CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name: Glutaraldehyde

EC Number: **203-856-5**

CAS Number: **111-30-8**

Index Number: **605-022-00-X**

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	glutaral; glutaraldehyde; 1,5-pentanedial
EC number:	203-856-5
CAS number:	111-30-8
Annex VI Index number:	605-022-00-X
Degree of purity:	≥ 48-52 %*
Impurities:	Confidential; No impurity is considered relevant for the classification of glutaraldehyde

* Glutaraldehyde is produced and placed on the market as an aqueous solution containing 50 % glutaraldehyde by weight. If the amount of glutaraldehyde in water exceeds 50 %, a change in composition of glutaraldehyde takes place because of gradual polymerization reaction of glutaraldehyde molecules. The highest concentration in which glutaraldehyde remains stable/monomeric for a long period of time (< 1 year) is 50 % aqueous glutaraldehyde. However, for classification purposes the (eco)toxicological endpoints are expressed as 100 % glutaraldehyde unless stated otherwise.

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation	**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	Acute Tox. 3*; H331 Acute Tox. 3*; H301 Skin Corr. 1B; H314 Resp. Sens. 1; H334 Skin Sens. 1; H317 Aquatic Acute 1: H400	T; R23/25 C; R34 R42/43 N; R50 Conc. limits: T; R25: C ≥ 50%

	SCLs and M-factors: Skin Corr. 1B; H314 : C ≥ 10% Skin Irrit. 2; H315: 0,5% ≤ C < 10% Eye Dam. 1; H318: 2% ≤ C < 10% Eye Irrit. 2; H319: 0,5% ≤ C < 2% STOT SE 3; H335: C ≥ 0,5 % Skin Sens. 1; H317: C ≥ 0,5%	Xn; R22: 2% ≤ C < 50% T; R23: C ≥ 25% Xn; R20: 2% ≤ C < 25% C; R34: C ≥ 10% Xi; R37/38-41: 2% ≤ C < 10% Xi; R36/37/38: 0,5% ≤ C < 2% R43: C ≥ 0,5%
Current proposal for consideration by RAC	Acute Tox 1; H330 Removal of asterisk (*) from Acute Tox 3: H301 Skin Sens. 1A Resp. Sens. 1 STOT SE 3; H335 Aquatic Chronic 2; H411 Supplemental labelling statement: EUH071 SCLs and M-factors: Skin Sens. 1 A: Removal of SCL of 0.5 % STOT SE 3; H335: C ≥ 0,00005 % M-factor M=10 to Aquatic Acute 1	T+; R26 R43: C ≥ 0,5% or C ≥ 0.1%[a)] Xi; R37: C ≥ 0,00005 % N; R50: C ≥ 2,5 %
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox. 1; H330 Acute Tox. 3; H301 Skin Corr. 1B ; H314 Resp. Sens. 1; H334 Skin Sens. 1A; H317 STOT SE 3; H335 Aquatic Acute 1; H400, Aquatic Chronic 2; H411 Supplemental labelling statement: EUH071 SCLs and M-factors: Skin Corr. 1B; H314 : C ≥ 10% Skin Irrit. 2; H315: 0,5% ≤ C < 10% Eye Dam. 1; H318:	T+; R26 T; R25 C; R34 Xi; R37 R42/43 N; R50 Conc. limits: T; R25: C ≥ 50% Xn; R22: 2% ≤ C < 50% C; R34: C ≥ 10% Xi; R38-41: 2% ≤ C < 10% Xi; R36/38: 0,5% ≤ C < 2% Xi; R37: C ≥ 0,00005% R43: C ≥ 0,5% or C ≥ 0.1% [a)]

	2% ≤ C < 10% Eye Irrit. 2; H319: 0,5% ≤ C < 2% STOT SE 3; H335: C ≥ 0,00005 % M=10	N; R50: C ≥ 2,5 %

[a)]It is proposed to either retain the existing SCL of C ≥ 0.5 % or align the SCL with the GCL of 1A (0.1%) according to the CLP criteria. Both options are justified.

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3: Proposed 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	-	-	-	Data conclusive but not sufficient for classification
2.2.	Flammable gases	-	-	-	Data lacking
2.3.	Flammable aerosols	-	-	-	Data lacking
2.4.	Oxidising gases	-	-	-	Data lacking
2.5.	Gases under pressure	-	-	-	Data lacking
2.6.	Flammable liquids	-	-	-	Data conclusive but not sufficient for classification
2.7.	Flammable solids	-	-	-	Data conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	-	-	-	Data conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	-	-	-	Data conclusive but not sufficient for classification
2.10.	Pyrophoric solids	-	-	-	Data conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	-	-	-	Data conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	-	-	-	Data conclusive but not sufficient for classification
2.13.	Oxidising liquids	-	-	-	Data conclusive but not sufficient for classification
2.14.	Oxidising solids	-	-	-	Data conclusive but not sufficient for classification
2.15.	Organic peroxides	-	-	-	Data conclusive but not sufficient for classification
2.16.	Substance and mixtures corrosive to metals	-	-	-	Data conclusive but not sufficient for classification

3.1.	Acute toxicity - oral	Acute Tox. 3: H301	-	Acute Tox. 3*; H301	
	Acute toxicity - dermal	-	-	-	Data conclusive but not sufficient for classification
	Acute toxicity - inhalation	Acute Tox. 1: H330	-	Acute Tox. 3*; H331	
3.2.	Skin corrosion / irritation			Skin Corr. 1B ; H314 Skin Corr. 1B; H314: C ≥ 10 % Skin Irrit. 2; H315: 0,5 % ≤ C < 10 %	
3.3.	Serious eye damage / eye irritation	-		Eye Dam. 1; H318: 2 % ≤ C < 10 % Eye Irrit. 2; H319: 0,5 % ≤ C < 2 %	
3.4.	Respiratory sensitisation	Resp. Sens. 1; H334	-	Resp. Sens. 1; H334	
3.4.	Skin sensitisation	Skin Sens. 1A; H317	Removal of SCL of 0.5 %	Skin Sens. 1; H317 Skin Sens. 1; H317: C ≥ 0,5 %	
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	STOT SE 3; H335	0,00005 %	STOT SE 3; H335: C ≥ 0,5 %	
3.9.	Specific target organ toxicity – repeated exposure	-	-	-	Data conclusive but not sufficient for classification
3.10.	Aspiration hazard	-	-	-	Data conclusive but not sufficient for classification
4.1.	Hazardous to the aquatic environment	Aquatic Acute 1: H400 Aquatic Chronic 2: H411	M=10	Aquatic Acute 1: H400	
5.1.	Hazardous to the ozone layer	-	-	-	Data conclusive but not sufficient for

					classification

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

Labelling: Signal word: Danger
Pictograms: GHS05, GHS06, GHS08, GHS09
Hazard statements: H301, H330, H314, H335, H334, H317, H410
Supplemental hazard statement: EUH071
Precautionary statements: No precautionary statements are proposed since they are not included in Annex VI of Regulation (EC) No 1272/2008

Proposed notes assigned to an entry:

None proposed.

