Committee for Risk Assessment

RAC

Annex 1
Background document
to the Opinion proposing harmonised classification and labelling at EU level of
potassium sorbate

EC number: 246-376-1
CAS number: 24634-61-5

CLH-O-0000002524-78-03/A1

Adopted
6 March 2013

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PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

Substance Name: **Potassium sorbate**

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

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

Registration number (s):

Purity: > 99 % w/w

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

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

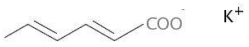
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

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 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 hexa-2,4-dienoate
Molecular Formula:	$C_6H_7KO_2$
Structural Formula:	



Molecular Weight:	150.22 g/mol
Typical concentration (% w/w):	≥ 99
Concentration range (% w/w):	99 – 100

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) Flammability in contact with water Pyrophoric properties	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)] not conducted (Testing can be waived)[2)] not conducted (Testing can be waived)[3)]	Franke, J (2003) report no. 20030852.01 BAM-II.2 (2010) 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 according to GHS

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 with Xi; R36 (according to the criteria of Annex VI of Dir. 67/548/EEC as last amended).

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 parameter	Inoculum			Additional substrate	Test substance conc.	Degradation		Reference
			Type	Concen-tration	Adaptation			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	Refer
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	Leusch J. (20 unpub report 16706

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, based on experience in humans (cf. section 5.9) classification/labelling as skin irritant is proposed

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

The CLH report included a Draize test conducted in rabbits (OECD 404) with 3333 mg/ml potassium sorbate (potassium (2E, 4E)-hexa-2,4-dienoate), purity > 99%) in 0.9% aqueous NaCl, vehicle solution (Hofman, 1987) that was found to be non-irritant. The DS based the justification for classification of the skin irritation effects of potassium sorbate by reading-across from sorbic acid and associated human skin reactions i.e NICU (non-imunological contact urticaria) extensively referenced in the CLH report, as well as a human case report on the development of contact dermatitis from exposure to airborne potassium sorbate powder (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). These positive skin reactions and effects reported in referenced sources mentioning sorbic acid as a potent contact skin irritant were extrapolated to the substance of interest, potassium sorbate, and considered as part of the weight of evidence approach justifying the classification for irritation

Therefore based on experience in humans, the dossier submitter proposes a classification for potassium sorbate as Skin Irrit. 2 – H315 under the CLP Regulation (Xi; R38 according to DSD).

Comments received during public consultation

Comments were received from three Member States, supporting the proposed classification for skin irritation.

Assessment and comparison with the classification criteria

RAC noted several issues of concern regarding the classification proposed.

- The reliability of the human studies on the potassium sorbate was uncertain, i.e. Le Coz et Abensour (2005) was not very well documented specifically regarding exposure. For Astvad (2004), it was not possible to gain access to the unpublished document.
- The proposed classification as skin irritant appears to have already been

implemented by industry
- The read across of potassium sorbate from sorbic acid may be questionable
- Hofmann, T (1987,unpublished) performed a Draize test according to OECD guidelines 404 using 3333 mg/ml potassium sorbate in 0,9% aqueous NaCl, in 3 albino New Zealand rabbits (sex not mentioned). After 24h and 48 h, no erythema and oedema were observed and the authors concluded that potassium sorbate was not irritating.

The justification for the classification as Skin Irrit. 2 – H315 proposed by the DS is based on human data with sorbic acid and extrapolation to potassium sorbate.

The RAC pointed out that direct comparison with the classification criteria as referred to in table 3.2.2. of Annex I to the CLP Regulation, is not possible for human data. However, he use of human data is discussed in general in paragraphs 1.1.1.3., 1.1.1.4., 1.1.1.5. of Annex I to the CLP Regulation where it is mentioned that all available information on the determination of hazard should be considered together (WoE), such as animal data, category approach (read-across, grouping), human experience such as occupational data, clinical studies, well documented case reports and observations, so that negative and positive findings shall be assembled together in a single weight of evidence determination. It is also stated that adequate, reliable and representative data on humans shall have precedence over other data. However, it is also mentioned that the quality and robustness of these studies need to be evaluated i.e. including confounding factors as well as the relevance for humans in terms of route of exposure and mechanism of action. The CLP Regulation also recommends that human data be evaluated with caution because these are not generated under controlled conditions for the purpose of hazard classification but rather as part of the risk assessment to confirm lack of effects seen in animal tests.

