CLH-Report

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **Potassium sorbate**

EC Number: **246-376-1**

CAS Number: **24634-61-5**

Submitted by: Germany

Version: November 2011 (post ACCheck)

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TABLES

PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **Potassium sorbate**

EC Number: **246-376-1**

CAS number: **24634-61-5**

Registration number (s): No registration dossiers were available for this substance on 28 November 2011.

Purity: > 99 % w/w

Impurities: This information is confidential and then provided in the confidential part of the dossier provided in Annex 1.

The current Annex VI entry and the proposed harmonised classification

	CLP Regulation (2^{nd} ATP)	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	-	-
Current proposal for consideration by RAC	Skin Irrit 2 H315 Eye Irrit 2 H319	Xi; R 36/38
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Skin Irrit 2 H315 Eye Irrit 2 H319	Xi; R 36/38

Proposed classification based on Directive 67/548/EEC:

Xi; R 36/38

Proposed classification based on Regulation (EC) No. 1272/2008:

Skin Irrit 2 H315: Causes skin irritation, Eye Irrit 2 H319: Causes serious eye irritation

Proposed labelling:

Dir. 67/548/EEC: Hazard symbol 'Harmful or irritant', Xi; R36/38

Reg. (EC) No. 1272/2008: Pictogram GHS07 (Warning); Skin Irrit 2/H315; Eye Irrit 2/H319

Proposed specific concentration limits (if any):

None

Proposed notes (if any):

None

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name: Potassium sorbate

EC Name: Potassium (E,E)-hexa-2,4-dienoate

CAS Number: 24634-61-5

IUPAC Name: Potassium (2E, 4E)-hexa-2,4-dienoate

1.2 Composition of the substance

Chemical Name: Potassium sorbate

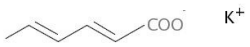
EC Number: 246-376-1

CAS Number: 24634-61-5

IUPAC Name: Potassium (2E, 4E)-hexa-2,4-dienoate

Molecular Formula: $C_6H_7KO_2$

Structural Formula:



Molecular Weight: 150.22 g/mol

Typical concentration (% w/w): ≥ 99

1.3 Physico-chemical properties

Table 1: Summary of physico- chemical properties of potassium sorbate

REACH ref Annex, §	Property	IUCLID section	Value	[enter comment/reference or delete column]
VII, 7.1	Physical state at 20°C and 101.3 kPa	4.1	White crystalline odorless powder	
VII, 7.2	Melting/freezing point	4.2	n.a. (decomposition above 200 °C)	Smeykal, H. (2002); report no. 20020015.01
VII, 7.3	Boiling point	4.3	n.a. (decomposition above 200 °C)	Smeykal, H. (2002); report no. 20020015.01
VII, 7.4	Relative density	4.4	1.36 at 23.5 °C	Smeykal, H. (2002); report no. 20020427.02
VII, 7.5	Vapour pressure	4.6	< 10^{-5} Pa at 25 °C	Smeykal, H. (2002); report no. 20020015.01
VII, 7.6	Surface tension	4.10	σ = 72.6 mN/m at 20°C (c = 1 g/l)	Wilfinger W (2003) report no. 0031475/01-PCST
VII, 7.7	Water solubility	4.8	pH 4: 1,96 g/l at 20°C pH 7: 543 g/l at 20°C pH 9: 563 g/l at 20°C	Heintze A (2002) report No. 0021005/01-PCSB
VII, 7.8	Partition coefficient n-octanol/water (log value)	4.7	pH 2,5: 1,32 at 20°C pH 6,5: -1,72 at 20°C (sorbic acid)	Heintze, A. (2002) report no. 0011364/01-PCPC
VII, 7.9	Flash point	4.11	not applicable.(solid).	BAM-II.2 (2010)
VII, 7.10	Flammability upon ignition (solids)	4.13	The test item could be ignited with a flame and then burned over a distance of 10 mm during 50 seconds, after which the flame went out (EC method A.10) [1)]	Franke, J (2003) report no. 20030852.01
	Flammability in contact with water		not conducted (Testing can be waived)[2)]	BAM-II.2 (2010)
	Pyrophoric properties		not conducted (Testing can be waived)[3)]	BAM-II.2 (2010)
VII, 7.11	Explosive properties	4.14	not conducted (Testing can be waived)[4)]	BAM-II.2 (2010)
VII, 7.12	Relative self-ignition temperature for solids	4.12	178 °C (EC method A.16)	Franke J (2003) report no.20030852.01,
VII, 7.13	Oxidising properties	4.15	not conducted (Testing can be waived)[5)]	BAM-II.2 (2010).
	Heat of decomposition	4.19	221 J/g (DSC)	Smeykal, H. (2002); report no. 20020015.01

[1)] The test item is not highly flammable according to Directive 67/548/EEC.

[2)] Testing can be waived based on a consideration of the chemical structure in accordance with REACH Column 2 of Annex VII, section 7.10: The classification procedure needs not to be applied because the organic substance is known to be soluble in water to form a stable mixture.

[3)] Testing can be waived in accordance with REACH Column 2 of Annex VII, section 7.10: The classification procedure needs not to be applied because the organic substance is known to be stable into contact with air at room temperature for prolonged periods of time (days).

[4)] Testing can be waived based on a consideration of the chemical structure in accordance with REACH Column 2 of Annex VII, section 7.11: The classification procedure needs not to be applied because there are no chemical groups present in the molecule which are associated with explosive properties.

[5)] Testing can be waived based on a consideration of the chemical structure in accordance with REACH Column 2 of Annex VII, section 7.13: The classification procedure needs not to be applied because the organic substance contains oxygen, which is chemically bonded only to carbon. Based on known experience of BAM II.2 in handling with similar organic substances the oxidising properties can be excluded.

2 MANUFACTURE AND USES

2.1 Manufacture

2.2 Identified uses

2.3 Uses advised against

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

Neither potassium sorbate nor its free acid, sorbic acid, are currently listed in Annex I of Dir. 67/548/EEC (up to the 31st ATP).

3.2 **Classification** in Annex VI of Regulation (EC) No. 1272/2008

Neither potassium sorbate nor its free acid, sorbic acid, are currently listed in Annex I of Regulation (EC) No. 790/2009 (1st ATP to Regulation (EC) No. 1272/2008)

3.3 Self classification(s)

The applicant under Dir. 98/8/EC proposed classification for toxicological hazards with Xi; R36 (according to the criteria of Annex VI of Dir. 67/548/EEC as last amended).

Proposed and current classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives				
2.2.	Flammable gases				
2.3.	Flammable aerosols				
2.4.	Oxidising gases				
2.5.	Gases under pressure				
2.6.	Flammable liquids				
2.7.	Flammable solids				
2.8.	Self-reactive substances and mixtures				
2.9.	Pyrophoric liquids				
2.10.	Pyrophoric solids				
2.11.	Self-heating substances and mixtures				
2.12.	Substances and mixtures which in contact with water emit flammable gases				
2.13.	Oxidising liquids				
2.14.	Oxidising solids				
2.15.	Organic peroxides				
2.16.	Substance and mixtures corrosive to metals				
3.1.	Acute toxicity - oral				Data conclusive but not sufficient for classification
	Acute toxicity - dermal				Data conclusive but not sufficient for classification
	Acute toxicity - inhalation				Data conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	Skin Irrit 2			
3.3.	Serious eye damage / eye irritation	Eye Irrit 2			
3.4.	Respiratory sensitisation				Data lacking
3.4.	Skin sensitisation				Data conclusive but not sufficient for classification
3.5.	Germ cell mutagenicity				Data conclusive but not sufficient for classification
3.6.	Carcinogenicity				Data conclusive but not sufficient for classification

3.7.	Reproductive toxicity				Data conclusive but not sufficient for classification
3.8.	Specific target organ toxicity –single exposure				Data conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure				Data conclusive but not sufficient for classification
3.10.	Aspiration hazard				Data lacking
4.1.	Hazardous to the aquatic environment				
5.1.	Hazardous to the ozone layer				

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: Pictogram GHS07 (Warning)
Hazard statements: Skin Irrit 2/H315: Causes skin irritation; Eye Irrit 2/H319: Causes serious eye irritation
Precautionary statements:

Proposed notes assigned to an entry:

Proposed and current classification according to DSD

Hazardous property	**Proposed classification**	**Proposed SCLs**	**Current classification [1)]**	**Reason for no classification [2)]**
Explosiveness				
Oxidising properties				
Flammability				
Other physico-chemical properties *[Add rows when relevant]*				
Thermal stability				
Acute toxicity				Data conclusive but not sufficient for classification
Acute toxicity – irreversible damage after single exposure				Data conclusive but not sufficient for classification
Repeated dose toxicity				Data conclusive but not sufficient for classification
Irritation / Corrosion	Xi; R36/38			
Sensitisation				Data conclusive but not sufficient for classification
Carcinogenicity				Data conclusive but not sufficient for classification
Mutagenicity – Genetic toxicity				Data conclusive but not sufficient for classification
Toxicity to reproduction – fertility				Data conclusive but not sufficient for classification
Toxicity to reproduction – development				Data conclusive but not sufficient for classification
Toxicity to reproduction – breastfed babies. Effects on or via lactation				Data conclusive but not sufficient for classification
Environment				

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Indication of danger: Hazard symbol "Harmful or irritant", Xi
R-phrases: R36/38
S-phrases:

4 ENVIRONMENTAL FATE PROPERTIES

4.1 Degradation

4.1.1 Biodegradation

The a.s. potassium sorbate is dissociated under environmentally relevant pH conditions by a reversible reaction with water. The sorbate anion is relevant for the degradation of the a.s. in water, therefore tests with sorbic acid can be used to determine the biodegradability of the a.s., if pH effects of the acid can be excluded (pH adjustment of test solution).