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness	-	-	-	Data conclusive but not sufficient for classification
Oxidising properties	-	-	-	Data conclusive but not sufficient for classification
Flammability	-	-	-	Data conclusive but not sufficient for classification
Other physico-chemical properties *[Add rows when relevant]*	-	-	-	-
Thermal stability	-	-	-	Data conclusive but not sufficient for classification
Acute toxicity	T+; R26 T; R25	Removal of SCLs from acute inhalation toxicity	T; R23/25 T; R25: C ≥ 50 % Xn; R22: 2 % ≤ C < 50 % T; R23: C ≥ 25 % Xn; R20: 2 % ≤ C < 25 %	
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; R37	Xi; R37 C ≥ 0,00005 %	C; R34 C; R34: C ≥ 10 % Xi; R37/38-41: 2 % ≤ C < 10 % Xi; R36/37/38: 0,5 % ≤ C < 2 %	
Sensitisation		R43: C ≥ 0,5 % or C ≥ 0.1%[a)]	R42/43 R43: C ≥ 0,5 %	
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		N; R50 C ≥ 2,5 %	N; R50	

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

[a)]It is proposed to either retain the existing SCL of C ≥ 0.5 % or align the SCL with the GCL of 1A (0.1%) according to the CLP criteria. Both options are justified.

Labelling: Indication of danger: T+, C, N
R-phrases: R26; R25; R34; R37; R42/43; R50
S-phrases: S1/2; S26; S36/37/39; S45; S61

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

The health hazard classification of glutaraldehyde according to Dangerous Substances Directive (DSD) 67/548/EEC was agreed in the Commission Working Group on the Classification and Labelling of Dangerous Substances in July 1995 meeting (ECBI/65/95) and the environmental hazard classification was agreed in the Environmental Effects Group in December 1995 meeting (ECBI/96/95). Glutaraldehyde was included in Annex I of DSD in the 22nd ATP (96/54/EC). In the 29th ATP (2004/73/EC) general environmental concentration limits were added to the N; R50 classification. The classification according to the DSD but without the general environmental concentration limit was transferred into Annex VI of the CLP Regulation.

According to DSD, glutaraldehyde is currently classified for its acute toxic effects via oral and inhalation routes as T; R23/25; for its corrosive effects as C; R34 with specific concentration limits and for its skin and respiratory sensitizing effects as R42/43. The corresponding classifications according to the CLP Regulation are Acute Tox. 3*; H301, Acute Tox. 3*; H331, Skin Corr. 1B; H314 with specific concentration limits, Skin Sens. 1; H317 and Resp. Sens. 1; H334.

Glutaraldehyde is being reviewed as an existing active substance under the Biocidal Products Directive (98/8/EC). The hazards of glutaraldehyde have been assessed by the Finnish Competent Authority as part of the Review Programme. The effects assessment (Document II-A of the Competent Authority Report) was discussed and agreed at the Biocides Technical Meeting III 2011. We consider that following this agreement, it is now an appropriate time to submit a harmonized classification and labelling proposal before the inclusion or non-inclusion to Annex I to Directive 98/8/EC.

The present proposal suggests to add an M-factor of 10 to the Aquatic Acute Category 1 CLP classification. Change of criteria in the 2nd ATP (286/2011) of the CLP Regulation leads to a proposal to classify glutaraldehyde to Aquatic Chronic Category 2. The proposal also includes revision of the acute toxicity classification. Removal of the asterisk from Acute Tox. 3; H301 is proposed as well as tightening the classification for the inhalation route from Acute Tox. 3* to Acute Tox. 1. In addition, data on skin, eye and respiratory tract irritation has been included and based on the data, classification as STOT SE 3; H335 with a SCL of 0,00005 % is proposed. The data on skin and respiratory sensitisation has been included and evaluated considering the new criteria for sub-categorisation of sensitisers in the 2nd ATP (286/2011) of the CLP Regulation. Based on data classification as Skin Sens. 1A and as Resp. Sens. 1 is proposed.

2.2 Short summary of the scientific justification for the CLH proposal

The classification proposal is based on the Document II-A and the Document III-A of the Competent Authority Report (CAR) which are provided in section 13 of the IUCLID file.

The available data on glutaraldehyde supports the revision of the current harmonised CLP classification from Acute inhalation toxicity 3 (H331) to Acute inhalation toxicity 1 (H330). In the inhalation study, a generation system for aerosol is described, but the resulting glutaraldehyde in the air is described as "very fine aerosol < 2.8 µm or as a vapour". This implies that the test atmosphere was a mixture of liquid and vapour phases, and therefore it would be prudent to apply the criteria for vapour. In order to clarify whether the test substance should be considered as aerosol or vapour,

the applicant performed a physical-chemical study mimicking the system used in the inhalation study (Wittmer 2012, BASF A6.01.3_01a). At measured concentrations of 0.224 and 0.349 mg/L, the vapour phase accounted for 65 and 68 % of the glutaraldehyde, respectively, supporting the use of the criteria for vapours. The LC50 values are 0.35 mg/L in male rats and 0.28 mg/L in female rats. These are both < 0.5 mg/L and therefore allocation to Category 1 for inhalation toxicity is appropriate.

The asterisk (*) indicating minimum CLP classification for Acute oral Toxicity 3 (H301) is no longer necessary since the data confirms the classification.

Glutaraldehyde is currently classified as Skin Corr. 1B with specific concentration limits for respiratory tract irritation STOT SE 3; H335: C ≥ 0,5%. This stems from the direct translation of R37 (at specific concentration limits) under Directive 67/548/EEC into the corresponding classification according to the CLP Regulation. However, the presented human and animal data in this CLH report confirm that glutaraldehyde causes respiratory tract irritation also via a specific mechanism, namely sensory irritation. Therefore, classification as STOT SE 3; H335 is proposed based on both corrosivity and sensory irritation in the respiratory tract.

Glutaraldehyde is currently classified as Skin Sens. 1 with a specific concentration limit of C ≥ 0.5% and as Resp. Sens. 1. The data on both skin and respiratory sensitisation has been included and evaluated according to the new criteria in the 2nd ATP. The presented human and animal skin sensitation data allow classification of glutaraldehyde into sub-category 1A. The existing SCL is superfluous to the 0.1% GCL of sub-category 1A and therefore it is proposed to be removed. The presented human data on respiratory sensitisation might be considered pointing towards sub-category 1B, however since the sub-category 1A cannot be excluded glutaraldehyde is proposed to be classified as Resp. Sens 1.

The Finnish CA considered also classification of glutaraldehyde as category 2 mutagen because of the strong *in vitro* evidence, but concluded that the evidence was not sufficient for classification. The *in vivo* genotoxicity studies suffered from the problem of fast reactivity of the test substance which resulted in uncertainty of whether the test substance and/or the reactive metabolites had reached the evaluated target tissue. Results of the *in vivo* studies were clearly negative except for one intraperitoneal micronucleus test, where cytotoxicity and an inconsistent pattern of slight increases in micronucleated polychromatic erythrocytes (PCEs) were seen. The conclusion on mutagenicity is that site of contact mutagenicity remains a possibility that has not been explored by the available mutagenicity studies, but for the purpose of biocide risk assessment the risk to humans was considered sufficiently covered based on the negative results of the carcinogenicity and reproductive toxicity studies. Further mutagenicity testing for the purpose of classification was not considered justifiable.

