restrictions
                  Accepted calculation method
Flag:             Critical study for SIDS endpoint
09-AUG-2004


2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow:          = -7.51 at 25 degree C

Method:           other (calculated)
   GLP:           no

Remark:           Estimated with Kowwin  (v1.67) program from US EPA (EPI
                  v3.11):
Reliability:      (2)  valid with restrictions
                  Accepted calculation method
Flag:             Critical study for SIDS endpoint
09-AUG-2004


2.6.1 Solubility in different media

Solubility in:    Water
Value:            = 30 g/l at 20 degree C
pH       value:   = 6 - 8.5
         Conc.:   1 vol% degree C

Method:           other: no data
   GLP:           no data
Test substance:   as prescribed by 1.1 - 1.4

Reliability:      (4)  not assignable
                  Data from an MSDS. No data on method used
Flag:             Critical study for SIDS endpoint
09-AUG-2004                                                          (9)

Solubility in:    Water
Value:            = 35 g/l at 25 degree C

Method:           other: no data
   GLP:           no data
Test substance:   as prescribed by 1.1 - 1.4

Reliability:      (4)  not assignable
                  Data from an MSDS. No data on method used
Flag:             Critical study for SIDS endpoint
```

09-AUG-2004 (4)

Solubility in: other: alcohol
Descr.: insoluble (< 0.1 mg/L)

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used
Flag: Critical study for SIDS endpoint
09-AUG-2004 (9)

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

2.9 Flammability

2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Dissociation Constant

Acid-base Const.: pKa=3.70

Method: other: no data
GLP: no data
Test substance: other TS

Remark: The dissociation in water is expected to be complete as the pKa values of gluconic acid found in literature range from 3.5 to 3.8
Test substance: gluconic acid
Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
12-AUG-2004 (20)

Acid-base Const.: pKa = 1.22

Method: other: no data specified
Year: 1964
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable

Secondary litterature. Old study
Flag: Critical study for SIDS endpoint
09-AUG-2004 (16)

2.13 Viscosity

2.14 Additional Remarks

11-JUN-2003

3.1.1 Photodegradation

Type: air

Method: other (calculated): Estimated with AOP (v1.91) program from US EPA (EPI v3.11)
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark:
OVERALL OH Rate Constant = 76.2553 E-12 cm3/molecule-sec

HALF-LIFE = 0.140 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 1.683 H
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
12-AUG-2004

3.1.2 Stability in Water

Type: abiotic

Method: other: no data
Year: 1993
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Stability constant for Ca2+ (25°C, μ=0.1) with gluconic acid = 1.22
Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
14-NOV-2005 (19)

Type: abiotic

Method: other: no data
Year: 1962
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Remark: Stability constant of Calcium with gluconic acid : pK= 1.22
Reliability: (4) not assignable
Secondary litterature. Old study
14-NOV-2005 (16)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III
Media: other
Method: other: calculated

Remark: Estimated with the Level III Fugacity Model program LEVEL3NT from US EPA (EPI v3.11)

Chem Name : D-Gluconic acid, calcium salt (2:1) Molecular Wt: 430.38
Henry's LC : 6.74e-029 atm-m3/mole (calc VP/Wsol)
Vapor Press : 1.19e-022 mm Hg (Mpbpwin program)
Liquid VP : 9.97e-020 mm Hg (super-cooled)
Melting Pt : 321 deg C (Mpbpwin program)
Log Kow : -7.51 (Kowwin program)
Soil Koc : 1.27e-008 (calc by model)

	Mass Amount	Half-Life	Emissions
	(percent)	(hr)	(kg/hr)
Air	1.06e-007	3.37	1000
Water	38.8	55.9	1000
Soil	61.2	55.9	1000
Sediment	0.0345	224	0

	Fugacity	Reaction	Advection	Reaction	Advection
	(atm)	(kg/hr)	(kg/hr)	(percent)	(percent)
Air	1.57e-032	5.12e-005	2.49e-006	1.71e-006	8.3e-008
Water	7.13e-035	1.13e+003	91.1	37.6	3.04
Soil	4.17e-033	1.78e+003	0	59.3	0
Sediment	3.17e-035	0.251	0.00162	0.00837	5.4e-005

Persistence Time: 78.3 hr
Reaction Time: 80.7 hr
Advection Time: 2.58e+003 hr
Percent Reacted: 97
Percent Advected: 3.04

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air: 3.367
Water: 55.92
Soil: 55.92
Sediment: 223.7
Biowin estimate: 3.848 (days)

Advection Times (hr):

Air: 100
Water: 1000
Sediment: 5e+004

Reliability: (3) invalid
Limited reliability because the Henry's LC can neither be calculated with the bond estimation method nor with the

group estimation method because of missing values for certain bonds/groups.

The Henry's LC is therefore estimated by VP/Wsol.

However, this program does not use the entered solubility (30 g/l) but the solubility determined by the WATERNT program (1000 g/l) for the estimation of the Henry's LC that is then used in the LEVEL3NT program.

Indeed the Henry's LC estimated with the entered solubility is:
Henrys LC [VP/WSol estimate using EPI values]:
HLC: 2.246E-027 atm-m3/mole

Whereas the Henry's LC estimated with the solubility determined by the WATERNT program is:
Henrys LC [VP/WSol estimate using EPI values]:
HLC: 6.739E-029 atm-m3/mole

25-JAN-2006

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: other (calculation)

Remark: Henry's law constant estimated with HENRY (v3.10) program from US EPA (EPI v3.11)

Can neither be calculated with the bond estimation method nor with the group estimation method because of missing values for certain bonds/groups.

Soil Adsorption Coefficient estimated with PCKOC (v1.66) program from US EPA (EPI v3.11)

First Order Molecular Connectivity Index : 12.487
Non-Corrected Log Koc : 7.2631
Fragment Correction(s):
2 Aliphatic Alcohol (-C-OH) : -3.0386
2 Misc (C=O) Group (aliphatic attach) : -2.4000
Corrected Log Koc . : 1.8245

Estimated Koc: 66.76
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2004

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type:	aerobic
Inoculum:	other: secondary effluent of a municipal sewage plant (Breisgauer Bucht, 500000 population equivalent), 0.4 ml/l
Concentration:	3 mg/l related to Test substance
Contact time:	28 day(s)
Degradation:	= 89 % after 28 day(s)
Result:	readily biodegradable
Kinetic:	3 day(s) = 61.13 % 7 day(s) = 74.35 % 14 day(s) = 66.09 % 21 day(s) = 71.94 % 28 day(s) = 88.88 %
Control Subst.:	Acetic acid, sodium salt
Kinetic:	3 day(s) = 67.15 % 28 day(s) = 80.93 %
Deg. product:	not measured
Method:	Directive 92/69/EEC, C.4-E
Year:	2001
GLP:	yes
Test substance:	other TS
Remark:	The 89% degradation indicated here relates to the Theoritical Oxygen Demand (ThOD). Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance:	Sodium gluconate: 99.0-101.0%
Reliability:	(1) valid without restriction study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag:	Critical study for SIDS endpoint

14-NOV-2005 (7)

Type:	anaerobic
Inoculum:	other: Digesting sludge of a municipal sewage plant (Breisgauer Bucht, 500000 population equivalent), 2.9 g total solids/l
Concentration:	303 mg/l related to Test substance
Contact time:	35 day(s)
Degradation:	= 100 % after 35 day(s)
Result:	readily biodegradable
Kinetic:	1 day(s) = 8 % 8 day(s) = 51 % 15 day(s) = 57 % 22 day(s) = 61 % 35 day(s) = 100 %
Control Subst.:	Benzoic acid, sodium salt
Kinetic:	8 day(s) = 6 % 35 day(s) = 100 %
Deg. product:	not measured
Method:	other: DIN EN ISO 11734
Year:	2001
GLP:	yes
Test substance:	other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
14-NOV-2005 (8)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: semistatic
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: > 100 -
LC0: > 100 -
Limit Test: yes

Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 2002
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate : 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
14-NOV-2005 (11)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: > 1000 -
EC100: > 1000 -
Limit Test: yes

Method: OECD Guide-line 202
Year: 2002
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate : 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
14-NOV-2005 (12)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: yes

NOEC: = 560 -
EC50: > 1000 -
Limit Test: yes

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 2002
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate : 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
14-NOV-2005 (13)

4.4 Toxicity to Microorganisms e.g. Bacteria

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

Species: other

Remark: No data available but exposure in sediment expected to be extremely limited according to the Level III Fugacity Model program LEVEL3NT from US EPA (EPI v3.11) on sodium gluconate
14-AUG-2003

4.6.2 Toxicity to Terrestrial Plants

Method: other

Remark: No data available
14-AUG-2003

4.6.3 Toxicity to Soil Dwelling Organisms

Method: other

Remark: no data available but due to the low intrinsic toxicity in