4.1.1.1 Screening tests

Ready biodegradability of sorbic acid was tested in the Closed Bottle Test (EC method C.4-E, OECD guideline 301 D).The pass-levels for ready biodegradability, i.e. > 60% removal of ThOD both within the 28-day period and within the 10-day window, are fulfilled. Sorbic acid is therefore considered to be readily biodegradable.

Table 2: Biodegradability of Sorbic acid

Guideline / Test method	Test type	Test para-meter	Inoculum			Additional substrate	Test substance conc.	Degradation		Refe-rence
			Type	Concen-tration	Adap-tation			Incubation period	Degree [%]	
EC C.4-E, OECD 301 D	Ready	Biochemical oxygen demand (BOD)	Activated sludge	2×10^4 cells/l	No	No	2 mg/l nominal	28 d 7 d	75 % 62 %	Dengler, D. (2002); report no. 20011364/ 01-AACB

4.1.2 Summary and discussion of persistence

Sorbic acid is considered to be readily biodegradable.

4.2 Bioaccumulation

Estimations on aquatic bioconcentration:

Basis for estimation	log $_{POW}$ (measured)	Estimated BCF for fish (freshwater)*	Reference
log K_{ow}	–1.72 (at pH = 6.5) 1.32 (at pH = 2.5)	0.007 2.6	Sendor, T. (2003)

* TGD, chapter 3.8.3.2, Equation 74: log BCF_{fish} = 0.85 x log K_{ow} – 0.70

Experimental studies on aquatic and terrestrial bioconcentration have not been performed. Instead, the BCF for fish was estimated based on the log Kow according to the TGD. Although, strictly speaking, the respective TGD equations are not applicable to log Kow values below the advised QSAR validity range, which is the case here, the calculated BCF´s reflect the order of magnitude

and are acceptable. These data have been derived for sorbic acid. However, the statement on the validity of the results in view of dissociation equilibrium also applies here. The potential of potassium sorbate to bioaccumulate in aquatic organisms is considered to be negligible.

5 HUMAN HEALTH HAZARD ASSESSMENT

Sorbic acid is the corresponding free acid to potassium sorbate. Under physiological conditions (pH of blood: 7.38, Frenking 2006) and given the pKa of 4.76 of sorbic acid (Hartmann-Schreyer 2004) the ratio of sorbate anion to free acid will be almost 420fold (in other words: less than 0.25 % will be available as the free acid). The results obtained for sorbic acid or other sorbates can therefore in general be extrapolated to potassium sorbate and vice versa. Thus below, for ease of reading, results are presented for potassium sorbate regardless of whether they were obtained using potassium sorbate itself, sorbic acid, or one of the other sorbates. However, NOAELs/LOAELs refer to the actual test item used in the respective study (which is given in the corresponding tables).

Unless otherwise noted, all studies were conducted under GLP conditions.

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Table 3: Summary of toxicokinetic studies

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels, Duration of exposure	Results (excretion via respiration, urine, faeces, bile, half-life time plasma, residues in tissue)	Remarks	Reference
Related to OECD 417 Non-GLP	Oral, gavage (single adminis-tration)	Mouse, 4 (F) low dose group, 2 (F) high dose group	40 or 3000 mg/kg bw sorbic acid, 1-^{14}C labelled, in water	Recovery of 84% in low dose group / 88% in high dose group, excretion via respiration as CO2 (80 – 83%), faeces (0 -1%) and urine (4 – 5%), sorbic acid (0.7%) and major metabolite muconic acid (0.4%) identified in urine	Post exposure period: 4 d	Westöö, G. (1964); Acta Chemica Scandinavica 18, 1373–1378
Related to OECD 417 Non-GLP	Oral, gavage (single adminis-tration)	Rat (Sprague Dawley), 13 groups, 1(F) per group	12.2, 24.4, 31.7, 50.2, 51.5, 52.2, 55.0, 56.0, 99.8, 106.9, 152.7, 199.9, 224.4 mg/ rat sorbic acid, 1-^{14}C labelled, in water	Recovery of 100%, excretion via respiration as CO2 (86%), radioactivity in urine (2-10%), mainly as urea, faeces (0.4%), intestines (2-4 %), muscle (2-4 %) and carcass (6 %). Excretion via lung starts approx. 10 min after application and is completed after max. 10 h	Post exposure period 4 - 20 hours, sacrifice after no more 14C determin-able in exhaled air	Fingerhut, M. et al. (1962); Biochemische Zeitschrift 336, 118-125
Non-GLP	Oral, gavage	Rat (F)	10 % sodium sorbate in water ca. 460-985 mg/animal/d Repeated administration twice daily over 5 d	Intermediary metabolism of sorbic acid is similar to that of common fatty acids. Sorbic acid is oxidised to CO_2 and H_2O.		Deuel, H.J. et al. (1954); Food Research 19, 13–19

Potassium sorbate is almost completely absorbed after oral application and is subsequently well distributed in the body. It is mainly oxidised to CO_2 and H_2O. Therefore excretion proceeds with 80-86% via the lung as CO_2. About 2-10% of the excreted radioactivity are found in the urine as urea and in minor concentration as sorbic acid and muconic acid. Excretion via the lung is complete 10 h after application.

Studies on *in vivo* or *in vitro* dermal absorption rates, performed with either sorbic acid or potassium sorbate, or a formulation of either of these, are not available. In the CA report for inclusion of potassium sorbate into Annex I of Dir. 98/8/EC, the RMS proposed to use a default value of 25% dermal absorption for risk characterisation based on read-across from acrylic acid (AA), a compound closely related to sorbic acid (SA) in terms of both chemical structure (AA is the C_3-homologue of SA) and metabolism in mammals.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

Table 4: Summary of acute oral toxicity studies

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/kg bw)	Value LD_{50} (mg/kg bw)	Classification, Remarks	Reference
Not stated, similar to OECD 401 Non-GLP	Oral, stomach tube	Rat, Wistar, 8M+8F	40% sorbic acid in 5% aqueous gum arabic 0-3800-5100-6900-9300-12500-16900	> 10000	None, Study report in Japanese, evaluation based on English translation submitted by the applicant under Dir. 98/8/EC	Uchida, O. (1985); Bull. Natl. Inst. Hyg. Sci. (Tokyo) 103, 166-171
Pre-guideline, Non-GLP	Oral, not specified	Rat, Sherman 5M+5F	Sorbic acid in 1% 'Tergitol Penetrant 7' and 0.25 % agar solution Dose levels not stated	10500	None, Rated additional information	Deuel, H.J. (1954); Food Research 19, 1-12
Pre-guideline, Non-GLP	Oral, not specified	Rat, Sherman 6M+F	Sorbic acid, unknown vehicle Dose levels not stated	7360	None, Rated additional information	Smyth, H.F. (1948) J. Ind. Hyg. Toxicol. 30 (1), 63 – 68

Potassium sorbate is not acutely toxic or harmful when administered orally to rats. Additional data regarding acute oral toxicity were provided which support the results above but are not suitable for risk assessment on their own.

5.2.2 Acute toxicity: inhalation

Table 5: Summary of acute inhalation toxicity studies

Method/Guideline	Route and duration of exposure	Test substance	Species, Strain, Sex, No/group	Dose levels (mg a.s./L air)	Value LC50 (mg a.s./L air)	Classification, Remarks	Reference
OECD 403	Inhalation nose-only, 4 hrs exposure	TC 3, 500 g potassium sorbate/kg, without further vehicle	Rat, CD® 5M+5F	5.15 (limit test)	> 5.15	None	Chevalier, F (2004); unpublished report no. 16706/03

A valid inhalation toxicity study using crystalline potassium sorbate was not provided. Instead, the potential for acute inhalation toxicity of potassium sorbate was assessed using a study with a biocidal product, i. e. a 50% (w/w) aqueous solution of potassium sorbate. Based on the potassium sorbate content of the test aerosol, the 4 h-LC_{50} was > 5.15 mg/L air.

5.2.3 Acute toxicity: dermal

Table 6: Summary of acute dermal toxicity studies

Method/ Guideline	Route	Species, Strain, Sex, No/group	Dose levels (mg/kg bw)	Value LD_{50} (mg/kg bw)	Risk Phrase/ Remarks	Reference
OECD 402	Dermal	Rat, Sprague-Dawley/ Crl:CD®BR 5M/5F	Sorbic acid in sesame oil 2000 (limit test)	> 2000	None	Leuschner, J. (2002); unpubished report no. 15270/02

Potassium sorbate is not acutely toxic or harmful when administered dermally. For the dermal study, a lipophilic vehicle was used, applying sorbic acid in its non-dissociated form. However, the results are seen as transferable to potassium sorbate as a worst case estimate because the salt, as a charged molecule, can be expected to penetrate the skin less readily than sorbic acid itself (thus displaying a lower acute dermal toxicity than the free acid).