The lowest aquatic acute toxicity value (0.07 mg/l) confirms the existing environmental hazard classifications (Aquatic Acute 1 according to CLP and N; R50 according to DSD) for glutaraldehyde and gives cause to set an M-factor of 10 to Aquatic Acute 1 classification and corresponding specific concentration limit (N; R50; C >2.5%) to N; R50 classification. The lowest chronic toxicity value 0.025 mg/l with the fact that glutaraldehyde is rapidly degradable leads to Aquatic Chronic 2 classification according to the criteria of the 2nd ATP of the CLP regulation.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Table 5: Current Annex VI Table 3.1 Classification and Labelling

Classification		Labelling		Specific Conc. Limits, M-factors
Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	
Acute Tox. 3 * Acute Tox. 3 * Skin Corr. 1B Resp. Sens. 1 Skin Sens. 1 Aquatic Acute 1	H331 H301 H314 H334 H317 H400	GHS06 GHS08 GHS05 GHS09 Dgr	H331 H301 H314 H334 H317 H400	Skin Corr. 1B; H314 : C ≥ 10% Skin Irrit. 2; H315: 0,5% ≤ C < 10% Eye Dam. 1; H318: 2% ≤ C < 10% Eye Irrit. 2; H319: 0,5% ≤ C < 2% STOT SE 3; H335: C ≥ 0,5% Skin Sens. 1; H317: C ≥ 0,5%

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Table 6: Current Annex VI Table 3.2 classification and labelling

Classification	Labelling	Concentration limits
T; R23/25 C; R34 R42/43 N; R50	T; N R: 23/25-34-42/43-50 S: (1/2-)26-36/37/39-45-61	T; R25: C ≥ 50% Xn; R22: 2% ≤ C < 50% T; R23: C ≥ 25% Xn; R20: 2% ≤ C < 25% C; R34: C ≥ 10% Xi; R37/38-41: 2% ≤ C < 10% Xi; R36/37/38: 0,5% ≤ C < 2% R43: C ≥ 0,5%

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

The existing harmonised classification was notified by a majority of the 1471 notifiers to the Classification and Labelling Inventory. Some notifiers (189; 13 %) classified the substance as Acute Tox. 2; H330 instead of Acute Tox 3*; H331 and 19 (1,3 %) notifiers as Acute Tox 1; H330 instead of Acute Tox 3*; H331. One notifier classified glutaraldehyde as Acute Tox. 4; H312. The EUH071 statement was notified by 45 (3 %) notifiers. STOT SE 3; H335 classification was notified by 94 (6,4 %) notifiers. STOT SE 1; H370 and STOT RE 1; H372 classification was notified by 1 notifier. Skin Sens. 1B and Resp. Sens. 1B classification was notified by 13 (0.9 %) notifiers, the rest of the notifiers classified glutaraldehyde as Skin Sens. 1 and as Resp. Sens. 1.

Aquatic Chronic 2; H411 classification was notified by 2 notifiers and Aquatic Chronic 1; H410 classification by 1 notifier (as the sole environmental classification).

In addition, classification as Met. Corr. 1; H290 was notified by 135 (10 %) notifiers. Seven notifiers classified glutaraldehyde as Flam. Liq. 3.

2.4.2 Current self-classification and labelling based on DSD criteria

Not applicable.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Glutaraldehyde is an active substance in the meaning of Biocidal Products Directive 98/8/EC and therefore subject to harmonised classification and labelling in accordance with Article 36(2) of the CLP Regulation.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

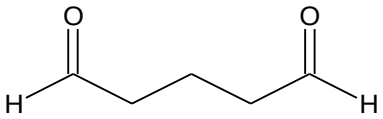
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 7: Substance identity

EC number:	203-856-5
EC name:	glutaral
CAS number (EC inventory):	
CAS number:	111-30-8
CAS name:	pentanedial
IUPAC name:	1,5-pentanedial
CLP Annex VI Index number:	605-022-00-X
Molecular formula:	$C_5H_8O_2$
Molecular weight range:	100.11 g/mol

Structural formula:



1.2 Composition of the substance

Table 8: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
glutaraldehyde	50 %	48-52 %	

Current Annex VI entry:

CLP: Acute Tox. 3*; H301, Acute Tox. 3*; H331, Skin Corr. 1B, Skin Sens. 1 and Resp. Sens. 1., Aquatic Acute 1; H400.

DSD: T; R23/25, C; R34, R42/43, N; R50

Table 9: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Confidential			

There is one impurity which is present at concentration ≤ 0.5 %. This impurity does not affect the classification of glutaraldehyde. The impurity is considered confidential and is therefore not given in this report but only in the IUCLID file and flagged confidential.

Table 10: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
water	stabilizer	50 %	48-52%	

1.2.1 Composition of test material

Glutaraldehyde is produced and placed on the market as an aqueous solution containing 50 % glutaraldehyde by weight. If the amount of glutaraldehyde in water exceeds 50 %, a change in composition of glutaraldehyde takes place because of gradual polymerization reaction of glutaraldehyde molecules. The highest concentration in which glutaraldehyde remains stable/monomeric for a long period of time (< 1 year) is 50 % aqueous glutaraldehyde. However, for classification purposes the (eco)toxicological endpoints are expressed as 100 % glutaraldehyde unless stated otherwise.

1.3 Physico-chemical properties

Table 11: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	Colourless liquid (50% glutaraldehyde)		
Melting/freezing point	Peak maximum ca. – 18 °C Extrapolated onset temperature ca. –33 °C; range about –50 to –15 °C	Schmidt, P. (2002) BASF A3.01.1_01	
	-18 to -21.2 ºC (performed at atmospheric pressure)	McKemie, T.H. (2000a) Dow A3.1.1	
Boiling point	101.5 °C at 987.1 hPa 101.95 °C at 1013.25 hPa 100.7 ºC at 1013 hPa	Siemann, L. (1999) BASF A3.01.2_01 Anonymous (1995) BASF A3.01.2_02 McKemie, T.H. (2000b) Dow A3.1.2	
Relative density	1.129 kg/dm^3	Siemann, L. (1999) BASF A3.01.2_01 McKemie, T.H. (2000c) Dow A3.1.3	
Vapour pressure	44 Pa (20 °C, 100 % GA)	Olson, J.D. (1998) BASF A3.02_03 Rick, D.L. and West, R.J. (2006) Dow 3.2	
Surface tension	ca. 68 mN/m at 20 °C (0.2% aqueous preparation of the test item corresponds to a 0.1% solution of pure glutaraldehyde) 72.4 mN/m at 20 ºC (1g/l corresponding to 0.5 g/l or 0.05% solution of pure glutaraldehyde)	Sametschek, E. (2004) BASF A3.13_01 McKemie, T.H. (2000e) Dow A3.13	
Water solubility	Glutaraldehyde is an aqueous solution and as such is fully soluble (≥ 51.3 g glutaraldehyde/100 ml)	Drögemüller, A. (2002) BASF A3.05_01 Wells, D.F (1994a) Dow A3.5	

Partition coefficient n-octanol/water	$logP_{ow}$ -0.41 (pH 5, temp. 23 +/- 1 °C) $logP_{ow}$ -0.36 (pH 7, temp. 23 +/- 1 °C) $logP_{ow}$ -0.80 (pH 9, temp. 23 +/- 1 °C) $logP_{ow}$ -0.33 (at 25 ºC, pH not reported)	Sametschek, E. (2002) BASF A3.09_01 Shepler, K. (1996) Dow A3.9	
Flash point	No flashpoint was observed for either sample at temperatures up to 95 °C 184.8 °F = 85 °C	Siemann, L. (1999) BASF A3.01.2_01 Fowler, T. (2009) Dow 3.12	
Flammability	Not flammable	Simms, R. (2006) BASF A3.10_02 Leder, J. (1989) Dow A3.11	
Explosive properties	Not applicable, Glutaraldehyde does not contain any reactive groups that might cause spontaneous explosive decomposition. Glutaraldehyde is not considered to present a danger of explosion.	Dow Gödde, M. (2004) BASF A3.10_01	
Self-ignition temperature	-	-	
Oxidising properties	No noticeable changes in temperature or evolution of gas were observed for any of the mixtures. The substance has no chemical groups indicating oxidizing properties. Not applicable, aldehydes by nature behave as reducing agents and are easily oxidised rather than reduced.	Siemann, L. (1999) BASF A3.01.2_01 Leder, J. (1989) Dow A3.11	
Granulometry	-	-	
Stability in organic solvents and identity of relevant degradation products	Not applicable as the products will not be formulated with organic solvents.	Dow BASF	