aquatic organisms, it is reasonable to expect a similar low toxic impact on terrestrial organisms.

09-AUG-2004

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

In Vitro/in vivo:	In vivo
Type:	Toxicokinetics
Species:	other: mice, dogs and monkeys

Method:	other: no data
Year:	1962
GLP:	no
Test substance:	as prescribed by 1.1 - 1.4

Result: The pharmacologic and toxic properties of calcium kinate gluconate, calcium gluconate, and calcium chloride have been studied in mice, dogs, and monkeys. The pharmacologic properties appeared to be based on the calcium concentration except for acute intravenous tolerance where calcium kinate gluconate was better tolerated than calcium gluconate. Calcium kinate gluconate and calcium gluconate injections produced transient decrease in blood clotting time, but increased platelet counts were observed only following calcium kinate gluconate injections. The calcium kinate gluconate effect on blood probably was attributable to the presence of calcium and kinic acid.

No toxic properties of calcium kinate gluconate and calcium gluconate were observed in a 6-month tolerance study in dogs. Good clinical tolerance of calcium kinate gluconate was reported on over 200 cases.

Reliability: (3) invalid
old comparative study not compliant with OECD guidelines, for reference only

14-NOV-2005 (1)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type:	LDLo
Species:	rat
Strain:	Crj: CD(SD)
Sex:	male/female
No. of Animals:	10
Vehicle:	no data
Doses:	500, 1000, 2000 mg/kg
Value:	> 2000 mg/kg bw

Method:	other: no data
Year:	1995
GLP:	no data
Test substance:	other TS

Test substance: sodium gluconate
Reliability: (2) valid with restrictions
Short abstract not well documented but key study for initial

	assessment
Flag:	Critical study for SIDS endpoint
14-NOV-2005	(15)

5.1.2 Acute Inhalation Toxicity

5.1.3 Acute Dermal Toxicity

5.1.4 Acute Toxicity, other Routes

Type:	other
Species:	dog
Strain:	no data
Sex:	no data
No. of Animals:	18
Vehicle:	no data
Doses:	no data
Route of admin.:	i.v.
Method:	other
Year:	1940
GLP:	no
Test substance:	as prescribed by 1.1 - 1.4

Method: 18 adult dogs were used. The animals received 10 mg/kg bw morphine sulfate subcutaneously 30 minutes before injection of the calcium salt was began. The calcium solutions (0.205 M) were injected through a cannula into the femoral vein at varying rates.

A blood sample was taken from the femoral vein just prior to cannulation and a second at death by direct cardiac puncture.

The concentration of calcium in the serum was determined by the method of Kramer and Tisdall (Kramer, B., and Tisdall, F. F.: A simple techniqe for the determination of calcium and magnesium in small amounts of serum, J. Biol. Che. 47: 475, 1921).

Electrocardiograms from Lead II were taken at frequent intervals during the injection.

Result: Appreciably larger quantities of calcium given as gluconate-idonate or calcium gluconate was necessary to produce death than are needed when calcium is given as the chloride. It is possible that the difference between the chloride and the sugar acid salts can be explained in part by the different amounts of calcium ions they yield.

Calcium gluconate-idonate and calcium gluconate differ very little in their toxicity for dogs.

Test substance: calcium gluconate, calcium gluconate-idonate and calcium chloride

Reliability: (3) invalid

very old study not compliant with OECD guidelines
14-NOV-2005 (17)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: other: no data on calcium gluconate. See gluconic acid

10-AUG-2004

5.2.2 Eye Irritation

Species: other: no data on calcium gluconate. See gluconic acid

10-AUG-2004

5.3 Sensitization

5.4 Repeated Dose Toxicity

Type: Sub-acute
Species: rat Sex: male/female
Strain: Crj: CD(SD)
Route of administration: gavage
Exposure period: 4 weeks
Frequency of treatment: daily
Doses: 0, 500, 1000, 2000 mag/kg bw
Control Group: yes, concurrent no treatment
NOAEL: = 1000 mg/kg bw
NOAEL females : = 2000 mg/kg bw

Method: other: no data
Year: 1995
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate
Reliability: (2) valid with restrictions
Secondary litterature but described in sufficient detail ina recognised WHO report. Acceptable for initial assessment
Flag: Critical study for SIDS endpoint
14-NOV-2005 (14)

Type: Chronic
Species: rat Sex: no data
Strain: no data
Route of administration: gavage
Exposure period: 70 days
Frequency of treatment: 6 days/weekly

Doses: 400 mg calcium/kg bw
Control Group: no data specified

Method: other: no data
Year: 1940
GLP: no
Test substance: other TS

Result: All the animals that received the equivalent of 2 g/kg bw calcium died after a single dose.

Administration of 1 g calcium /kg bw as calcium chloride produced death after one or two doses and 4 animals from the calcium gluconate-idonate group receiving the equivalent of 1 g calcium survived throughout the experience.

At a dose of 0.4 g calcium/kg bw, 5 out of 10 animals survived in the calcium chloride group while all the animals receiving calcium gluconate-idonate survived. 2 of the gluconate animals died (at 56 and 63 days) but the entire gluconate-idonate group was still alive.

The heart, kidney, and liver tissue examinations did not show any abnormality which could be ascribed to the effect of the drug.

Toxicity of calcium chloride is higher than calcium gluconate-idonate or calcium gluconate. Calcium gluconate and calcium gluconate-idonate differ very little in their toxicity.

Test condition: Calcium gluconate-idonate, calcium chloride and calcium gluconate were all given in amounts equivalent to 0.4 g calcium per kg bw daily in solution for the gluconate-idonate and chloride salts and in heavy suspension for calcium gluconate. Calcium gluconate-idonate and calcium chloride were also tested at levels equivalent to 1 and 2 g calcium/kg bw /day.

Each group of animals contained 10 animals except the one receiving the equivalent of 1 g calcium/kg bw calcium gluconate-idonate which contained 20 animals.

Test substance: calcium gluconate, calcium gluconate-idonate and calcium chloride

Reliability: (3) invalid
very old study not compliant with OECD guidelines

14-NOV-2005 (17)

5.5 Genetic Toxicity 'in Vitro'

Type: other: saccharomyces cervisiae and salmonella typhimurium reverse mutation assay
System of testing: bacterial and non bacterial
Concentration: bacteria: 1.25%, 2.50 %, 5.00 % and yeast: 0.75%, 1.50% and 3.00%
Cytotoxic Concentration: 50% survival in bacteria calculated was at 5.00 % test substance and 3.00% for yeast

Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
Year: 1975
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: A. Toxicity:

The solubility, toxicity and doses for all chemicals were determined prior to screening.

Each chemical was tested for survival against the specific strains over a range of doses (10, 1.0, 0.1, 0.01, 0.001 %) to determine the 50% survival dose. Bacteria were tested in phosphate buffer, pH 7.4 for one hour at 37°c on a shaker.

Yeasts were tested in phosphate buffer, pH 7.4 for 4 hours at 30°c on a shaker. The 50% survival curve and the 1/4 and 1/2 50% doses calculated. If no toxicity was obtained for a chemical with a given strain, a maximum dose of 5% (w/v) was used. The doses calculated for the tests in buffer were applied to the activation tests. The solubility of the test substance under treatment conditions was measured and Calcium gluconate is not completely soluble at treatment concentrations in a suspension 10% saline.

B. Plate tests

In the non activation procedure, approximately 10 exp9 cells from a log-phase culture of the bacterial indicator strains were spread over the surface of a minimal plate, and a measured amount of the test chemical was placed in the center of the test plate.

In activation tests, the test chemical was added to the cells, and an aliquot of the mixture was spread on the surface of the test plate. The reaction mixture (0.1 ml) plus tissue extract was then spotted on the surface of the plate.

All plates were incubated for 4 days at 37°C, and then scored. Each compound, (test, positive and solvent controls were run with each assay.

C. Suspension tests

1. Non activation

Log phase bacteria and stationary-phase yeast cultures of the indicator organisms were grown in complete broth, washed and resuspended in 0.9% saline to densities of 1 x 10 exp9 cells/ml and 5 x 10 exp7 cells/ml respectively.

Tests were conducted in plastic tissue culture plates. Cells plus chemicals were added to the wells to give a final volume of 1.5 ml. The solvent replaced the test chemical in the negative controls. Treatment was at 30°C for 4 hours for yeast tests and at 37°c for one hour for bacterial tests. All flasks were shaken during treatment.