5.2.4 Acute toxicity: other routes

No data are available.

5.2.5 Summary and discussion of acute toxicity

Potassium sorbate is not acutely toxic or harmful when applied by the oral, dermal, or inhalative route. No specific classification/labelling for acute (systemic) toxicity is required.

5.3 Irritation

5.3.1 Skin

Table 7: Summary of skin irritation studies

Method/ Guideline	Species, Strain, Sex, No/group	Average score 24, 48 h		Reversibility yes/no	Results	Classification, Remarks	Reference
		Erythe-ma	Oedema				
OECD 404	Rabbit, albino New Zealand 3 (sex not mentioned)	0	0	-	Not irritating	None, performed using potassium sorbate in 0.9 % aqueous NaCl	Hofmann, T. (1987); unpublished report no. 87.0372

Potassium sorbate was non-irritant in the Draize test with rabbits. However, reversible skin reactions have frequently been reported for humans (cf. section 5.9.1 and table 15 for selected publications). Based on experience in humans, classification/labelling as skin irritant is proposed (section 5.9.1).

5.3.2 Eye

Table 8: Summary of eye irritation studies

Method/ Guideline	Species, Strain, Sex, No/group	Average Score over 24, 48, 72h				Reversi-bility yes/no	Results	Classification, Remarks	Reference
		Cornea opacity	Iris	Redness Conjunc-tiva	Chemosis				
OECD 405	Rabbit, albino New Zealand 3 (sex not mentioned)	All animals: 0.4 Individual animals: 1) 1.0 2) 0.3 3) 0.0	All animals: 0.4 Individual animals: 1) 0.3 2) 0.7 3) 0.3	All animals: 1.6 Individual animals: 1) 2.3 2) 2.3 3) 0.3	All animals: 2.1 Individual animals: 1) 2.3 2) 2.0 3) 2.0	Yes (within 21 days)	Irritating	R36 Performed using potassium sorbate without further vehicle; washout 24 h after application	Hofmann, T. & Jung R. (1987); report no. 87.0501

In a study conducted by Hofmann & Jung (1987) according to OECD 405, potassium sorbate proved to be irritating to the eyes of rabbits. Potassium sorbate was applied without vehicle, and a washout performed with 0.9% NaCl 24 hours after application. Eyes were examined 1, 24, 48 and 72 hours after application. Mean values of scoring over 24, 48 and 72 hours are compiled in Table 8 for all 3 animals as well as for the individual rabbits. Clear to white mucous discharge was observed 1 to 48 hours following application. All animals displayed reddened irises from 1 to 24 hours after application, one animal showed a reddened iris until 48 hours. Conjunctival bleeding was observed between 48 h and 7 days after application, and was still present in one animal 14 days following application. All eye reactions were fully reversible within 21 days.

Medical surveillance and human case reports (summarised in 5.9.1) provide evidence for an eye irritating potential of sorbic acid. Incidences of irritation to eyes were reported at a production site for potassium sorbate (Astvad, 2004: "Irritation from eyes, skin and respiratory passages were seen when working with sorbic acid"). In addition, adverse ocular reactions have been reported for individuals applying contact lens care solutions containing sorbic acid as a preservative (a. o. Josephson & Caffery 1986; Herbst & Maibach 1991; Herbst & Maibach, 1992). In section 5.9.1.4 of this CLH report, both immunological and non-immunological (irritant) reactions to sorbic acid are discussed as possible underlying mechanisms for eye effects in humans.

Classification/labelling according to Directive 67/548/EEC:

Classification/labelling as "**irritating to eyes" (Xi; R36)** is proposed for potassium sorbate, based on the animal study by Hofmann & Jung, 1987, performed with potassium sorbate. The ocular lesions observed in this study are regarded as being significant, since the overall mean score for

oedema of the conjunctivae (chemosis) was greater than 2, and all three animals displayed individual scores of equal to or greater than 2 for this endpoint. Criteria, however, for classification/labelling as "causing serious eye damage" are not fulfilled for the animal study, since the observed eye reactions were fully reversible within 21 days.

Classification/labelling according to the CLP Regulation:

Classification/labelling as "irritating to eyes", category 2 is proposed for potassium sorbate, based on the animal study by Hofmann & Jung, 1987, in which potassium sorbate caused relevant ocular lesions that were reversible within 21 days following application. A positive response in terms of conjunctival redness (individual scores > 2) and conjunctival oedema (individual scores ≥ 2) was observed for 2 out of 3 and 3 out of 3 test animals, respectively.

5.3.3 Respiratory tract

No experimental animal data are available. While potassium sorbate has been produced and marketed for decades, respiratory irritation in humans due to direct exposure to potassium sorbate has not been reported. Nevertheless, in a declaration of medical surveillance procedures for manufacturing personnel at a potassium sorbate production plant, it is stated that "Irritation from eyes, skin and respiratory passages were seen when working with sorbic acid", although further detail is not provided (Astvad 2004, cf. 5.9.1, Medical data). Overall, this information is not regarded as sufficient for proposing classification/labelling of potassium sorbate as respiratory irritant along Directive 67/548/EEC or CLP Regulation.

5.3.4 Summary and discussion of irritation

The following classification/labelling for local irritation is proposed:

Classification/labelling according to Directive 67/548/EEC:
Xi; R36/38

Classification/labelling according to the CLP Regulation:
Skin Irrit 2/H315: Causes skin irritation;
Eye Irrit 2/H319: Causes serious eye irritation

5.3.5 Corrosivity

Potassium sorbate is not corrosive as proven by the results obtained in Draize tests for skin and eye irritation in rabbits.

5.4 Sensitisation

5.4.1 Skin

Table 9: Summary of skin sensitisation studies

Method/ Guideline	Species, Strain, Sex, No/group	Number of animals sensitised/ total number of animals	Results	Classification, Remarks	Reference
Not stated, related to OECD 406; similar to GPMT Non-GLP	Guinea pig, Pirbright white, 10M/10F (treated) 10M/10F (neg. control) 10M/10F (pos. control)	1st challenge (intradermal): 4/20 (treated); 0/20 (neg. control); 18/20 (pos. control) 2nd challenge (topical): 0/20 (treated); 0/20 (neg. control); 4/20 (pos. control)	Not sensitising	None, Performed using 0.1 % sorbic acid in physiol. saline (first challenge, intradermal) and 1% sorbic acid in soft white petrolatum (second challenge, topical)	Maurer, T. (1979); Contact Dermatitis 5, 1–10

The skin sensitising potential of sorbic acid was tested in guinea pigs according to a maximisation procedure related to OECD 406. While the first challenge involved intradermal application, the second challenge was applied topically (epidermal occlusion for 24 hours). As summarised in table 9, 4 out of 20 animals (20 %) treated with sorbic acid showed positive skin reactions after the first challenge. After the second (epidermal) challenge to sorbic acid, no response in terms of skin findings were observed.

No classification for skin sensitisation is required for sorbic acid according to the criteria for animal test results laid down in Annex VI to Dir. 67/548/EEC or in the 2nd ATP to CLP, since the proportion of animals with positive skin findings resulting from the first, intradermal challenge application (20 %) was below the threshold for classification (i. e. 30% animals with positive skin reactions).

Supplementary to the key study mentioned above, additional data reporting results of human allergenicity patch testing are available for sorbic acid which support this conclusion (cf. section 5.9.1). In rare cases, also true allergic eczematous reactions to sorbic acid were observed. Even in large collectives of some thousands of patients the number of positive patch test results rarely exceeded 1%. Given the almost ubiquitous pre-exposure with sorbic acid via food or cosmetics, these findings indicate at most a very weak sensitising potential of sorbic acid, which would not call for classification and labelling as a sensitiser. However, evidence has been provided that sorbic acid may more commonly trigger transient skin reactions when applied to human skin via a reaction regarded as non-immunologic contact urticaria or non-immune immediate contact reaction (cf. section 5.9.1).

In conclusion, considering both DSD and CLP (2nd ATP) criteria, no classification/labelling of potassium sorbate/sorbic acid is proposed for skin sensitisation.

5.4.2 Respiratory system

No data are available. Respiratory sensitisation in humans has not been reported while potassium sorbate has been produced and marketed for decades.

5.4.3 Summary and discussion of sensitisation

Potassium sorbate does not require classification/labelling for sensitisation.