Dissociation constant	Due to the nature of the test substance, determinations were not possible Does not have any ionisable/dissociable groups therefore not applicable	Siemann, L. (1999) BASF A3.01.2_01 Dow	
Viscosity	12.75 mm^2/s at 25 °C 20.15 mPa/s (at 20 ºC) 4.72 mPa/s (at 40 ºC)	Siemann, L. (1999) BASF A3.01.2_01 McKemie, T.H. (2000f) Dow A3.14	

2 MANUFACTURE AND USES

2.1 Manufacture

2.2 Identified uses

Glutaraldehyde is used as a biocidal active substance in disinfection and in product and process preservation. It has a broad spectrum activity against Gram-positive and Gram-negative bacteria, bacterial spores, fungi (yeasts and moulds) and viruses. Besides biocidal use, glutaraldehyde is used as a laboratory reagent, in development of X-ray film, and in cross linking.

Glutaraldehyde is a registered substance under the REACH Regulation (1907/2006). The registration dossiers have been considered when preparing the CLH dossier (last date for checking 24/05/2012). No new relevant data is presented in the registration dossiers. There are, however, relevant data used in the biocide assessment that is not included in REACH registration dossiers.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

No classification is proposed based on the evaluated data in the CAR.

4 HUMAN HEALTH HAZARD ASSESSMENT

The Document II-A (Draft, December 2012) of the Competent Authority Report (CAR) including the health hazard assessment is provided in section 13 of the IUCLID file.

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

Table 12: Toxicokinetic and metabolism studies

Route **Guideline** **GLP**	**Species** **Strain** **Sex** **No of animals**	**Dose levels** **Frequency of application** **Label**	**Investigations**	**Reference**
Oral (gavage) OECD 417 GLP	Rat Wistar (CrlGlxBrlHan:Wl) 4 ♂ + 4 ♀ per group in balance/excretion study, blood/plasma level study, bile excretion study 3 ♂ + 3 ♀ per group in tissue distribution study,	Single oral dose of 5 or 75 mg/kg [2,4-^{14}C]-glutaraldehyde	Balance/excretion Blood/plasma level Tissue distribution Bile excretion	Beimborn, D.B. and Leibold, E. (2004) Dow A6.02/01, BASF A6.02_01 Key study
Oral (gavage), Dermal Similar to OECD 417 GLP	Rat Fischer 344 4 ♀ per group (*in vivo* experiments) 15 ♀ (*in vitro* experiment)	Single oral dose of 5 or 75 mg/kg Single dermal application, 120 µl of 0.75 % or 7.5 % solutions No labelling	*In vivo* oral pharmacokinetics *In vivo* dermal pharmacokinetics *In vitro* partitioning between red blood cells, plasma protein and free glutaraldehyde	Mendrala A.L., Clark A.J., Sushynski, J.M. (2004) Dow A6.02/02 BASF A6.02_02 Key study

Route **Guideline** **GLP**	**Species** **Strain** **Sex** **No of animals**	**Dose levels** **Frequency of application** **Label**	**Investigations**	**Reference**
Oral *via* drinking water OECD 417 GLP	Rat Crl:W1(Han) 4 ♀ per group (12 ♀ per dose level)	50 ppm and 1000 ppm for 24 h (equivalent to a mean dose of 6.8 and 87 mg/kg bw) [2,4-^{14}C]-glutaraldehyde (also non-labelled glutaraldehyde)	Excretion/Balance Blood/plasma level Tissue distribution Metabolite identification (intended)	Hansen, S.C., Clark, A.J, McClymont, E.L., Staley, J.L. (2007) Dow A6.02/03 BASF A6.2_09
In vitro Skin penetration No guideline GLP	Fischer 344 rats (♂, ♀) CD®-1 mice (♂, ♀) Albino Hartley guinea pigs (♂, ♀) New Zealand White rabbits (♂, ♀) Human (♀)	Single 6 h application of 250 µl of 0.75 % and 7.5 % solutions [1,5-^{14}C]-glutaraldehyde	*In vitro* percutaneous absorption through skin *(Supportive information only due to major methodological problems)*	Tallant, M.J., Beskitt, J.L., and Frantz, S.W. (1991) Dow A6.02/4 (full report)
				Frantz, S.W., Beskitt J.L., Tallant, M.J. (1993) BASF A6.02_6 (published report)
Oral (gavage) OECD 417 GLP	Rat Wistar 3 ♂ + 3 ♀ per group	Single oral dose of 5 or 75 mg/kg [2,4-^{14}C]-glutaraldehyde	Excretion in urine, faeces, CO_2 Metabolite identification (intended)	Zhang, F., Hansen, S.C., Clark, A.J. (2007) Dow A6.02/05 BASF A6.02_5
In vivo skin penetration and pharmacokinetics Comparable to OECD 427 No GLP	Fischer 344 rats 4 ♂ + 4 ♀ per dose level and experiment New Zealand White rabbits 1 ♂ + 1 ♀ per dose level and experiment	Single 24 h application of 0.075, 0.75 or 7.5 % glutaraldehyde (rats) Single 24 h application of 0.75 or 7.5 % glutaraldehyde (rabbits) [1,5-^{14}C]-glutaraldehyde	*In vivo* skin penetration Material retained in skin and tissues *(Supportive information only due to major methodological problems)*	McKelvey, J.A., Anuszkiewicz, C. M. and Tallant, M..J. (1985) Dow A6.02/6

Oral absorption. The test substance was rapidly but incompletely absorbed from the gastrointestinal tract, with no remarkable differences between sexes. Bioavailability was calculated to be 37 % after a single dose of 75 mg/kg bw, and about 51 % after a single dose of 5 mg/kg bw. Based on presented data, oral absorption of 40 % is used for estimating the systemic dose. Glutaraldehyde mostly absorbs as molecules other than glutaraldehyde (or is rapidly converted after absorption), as at the time of C_{max} the rat blood contained approximately 0.16 % and 1.6 % of the total dose as glutaraldehyde following low and high dose, respectively.

Dermal absorption. None of the studies can be considered to give sufficient information for establishing a value for dermal absorption due to methodological problems. It can be considered that most of the glutaraldehyde in the skin will react immediately, leaving little free glutaraldehyde for absorption. Nevertheless, the absorption of metabolites needs to be considered as well, and furthermore it was shown that small amounts of free glutaraldehyde can also be detected from the blood after dermal dosing (Mendrala et al. 2004, BASF A6.02_02/Dow A6.02/02). In the study using human skin (Tallant et al. 1991, Dow A6.02/4), the total combined radioactivity in the receptor fluid and in the full combusted skin sample was 6.6 % for a 0.75 % glutaraldehyde solution, and 4.8 % for a 7.5 % glutaraldehyde solution. A conservative value of 10 % for dermal absorption is proposed.