After treatments, the plates wereset on ice. Aliquots of cells were removed, diluted in sterile saline (4°c) and plated on the appropriate complete media. Undiluted samples from flasks containing the bacteria were plated on minimal selective medium in reversion experiments. Samples from a 1/10 dilution of treated cells were plated on the selected media for enumeration of gene conversion with strain D4.

Bacterial plates were scored after incubation for 48 hours at 37°C. The yeast plates were incubated at 30°C for 3-5days before scoring.

2. Activation

Bacteria and yeast cells were grown and prepared as described in the non activation tests. Measured amounts of the test and control chemicals plus 0.25 ml of the stock-cell suspension were added to wells of the Linbro plate containing the appropriate tissue fraction and reaction mixture. All flasks (bacteria and yeast) were incubated at 37°c in an oxygen atmosphere with shaking. The treatment times, dilutions, plating procedure and scoring of the plates were the same as described for non activation tests.

Result: A. Salmonella typhimurium:

1. Plate tests: negative

2. Nonactivation suspension tests: negative

3. Activation suspension tests: negative (some tests using mouse and rat tissues with TA-1538 appeared slightly increased but were not considered positive. One high dose with primate tissue was repeated. The results were negative. The positive and negative control values for TA-1537 and TA-1538 tests were lower than usual.

No information or discussion are reported on the results from the positive controls, nor on their origin (same laboratory ?)

B. Saccharomyces cerevisiae

1. Non-activation suspension tests: negative

2. Activation suspension tests: negative (A higher than normal spontaneous background at the TRY locus was observed in these tests.)

Conclusion: Calcium gluconate did not exhibit genetic activity in any of the assays employed in study.

Test condition: Strains tested:
Yeast: Saccharomyces Cerevisiae, Strain D4
Bacteria: Salmonella typhimurium, strains: TA1535, TA1537,TA1538

Reaction mixture:

Component:	Final concentration/ml
TNP (sodium salt)	6 µM
Isocitric acid	49µM
Tris buffer, pH 7.4	28 µM
MgCl2	1.7 µM
Tissue homogenate fraction	72 mg

Tissue homogenates and supernatants:The tissue homogenates and supernatants (9000 g) were prepared from tissues of mouse (ICR random bred adult males); rat (Sprague-Dawnley adult males) and monkey (Macaca mulatta adult males)

Positive controls in direct and activation assays:

Non-activation:

Chemical	Solvent	Probable mutagenic specificity
Ethyl methanesulfonate (EMS)	water or saline	base-pair substitution
2-nitrofluorene (NF)	dimethylsulfoxide	frameshift
Quinacrine mustard (QM)	water or saline	Frameshift

****

Activation:

Chemical	Solvent	Probable mutagenic specificity
Dimethylnitrosamine (DMN)	water or saline	base-pair substitution
2-acetylaminofluorene (AAF)	dimethylsulfoxide	Frameshift

Concentration of positive controls:

Non activation:
TA-1535 EMS 10µl/plate
TA-1537 QM 20 µg/plate
TA-1538 NF 100 µg/plate

Activation:
TA-1535 DMN 50 µM/plate
TA-1537 AAF 100 µg/plate
TA-1538 AAF 100 µg/plate

Test substance: calcium gluconate

Reliability: (2) valid with restrictions
OECD guideline 471 recommend 5 strains of bacteria at least to be tested: 4 strains of S. typhimurium (TA1535,TA1537 or

TA97 or TA97a, TA98, TA100) and E. Coli WP2uvrA or E. Coli WP2uvrA (pKM101) or S.typhirmurium TA102.

The study was made on one yeast strain : saccharomyces cerevisiae, strain D4 and 3 bacteria strains: S. typhimuriumTA1535, TA1537 and TA 1538

Positive controls different from the ones recommended in OECD guideline 471.

At least 5 concentrations should be tested, the study only test 3 concentrations.

Flag: Critical study for SIDS endpoint
25-JAN-2006 (10)

5.6 Genetic Toxicity 'in Vivo'

Type:	other: in vivo chromosomal aberration test with mouse bone marrow cells
Species:	mouse Sex: male
Strain:	C57BL
Route of admin.:	oral feed
Exposure period:	single dose and 4 days
Doses:	single dose administration : 2.5, 5 and 10 g/kg. 4 day repeated dose: 1.25 and 2.5 g/kg
Result:	negative
Method:	other: no data specified
Year:	1974
GLP:	no data
Test substance:	other TS
Remark:	Data for the category: see details of study under sodium gluconate SIDS dossier
Test substance:	sodium gluconate
Reliability:	(2) valid with restrictions translation of a report not fully documented but acceptable for initial assessment

Flag: Critical study for SIDS endpoint
14-NOV-2005 (18)

5.7 Carcinogenicity

5.8.1 Toxicity to Fertility

5.8.2 Developmental Toxicity/Teratogenicity

Species:	rat Sex: female
Strain:	Wistar
Route of administration:	gavage
Exposure period:	from day 6 to day 15 of gestation
Frequency of treatment:	daily
Duration of test:	10 days
Doses:	0, 5.94, 27.6, 128.0, 594.0 mg/kg

Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 594 mg/kg bw
NOAEL Teratogenicity: > 594 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-NOV-2005 (3)

Species: mouse Sex: female
Strain: CD-1
Route of administration: gavage
Exposure period: from day 6 to day 15 of gestation
Frequency of treatment: daily
Duration of test: 10 days
Doses: 0, 6.95, 32.5, 150, 695 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 695 mg/kg bw
NOAEL Teratogenicity: > 695
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-NOV-2005 (3)

Species: rabbit Sex: female
Strain: Dutch
Route of administration: gavage
Exposure period: from day 6 to 18 of gestation
Frequency of treatment: daily
Duration of test: 13 days
Doses: 0, 7.80, 36.2, 168.5, 780.0 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 780 mg/kg bw
NOAEL Teratogenicity: > 780 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-NOV-2005 (3)

Species: hamster Sex: female
Route of administration: gavage
Exposure period: from day 6 to day 10 of gestation
Frequency of treatment: daily
Duration of test: 5 days
Doses: 0, 5.60, 26.0, 121, 560 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 560 mg/kg bw
NOAEL Teratogenicity: > 560 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (1) valid without restriction
Flag: Critical study for SIDS endpoint
14-NOV-2005 (3)

Species: rat Sex: female
Strain: Sprague-Dawley
Route of administration: oral unspecified
Exposure period: from day 6 to day 15 of gestation
Frequency of treatment: daily
Duration of test: 10 days
Doses: 1000 and 4000 mg/kg
Control Group: no data specified
NOAEL Maternal Toxity: > 4000 mg/kg bw
NOAEL Teratogenicity: > 4000 mg/kg bw
Result: non teratogen

Method: other: No data specified
Year: 1978
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (2) valid with restrictions
short abstract but acceptable for initial assessment.
Flag: Critical study for SIDS endpoint
14-NOV-2005 (5)

Species: mouse Sex: female

Strain: ICR
Route of administration: oral unspecified
Exposure period: from day 6 to day 15 of gestation
Frequency of treatment: daily
Duration of test: 10 days
Doses: 1000 and 4000 mg/kg
Control Group: no data specified
NOAEL Maternal Toxity: > 4000 mg/kg bw
NOAEL Teratogenicity: > 4000 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1978
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (2) valid with restrictions
short abstract but acceptable for initial assessment.
Flag: Critical study for SIDS endpoint
14-NOV-2005 (6)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Type of experience: Direct observation, clinical cases

Remark: In cases of hypocalcemia in premature neonates, treatment by
intraveinous administration of calcium gluconate is given (scalp-vein infusion).

The author reports observation of localised skin necrosis of
the scalp on 4 premature infants out of 45 who received calcium gluconate infusions via scalp veins. The infusions lasted up to 15 days with frequent changes of the cannulation sites. All the lesions developed at the site of
the last infusion, usually during the first 48 hours after removal of the needle. The necrosis never appeared during the infusion.

The areas of necrosis were 2-4 cm2 and were treated by wet dressings and healed well after 15 to 40 days.

The author assumes that this local necrosis appearing after the last infusion (which is usually the longest) is probably
due 1) to the long duration which may lead to phlebitis, 2)

a minor degree of leakage during the infusion,and 3) a sudden extravasation which occurs after removal of the needle.

Advise is given as to avoid administration of calcium gluconate into scalp veins except for the most stringent indications and if unavoidable, it is suggested that the infusion site is changed frequently

14-AUG-2003 (21)

Type of experience: Human - Medical Data

Remark: Calcium gluconate is the treatment of choice in case of hydrofluoric acid burns.

Calcium gluconate is used in calcium supplements.

Company	Product	Calcium gluconate content
Adams Labs Ltd	Calcium gluconate Tab 10gr	648 mg
AstraZeneca Canada Inc	Calcium gluconate 10% Inj 100 mg/ml	100 mg/ml
Pharmetics Inc	Calcium gluconate tablets USP 650 mg	60 mg
D.C. Labs Ltd	Calcium gluconate Tab 650 mg	650 mg
Pharmaceutical Partners of Canada	Calcium gluconate Injection USP 10%	94 mg/ml