Taking all the information available in the dossier together, the RAC considered that:

- reading-across from the free acid to the sorbate anion can be generally accepted. However concerning the specific endpoint of skin irritation, consideration has to be given to the Draize study with rabbits performed with potassium sorbate according to OECD 404 and which showed negative results.
- the reliability of the human cases reported with potassium sorbate (Le Coz & Abensour, 2005) is insufficient, namely in relation to the accurate identification of the substance of interest, description of the exposure conditions and assessment of confounding factors (i.e. moistened skin, mixed exposure). This leads to uncertainty as to whether and to what extent the effect (NICU contact dermatitis) and its magnitude can be reliably attributed to the intrinsic properties of potassium sorbate.
- as a charged molecule, potassium sorbate is expected to penetrate the skin less readily. Therefore read-across from sorbic acid skin irritation effects is considered to overestimate the hazard.

Considering the above weight-of-evidence, RAC concluded that the criteria for classification of potassium sorbate for skin irritant effects are not met and that no classification is warranted.

5.3.2 Eye

Table 8: Summary of eye irritation studies

Method/ Guideline	Species, Strain, Sex, No/group	Average Score 24, 48, 72h				Reversi-bility yes/no	Results	Classification, Remarks	Refe
		Cornea opacity	Iris	Redness Conjunc-tiva	Chemosis				
OECD 405	Rabbit, albino New Zealand 3 (sex not mentioned)	0.4	0.4	1.6	2.1	Yes (within 21 days)	Irritating	R36 Performed using potassium sorbate without further vehicle	Hofm T. (19 repor 87.05

Potassium sorbate proved to be irritating to the eyes of rabbits. Since the observed eye reactions were of a moderate degree and were fully reversible within 21 days, classification/labelling as 'irritating to eyes' but not as 'causing serious eye damage' is proposed.

RAC evaluation of eye irritation

Summary of the Dossier submitter's proposal

The DS proposed classification as Eye Irrit. 2 – H319 - "irritating to eyes" according to CLP (Xi; R36 according to DSD) for potassium sorbate based on the OECD 405 animal study by Hofmann & Jung, 1987. The ocular lesions observed are described below.

Comments received during public consultation

Comments were received from three Member States, supporting the proposed classification for skin irritation.

Assessment and comparison with the classification criteria

The justification for classification as "irritating to eyes" Xi; R36 under DSD and Eye irrit 2; H319 under CLP was obtained from the rabbit study by Hofmann & Jung, 1987, with potassium sorbate without a vehicle and with wash-out 24h after application, where the eye irritant effects observed showed a positive reaction in terms of conjunctival redness (individual scores > 2) and conjunctival oedema (individual scores ≥ 2) for 2 of 3 and 3 of 3 test animals, respectively. These ocular lesions were reversible within 21 days following application. Therefore, they did not trigger the more stringent classification of Eye Dam. 1.

RAC agrees with the dossier submitter's proposal to classify potassium sorbate as Eye irritant 2 –H319 under CLP (Xi: R36 under DSD).

5.3.3 Respiratory tract

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

5.3.4 Summary and discussion of irritation

The following classification/labelling for local irritation is proposed:

Xi; R36/38

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 sorbic acid in physiol. saline	Maurer, T. (1979); Contact Dermatitis 5, 1–10

According to the criteria of Annex VI to Dir. 67/548/EEC, potassium sorbate displayed no skin-sensitising potential in a modified guinea pig maximisation test, since the proportion of animals with positive skin findings resulting from the first, intradermal challenge application was below the threshold for classification (i. e. 30% animals with positive skin reactions). After the second, topical challenge, the proportion of animals showing skin irritation was even lower than the first time.

Supplementary to the study mentioned above, additional data reporting human test results are available which support this conclusion (cf. section 5.9).

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. typhi-murium, 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

Method/ Guideline	Test system (Organism, strain)	Concentra-tions tested (give range)	Results		Remarks	Reference
			+ S9	- S9		
No guideline indicated Non-GLP	Bacterial reverse mutation assay (S. typhi-murium, 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 submitted by the applicant	Fujita, H., Sasaki, M. (1986), Ann. Rep. Tokyo. Metr. Res. Lab. P.H. 37, 447 – 452
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).