Distribution. Free glutaraldehyde is rapidly removed from circulation, presumably through macromolecular binding or metabolism. When using radioactive labelling, the label was distributed in all organs and tissues (Beimborn and Liebold 2004, BASF A6.02_01 and Dow A6.02/01), while free glutaraldehyde is mostly assumed to be rapidly metabolised. Free glutaraldehyde could be detected in blood after a high dose, while only trace amounts or none were seen after a low dose, the majority of glutaraldehyde having been metabolised and/or bound. The concentration in the blood decreases rapidly (Mendrala et al. 2004, BASF A6.02_02 and Dow A6.02/02). The radioactive label, representing metabolites and/or breakdown products, was still detectable at 168 h after administration.

Metabolism. It has been demonstrated that glutaraldehyde is largely metabolised either before or soon after absorption, but no detailed metabolic pathways have been suggested. Furthermore, the only metabolite identified is glutaric acid. The scheme presented in Figure 1 is based on the proposals of Ballantyne and Jordan (2001), Beauchamp R.O *et al*. (1992) and Salway J. G. (1994). The scheme is poorly substantiated with regard to the pathway from glutaraldehyde to glutaryl CoA, and the scheme as a whole should be considered as one of the possible alternatives of probably multiple reaction pathways that depend on the initial reaction, among other things. Acetyl CoA is an important branching point for several routes in metabolism, including fatty acid synthesis. Due to very fast metabolism, the relevant metabolites can be assumed to have been taken into account in the toxicological studies.

Excretion. The excretion of radioactivity was rapid and occurred mainly via faeces, where around 62 % of the total dose was found after a single dose of 75 mg glutaraldehyde/kg bw. In exhaled air and urine, there were around 20 and 11 % of the administered dose, respectively (Beimborn and Liebold 2004, BASF A6.02_01, Dow A6.02/01). Similar results were obtained using a 15-fold lower dose of 5 mg glutaraldehyde/kg bw, with the difference that exhaled air and urine now contained 29 and 14 % of the administered dose, respectively, indicating higher bioavailability. In bile duct cannulated animals, the total amount excreted in bile was 2.6 % at high dose and 1.8 % at low dose. There was no indication of bioaccumulation in any of the tissues (Beimborn and Liebold 2004, BASF A6.02_01, Dow A6.02/01).

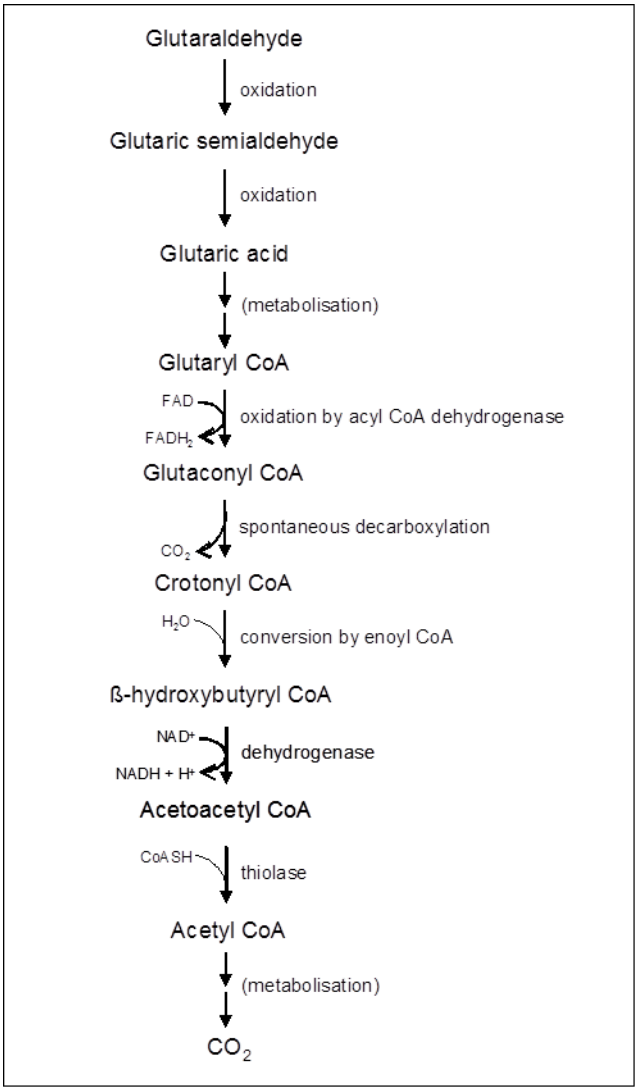


Figure 1: Proposed metabolic pathway

4.1.2 Human information

No data available.

4.1.3 Summary and discussion on toxicokinetics

Table 13: Summary of toxicokinetics

Oral absorption	Rapid but partial absorption from the gastrointestinal tract; no remarkable differences between sexes. Bioavailability after a single dose: 37 and 51 % for 75 and 5 mg/kg bw, respectively. Oral absorption of 40 % is used for estimating the

	systemic dose. Glutaraldehyde is mostly absorbed as compounds other than glutaraldehyde (or is rapidly converted after absorption). At C_{max} the rat blood contained 0.16 and 1.6 % of the total dose as glutaraldehyde following low and high dose, respectively.
Dermal absorption	None of the studies is of sufficient quality for establishing a value for dermal absorption. Most of the glutaraldehyde absorbing in the skin will react immediately, but small amounts of free glutaraldehyde can be detected from the blood after dermal dosing. Human skin *in vitro* study: total radioactivity in receptor fluid + full combusted skin sample was 6.6 % for a 0.75 % glutaraldehyde solution, and 4.8 % for a 7.5 % glutaraldehyde solution. A conservative value of 10 % is used unless further information is provided.
Distribution	Radioactive label was distributed in all organs and tissues, while free glutaraldehyde is mostly assumed to be rapidly metabolised. Free glutaraldehyde was detected in blood after a high dose, while only trace amounts or none were seen after a low dose. The concentration in the blood decreases rapidly. The radioactive label, representing metabolites and/or breakdown products, was still detectable at 168 h after administration.
Metabolism	Glutaraldehyde is largely metabolised either before or soon after absorption, but no detailed metabolic pathways have been suggested. Furthermore, the only metabolite identified is glutaric acid. Relevant metabolites are assumed to have been taken into account in the toxicological studies.
Excretion	Single high dose of 75 mg/kg bw: Rapid excretion of radioactivity via faeces (62 % of total dose), exhaled air (20 %) and urine (11 %). Single low dose of 5 mg/kg bw: Similar results as above, but exhaled air and urine contained 29 and 14 % of the administered dose, respectively. Bile duct cannulated animals: 2.6 % was excreted in bile at high dose and 1.8 % at low dose. No indication of bioaccumulation in any tissue.