Abbott Laboratories Ltd	Calcium gluconate Inj 100mg/ml	100 mg/ml
Novopharm Ltd	Calcium gluconate Tab 650 mg	650 mg
Hall Laboratories Ltd	Calcium gluconate Tab 648 mg	648 mg
Professional Veterinary Laboratories	Dextrose Calcium Gluconate Magnesium Phos	100 g / 500 ml

And many others at
http://www.hc-sc.gc.ca/hpb/drugs-dpd/

20-OCT-2003

5.11 Additional Remarks

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I U C L I D

D a t a S e t

Existing Chemical	ID: 299-27-4
CAS No.	299-27-4
EINECS Name	potassium gluconate
EC No.	206-074-2
Molecular Formula	C6H12O7.K

Producer Related Part	
Company:	Keller and Heckman LLP
Creation date:	02-APR-2003
Substance Related Part	
Company:	Keller and Heckman LLP
Creation date:	02-APR-2003
Memo:	OECD HPV Chemicals Programme, SIDS Dossier, approved at SIAM 18 (20-23 April 2004)

Printing date:	25-JAN-2006
Revision date:	
Date of last Update:	25-JAN-2006

Number of Pages:	39

Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 Applicant and Company Information

Type: lead organisation
Name: The Gluconic acid and its sodium, potassium and calcium salts and glucono-delta-lactone consortium
Contact Person: Jean-Philippe Montfort Date: 02-APR-2003
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Remark: Sponsor Country for this Category: Belgium; Co-sponsor country: Japan.
12-DEC-2005

Type: manufacturer
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Contact Person: Ph.D. Shinichi Sugita Date:
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03-AUG-2004

Type: manufacturer
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17-OCT-2003

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31-JUL-2003

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03-AUG-2004

1.0.2 Location of Production Site, Importer or Formulator

1.0.3 Identity of Recipients

1.0.4 Details on Category/Template

Remark: Glucono-delta-lactone, gluconic acid and its sodium, calcium and potassium salts have been proposed in a category, as the salts of gluconic acid freely dissociate to the gluconate anion and the respective cation.

Glucono-delta-lactone (GDL) is the inner ester of gluconic acid formed by the removal of water.

When glucono-delta-lactone is used in aqueous solution, it is slowly hydrolysed until an equilibrium is reached between gluconic acid and its delta-lactone.

12-AUG-2004

1.1.0 Substance Identification

IUPAC Name: potassium penta-hydroxy hexanoate anhydrate
Smiles Code: [K]OC(=O)C(O)C(O)C(O)C(O)CO
Mol. Formula: C6H11O7K
Mol. Weight: 234.25

20-OCT-2003

1.1.1 General Substance Information

Purity type: typical for marketed substance
Substance type: organic
Physical status: solid
Purity: ca. 97 - 103 % w/w
Colour: white
Odour: none

06-AUG-2004

1.1.2 Spectra

1.2 Synonyms and Tradenames

potassium penta-hydroxyhexanoate anhydrate

06-AUG-2004

1.3 Impurities

Purity type: typical for marketed substance

Remark: For food and/or medical applications the level of impurities complies with the restrictions laid down in the corresponding EU Directives.
09-AUG-2004

1.4 Additives

Remark: For all the chemicals of the category: no additives used
10-NOV-2005

1.5 Total Quantity

Quantity: ca. 1000 - 2000 tonnes produced in 2000

Flag: confidential
06-AUG-2004

1.6.1 Labelling

Remark: For all the chemicals in the category: proposal of Industry: no labelling required
10-NOV-2005

1.6.2 Classification

Classified: other, as in legislation

Remark: For all chemicals of the category: proposal of Industry: no classification required
10-NOV-2005

1.6.3 Packaging

1.7 Use Pattern

Type: type
Category: Non dispersive use

Remark: Data for the category: see sodium gluconate
14-AUG-2003

Type: type

Category: Wide dispersive use

Remark: Data for the category: see sodium gluconate
14-AUG-2003

1.7.1 Detailed Use Pattern

1.7.2 Methods of Manufacture

1.8 Regulatory Measures

1.8.1 Occupational Exposure Limit Values

1.8.2 Acceptable Residues Levels

1.8.3 Water Pollution

1.8.4 Major Accident Hazards

1.8.5 Air Pollution

1.8.6 Listings e.g. Chemical Inventories

1.9.1 Degradation/Transformation Products

1.9.2 Components

1.10 Source of Exposure

Source of exposure: other

Remark: Data for the category: see sodium gluconate
14-AUG-2003

1.11 Additional Remarks

Memo: Regulatory status

Remark: Potassium gluconate is the potassium salt of gluconic acid, obtained from glucose by fermentation.

In the European Parliament and Council Directive 95/2/EC, potassium gluconate is listed as a generally permitted food additive (E577) and may be added to all foodstuffs, following the "quantum satis" principle, as long as no

special regulations restrict the use.

The US Food and Drug Administation (FDA) assigned potassium gluconate the "generally recognised as safe" (GRAS) status and permitted its use in food without limitation other than the current good manufacturing practice.

06-AUG-2004

1.12 Last Literature Search

1.13 Reviews

2.1 Melting Point

Decomposition: yes at = 180 degree C

Method: other: no data specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
12-AUG-2004 (20)

Value: ca. 174 - 176 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
12-AUG-2004 (12)

2.2 Boiling Point

Value: = 613.1 degree C

Method: other: calculated
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with MPBPWIN (v1.41) program from US EPA (EPI v3.11)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2004

2.3 Density

Type: bulk density
Value: ca. 800 kg/m3

Method: other: no data
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
09-AUG-2004 (12)

2.3.1 Granulometry

2.4 Vapour Pressure

Value: = 0 hPa at 25 degree C

Method: other (calculated)
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with MPBPVP (v1.41) program from US EPA (EPI v3.11):

Vapor Pressure Estimations (25 deg C):
(Using BP: 613.05 deg C (estimated))
(Using MP: 174.00 deg C (user entered))
VP: 3.11E-022 mm Hg (Antoine Method)
VP: 8.94E-017 mm Hg (Modified Grain Method)
VP: 2.39E-012 mm Hg (Mackay Method)
Result: Selected VP: 8.94E-017 mm Hg = 11.89E-017 hPa (Modified Grain Method)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
06-AUG-2004

2.5 Partition Coefficient

Partition Coeff.: octanol-water
log Pow: = -5.99

Method: other (calculated)
GLP: no

Remark: Estimated with Kowwin (v1.67) program from US EPA (EPI v3.11)
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
06-AUG-2004

2.6.1 Solubility in different media

Solubility in: Water
Value: = 450 g/l at 20 degree C
pH value: ca. 6.8 - 8.3
Conc.: 10 vol% at 20 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4
Deg. product: not measured

Reliability: (4) not assignable
Data from an MSDS. No data on method used.
Flag: Critical study for SIDS endpoint
06-AUG-2004 (12)

Solubility in: Water
Value: = 1000 g/l at 25 degree C

Method: other: no data
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (4) not assignable
Data from Commercial brochure
Flag: Critical study for SIDS endpoint
12-AUG-2004 (8)

Solubility in: Water
Descr.: other: freely soluble

Method: other: no data specified
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions
Data from Handbook or collection of data
Flag: Critical study for SIDS endpoint
12-AUG-2004 (20)

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

2.9 Flammability

2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Dissociation Constant

Acid-base Const.: pka = 3.70

Method: other: no data
GLP: no data
Test substance: other TS

Remark: The dissociation in water is expected to be complete as the pKa values of gluconic acid found in literature range from 3.5 to 3.8
Test substance: gluconic acid
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint

12-AUG-2004 (23)

2.13 Viscosity

2.14 Additional Remarks

3.1.1 Photodegradation

Type: air

Method: other (calculated): Estimated with AOP (v1.91) program from US EPA (EPI v3.11)
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Remark: Estimated with AOP (v1.91) program from US EPA (EPI v3.11)

OVERALL OH Rate Constant = 38.1277 E-12 cm3/molecule-sec

HALF-LIFE = 0.281 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE = 3.366 Hrs
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
12-AUG-2004

3.1.2 Stability in Water

Type: abiotic

Remark: The dissociation in water is expected to be complete as the pKa values of gluconic acid found in literature range from 3.5 to 3.8
Reliability: (2) valid with restrictions
Flag: Critical study for SIDS endpoint
14-NOV-2005 (23)

3.1.3 Stability in Soil

3.2.1 Monitoring Data (Environment)

3.2.2 Field Studies

3.3.1 Transport between Environmental Compartments

Type: fugacity model level III
Media: other
Method: other: calculated

Remark: Estimated with the Level III Fugacity Model program LEVEL3NT from US EPA (EPI v3.11)

Chem Name : Potassium gluconate
Molecular Wt: 234.25
Henry's LC : 2.76e-023 atm-m3/mole (calc VP/Wsol)
Vapor Press : 8.94e-017 mm Hg (Mpbpwin program)
Liquid VP : 2.66e-015 mm Hg (super-cooled)
Melting Pt : 174 deg C (user-entered)