5.5 Repeated dose toxicity

5.5.1 Repeated dose toxicity: oral

Table 10: Summary of oral repeated dose toxicity studies

Method/ Guideline	Route of exposure, Duration	Species, Strain, Sex, No/group	Dose levels (ppm)	NO(A)EL ppm (mg/kg bw /d)	LO(A)EL ppm (mg/kg bw /d)	Results Main effects/ Target organs	Reference
OECD 407	Oral/diet 28 days	Rat, SD, 5M/5F, 10M/10F in dose group 0 and 100 000 ppm Range finding study + 15 days recovery group: 5 M+F/ control and 100 000 ppm	Sorbic acid without further vehicle 0-25 000-50 000-100 000	100 000 (M: 9200, F: 8600)	> 100 000	No adverse effects	Ehling, G. (2003); Report No. PT02-0039
OECD 408	Oral/diet 90-92 days	Rat, SD, 20M/20F	Sorbic acid without further vehicle 0-25 000-50 000-100 000	100 000 M/F, (M: 6800, F: 7200)	> 100000	No adverse effects	Ehling, G. (2004); Report No. PT02-0040
Related to OECD 409, Non-GLP	Oral/diet 88-91 days	Dog (half-cocker, mixed cocker, terrier), 2M/1F	Sorbic acid without further vehicle 0-40 000	40 000 (ca. 1000 mg/kg bw/d*)	> 40 000	No adverse effects	Deuel, H.J. et al. (1954), Food Research 19: 1–12

Method/ Guideline	Route of exposure, Duration	Species, Strain, Sex, No/group	Dose levels (ppm)	NO(A)EL ppm (mg/kg bw /d)	LO(A)EL ppm (mg/kg bw /d)	Results Main effects/ Target organs	Reference
Pre-guideline Non-GLP	Oral, diet, 18 mo.	Mouse, ASH/CS1, 48 M and 50 F per group	Sorbic acid without further vehicle 0-10000-50000-100000 ppm (0-1400-7000-14000 mg/kg bw, based on estimation)	Reduced terminal body weight, increased organ weight (liver, kidney); No carcinogenic potential	10000 (1400)	50000 (7000)	Hendy, R.J. (1976), Fd. Cosmet. Toxicol. 14, 381-386
Pre-guideline Non-GLP	Oral, diet, 2 yrs	Rat, Wistar SPF breed, M + F, 48	Sorbic acid without further vehicle 0-15000 100000 ppm (0-750-5000 mg/kg bw/d)	Reduced body weight (gain), increased organ weights (liver, kidney, thyroid); focal fatty changes in livers of female animals No carcinogenic potential	15000 (750)	100000 (5000)	Gaunt, I.F. et al. (1975), Fd. Cosmet. Toxicol. 13, 31-45
No guideline indicated Non-GLP Unsuitable for risk assessment	Oral, pelleted diet, 106 weeks (rats, mice: not specified)	Rat, Donryu, Wistar, Sprague-Dawley and Fisher; Mouse, ICR and B6C3F1	Potassium sorbate, vehicle unknown (if any) 2.5-5.0 %	No carcinogenicity observed	Not applicable	Not applicable	Odashima,S. (1980) in: Montesano et al. (eds.): Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Sci. Publ., Lyon/France, 315-322

* estimated using a standard conversion factor of 0.025

5.5.1.1 Subacute to subchronic

No substance-related adverse effects could be observed in repeated dietary administration tests in rats and dogs up to a dietary content of 100000 ppm (10%) sorbic acid.

5.5.1.2 Chronic

Only weak, borderline effects on body and organ weight were seen after treatment of rats and mice for 24 and 18 months, respectively. Focal fatty changes in the liver of female rats were the only effect observed upon histopathological examination.

5.5.2 Repeated dose toxicity: inhalation

No data are available. Poisoning of humans by repeated exposure via inhalation has not been reported in the published literature, while potassium sorbate has been produced and marketed for decades.

5.5.3 Repeated dose toxicity: dermal

No data are available. Poisoning of humans after repeated dermal exposure has not been reported in the published literature, while potassium sorbate has been produced and marketed for decades.

5.5.4 Other relevant information

None

5.5.5 Summary and discussion of repeated dose toxicity

A NOAEL of 750 mg/kg bw/d for long-term toxicity is derived from the 2-yr study in rats. However, taking into account the large dose-spacing used in this study as well as the marginal nature of the effects observed at the high-dose level, the RMS proposes that the limit dose level of 1000 mg/kg bw/d which proved safe in the 90-d study in dogs as well as in the multi-generation studies in rats and which was also exceeded by the NOAEL in the 18-mo. mouse study, should be used as the starting point for deriving any toxicological limit values for long-term exposure in humans.

5.6 Mutagenicity

5.6.1 *In vitro* data

Table 11: Summary of *in vitro* mutagenicity studies

Method/ Guideline	Test system (Organism, strain)	Concentra-tions tested (give range)	Results		Remarks	Reference
			+ S9	- S9		
Pre-guideline Non-GLP	Bacterial reverse mutation assay (S. typhimurium, TA 98, TA 100, TA 1535, TA 1537)	Potassium sorbate in different solvents (DMSO, ethanol, dist. water) No information on applied concentration	Negative	Negative	Not suitable for risk assessment No further specification of the technical material	Engelbart, K. (1979), report No. 417/79 A
No guideline indicated Non-GLP	Bacterial reverse mutation assay (S. typhimurium, TA 97a, TA 1538)	Potassium sorbate in dist. water 0-10 mg/plate	Negative	Negative	Study with deficiencies* Study report in Japanese, evaluation based on English translation sub-mitted by the applicant	Fujita, H., Sasaki, M. (1986), Ann. Rep. Tokyo. Metr. Res. Lab. P.H. 37, 447 – 452

Method/ Guideline	Test system (Organism, strain)	Concentra-tions tested (give range)	Results		Remarks	Reference
			+ S9	- S9		
Pre-guideline Non-GLP	Bacterial reverse mutation assay (S. typhimurium), TA 1535, TA 1537, TA 1538; Saccharomyces cerevisiae D4)	Potassium sorbate in phosphate buffer 0-2.5% (plate tests) 0-2.5-5.0 % (suspension tests)	Negative	Negative	Study with deficiencies* Metabolic activation mixtures were prepared using tissue homogenates of liver, lung, and testes from ICR mice, Sprague-Dawley rats, and rhesus monkeys (macaca mulatta)	Brusick, D. (1974), Report No. 2468
No guideline indicated No GLP statement	Bacterial reverse mutation assay (S. typhimurium, TA98, TA100)	Potassium sorbate, sodium sorbate 0, 0.01, 0.1, 0.5, 1.0 and 2.0 mg/plate	Negative	Negative	Additional study	Münzner, R. et al. (1990) Fd Chem. Toxic. 28, 397 – 401 (see also below)
Pre-guideline Non-GLP	Bacterial reverse mutation assay (S. typhimurium TA98, TA100, TA 1535, TA 1537, TA 1538; S. cerevisiae D4; E. coli w3110, 3478)	Sorbic acid - sodium nitrite reaction products without further vehicle	Negative	Negative	Not suitable for risk assessment, as basic bibliographic information is missing and relevant tables are unreadable.	Litton Bionetics (1976), Litton Bionetics Inc., Kensington, USA, Report No.: Not stated (unpublished).
Pre-guideline Non-GLP	Bacterial reverse mutation assay (S. typhimurium), TA98, TA100, TA 1535, TA 1537, TA 1538; S. cerevisiae D4)	Calcium sorbate in phosphate buffer at 24, 47, and 94%, resp.	Negative	Negative	Additional study Relevance of test item questionable	Brusick, D. (1977), Report No. 2672 (unpublished).
Similar to method B.10 (2000/32/EC) Non-GLP	In vitro mammalian chromosome aberration test (CHL cells)	Potassium sorbate in physiol. saline 0-4 g/L Sorbic acid 0-1 g/L	Not tested Not tested	Equivocal Negative	Weakly positive at 4.0 mg/mL (cytotoxic range); most likely due to high osmolality	Ishidate, M., Odashima, S. (1977) Mutation Research 48, 337 – 354
No guideline indicated No GLP statement	Chromosome aberrations, sister chromatid exchanges and gene mutations in cultured Chinese hamster cells (CHO, V79 cells)	Sorbic acid in ethanol 0-1.05 g/L Potassium sorbate in water 0-20 g/L Sodium sorbate in water 0-0.8 g/L	Not tested	Equivocal	Additional study Potassium sorbate: weakly positive in the chromosome aberration test at high concentrations	Hasegawa, M. et al. (1984), Fd Chem. Toxicol. 22, 501 – 507 (published).