4.2 Acute toxicity

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Table 14: Summary table of relevant acute oral toxicity studies

Method **Guideline** **GLP**	**Species** **Strain** **Sex** **No/group**	**Dose levels** **Duration of exposure**	**Value** **LD_{50}/LC_{50}**	**Remarks**	**Reference**
OECD 401, GLP	Rat Sprague-Dawley Albino 5 ♂ + 5 ♀ per group	Test substance: 50 % glutaraldehyde 100, 200, 400 mg/kg bw in ♂ (test substance) 100, 141, 200 mg/kg bw in ♀ (test substance) 14 day post exposure period	LD_{50} ♂ 123 mg glutaraldehyde/kg bw LD_{50} ♀ 77 mg GA/kg bw LD_{50} ♂ + ♀ 100 mg glutaraldehyde/kg bw Respective values for 50 % test substance: 246, 154, 200 mg/kg bw	**Spontaneously dying animals**: necropsy findings included red, mottled lungs, red stomachs, discoloured intestines, dark red kidneys **Survivors**: no remarkable gross lesions	Myers, R.C. and Christopher, S.M (1992) Dow A6.1.1 Key study
Similar to OECD 401 No GLP	Rat Sprague-Dawley 5 ♂ + 5 ♀ per group	Test substance: 50 % glutaraldehyde Test doses: 215, 316, 464 and 1470 mg/kg bw (test substance) 14 day post-exposure period	LD_{50} ♂ 158 mg glutaraldehyde/kg bw LD_{50} ♀ 143 mg glutaraldehyde/kg bw LD_{50} ♂ + ♀ 151 mg glutaraldehyde/kg bw Respective values for 50 % test substance: 316, 285, 301 mg/kg bw	**Spontaneously dying animals**: • Acute congestion; the stomach of these animals was dilated and the wall of the glandular stomach was thickened • In forestomach and glandular stomach, there were leathery bloody ulcerations, purulent abscesses and purulent fibrinous coatings • The mucosa of the small intestines partly appeared reddened and the intestinal contents were tinged with blood **Survivors**: no abnormalities	Jaeckh, R. (1994a) BASF A6.01.1_01 Key study

Glutaraldehyde was toxic when administered by the oral route. The toxic effects are considered to be caused by the corrosive effect on the mucosal surfaces of the GI tract.

In the study provided by Dow, an LD_{50} of 77 mg/kg bw in the rat was derived for pure glutaraldehyde (154 mg/kg bw/day of the test substance; Myers and Christopher 1992, Dow A6.1.1). Male rats were treated with doses of 100, 200 and 400 mg/kg (test substance), and female rats with doses of 100, 141 and 200 mg/kg (test substance). Mortalities occurred on days 1 and 2 post dosing at all dose levels except for 100 mg/kg bw. Survivors recovered within 4-5 days. Signs of toxicity included sluggishness, lacrimation, piloerection, diarrhoea, and a trace amount of blood in the urine of 2 animals. Red, perinasal soiling and perineal soiling was also noted. Necropsy findings of mortalities revealed red, mottled lungs, red stomachs (some haemorrhaged, 1 full of red liquid), discoloured intestines, and dark red kidneys. Necropsy revealed no remarkable gross lesions on the examination of survivors.

In the study provided by BASF, an LD_{50} of 143 mg/kg bw for the rat was derived for pure glutaraldehyde (285 mg/kg bw/day of the test substance; Jaeckh 1994a, BASF A6.01.1_01). Rats of both sexes were treated with test substance doses ranging from 215 to 1470 mg/kg bw. Mortalities were seen at all tested doses, and all treated animals suffered from symptoms indicative of generalized toxicity. Observations included poor general state, dyspnea, apathy, piloerection, staggering, trembling and exsiccosis. Necropsy of the rats that died revealed acute congestion, dilation of the stomach and thickening of the wall of the glandular stomach; furthermore, both in the forestomach and the glandular stomach, leathery bloody ulcerations as well as purulent abscesses and purulent fibrinous coatings were seen. The mucosa of the small intestines partly appeared reddened and the intestinal contents were tinged with blood.

4.2.1.2 Acute toxicity: inhalation

Table 15: Summary table of relevant acute inhalation toxicity studies

Method **Guideline** **GLP**	**Species** **Strain** **Sex** **No/group**	**Dose levels** **Duration of exposure**	**Value LD_{50}/LC_{50}**	**Remarks**	**Reference**
Similar to OECD 403 No GLP	Rat Sprague-Dawley 10 ♂ + 10 ♀ per group	50 % glutaraldehyde (, 49.5 % water) Nominal concentrations: 0.23, 0.41, 0.53, 0.68, 0.9 mg/l Analytical concentrations: 0.10, 0.18, 0.28, 0.39 and 0.44 mg/l Exposure: 4 h Post-exposure observation period: 14 days	LC_{50} ♂ 0.35 mg/l LC_{50} ♀ 0.28 mg/l ♂ + ♀: 0.28 mg/l < LC_{50} < 0.39 mg/l Values are based on analytical GA aerosol/vapour concentrations and need not be corrected for 50 % glutaraldehyde used	Necropsy of the animals that died during the experiment: acute congestion, pronounced emphysema of the lungs, edematization and infarctoid hyperemia. Surviving animals: no pathological abnormalities reported	Klimisch, H.J. (1994) BASF A6.01.3_01 Key study

Method **Guideline** **GLP**	**Species** **Strain** **Sex** **No/group**	**Dose levels** **Duration of exposure**	**Value LD_{50}/LC_{50}**	**Remarks**	**Reference**
Similar to OECD 403 No GLP	Rat Sprague-Dawley 10 ♂ + 10 ♀ per group	50 % glutaraldehyde (, 49.5 % water) Nominal concentrations: 0.35, 0.58 and 0.72 mg/l Analytical concentrations: 0.22, 0.31and 0.63 mg/l Exposure: 4 h Post-exposure observation period: 14 days	LC_{50} ♂ 0.52 mg/l LC_{50} ♀ 0.45 mg/l LC_{50} ♂ + ♀ 0.49 mg/l Values are based on analytical glutaraldehyde aerosol/vapour concentrations and need not be corrected for 50 % glutaraldehyde used	Necropsy of the animals that died during the experiment: general congestion and slightly increased blood content, small emphysema areas in the lung, 3 cases of pronounced emphysema of the lungs. Surviving animals: no pathological abnormalities reported	Klimisch, H.J. (2001) BASF A6.01.3_02
Non-guideline No GLP	Rat Fischer 344 6 ♂ + 6 ♀ per group	0, 10, 20 and 50 ppm 4 h exposure with 14-day post exposure period	LC_{50} ♂ 0.090 mg/l LC_{50} ♀ 0.16 mg/l LC_{50} ♂ + ♀ 0.125 mg/kg bw	Study concerns glutaraldehyde heated to approximately 65 ˚C, and is therefore not usable for classification purposes. 50 ppm and 20 ppm groups: patchy or general colour change in the lungs, perinasal and periocular encrustation. 10 ppm and control groups: No significant gross lesions.	Greenspan, B.J., Longo, L. and Eisler, D.L. (1982) Dow A6.1.3
OECD 403 (but only one dose level and additional minor deficiencies) GLP	Rat Sprague Dawley 5 ♂ + 5 ♀ per group	Single dose level: 27 ppm (0.11 mg/L) 4 h exposure with 14-day post exposure period	Not determined due to a single dose level LC_{50} > 0.11 mg/L	Necropsy findings at 14 days: rhinitis and goblet cell hyperplasia in the nasal cavity No mortalities High humidity (76-77 %) might have reduced the irritant effects Additionally, the study determined the LC_{50} for glutaraldehyde heated to 60 ˚C (44 ppm = 0.18 mg/L)	Norris, J.C. and Kintigh, W.J. (1995) Dow A6.1.3/2

Glutaraldehyde was very toxic when administered by inhalation.