```
Log Kow     : -5.99  (Kowwin program)
Soil Koc    : 4.2e-007  (calc by model)

          Mass Amount    Half-Life    Emissions
          (percent)        (hr)       (kg/hr)
-------------------------------------------------
 Air       4.78e-007       6.73         1000
 Water     42.8            208          1000
 Soil      57.1            208          1000
 Sediment  0.0638          832          0
_________________________________________________


      Fugacity    Reaction    Advection   Reaction  Advection
(atm)      (kg/hr)    (kg/hr)    (percent)   (percent)
-------------------------------------------------------------
Air    1.18e-026  0.000393    3.82e-005  1.31e-005 1.27e-006
Water  2.01e-028  1.14e+003   342          37.9       11.4
Soil   9.94e-027  1.52e+003   0           50.7        0
Sediment 1.5e-028  0.424      0.0102      0.0141    0.00034
_____________________________________________________________

Persistence Time: 266 hr
Reaction Time:    300 hr
Advection Time:   2.34e+003 hr
Percent Reacted:  88.6
Percent Advected: 11.4

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):

Air:      6.732
Water:    208.1
Soil:     208.1
Sediment: 832.3
Biowin estimate: 3.481  (days-weeks  )

Advection Times (hr):
Air:      100
Water:    1000
Sediment: 5e+004
```

Reliability: (3) invalid
Limited reliability because the Henry's LC can neither be calculated with the bond estimation method nor with the group estimation method because of missing values for certain bonds/groups.

The Henry's LC is therefore estimated by VP/Wsol.

However, this program does not use the entered solubility (500 g/l) but the solubility determined by the WATERNT program (1000 g/l) for the estimation of the Henry's LC that is then used in the LEVEL3NT program.

25-JAN-2006

3.3.2 Distribution

Media: air - biota - sediment(s) - soil - water
Method: other (calculation)

Remark: Henry's law constant estimated with HENRY (v3.10) program from US EPA (EPI v3.11)

Can neither be calculated with the bond estimation method nor with the group estimation method because of missing values for certain bonds/groups.

Soil Adsorption Coefficient estimated with PCKOC (v1.66) program from US EPA (EPI v3.11)

NOTE: THE METAL (Na, Li or K) HAS BEEN REMOVED TO ALLOW ESTIMATION!

First Order Molecular Connectivity Index : 5.913
Non-Corrected Log Koc : 3.7674
Fragment Correction(s):
* Organic Acid (-CO-OH) : -1.7512
2 Aliphatic Alcohol (-C-OH) : -3.0386
Corrected Log Koc : -1.0224

Over Correction Adjustment to Lower Limit Log Koc : 1.0000

Estimated Koc: 10

NOTE: The Koc of this structure may be sensitive to pH!
Reliability: (2) valid with restrictions
Accepted calculation method
Flag: Critical study for SIDS endpoint
09-AUG-2004

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type: aerobic
Inoculum: other: secondary effluent of a municipal sewage plant (Breisgauer Bucht, 500000 population equivalent), 0.4 ml/l
Concentration: 3 mg/l related to Test substance
Contact time: 28 day(s)
Degradation: = 89 % after 28 day(s)
Result: readily biodegradable
Kinetic: 3 day(s) = 61.13 %
7 day(s) = 74.35 %
14 day(s) = 66.09 %
21 day(s) = 71.94 %
28 day(s) = 88.88 %
Control Subst.: Acetic acid, sodium salt
Kinetic: 3 day(s) = 67.15 %
28 day(s) = 80.93 %
Deg. product: not measured

Method: Directive 92/69/EEC, C.4-E

```
  Year:           2001
   GLP:           yes
Test substance:   other TS

Remark:           The 89% degradation indicated here relates to the
                  Theoritical Oxygen Demand (ThOD)
                  Data for the category: see details of study under  sodium
                  gluconate SIDS dossier.
Test substance:   Sodium gluconate: 99.0-101.0%
Reliability:      (1)  valid without restriction
                  study conducted according to OECD guidelines, valid
                  test,quality assurance and GLP certificates
Flag:             Critical study for SIDS endpoint
14-NOV-2005                                                          (10)

Type:             anaerobic
Inoculum:         other: Digesting sludge of a municipal sewage plant
                  (Breisgauer Bucht, 500000 population equivalent), 2.9 g total
                  solids/l
Concentration:    303 mg/l related to Test substance
Contact time:     35 day(s)
Degradation:      = 100 % after 35 day(s)
Result:           readily biodegradable
Kinetic:              1 day(s)    = 8 %
                      8 day(s)    = 51 %
                     15 day(s)    = 57 %
                     22 day(s)    = 61 %
                     35 day(s)    = 100 %
Control Subst.:   Benzoic acid, sodium salt
Kinetic:              8 day(s)    = 6 %
                     35 day(s)    = 100 %
Deg. product:     not measured