Method/ Guideline	Test system (Organism, strain)	Concentra-tions tested (give range)	Results		Remarks	Reference
			+ S9	- S9		
No guideline indicated Non-GLP	Chromosome aberrations and sister chromatid exchanges in Don Chinese hamster cells exposed to various chemicals	Potassium sorbate in HBSS (Hank's balanced salt solution) 0-0.04 mol/L	Not tested	Equivocal	Additional study Potassium sorbate: equivocal result in the chromosome aberration test at high concentrations	Abe, S. and Sasaki, M. (1977) J. Natl. Cancer Inst. 58, 1635 – 1641 (published).
No guideline indicated No GLP statement	Effects on cell cycle in vitro in V79 cells and somatic mutations in drosophila melanogaster	Potassium sorbate in water 0-2.5 g/L Sodium sorbate (produced from sorbic acid with NaOH) in water 0-2.5 g/L	Not tested/ not applicable	Negative Equivocal	Additional study Sodium sorbate: weakly positive in the V79 cell test at the highest concentration	Schlatter, J. et al. (1992) Fd Chem. Toxic. 30, 843 - 851 (published).
No guideline indicated No GLP statement	Syrian hamster embryo (SHE) fibroblast micronucleus and cell transformation test	Sorbic acid, sodium sorbate, and potassium sorbate (all in water, all 0-1.2 g/L)	Not tested	Negative	Additional study	Schiffmann, D., Schlatter, J. (1992) Fd Chem. Toxic. 30, 669 - 672 (published)
Similar to method B.18 (88/303/EC). GLP-compliant	Unscheduled DNA synthesis in mammalian cells in vitro (human cell line A 549)	Sorbic acid in DMSO 0-2 g/L	Negative	Negative	None	Müller, W. (1989), Report No. 89.0890
Similar to method B.17 (2000/32/EC) Non-GLP	HGPRT-test (CHO-K1-BH4 cells)	Potassium sorbate in water 0-20 g/L	Negative	Negative	None	Münzner, R. et al. (1990) Fd Chem. Toxic. 28, 397 – 401
No guideline indicated No GLP statement	Alkaline elution assay (human tumour cell line A 549)	Sorbic acid in DMSO 0-1 g/L	Negative	Negative	Additional study	Cojocel, C. (1989), Report No. 89 1188 (unpublished)

* Both studies showed deficiencies (insufficient number of strains tested according to current guidelines). However, based on a synopsis of all submitted data, no further study is required.

5.6.2 In vivo data

Table 12: Summary of *in vivo* mutagenicity studies

Method/ Guideline	Species, Strain, Sex, No/group	Route and Frequency of application	Sampling times	Dose levels mg/kg bw	Results	Remarks	Reference
OECD 474 GLP-compliant Mouse	Mouse, NMRI, 5/sex/group	Oral, gavage, single dose	24, 48, 72 h	Sorbic acid in sesame oil 0-500-1500-5000	Negative	None	Müller, W. (1989), Report No. 89.1023*

Method/ Guideline	Species, Strain, Sex, No/group	Route and Frequency of application	Sampling times	Dose levels mg/kg bw	Results	Remarks	Reference
micronucleus test	Bone marrow						
US-EPA GLP-compliant SCE test	Mouse, NMRI, 5/sex/group Bone marrow	Oral, gavage, single dose	24 h	Sorbic acid in 1 % CMC 0-500-1500-5000	Negative	None	Völkner, W. (1989), Report No. 89.1433*
No guideline indicated No GLP statement Test for chromosomal damage	Male Swiss albino mice Bone marrow	Oral, gavage, daily for 30 d	24 h after last dose	Sorbic acid in dist. water 15	Negative	Additional study	Banerjee, T.S., Giri, A.K. (1986) Toxicology Letters 31, 101 – 106, 1986 (published)
No guideline indicated No GLP statement Test for micronucleus formation, chromosomal aberrations, and SCE	Chinese hamsters, C1H mice Bone marrow cells	Oral, gavage or i.p. single dose	24-30 h (micronuc-leus test) 20-24-30 h (chromosome aberration test) 24 h (SCE)	Potassium sorbate, sodium sorbate all in water 100-200 (expressed as sorbic acid)	Negative	Additional study	Münzner, R. et al. (1990) Fd Chem. Toxicol. 28, 397 – 401
No guideline indicated No GLP statement Alkaline elution assay (test for DNA strand breaks)	Male Wistar rats (4/dose group) Isolated liver cells	i.p.	2 h after administr-ation	Potassium sorbate in DMSO 400-800-1200	Negative	Additional study	Cojocel, C. (1989), Report No. 89 1188 (unpublished).*

* These results were also summarised in the following publication, which was submitted by the applicant under Dir. 98/8/EC as an additional study: Jung R et al. (1992), Fd Chem. Toxic. 30, 1 – 7.

5.6.3 Human data

Genotoxicity of potassium sorbate in humans has not been reported in the published literature, while potassium sorbate has been produced and marketed for decades.

5.6.4 Other relevant information

None

5.6.5 Summary and discussion of mutagenicity

Potassium sorbate did not display a genotoxic potential either *in vitro* or *in vivo*. No classification/labelling for genotoxicity is needed.

5.7 Carcinogenicity

5.7.1 Carcinogenicity: oral

For a summary of chronic/carcinogenicity studies, please cf. section on repeated dose toxicity above.

Potassium sorbate did not display a carcinogenic potential in any of the available oral chronic studies in rats or mice.

5.7.2 Carcinogenicity: inhalation

No data available

5.7.3 Carcinogenicity: dermal

No data available

5.7.4 Carcinogenicity: human data

Carcinogenicity in humans related to an exposure to potassium sorbate or sorbic acid has not been reported in the published literature, while these substances have been produced and marketed for decades.

5.7.5 Other relevant information

None

5.7.6 Summary and discussion of carcinogenicity

Potassium sorbate is not considered carcinogenic and thus does not require classification/labelling for carcinogenicity.

5.8 Toxicity for reproduction

5.8.1 Effects on fertility

Table 13: Summary of effects on fertility studies

Method/ Guideline	**Route of exposure**	**Species, Strain, Sex, No/group**	**Dose levels mg/kg bw/d**	**Critical effect 1) Parental, 2) Offspring (F1, F2)**	**NO(A)EL mg/kg bw/d 1) Parental toxicity 2) Reproductive toxicity 3) Offspring toxicity**	**Reference**
OECD 416	Oral, gavage	Rat, CD, 30 M/30 F	Sorbic acid in aqueous hydroxylpropyl methyl cellulose gel (Methocel E 4 M) 0-300-1000-3000	1) - 2) Reduced postnatal body weight gain, retarded development, behavioural changes	3000 3000 1000	Cordts, R. (2004), Report No. 16645/03

In the multi-generation study in rats, there were no treatment-related adverse effects on P-generation animals or reproduction up to a dose level of 3000 mg/kg bw/day. Adverse effects on growth, attainment of developmental landmarks, and behavioural changes were observed in the offspring at 3000 mg/kg bw/day. The dose of 1000 mg/kg bw/d is considered the relevant NOAEL for offspring toxicity.

5.8.2 Developmental toxicity

Table 14: Summary for developmental toxicity studies

Method/ Guideline	**Route of exposure, Duration**	**Species, Strain, No/group**	**Dose levels, mg/kg bw/d**	**Critical effects 1) dams 2) fetuses**	**NO(A)EL mg/kg bw/d 1) Maternal toxicity 2) Embryotoxicity 3) Teratogenicity**	**Remarks**	**Reference**
Pre-guideline Non-GLP	Oral, gavage, day 6-15 pc	Rat, Wistar, 19-22 F	Potassium sorbate in water 0-3.4-15.8-73.3-340	1) none 2) none	1) 340 2) 340 3) 340	None	Bailey, D.E. (1975), Report No. PB 245 520

Method/ Guideline	**Route of exposure, Duration**	**Species, Strain, No/group**	**Dose levels, mg/kg bw/d**	**Critical effects 1) dams 2) fetuses**	**NO(A)EL mg/kg bw/d 1) Maternal toxicity 2) Embryotoxicity 3) Teratogenicity**	**Remarks**	**Reference**
OECD 414	Oral, gavage, day 6-29 pc	Rabbit, Himalayan, 24-38 F	Sorbic acid in 0.5 % aqueous hydroxypropyl methylcellulose gel 0-300-1000-3000	1) ≥ 1000 mg/kg bw/d: Reduced food consumption and body wt gain, clinical signs, coarse spleen surface; 3000 mg/kg bw/d: Decr. body wt, decreased gravid uterus wt, reduced spleen size, mortality 2) ≥ 1000 mg/kg bw/d: Decreased foetal body wt, increased post-partal mortality 3000 mg/kg bw/d (with severe maternal toxicity): Increased no. of resorptions and abortions, decr. number of live foetuses, mortality, malformations	1) 300 2) 300 3) 1000	The effects observed after gavage bolus of doses at or above limit dose level were considered as irrelevant for human exposure in the context of this dossier	Cordts, R. (2004), Report No. 16972/03

The available studies do not indicate any specific embryo-/foetotoxic potential of potassium sorbate. In rats, no adverse effects in dams or foetuses were noted up to the highest dose tested, i. e. 340 mg/kg bw/d.

Foetal growth retardation and embryo-foetal death and/or reduced viability were present in rabbits at a dose of 1000 mg/kg bw/d, which also induced slight maternal toxicity (increased respiration rate, decreased food consumption and body weight gain, coarse spleen surface). A dose of 3000 mg/kg bw/d resulted in maternal lethality and increased morphologic abnormalities (brain, limbs) in the foetuses of surviving does. The dose of 300 mg/kg bw/d is considered the relevant NOAEL for maternal and embryofoetal toxicity. The severe effects on offspring and maternal animals that were observed in this study were most likely attributable to damage of the gastro-intestinal tract, which was caused by high local concentrations of sorbic acid after bolus gavage administration, and to which this species seemed especially amenable (as in the rat multigeneration gavage study comparable findings were not observed). As a consequence, both the design

(unusually high gavage dose levels at and above the limit dose level) and the results obtained from this study were seen as bearing little relevance to exposure scenarios to be expected for humans, where oral bolus ingestion is highly unlikely.