In the two acceptable studies provided by BASF, the LC_{50} was between 0.28 mg/L and 0.52 mg/L (males 0.35 and 0.52 mg/L; females 0.28 and 0.45 mg/L). In the high dose group (0.63 mg/L), 15 animals of 20 died within 2 days after the exposure, and no further mortalities occurred. In the medium dose group (0.31 mg/L), 3 animals died between days 3 and 7 after the exposure. There were no mortalities in the low dose group of 0.22 mg/L. A generation system for aerosol is described, but the resulting glutaraldehyde in the air was described as "very fine aerosol < 2.8 µm or as a vapour". In order to clarify whether the test substance should be considered as aerosol or vapour, the applicant performed a physical-chemical study mimicking the system used in the

inhalation study. At measured concentrations of 0.224 and 0.349 mg/L, the vapour phase accounted for 65 and 68 % of the glutaraldehyde, respectively.

In the study provided by Dow (Greenspan et al. 1982, A6.1.3), glutaraldehyde vapour was generated using air heated to around 65 ˚C. The study report does not describe any means of cooling down the vapour, and therefore it is concluded that the study is not usable for classification purposes because of the unknown temperature of glutaraldehyde vapour. The study is nevertheless included here as supportive information. The LC_{50} for heated glutaraldehyde was 0.090 mg/L in male rats and 0.16 mg/L in female rats. In the high dose group (50 ppm), one male died during exposure and all other males during the following 3 days, and 3/6 females died during the 3 days after exposure. In the 20 ppm group, 2 males and 2 females died during the post-exposure period. Altogether, 12 mortalities occurred during the first 3 days and one on day 7. The other study by Dow (Norris and Kintigh 1995, A6.1.3/2) only concerned one dose level of 0.11 mg/L which was close to the LC_{50} indicated above. No mortalities occurred, but there were rhinitis and goblet cell hyperplasia in the nasal cavity of 3 males and 2 females out of the 4 animals investigated for each sex. The relative humidity in this study was 76-77 %, which is higher than required and might possibly have reduced the irritant effect.

4.2.1.3 Acute toxicity: dermal

Table 16: Summary table of relevant acute dermal toxicity studies

Method **Guideline** **GLP**	**Species** **Strain** **Sex** **No/group**	**Dose levels** **Duration of exposure**	**Value** **LD_{50}/LC_{50}**	**Remarks**	**Reference**
Non-guideline, non-GLP	Rabbit; 4 groups of 4 ♂ with 50 % solution; 4 groups of 4 ♂ with 25 % solution; 1 group of 6 ♂ with 5 % solution	50 % solution: 0.5, 1.0, 2.0 and 4.0 ml/kg; single application with 14 day post exposure period 25 % solution: 2, 4, 8 and 16 ml/kg; single application with 14 day post exposure period 5 % solution: 16 ml/kg; single application with 14 day post exposure period	GA pure: LD_{50} 875 mg/kg for ♂ (as calculated from LD_{50} for 50 % solution) GA 50 %: LD_{50} 1.75 g/kg	Spontaneously dying animals: • Red lungs • Mottled, red and light red or tan livers • Dark red spleens • Mottled red and tan kidneys; kidney sections red • Intestines opaque • Effects were linked to concentration: the lowest concentration (5 %) resulted in no mortalities and milder effects in fewer animals. No effects were reported for 4/6 animals.	Myers, R.C. (1981) Dow A6.1.2 Key study

Method Guideline **GLP**	**Species** **Strain** **Sex** **No/group**	**Dose levels** **Duration of exposure**	**Value LD_{50}/LC_{50}**	**Remarks**	**Reference**
(Reportedly EPA Pesticide Assessment Guidelines, Section 81-2)	Rabbit New Zealand white 5 ♂ + 5 ♀ per group	50.2 % glutaraldehyde Test doses: 2000 mg/ kg bw Post-exposure observation period: 14 days	GA pure: LD_{50} > 1000 mg/kg bw for ♂ + ♀ (as calculated from LD_{50} for 50 % solution) GA 50 %: LD_{50} > 2000 mg/kg	Mortalities: none. Clinical signs: mucoid faeces (days 1 and 2), wet brown urogenital staining (4 h after application). Local skin effects: Severe erythema, moderate to severe edema and eschar with subsequent exfoliation (all animals). In addition, there were signs of corrosion, fissuring and desquamation. Signs of severe skin irritation persisted in all animals over the complete observation period.	Kiplinger, G.R. (1995) BASF A6.01.2_01 Key study
Similar to OECD 402	Rat Sprague-Dawley 5 ♂ + 5 ♀ per group	50 % glutaraldehyde (0.5 % methanol, 49.5 % water) Test doses: 400, 1000 and 2000 mg/kg bw Post-exposure observation period: 14 days	GA pure: LD_{50} > 1000 mg/kg bw for ♂ + ♀ (as calculated from LD_{50} for 50 % solution) GA 50 %: LD_{50} > 2000 mg/kg	Highest dose group: one mortality. Clinical signs of toxicity were observed in all test groups and included a poor general state, dyspnea, apathy, excitation, staggering, atony, trembling, ruffled fur and diarrhoea. Local effects were seen in all test groups and included necrosis and oedema of different levels of severity. The LD_{50} value is valid for the test substance as tested in a 50 % aqueous solution	Jaeckh, R. (1994b) BASF A6.01.2_02

Glutaraldehyde caused local effects when administered by the dermal route. One study showed a calculated LD50 of 875 (386-1975) mg/kg in the rabbit (Myers, R.C. 1981, Dow 6.1.2), while in two other studies the LD50 was above 1000 mg/kg in both the rabbit and the rat (Kiplinger, G.R. 1995, BASF 6.1.2_1 and Jaeckh, R. 1994b, BASF 6.1.2_2). All the data is generally well in line, but the somewhat higher mortality in the non-GLP study (Myers, R.C. 1981, Dow 6.1.2) can be concluded to be partially due to the poor treatment of the animals, as the rabbits were immobilized for 24 h during treatment with a corrosive substance. Although the humaneness of the study can be questioned and the resulting mortality may be disproportionate, the study should be considered

acceptable for the data requirement. Judging by the full data set, it is concluded that the LD50 of 875 mg/kg is not reliable and the LD50 is set at above 1000 mg/kg bw.

The results (Myers, R.C. 1981, Dow 6.1.2 in particular) indicate that the effects were more directly linked to concentration than to a systemic dose level: 0.5 ml/kg of a 50 % solution (corresponding to 0.25 ml of 100 % glutaraldehyde) caused severe skin damage and one mortality, while 16 ml/kg of a 5 % solution (corresponding to 0.8 ml of 100 % glutaraldehyde) caused no mortalities and milder effects, and no effects were reported for 4/6 animals. The same concentration dependence is seen in repeated dose toxicity studies by the dermal route.

Due to the direct corrosive effect there is a danger of irreversible damage to the skin upon exposure to the undiluted solution. Toxicity is considered to be secondary to the local tissue damage rather than a result of percutaneously absorbed material.

4.2.1.4 Acute toxicity: other routes

Not evaluated in this dossier.

4.2.2 Human information

No information available.

4.2.3 Summary and discussion of acute toxicity

Glutaraldehyde was found moderately toxic when tested via the oral route (LD50 of 77 mg/kg bw in the rat was derived for pure glutaraldehyde (154 mg/kg bw/day of the test substance). The toxic effects are considered to be caused by the corrosive effect on the mucosal surfaces of the GI tract.