Method:           other: DIN EN ISO 11734
  Year:           2001
   GLP:           yes
Test substance:   other TS

Remark:           Data for the category: see details of study under sodium
                  gluconate SIDS dossier.
Test substance:   sodium gluconate
Reliability:      (1)  valid without restriction
                  study conducted according to OECD guidelines, valid
                  test,quality assurance and GLP certificates
Flag:             Critical study for SIDS endpoint
14-NOV-2005                                                          (11)
```

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: semistatic
Species: Oryzias latipes (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: > 100 -
LC0: > 100 -
Limit Test: yes

Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: 2002
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate : 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
14-NOV-2005 (14)

4.2 Acute Toxicity to Aquatic Invertebrates

Type: static
Species: Daphnia magna (Crustacea)
Exposure period: 48 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: > 1000 -
EC100: > 1000 -
Limit Test: yes

Method: OECD Guide-line 202
Year: 2002
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate : 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
14-NOV-2005 (15)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Selenastrum capricornutum (Algae)
Endpoint: growth rate
Exposure period: 72 hour(s)
Unit: mg/l Analytical monitoring: yes
NOEC: = 560 -

EC50: > 1000 -
Limit Test: yes

Method: OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year: 2002
GLP: yes
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: Sodium gluconate: 99.6%
Reliability: (1) valid without restriction
study conducted according to OECD guidelines, valid test,quality assurance and GLP certificates
Flag: Critical study for SIDS endpoint
14-NOV-2005 (16)

4.4 Toxicity to Microorganisms e.g. Bacteria

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Sediment Dwelling Organisms

Species: other

Remark: No data available but exposure in sediment expected to be extremely limited according to the Level III Fugacity Model program LEVEL3NT from US EPA (EPI v3.11).
09-AUG-2004

4.6.2 Toxicity to Terrestrial Plants

Method: other

Remark: No data available
14-AUG-2003

4.6.3 Toxicity to Soil Dwelling Organisms

Method: other

Remark: no data available but due to the low intrinsic toxicity in aquatic organisms, it is reasonable to expect a similar low toxic impact on terrestrial organisms
19-JAN-2004

4.6.4 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.0 Toxicokinetics, Metabolism and Distribution

In Vitro/in vivo:	In vivo
Type:	Absorption
Species:	rat
No. of animals, males:	9
Doses, males:	2.1 and 6.4 mEq/kg/day
Vehicle:	no data
Route of administration:	oral unspecified

Method:	other: no data specified
Year:	1975
GLP:	no data
Test substance:	as prescribed by 1.1 - 1.4

Result:

1. After oral administration of 2.1 mEq/kg of potassium gluconate and potassium chloride, the potassium ion concentrations in the serum in both the potassium gluconate and potassium chloride groups started to increase, reached the maximum in 3 hours and recovered to the initial value in 9 hours. During this time, the potassium ion concentration in the urine increased with time, reached the maximum in 6 hours and recovered almost to the normal level in 10 hours. The concentration of the potassium ion in the serum and the urine increased more by potassium gluconate than by potassium chloride.

2. Distribution of the potassium ion in the organs in 3 and 7 hours after oral administration of 2.1 mEq/kg of potassium gluconate and potassium chloride was examined and an increase in the potassium ion contents in the liver, kidneys, heart, cerebrum, diaphragm and serum were observed. The potassium ion contents in the kidneys and the serum were larger in the potassium gluconate group than in the potassium chloride group whereas there was no differences detected in the potassium ion contents in the other organs between the two groups. Also, the distribution of the potassium ion in the organs was found larger when examined in 3 hours after the administration than when examined in 7 hours after the administration.

3. With the continuous oral administration of 6.4 mEq/kg of potassium gluconate and potassium chloride, potassium concentrations both in the serum and the urine increased and reached the maximum on the 3rd day, but the concentrations decreased thereafter and maintained a constant value. During this time, urinary excretion increased with the number of days for medication. The increase in concentrations of potassium ion in the serum and the urine induced by potassium gluconate was almost the same as the one induced by potassium chloride. However, the urinary excretion increased more with potassium gluconate than with potassium chloride. Also, the continous administration of potassium gluconate and potassium chloride did not cause

changes in the concentrations of the sodium ion in the serum and in the urine.

4. When 2.1 mEq/kg and 6.4 mEq/kg of potassium gluconate and potassium chloride were daily administered to aldosteronized rats having reduced concentrations of the potassium ion in the serum and the urine, concentrations of the potassium ion both in the serum and the urine recovered to the normal level in all cases. There was no difference observed in the state of recovery between the potassium gluconate groups and the potassium chloride groups. Urinary excretion increased in all groups. Further, when the administration of the drugs was withheld, the concentrations of the potassium ion in the serum and the urine decreased but the rate of decrease was faster in the potassium gluconate group than the potassium chloride.

Concentration of the sodium ion in the serum and urine did not change during and after administration of potassium gluconate and potassium chloride.

Many studies relating to the in vivo variations of gluconic acid in potassium gluconate used as a potassium supplement (Stetten and Steen 1950, Stetten and Topper 1953) showed that gluconic acid did not only migrates in the body in its original form but also transforms to a nucleic acid, glycogen and glucose, or may change to CO2 and be excreted during the expiratio

Test condition: Wistar male rats were used.

They were raised in thermo-hygrostat metabolic cages where room temperature was kept at 23+/- 1 °C and the humidity was kept at 55 +/- 5%. After oral administration of potassium gluconate / potassium chloride, the potassium ion contents in the serum, organs and urine were measured by a flame spectrometer.

The tests were conducted using 3 rats to a group and the average value was designated as the value.

Reliability: (2) valid with restrictions
report not well documented. No GLP.

14-NOV-2005 (22)

In Vitro/in vivo:	In vivo
Type:	Toxicokinetics
Species:	rat
Doses, males:	2.3 g/kg bw

Method:	other: no data specified
Year:	1957
GLP:	no
Test substance:	as prescribed by 1.1 - 1.4

Remark: Quantitative nutritional studies on water-soluble, chemically defined diets have been conducted by Greenstein

et al. (1957). Their basal diet, containing the equivalent of 23 g of potassium gluconate per kg, was supplemented with various amino acid mixtures and fed (daily intake of potassium gluconate about 2.3 g/kg body weight assuming an average animal weight of 100 g) to Sprague-Dawnley rats for 60-100 days without evidence of adverse effects.

Reliability: (3) invalid
secondary litterature, old study

14-NOV-2005 (9)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: rat
Strain: Wistar
Sex: male/female
No. of Animals: 50
Vehicle: water
Doses: 3000, 3600, 4320, 5190, 6210 mg/kw bw
Value: = 6060 mg/kg bw

Method: other: no data specified
Year: 1978
GLP: no data
Test substance: as prescribed by 1.1 - 1.4

Method: After some preliminary observations, the test compound was given by gavage, as a 30% (w/v) aqueous solution to groups of five males and five females in single doses.

After treatment, the rats received stock diet and tap water ad libitum. They were observed for signs of intoxication during a 14-day period, after which autopsies were carried out on the survivors.

The LD50 was calculated according to the method of Weil.

Remark: We note that the doses of the test substance were high and and the observations made at the highest doses (from which the LD50 was determined) occur above the accepted limit dose of 5000 mg/kg bw. Those results could therefore be linked to the high dosage.

Result: Within a few hours after dosing, the rats showed sluggishness, humpback behavior and severe diarrhoea. Deaths occurred between 5 and 21 hours after treatment. Afterwards the survivors recovered gradually and looked quite healthy again at the end of the observation period. Macroscopic examination of the survivors at autopsy revealed no treatment-related gross alterations.

Dose		Mortality		
Solution (ml/kg)	test substance (g/kg)	Number males	females	%

10.0	3.00	0/5	0/5	0
12.0	3.60	0/5	0/5	0
14.4	4.32	0/5	0/5	0
17.3	5.19	1/5	1/5	20
20.7	6.21	4/5	3/5	70

From the mortality figures, the LD50 of potassium gluconate was calculated to be 6.06 g/kg bw with 5.64 and 6.51 as the 95 % confidence limit.

Test condition: Young adult albino rats (wistar derived) from the Institute's colony were used.

Body weights:
Males : from 240 to 382 g
Females: from 156 to 206 g

Rats were housed in groups of five in screen-bottomed, stainless steel cages, in a well-ventilated room, maintained at 23-25°C. Before dosing the rats were fasted overnight

Reliability: (2) valid with restrictions
No data on method, GLP etc.

Flag: Critical study for SIDS endpoint

14-NOV-2005 (21)

Type: LDLo
Species: rat
Strain: Crj: CD(SD)
Sex: male/female
No. of Animals: 10
Vehicle: no data
Doses: 500, 1000, 2000 mg/kg
Value: > 2000 mg/kg bw

Method: other: no data
Year: 1995
GLP: no data
Test substance: other TS

Test substance: sodium gluconate

Reliability: (2) valid with restrictions
Short abstract not well documented but key study for initial assessment

Flag: Critical study for SIDS endpoint

14-NOV-2005 (18)

5.1.2 Acute Inhalation Toxicity

5.1.3 Acute Dermal Toxicity

5.1.4 Acute Toxicity, other Routes

Type: other: intestinal toxicity
Species: dog
Strain: no data
Sex: no data

No. of Animals: 7
Vehicle: no data
Doses: tablets containing 10 meq (2.3g), 15 meq (3.5 g) and 30 meq (7.0 g) potassium gluconate.
Route of admin.: other: tablets of test substance fixed in the ileum or distal jejunum

Method: no data
Year: 1967
GLP: no
Test substance: as prescribed by 1.1 - 1.4

Method: Tablets of potassium gluconate, potassium citrate and potassium chloride were fixed within the ileum or distal jejunum of dogs so that their dissolution and absorption occurred within a limited segment of the intestine. Tablets containing 10 meq potassium gluconate (2.3g) were implanted in 2 dogs, 15 meq (3.5 g) in three dogs and 30 meq (7.0 g) in 2 dogs. The dogs were killed 5 to 7 days later and microscopic examinations performed on all tissue surrounding the tablet site.
Result: Minimal superficial hemorrhage was noted at two sites (of five) where 30 meq potassium gluconate had been given and in one (of ten) site with 15 meq potassium gluconate tablets. The pathology was much less marked than with potassium chloride.
Reliability: (3) invalid
secondary litterature, old study.
14-NOV-2005 (1)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: other: no data on potassium gluconate. See gluconic acid

10-AUG-2004

5.2.2 Eye Irritation

Species: other: no data on potassium gluconate. See gluconic acid

10-AUG-2004

5.3 Sensitization

5.4 Repeated Dose Toxicity

Type: Sub-acute
Species: rat Sex: male/female
Strain: Crj: CD(SD)
Route of administration: gavage

Exposure period: 4 weeks
Frequency of treatment: daily
Doses: 0, 500, 1000, 2000 mg/kg bw
Control Group: yes, concurrent no treatment
NOAEL: = 1000 mg/kg bw
NOAEL females : = 2000 mg/kg bw

Method: other: no data
Year: 1995
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate
Reliability: (2) valid with restrictions
Secondary litterature but described in sufficient detail ina recognised WHO report. Acceptable for assessment.
Flag: Critical study for SIDS endpoint
14-NOV-2005 (17)

5.5 Genetic Toxicity 'in Vitro'

Type: other: Saccharomyces Cerevisiae and Salmonella typhimurium reverse mutation assay
System of testing: bacterial and non bacterial
Concentration: bacteria: 0.006%, 0.0012 %, 0.0024 % and yeast: 1.25%, 2.50% and 5.00%
Cytotoxic Concentration: 50% survival in bacteria calculated was at 0.0024 % test substance and 5% for yeast
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471
Year: 1975
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
This study was conducted using 3 bacteria strains (salmonella typhimurium) and one yeast strain (saccharomyces cervisiae) rather than a fourth bacteria strain as indicators for this in vitro microbial assay with and without metabolic activation. Therefore, the results of this report on bacteria and yeast are included in the same entry.
Test substance: sodium gluconate
Reliability: (2) valid with restrictions
OECD guideline No. 471 followed except that the study was made on one yeast strain : saccharomyces cerevisiae, strain D4 and 3 bacteria strains: S. typhimurium TA1535, TA1537 and TA 1538.

Positive controls different from the ones described in the OECD guideline No 471.

The study was made only on 3 test concentrations.
Flag: Critical study for SIDS endpoint
14-NOV-2005 (13)

5.6 Genetic Toxicity 'in Vivo'

Type: other: in vivo chromosomal aberration test with mouse bone marrow cells
Species: mouse Sex: male
Strain: C57BL
Route of admin.: oral feed
Exposure period: single dose and 4 days
Doses: single dose administration : 2.5, 5 and 10 g/kg. 4 day repeated dose: 1.25 and 2.5 g/kg
Result: negative

Method: other: no data specified
Year: 1974
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under sodium gluconate SIDS dossier.
Test substance: sodium gluconate
Reliability: (2) valid with restrictions
translation of a report not fully documented but acceptable for initial assessment
Flag: Critical study for SIDS endpoint
14-NOV-2005 (19)

5.7 Carcinogenicity

5.8.1 Toxicity to Fertility

5.8.2 Developmental Toxicity/Teratogenicity

Species: rat Sex: female
Strain: Wistar
Route of administration: gavage
Exposure period: from day 6 to day 15 of gestation
Frequency of treatment: daily
Duration of test: 10 days
Doses: 0, 5.94, 27.6, 128.0, 594.0 mg/kg
Control Group: yes, concurrent vehicle
NOAEL Maternal Toxity: > 594 mg/kg bw
NOAEL Teratogenicity: > 594 mg/kg bw
Result: non teratogen

Method: other: no data specified
Year: 1973
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under