5.8.3 Human data

Developmental toxicity or impairment of fertility in humans related to exposure towards potassium sorbate has not been reported in the published literature while this substance has been produced and marketed for decades.

5.8.4 Other relevant information

None

5.8.5 Summary and discussion of reproductive toxicity

Potassium sorbate is not considered toxic to reproduction (fertility, development of offspring) and thus does not require classification/labelling for reproduction toxicity.

5.9 Other effects

5.9.1 Medical data

Table 15: Summary of medical data

Kind of study (e.g. case reports)	Examination methods, number of individuals examined	Results	References
Declaration of medical surveillance procedures for manufacturing plant personnel (Nutrinova)	Blood and urine analyses including blood count, blood glucose and liver status parameters, technical medical check-ups such as hearing, vision, and lung function tests, ECG. All workers concerned, in regular intervals (not specified).	No negative health effects under regular medical surveillance.	Dosch, E. (2004), unpublished report (no designation)
Declaration of medical surveillance procedures for manufacturing plant personnel (Cheminova)	Blood pressure, weight and height (BMI), vision test, hearing test, lung function tests, and a general objective health check-up. All workers concerned, check-up repeated every 3 years.	Incidences of irritation of eyes, skin, and respiratory tract were observed at a production site for potassium sorbate. Otherwise, no negative health effects under regular medical surveillance.	Astvad, K. (2004), unpublished report (no designation)
Declaration of medical surveillance procedures for manufacturing plant personnel (Daicel)	Blood pressure, height, body weight (BMI), differential blood count, blood glucose, blood neutral lipid, blood Cholesterol, HDL-C, creatinine, liver status parameters (GOT, GPT, gamma-GTP, urinary urobilinogen), haematocrit, urinary protein, urinary glucose, uric acid, occult blood. Furthermore, technical medical check-ups are carried out such as hearing tests, vision tests, lung function tests, x-ray investigations of the chest, ECG, and tests on olfactory nerves. All workers concerned, twice a year.	No negative health effects under regular medical surveillance.	Terakawa, T. (2004), unpublished report (no designation)

Kind of study (e.g. case reports)	**Examination methods, number of individuals examined**	**Results**	**References**
Study on sorbic acid - induced erythemata and oedemata in humans	Up to 17 subjects were tested in different experimental settings.	Sorbic acid concentrations in propan-2-ol/water (50:50) produced transient erythema with oedema and flare after open or closed application to human skin. Reactions were most intense on the face (at as low as 0.05%), but also could be produced on the back, forearm, and deltoid areas. 100 % of sites treated on upper back with 1 % sorbic acid displayed intense reactions.	Soschin, D., Leyden J.J. (1986), J. Acad. Dermatol. 14, 234-241 (published)
Review on the etiology of immediate contact reactions in the skin, including non-immunological contact urticaria	Not applicable	Sorbic acid is among the most potent and best studied substances causing non-immunological contact reactions.	Lahti, A., Maibach, H.I. (1987), Sem. Dermatol. 6, 313-320 (published)
Mechanistic study on mediators for skin reactions caused by sorbic acid	4 human volunteers	Slight erythemata were elicited by 0.1%, maximum skin reactions by 1% sorbic acid dissolved in propan-2-ol/water (50:50). The cutaneous vasodilation that occurs following the administration of sorbic acid is primarily due to a release of prostaglandin D_2 from a cellular source in the skin.	Morrow, J.D. et al. (1994), Arch. Dermatol. 130, 1408-1412 (published) Roberts, L.J., Morrow, J.D. (1997), Contact Urticaria Synd. 1997, 77-88 (published)
Extensive study on non-immunological contact urticaria (NICU) caused by sorbic acid a. o.	A) <u>Course of reactions (open test)</u>: 103 subjects (29 atopics and 74 non-atopics) B) <u>Effects of vehicles (chamber test method):</u> 26 subjects (13 atopics and 13 non-atopics)	A) Most of the skin reactions in the open test to 2.5% sorbic acid in petrolatum appeared within 45 min and disappeared within two hours. No significant differences were found in the frequency or strength of the NICU reaction between atopics and non-atopics. Contact urticarial reactions: Atopics: 20/29 (69 %) Non-atopics: 40/74 (54 %) B) Sorbic acid elicited reactions most easily in water and, in decreasing order, in water/oil emulsion, petrolatum, and oil/water emulsion. The lowest concentrations of sorbic acid eliciting wheal and flare reactions were 0.050% in water, 0.10% in W/O emulsion, 0.25% in petrolatum, and 0.50% in O/W emulsion.	Lahti, A. (1980), Acta Derm. Venereol. 60, Suppl. 91, 1-49 (published)
Human assay for NICU	3 panels of 12 subjects each	Depending on concentration, mild to strong reactions were observed for sorbic acid.	Gollhausen, R., Kligman, A.M. (1985), Contact Dermatitis 13, 98-106 (published)

Kind of study (e.g. case reports)	**Examination methods, number of individuals examined**	**Results**	**References**
Review on contact dermatitis as a reaction to some commonly used preservatives	50 patients	In more than half of the patients, brisk erythema could be produced on the forearms with 5% sorbic acid in petrolatum	Fisher, A.A. (1980). Cutis 26, 136-148 (published)
Case study	18 nursery school children (accidentally exposed to sorbic and benzoic acid-containing salad periorally) and 10 adults + 2 children (exposed deliberately to serve as reference group)	Sorbic acid (and benzoic acid) caused perioral contact urticaria in the majority of patients/probands.	Clemmensen, O., Hjorth, N. (1982), Contact Dermatitis 8, 1-6 (published)
Case report on occupational contact dermatitis from potassium sorbate in milk transformation plant	Patch test for allergenicity performed with 2% sorbic acid pet. after recovery from dermatitis; readings at days 2, 4, 7 Subsequent ROAT (repeated open application test) performed with 2% sorbic acid pet.	35-year-old man, exposed to airborne potassium sorbate powder, developed severe dermatitis at exposed skin areas. A weakly positive test reaction to sorbic acid in patch testing on day 7 was not confirmed by repeated testing (ROAT), “strongly suggesting irritant role of powdery potassium sorbate in the dermatitis”.	Le Coz, C.J, Abensour, M. (2005), Contact Dermatitis 53, 176-177 (published)
Patch test allergenicity study with 5% sorbic acid in petrolatum	100 subjects	1 out of 100 subjects exposed to sorbic acid displayed a positive reaction.	Fisher, A.A. et al. (1971), Arch. Derm. 104, 286-290 (published)
Patch test allergenicity study with 2.5% sorbic acid in Eucerin	1537 subjects	49 patients (3.2%) were tested positive	Klaschka, F. (1966), Fette - Seifen - Anstrichmittel 9, 756-760 (published)
	A subgroup of 736 patients with eczema (subgroup of the 1537 subjects mentioned above)	16 patients with contact eczema, 3 patients with allergic contact eczema	Klaschka, F., Beiersdorff, H.U. (1965), Münch. Med. Wschr. 107, 185-188 (published)
Patch test allergenicity study with 2.0% sorbic acid in petrolatum	11437 subjects	85 positive cases (0.7%) and another 93 with questionable result, but signs of irritation	Schnuch, A. et al. (1998), Brit. J. Dermatol. 138, 467-476 (published)
Patch test allergenicity study with 2.5% sorbic acid in petrolatum	627 subjects	2 positives (0.3%)	DeGroot, A.C. et al. (1986), Contact Dermatitis 14, 120-122 (published)
Patch test allergenicity study with sorbic acid	2912 subjects, patches were applied for 2 consecutive days and read on days 2 and 4.	20 positives (0.7%), of which 7 had a negative day 2 reading	Shehade, S.A. et al. (1991), Contact Dermatitis 24, 119-122 (published)
Patch test allergenicity study with 2.0% sorbic acid in petrolatum	2852 subjects	7 positives. Sensitisation via daily use of cosmetic was accomplished at concentrations as low as 0.15%.	Ramsing, D.W., Menné, T. (1993), Contact Dermatitis 28, 124-125 (published)