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), 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).
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).

Method/ Guideline	Test system (Organism, strain)	Concentra-tions tested (give range)	Results		Remarks	Reference
			+ S9	- S9		
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 micronucleus test	Mouse, NMRI, 5/sex/group Bone marrow	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*
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 (chromo-some 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 hydroxyl-propyl 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)

Kind of study (e.g. case reports)	**Examination methods, number of individuals examined**	**Results**	**References**
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)
Study on sorbic acid - induced erythemata and oedemata in humans	Up to 17 subjects were tested in different experimental settings.	Sorbic acid concentrations as low as 0.1% produced transient erythema with oedema and flare after open or closed application to human skin. Reactions were most intense on the face but also could be produced on the back, forearm, and deltoid areas.	Soschin, D. et al. (1986), J. Acad. Dermatol. 14, 234-241 (published)

Kind of study (e.g. case reports)	**Examination methods, number of individuals examined**	**Results**	**References**
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	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)	26 subjects (13 atopics and 13 non-atopics)	Most of the skin reactions in the open test to 2.5% sorbic acid appeared within 45 min and disappeared within two hours. 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)
Patch test allergenicity study	100 subjects	1 out of 100 subjects exposed to 5% sorbic acid in petrolatum displayed a positive reaction.	Fisher, A.A. et al. (1971), Arch. Derm. 104, 286-290 (published)

Kind of study (e.g. case reports)	**Examination methods, number of individuals examined**	**Results**	**References**
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 concentr-ations as low as 0.15%.	Ramsing, D.W., Menné, T. (1993), Contact Dermatitis 28, 124-125 (published)
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	Brasch, J. et al. (1993), Dermatosen 41 (2), 71-76 (published)

Kind of study (e.g. case reports)	**Examination methods, number of individuals examined**	**Results**	**References**
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	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)

Kind of study (e.g. case reports)	**Examination methods, number of individuals examined**	**Results**	**References**
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)
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)
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)
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 (0.5 and 2.0% 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)

Kind of study (e.g. case reports)	Examination methods, number of individuals examined	Results	References
Patch test allergenicity and contact urticaria study with acrylate and contact lens solution test batteries	20 patients with contact lens intolerance	6 patients with contact urticaria following application of sorbic acid onto intact and abraded skin.	Podmore, P., Storrs, F.J. (1989), Contact Dermatitis 20, 98-103 (published)
Case study	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	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)
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)

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. Based on this experience and in accordance with Annex VI of Directive 67/548/EEC, the applicant under Dir. 98/8/EC proposed to classify potassium sorbate as 'irritating to the skin' and label it with the risk phrase 38, which is supported by the RMS.

A multitude of publications was submitted regarding medical experience with topical applications/exposure of human skin and eyes to sorbic acid and its salts. Four main ways of toxic action were identified:

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. While not proven in a narrow sense,

some mechanistic evidence was presented, that these skin reactions are mediated by release of vasoactive substances (mainly prostaglandin D_2). An immunological, T-cell mediated mechanism is ruled out, also because no systemic reaction has been observed in the respective patients.

Together with the findings in the medical surveillance report described above, and in accordance with the view of the applicant, these results are regarded by the RMS to provide sufficient evidence to justify labelling potassium sorbate with R38 ('irritant to the skin').

5.9.1.2 Immunological contact urticaria

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.

5.9.1.3 Burning mouth syndrome

From the data submitted with this dossier, it appears that the etiology of this syndrome is, at present, not completely understood. Some of the patients displaying 'burning mouth syndrome' were tested positive for sorbic acid in epicutaneous patch tests. Dietary avoidance of sorbic acid brought relief in some cases. Other confounding factors seem to contribute to the syndrome (e.g. women after the menopause are affected more often). 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

In accordance with the irritating properties of sorbic acid to the eye which were reported in the corresponding animal experiment, conjunctival contact sensitivity was observed in individuals applying contact lens care solutions containing sorbic acid as a preservative.

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

Not relevant for this type of dossier.

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 design	Exposure duration	Results	Remarks	Reference
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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