```
                  glucono-delta-lactone SIDS dossier.
Test substance:   Glucono-delta-lactone
Reliability:      (1)  valid without restriction
Flag:             Critical study for SIDS endpoint
14-NOV-2005                                                          (4)

Species:                    mouse                          Sex: female
Strain:                     CD-1
Route of administration:    gavage
Exposure period:            from day 6 to day 15 of gestation
Frequency of treatment:     daily
Duration of test:           10 days
Doses:                      0, 6.95, 32.5, 150, 695 mg/kg
Control Group:              yes, concurrent vehicle
NOAEL Maternal Toxity:      > 695 mg/kg bw
NOAEL Teratogenicity:       > 695 mg/kg bw
Result:                     non teratogen

Method:           other: no data specified
  Year:           1973
   GLP:           no
Test substance:   other TS

Remark:           Data for the category: see details of study under
                  glucono-delta-lactone SIDS dossier.
Test substance:   Glucono-delta-lactone
Reliability:      (1)  valid without restriction
Flag:             Critical study for SIDS endpoint
14-NOV-2005                                                          (4)


Species:                    rabbit                         Sex: female
Strain:                     Dutch
Route of administration:    gavage
Exposure period:            from day 6 to 18 of gestation
Frequency of treatment:     daily
Duration of test:           13 days
Doses:                      0, 7.80, 36.2, 168.5, 780.0 mg/kg
Control Group:              yes, concurrent vehicle
NOAEL Maternal Toxity:      > 780 mg/kg bw
NOAEL Teratogenicity:       > 780 mg/kg bw
Result:                     non teratogen

Method:           other: no data specified
  Year:           1973
   GLP:           no
Test substance:   other TS