Kind of study (e.g. case reports)	**Examination methods, number of individuals examined**	**Results**	**References**
Patch test allergenicity study with sorbic acid (up to 10%)	1489 subjects	5 clear, 5 dubious positives, poor documentation	Hjorth, N., Trolle-Lassen, C. (1962), American Perfumer 77, 43-46 (published)
Retrospective study on patch test data with 2.0% sorbic acid in petrolatum	2044 subjects	9 positives (0.44 %)	Brasch, J. et al. (1993), Dermatosen 41 (2), 71-76 (published)
Patch test allergenicity study with 2.5% sorbic acid in petrolatum	606	5 positives (0.8%)	Hannuksela, M. et al. (1976), Contact Dermatitis 2, 105-110 (published)
Patch test allergenicity study with sorbic acid	1000 subjects	6 positives (0.6%)	Brun, R. (1975), Contact Dermatitis 1, 214-217. (published)
Patch test allergenicity study with 5% sorbic acid	776 subjects	8 positives (1.0%)	Iden, D.L., Schroeter, A.L. (1977), Contact Dermatitis 3, 122-126 (published)
Reviews on 'burning mouth syndrome'	Not applicable	Some patients with burning mouth syndrome were reported to have been tested positively in patch tests with sorbic acid.	Huang, W. et al. (1996), J. Am Acad. Dermatol. 34, 91-98 (published) Tourne, L.P.M., Fricton, J.R. (1992), Oral Surg. Oral Med. Oral Pathol. 74, 158-167 (published)
Patch test allergenicity study (among other tests) / Case study on a patient tested positive	33 type 3 burning mouth syndrome patients	1 patient tested positive with sorbic acid (and propylene glycol) who was rendered asymptomatic by dietary avoidance.	Lamey, P.-J. et al. (1994), J. Oral Pathol. Med. 23, 216-219 (published) Lamey, P.-J. et al. (1987), Contact Dermatitis 17, 242-243 (published)
Case study	1 patient with burning mouth syndrome	The patient tested positive with sorbic acid and potassium sorbate (both 2% in petrolatum) in the patch test (also positive for benzyl and propyl nicotinate).	Haustein, U.-F. (1988), Contact Dermatitis 19, 225-226 (published)
Patch test allergenicity study in the buccal mucosa, using 5 or 10% sorbic acid in water	11 subjects	Signs of erythema/oedema, but unclear results regarding sensitisation	Clemmensen, O.J., Schiodt, M. (1982), Contact Dermatitis 8, 341-342 (published)

Kind of study (e.g. case reports)	Examination methods, number of individuals examined	Results	References
Oral challenge study with food additives (incl. sorbic acid)	101 patients suspected of food-related dermatitis	Test design turned out to be inadequate to detect reactions to specific food additives.	Veien, N.K. et al. (1987), Contact Dermatitis 17, 100-103 (published)
Patch test allergenicity study with 2.5% sorbic acid in vaseline	25 patients with suspected allergic periorbital eczema	3 patients tested positive for sorbic acid	Maucher, O.M. (1974), Klin. Mbl. Augenheilk. 164, 350-356 (published)
Literature review on cases of contact dermatitis caused by allergy to ophthalmic drugs and contact lens solutions	Not applicable	6 cases reported with contact conjunctivitis (2.0% and 5% sorbic acid), 3 displaying contact dermatitis (2.5% sorbic acid)	Herbst, R.A., Maibach, H.I. (1991), Contact Dermatitis 25, 305-312 (published) Herbst, R.A., Maibach, H.I. (1992), Akt. Dermatol., 18, 36-40. (published)
Review on type IV allergy against ingredients of ophthalmica	Not applicable	No specified results for sorbic acid	Riedl, B. et al. (1991), Klin. Mbl. Augenheilk. 198, 251-254 (published)
Patch test allergenicity and contact urticaria study with acrylate and contact lens solution test batteries	20 patients with contact lens intolerance	No positive delayed reactions observed in allergenicity patch test with sorbic acid (5% in petrolatum) 5 patients showed contact urticaria following application of sorbic acid onto intact and abraded skin for 30 minutes.	Podmore, P., Storrs, F.J. (1989), Contact Dermatitis 20, 98-103 (published)
Patch test allergenicity study with ingredients of contact lens solutions	8 patients with pruritic conjunctivitis as a consequence of using contact lens solutions	1 patient patch-tested positive for sorbic acid (2% in petrolatum)	Fisher, A.A. (1985), Cutis 85, 209-211 (published)
Patch test allergenicity study with 2% sorbic acid in petrolatum	100 subjects with various forms of conjunctivitis	No positives	Rudzki, E. et al. (1995), Contact Dermatitis 33, 270 (published)
Study of adverse ocular reactions in patients using contact lens care solutions containing sorbic acid	135 subjects	15% of the patients reported symptoms such as stinging on insertion of lenses, dryness, irritation, redness, and/or showed signs of corneal staining, limbal vessel dilation, epithelial infiltrates or hyperaemia.	Josephson, J.E., Caffery, B. (1986), J. Am. Optometric Ass. 57 (3), 188-189 (published)

Three reports from production plants were submitted concerning the regular medical surveillance of production staff handling potassium sorbate. No negative impact on workers was observed in two of these examinations. However, one report (Astvad, 2004, cf. above table) states that “Irritation from eyes, skin and respiratory passages were seen when working with sorbic acid” at a potassium sorbate production plant. This experience is also further discussed under section 5.9.1.1 as part of a weight of evidence approach, which forms the basis for the proposal to classify potassium sorbate as a skin irritant.

A multitude of publications was submitted regarding medical experience with topical applications/exposure to/of human skin and eyes, particularly to sorbic acid. For local dermal effects, two main ways of toxic action, resulting either in non-immunological (irritant) contact urticaria or immunological contact reactions, are discussed.

5.9.1.1 Non-immunological contact urticaria (NICU)

Transient, but nevertheless intense erythema and oedema are regularly evoked by sorbic acid when applied to human skin in various parts of the body. Sorbic acid and its salts are capable of causing non-immune immediate contact reactions (NIICR) and non immunologic contact urticaria (NICU). Per definition, non-immunologic immediate contact reactions are considered irritant reactions (Lahti & Basketter, 2006). While immunologic (allergic) contact reactions involve specific IgE antibodies, NIICR of the skin are dose-dependent inflammatory reactions that occur within a short time of contact with the eliciting substance, without requiring previous sensitisation. These non-immunologic contact reactions typically remain localised without becoming systemic. Susceptibility of the exposed individuals may vary widely. Contact reactions may involve development of erythema, oedema or appearance of wheals (Lahti & Basketter, 2006). It is assumed that vasoactive substances are involved in mediating these effects.

Sorbic acid belongs to the most potent and best studied substances causing immediate non-immunologic contact reactions. Under optimal conditions, the majority (more than half) of subjects develop skin reactions within 45 minutes of topical application, with symptoms typically resolving within a few hours (Lahti 1980, Lahti and Maibach, 1987). For example, application of 2.5 % sorbic acid in petrolatum according to an open test procedure led to reactions in 58 % of the test subjects, the frequency in reactions being similar between atopic and non-atopic subjects (Lahti 1980). In the study by Soschin & Leyden, 1986, 100 % of sites treated on the upper backs with 1 % sorbic acid developed intense reactions.

Reactions have been observed with sorbic acid concentrations as low as 0.05-0.1% (Lahti 1980; Soschin & Leyden, 1986; Morrow et al., 1994), the sensitivity also clearly depending on the site of application (Soschin & Leyden, 1986).

An immunological mechanism appears less likely for these rapid skin reactions, also because no systemic reaction has been observed in the respective patients. Histological investigation of skin biopsies of subjects topically exposed to sorbic acid did not reveal significant involvement of mast cell degranulation (Soschin & Leyden, 1986). Acetylsalicylic acid (Aspirin) was found to block the erythematous, but not the oedematous reaction caused by sorbic acid, indicating that prostaglandins might play a role in mediating at least the erythematous reaction (Soschin & Leyden, 1986). Additional mechanistic evidence has been presented that the release of vasoactive prostaglandin D2 from a cellular source in the skin is involved in erythema development in response to sorbic acid (Morrow et al., 1994; Roberts & Morrow, 1997).

Sorbic acid is the corresponding acid to potassium sorbate. Since protonated sorbic acid and sorbate anion are in equilibrium in solutions and the concentration of non-dissociated in relation to dissociated form depends on the pH, the results obtained for sorbic acid can generally be extrapolated to potassium sorbate. This is supported by a case report (Le Coz & Abensour, 2005), in which an individual developed severe contact dermatitis as a result of occupational exposure to potassium sorbate powder. Based on the outcome of subsequent patch testing with sorbic acid, the authors of this report suggested an irritant mechanism as underlying cause for the preceding reaction to potassium sorbate.

Classification/labelling, based on human data:

Potassium sorbate was not found to be irritant in the Draize skin test with rabbits (cf. section 5.3.1). Following a weight of evidence approach, however, practical observations in humans are regarded by the RMS to sufficiently justify classification/labelling of potassium sorbate with Xi; R38 ("irritating to skin") according to Dir. 67/548/EEC. Existing experience and data for humans are also considered consistent with classification/labelling as Skin Irrit 2/H315: "Causes skin irritation" in accordance with the CLP Regulation. Evidence from human data is based on a number of publications on the potential of sorbic acid to elicit non-immunologic contact (irritant) reactions in humans, the case report regarding development of contact dermatitis under potassium sorbate (Le Coz & Abensour, 2005) and the findings in the medical surveillance report on workers exposed to sorbic acid in a potassium sorbate production facility (Astvad, 2004).

5.9.1.2 Immunological contact urticaria

In rare cases, also true allergic eczematous reactions to sorbic acid were observed in patch test allergenicity studies (cf. table 15). However, even in large collectives of some thousands of patients the number of positive patch test results rarely exceeded 1%. Given the almost ubiquitous pre-exposure with sorbic acid via food or cosmetics, these findings indicate at most a very weak sensitising potential of sorbic acid, which would not call for classification and labelling as a sensitiser.

5.9.1.3 Burning mouth syndrome

Burning mouth syndrome involves oral discomfort, i. e. burning sensations within the mouth and of the tongue, in the absence of evident mucosal abnormalities (Lamey, 1994; Huang et al., 1996). From the data submitted with this dossier, it appears that the etiology of this syndrome is, at present, not completely understood. Several factors seem to contribute to the syndrome, for example, peri- and postmenopausal women appear to be affected more often (Huang et al, 1996). Some of the patients displaying "burning mouth syndrome" were tested positive for sorbic acid (Haustein, 1988; Lamey et al., 1994) or potassium sorbate (Haustein, 1988) in epicutaneous allergenicity patch tests. Dietary avoidance of sorbic acid has been reported to bring relief in a patient tested positive with sorbic acid (Lamey et al., 1994). These data indicate that, in a small subset of patients suffering from burning mouth syndrome, the burning sensation may represent a reaction to one or more food additives, e. g. sorbic acid. In any case, due to the oral exposure route involved in this effect, this is not seen as being especially relevant in the context of the current dossier.

5.9.1.4 Ocular effects

Adverse ocular reactions, including contact conjunctivitis, transient stinging, irritation, redness and corneal staining, have been reported in individuals using ophthalmic drugs or contact lens care solutions containing sorbic acid as a preservative (Josephson & Caffery 1986; Herbst & Maibach 1991; Herbst & Maibach, 1992). Principally, immunological/allergic reactions may be considered as underlying mechanisms. The data reviewed within this dossier indicates that delayed type reactions to sorbic acid as tested via the patch allergenicity assay may be rarely linked to contact conjunctivitis. While patch testing of 100 subjects with various forms of conjunctivitis yielded no positive reactions to sorbic acid (Rudzki et al., 1995), a single case of positive patch testing for sorbic acid among 8 contact lens users affected by conjunctivitis has been described by Fisher (1985). Other underlying mechanisms should therefore be considered for eye effects, including those responsible for manifestation of non-immunological contact dermatitis. An irritating potential of sorbic acid to the human eye would be in accordance with the eye-irritating properties of

potassium sorbate that have been reported in the corresponding animal experiment (Hofmann & Jung, 1987), and which are presented as the basis for the proposal for classification/labelling of potassium sorbate as an eye irritant (cf. section 5.3.2).

5.10 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

Not relevant for this type of dossier

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6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

6.1 Explosivity

No experimental data on explosive properties:

Testing can be waived based on a consideration of the chemical structure in accordance with REACH Column 2 of Annex VII, section 7.11:

The classification procedure needs not to be applied because there are no chemical groups present in the molecule which are associated with explosive properties.

No classification for explosivity is proposed.

6.2 Flammability

Experimental data on flammability upon ignition for solids and the relative self-ignition temperature for solids:

In a standard study according EC method A.10 (Franke, J, 2003) report no. 20030852.01) Potassium sorbate could be ignited with a flame and then burned over a distance of 10 mm during 50 seconds, after which the flame went out. In a standard study according EC method A.16 (Franke, J, 2003) report no. 20030852.01 the relative self-ignition temperature for solids is 178 °C.

No experimental data on flammability in contact with water and pyrophoric properties:

Testing can be waived based on a consideration of the chemical structure in accordance with REACH Column 2 of Annex VII, section 7.10.
Flammability in contact with water: The classification procedure needs not to be applied because the organic substance is known to be soluble in water to form a stable mixture.
Pyrophoric properties: The classification procedure needs not to be applied because the organic substance is known to be stable into contact with air at room temperature for prolonged periods of time (days).

No classification for flammability is proposed.

6.3 Oxidising potential

No experimental data on oxidising properties:

Testing can be waived based on a consideration of the chemical structure in accordance with REACH Column 2 of Annex VII, section 7.13.
The classification procedure needs not to be applied because the organic substance contains oxygen, which is chemically bonded only to carbon. Based on known experience of BAM II.2 in handling with similar organic substances the oxidising properties can be excluded.

No classification for oxidising properties is proposed.

7 ENVIRONMENTAL HAZARD ASSESSMENT

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

7.1.1.1 Fish

Short-term toxicity to fish

Guideline /Test method	Species	Endpoint / Type of test	Exposure		Results	Remarks	Reference
			design	duration			
OECD 203 EC C.1 (92/69/EEC)	*Oncorhynchus mykiss*	mortality	static	96 h	LC_0 = 1000 mg/l LC_{50} > 1000 mg/l LC_{100}> 1000 mg/l	Measured conc. > 80 % of nominal	Staebler, D. (2004)a; report no. 20031274/01-AAOm

From the available data it can be concluded that potassium sorbate did not induce mortality in fish up to concentrations of 1000 mg/l.

Long-term toxicity to fish

No information available.

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

Guideline /Test method	Species	Endpoint / Type of test	Exposure		Results	Remarks	Reference
			design	duration			
OECD 202 EC C.2 (92/69/EC)	*Daphnia magna*	immobilisation	static	48 h	EC_0 = 804 mg/l EC_{50} = 982 mg/l EC_{100} > 1000 mg/l	measured conc. > 80 % of nominal	Staebler, D. (2004)b; report no. 20031274/01-AADm

From the available data it can be concluded that potassium sorbate exhibits a low acute toxicity to invertebrates with a 48h-EC_{50} of 982 mg/l.

Long-term toxicity to aquatic invertebrates

No information available.

7.1.1.3 Algae and aquatic plants

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results	Remarks	Reference
			design	*duration*			
OECD 201	*Desmodesmus subspicatus*	Growth inhibition	Static	48 h	NOEC = 97 mg/l ErC50 = 480 mg/l	analytical monitoring showed decrease in TS concentration over the exposure period; test result related to mean measured conc.	Dengler, D. (2005); report no. 20051092/01-AADs

An algae growth inhibition study with potassium sorbate as test substance and *Desmodesmus subpicatus* is available. The growth of the control cultures did not show an exponential pattern over the whole exposure period of 72 h. Growth was monoton exponential between 0 and 48 h, but the curves deviate from exponential growth after this time period. The mean coefficient of variation for section-by-section specific growth rates was about 53 % and thus well above the value of 35 % given in the updated OECD 201 (2006). Possible reasons for this decline may be nutrient limitation due to rather high growth rates of algae at the first 48 h of the test.

To allow the estimation of algae growth inhibition by potassium sorbate, it is proposed to evaluate the available study for an exposure period of 48 instead of 72 h. This seems acceptable based on the overall low ecotoxicity of potassium sorbate.

The concentration course in test medium during the main test showed that the test item was not stable over the period of the test and decreased below 80 % of nominal. Therefore, effect values are based on mean measured concentrations for 4 concentration levels. For the considered exposure period of 48 h the geometric mean of the recoveries for the 4 concentration levels was 77.5 %. Therefore, the nominal concentrations are corrected with this mean recovery.

After 48 h the inhibition in growth rate at the highest concentration (500 mg/l nominal) was < 50 % (about 38 %). Using probit analysis a 48 h-E_rC_{50} of 620 mg/l (nominal) was derived. The 48 h-NOEC for growth rate inhibition was found to be 125 mg/l (nominal). Applying the recovery of 77.5 % results in a 48 h-E_rC_{50} of 480 mg/l and a 48 h-NOEC of 97 mg/l.

7.2 Terrestrial compartment

Not relevant for this type of dossier.

7.3 Atmospheric compartment

Not relevant for this type of dossier.

7.4 Microbiological activity in sewage treatment systems

Not relevant for this type of dossier.

7.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC_oral)

Not relevant for this type of dossier.

7.6 Conclusion on the environmental classification and labelling

Sorbic acid is readily biodegradable with a ThOD removal of 75 % within 28 days fulfilling the 10-day window.

Potassium sorbate has a log K_{ow} of –1.72 (at pH = 6.5) and 1.32 (at pH = 2.5). No BCF study is available.

The acute toxicity of potassium sorbate to aquatic organisms is above the trigger value of 100 mg/L.

Conclusion of environmental classification according to Directive 67/548/EEC

In acute aquatic toxicity studies, all effect values are above 100 mg/L. Potassium sorbate is readily biodegradable and the log K_{ow} is below the trigger value of 3 thus indicating a low potential for bioaccumulation. Therefore, an environmental classification and labelling according to Directive 67/548/EEC is not required.

Conclusion of environmental classification according to Regulation (EC) 1272/2008

In acute aquatic toxicity studies, all effect values are above 100 mg/L. Potassium sorbate is readily biodegradable and the log K_{ow} is below the trigger value of 4 thus indicating a low potential for bioaccumulation. Therefore, an environmental classification and labelling according to Regulation (EC) 1272/2008 is not required.

JUSTIFICATION THAT ACTION IS REQUIRED ON A COMMUNITY-WIDE BASIS

There was agreement on Community Level that for active ingredients in biocidal and plant protection products harmonised C & L should be sought for all phys.-chem., toxicological, and ecotoxicological endpoints addressed by the corresponding legislations.

OTHER INFORMATION

The data and conclusions presented here have already undergone a peer review by experts from the company applying for Annex I inclusion, the European Member States, and the European Commission (ECB) in the context of the inclusion procedure for potassium sorbate into Annex I of Dir. 98/8/EC.

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