Remark:           Data for the category: see details of study under
                  glucono-delta-lactone SIDS dossier.
Test substance:   Glucono-delta-lactone
Reliability:      (1)  valid without restriction
Flag:             Critical study for SIDS endpoint
14-NOV-2005                                                          (4)

Species:                    hamster                        Sex: female
Route of administration:    gavage
Exposure period:            from day 6 to day 10 of gestation
```

```
Frequency of treatment:    daily
Duration of test:          5 days
Doses:                     0, 5.60, 26.0, 121, 560 mg/kg
Control Group:             yes, concurrent vehicle
NOAEL Maternal Toxity:     > 560 mg/kg bw
NOAEL Teratogenicity:      > 560 mg/kg bw
Result:                    non teratogen

Method:           other: no data specified
  Year:           1973
   GLP:           no
Test substance:   other TS

Remark:           Data for the category: see details of study under
                  glucono-delta-lactone SIDS dossier.
Test substance:   Glucono-delta-lactone
Reliability:      (1)  valid without restriction
Flag:             Critical study for SIDS endpoint
14-NOV-2005                                                          (4)


Species:                   rat                              Sex: female
Strain:                    Sprague-Dawley
Route of administration:   oral unspecified
Exposure period:           from day 6 to day 15 of gestation
Frequency of treatment:    daily
Duration of test:          10 days
Doses:                     1000 and 4000 mg/kg
Control Group:             no data specified
NOAEL Maternal Toxity:     > 4000 mg/kg bw
NOAEL Teratogenicity:      > 4000 mg/kg bw
Result:                    non teratogen

Method:           other: No data specified
  Year:           1978
   GLP:           no data
Test substance:   other TS

Remark:           Data for the category: see details of study under
                  glucono-delta-lactone SIDS dossier.
Test substance:   Glucono-delta-lactone
Reliability:      (2)  valid with restrictions
                  short abstract but acceptable for initial assessment.
Flag:             Critical study for SIDS endpoint
14-NOV-2005                                                          (6)

Species:                   mouse                            Sex: female
Strain:                    ICR
Route of administration:   oral unspecified
Exposure period:           from day 6 to day 15 of gestation
Frequency of treatment:    daily
Duration of test:          10 days
Doses:                     1000 and 4000 mg/kg
Control Group:             no data specified
NOAEL Maternal Toxity:     > 4000 mg/kg bw
NOAEL Teratogenicity:      > 4000 mg/kg bw
Result:                    non teratogen
```

Method: other: no data specified
Year: 1978
GLP: no data
Test substance: other TS

Remark: Data for the category: see details of study under glucono-delta-lactone SIDS dossier.
Test substance: Glucono-delta-lactone
Reliability: (2) valid with restrictions
short abstract but acceptable for initial assessment
Flag: Critical study for SIDS endpoint
14-NOV-2005 (7)

5.8.3 Toxicity to Reproduction, Other Studies

5.9 Specific Investigations

5.10 Exposure Experience

Type of experience: Human - Medical Data

Remark: Potassium gluconate is used clinically to replenish potassium in patients experiencing hypokalemia. The usual adult dose is about 9 gr in equal portions after meals and at bedtime (Physicians' Desk Reference, 1978).
Reliability: (4) not assignable
20-OCT-2003 (2)

Type of experience: other

Remark: Circumferential small-bowel ulcers have been associated with
the irritant effects of potassium chloride used in potassium
replenishment therapy (Morgenstern et al., 1965).

Potassium gluconate appears to be less irritating in this respect. This has been tested by fixing tablets within the ileum or distal jejunum of dogs so that absorption would occur within a limited segment of the intestine (Boley et al., 1967).

The dogs were sacrificed after 5-7 days and all tissues surrounding the tablet site were examined microscopally. No
remarkable gross changes were seen at any of the sites where
potassium gluconate was implanted. Minimal superficial hemorrhage was noted in 40% of the sites where tablets containing 7.0 g potassium gluconate where used; 10% of the sites with 3.5 g tablets; none of the sites with 2.3 g tablets. While histologic changes were minimal, the authors
suggested that high concentration of potassium ions was not

completely without physiologic and anatomic effect on the bowel. Pathological changes were less with potassium gluconate tablets than with potassium chloride tablets at the same dose level.

Reliability: (3) invalid
secondary litterature, old study.

14-AUG-2003 (2)

Type of experience: Direct observation, clinical cases

Remark: Potassium gluconate in syrup was tested:

1 aromatized syrup (oral route) : a soup spoon corresponds to 9.5 mEq of potassium or 0.375 g

Patients suffering from cardiac insufficiency (and subject to different saluretics) were given potassium gluconate in syrup for 6 months. From these numerous clinical material, 10 cases were observed and studied on the ionic side.

In 4 cases, the patients were already given saluretics with an insufficient potassium recharge but without signs of potassium deficiency.

In 4 other cases, patients were not given recently saluretics.

The 2 last cases concerned patients entered into the service
with a clinical and biological picture of potassium deficiency.

All were subjected to a hospital regime without salt which brings for 24 hours (average) 40 mEq potassium. This average has been calculated on one week taking into account the loss of nutrition due to cooking.

Control of the treatment:

Minor consideration was given to the dosage of electrolytes in blood as a normal kaliemia or a slightly high kaliemia coincidates oftenly with an hypokalicytia, and, under some therapeutic circumstances, ie. injection of intraveinous glucose, an hypokaliemia can show a positive potassium result.

Therefore, the balance method was used. The admissions are

represented by 40 mEq food requirements to which is added the quantity of potassium ingested in the form of syrup.

The outlets are established on the basis of urinary potassium determined each day in the 24 hour urine. The 10% fecal potassium as well as sweat potassium from patients (none of them have shown important sudoral crises) were not taken into account. However, frequent plasmatic dosages

were undergone and except for 2 cases, there was no perturbation.

Observations:

The product is remarkably tolerated. No digestive intolerance was observed which is appreciable for a potassium therapy applied per os. Also, no surcharge accident and no metabolic trouble were observed.

The doses varied between 3 and 6 soup spoons per day, which represent a potassium intake of 28-56 mEq. The therapy started several days after the beginning of the diuretic treatment in order to prevent an oveload accident in the case of marked oliguria.

The efficiency of potassium gluconate was clearly demonstrated by 2 cases where clinically evident hypokalemia
is spectacularly improved after a few days of treatment.

Reliability: (3) invalid
09-AUG-2004 (5)

Type of experience: Human - Medical Data

Remark: Potassium gluconate is used in potassium supplements

Company	Product	Potassium gluconate Content
Pharmetics Inc	Potassium gluconate 550 mg tablets USP	92 mg
Trophic Canada Ltd	Potassium gluconate Tab 1g	1 g
Pharmascience Inc	PMS- Potassium gluconate solution	20 meq/15 ml
General Nutrition Canada Inc	Timed Release Potassium 100mg	100 mg
Rheingold Food International Ltd	Potassium Tab 99 mg	99 mg

And many others at http://www.hc-sc.gc.ca/hpb/drugs-dpd/
20-OCT-2003

5.11 Additional Remarks

Type: other: Opinion of the Select Committee on GRAS substances on the health aspects of using potassium gluconate as a food ingredient

Remark: The Select Committee on GRAS substances has concluded that there is no evidence in the available information on potassium gluconate that demonstrates or suggests reasonable

grounds to suspect a hazard to the public should it be used as a food ingredient at levels now used for sodium gluconate, or that might be expected in the future.

Indeed, potassium, the cation of potassium gluconate, is an essential nutrient. It is widely distributed in foods and 2-6 g are consumed by adults daily from all sources. Gluconic acid, the anion of potassium gluconate, is a normal metabolic product of glucose metabolism, 25-30 g being produced daily. For these reasons, and because potassium gluconate is widely used therapeutically as a source of potassium in cases of hypokalemia, conventional toxicological studies of potassium gluconate have not been regarded as necessary, explaining the lack of direct animal data on the compound. Orally administered gluconate is absorbed rapidly; a major part is excreted in the urine and the remainder is metabolized.

Reliability: (4) not assignable

09-AUG-2004 (3)

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