Glutaraldehyde was very toxic via the inhalation route (The LC50 values were 0.35 mg/L in male rats and 0.28 mg/L in female rats; values are based on analytical glutaraldehyde aerosol/vapour concentrations and need not be corrected for 50 %).

The dermal LD50 of the active substance, 50 % glutaraldehyde, is above 2000 mg/kg bw. The toxicity is based on local effects and is dependent on the concentration of the substance. It is reported that concentrations above 50 % will not be manufactured or used. The assessment of the 50 % active substance can therefore be considered as the worst-case assessment. Glutaraldehyde (50 %) does not warrant classification for acute dermal toxicity according to Directive 67/548/EEC, or according to the CLP regulation 1272/2008.

4.2.4 Comparison with criteria

The LD50 value from acute oral toxicity studies was 77 mg glutaraldehyde/kg bw (154 mg/kg bw for the test substance). This LD50 value is within the range of 50-300 mg/kg for classification as Acute Tox. 3; H301 under the CLP Regulation, and 25-200 mg/kg for classification as T; R25 under Directive 67/548/EEC. The asterisk (*) indicating minimum CLP classification for Acute oral Toxicity 3; H301 is no longer necessary since the data confirms the classification.

In the inhalation study, a generation system for aerosol is described, but the resulting glutaraldehyde in the air was described as "very fine aerosol < 2.8 µm or as a vapour". This implies that the test atmosphere was a mixture of liquid and vapour phases, and therefore it would be prudent to apply the criteria for vapour. In order to clarify whether the test substance should be considered as aerosol or vapour, the applicant performed a physical-chemical study mimicking the system used in the inhalation study. At measured concentrations of 0.224 and 0.349 mg/L, the vapour phase accounted for 65 and 68 % of the glutaraldehyde, respectively, supporting the use of the criteria for vapours. The LC50 values are 0.35 mg/L in male rats and 0.28 mg/L in female rats. These are both < 0.5 mg/L which is the classification limit for vapours in category Acute Tox. 1 under the CLP Regulation and limit for classification as "very toxic" under Directive 67/548/EEC. Therefore classification of glutaraldehyde as Acute Tox. 1; H330 is appropriate under the CLP Regulation and as T+; R26 under Directive 67/548/EEC. No specific concentration limit for acute inhalation toxicity is suggested under the Directive 67/548/EEC, since the calculated value (4 %) is very close to the general concentration limit of 7% for R26 (Calculation carried out as follows: Rat acute inhalation LC50 = 0.28 mg/L/4h. Cut off for R26 is 0.5 mg/L/4h (vapour); 0.5/0.28 = 1.8. The general concentration limit is 7% therefore SCL would be 7/1.8= 4.0 %). Since the mechanism of inhalation toxicity is corrosivity, glutaraldehyde should also be labelled as EUH071 (Corrosive to the respiratory tract) according to the CLP Regulation, Annex I, section 3.1.2.3.3 and Note 1 in section 3.1.4.1.

No classification is proposed via the dermal exposure route since the obtained LD50 value is above 2000 mg/kg bw. The criteria for classification as Acute Tox. 4; H312 under CLP is 1000 < ATE < 2000 mg/kg bw and the criteria for classification as Xn; R21 under DSD is 400 < LD_{50} ≤ 2000 mg/kg.

4.2.5 Conclusions on classification and labelling

CLP: Acute Tox. 3; H301 and Acute Tox. 1; H330. A supplemental hazard statement EUH071 is also proposed.

DSD: T; R25 and T+; R26

4.3 Specific target organ toxicity – single exposure (STOT SE)

See section 4.4.3

4.4 Irritation

4.4.1 Skin irritation

4.4.1.1 Non-human information

Table 17: Summary table of skin irritation studies

Species	Method Test substance	Average score 24, 48, 72 h		Reversibility yes/no	Result	Reference
		Erythema	Edema			
Rabbit, New Zealand White	OECD 404 GLP Male and female 3/sex/group 50 % GA	2.8, 3.0, 2.7	3.2, 2.7, 2.0	Not reversible Necrosis and desquamation were present at day 10	Corrosive	Myers, R.C. (1988) Dow A6.1.4(s) Key study
Rabbit, White Vienna	No guideline Glutaraldehyde 50 % aq. solution applied undiluted for 4 h, then removed by rinsing with Lutrol and 1:1 Lutrol in water 3 males and 1 female	2.0, 2.0, not assessed (the scale is different from the OECD scale: 0 = none 1 = questionable 2 = slight 3 = distinct 4 = very distinct)	2.5, 1.75, not assessed (the scale is different from the OECD scale: 0 = none 1 = questionable 2 = slight 3 = distinct 4 = very distinct)	Not reversible Necrosis, erythema and oedema were present at day 8 (necrosis confirmed by gross pathology)	Corrosive	Grundler, O.J. (1994a) BASF A6.01.4_01
Rabbit, White Vienna	No guideline Glutaraldehyde 50 % aq. solution applied undiluted for 1 h, then removed by rinsing with Lutrol and 1:1 Lutrol in water. 2 females	not assessed, 2.0, not assessed (the scale is different from the OECD scale: 0 = none 1 = questionable 2 = slight 3 = distinct 4 = very distinct)	2.0, 2.0, not assessed (the scale is different from the OECD scale: 0 = none 1 = questionable 2 = slight 3 = distinct 4 = very distinct)	Not reversible There was severe scaling at 8 days, as well as erythema and edema	Irritating (but after exposure of only 1 h)	Grundler, O.J. (1994b) BASF A6.01.4_02

In the study provided by Dow (Myers 1988, A6.1.4(s)), 50 % glutaraldehyde produced severe skin irritation: necrosis, desquamation, scabs and alopecia when applied dermally to rabbit for 4 h. In the same study, a parallel test was performed with exposure times of 1 h and 3 min. Following an exposure of 1 h, necrosis was observed in 2 and desquamation in 4 of the 5 surviving animals (one animal died on day 5, but there were no indications that death was related directly to treatment). These effects persisted until the end of the observation period of 7 days. An exposure of 3 min resulted in minor erythema in 1 animal, and no other effects were observed.

The studies provided by BASF (Grundler 1994a, A6.01.4_01 and Grundler 1994b, A6.01.4_02) were not performed according to the OECD guideline: the observation period was only 8 days, the scaling system was different and observations were not done at 72 h. Regardless of the methodology, the results are scientifically clear and in line with the results provided by Dow. Exposure time of 4 h (Grundler 1994a, BASF A6.01.4_01) resulted in necrosis, erythema and edema in all animals. In addition, an exposure of 1 h was used (Grundler 1994b, BASF A6.01.4_02)

resulting in erythema and edema, and at the end of the observation period of 8 days, there was severe scaling in both of the 2 animals tested. An exposure of 3 min resulted in no edema, and erythema that was considered questionable, but at the end of the observation period of 8 days, there was scaling in 1 of the 2 animals.

4.4.1.2 Summary and discussion of skin irritation

Glutaraldehyde 50% was found to be corrosive when tested on rabbit skin. Glutaraldehyde has an existing classification as Skin Corr. 1 B; H314 according to the CLP Regulation and C; R34 according to the DSD, both with specific concentration limits. The present studies thus confirm the existing classification.

4.4.1.3 Comparison with criteria

Glutaraldehyde 50 % was found to cause necrosis when applied to rabbit skin for 1 h, however shorter exposure times (3 min) did not cause necrosis. This finding fulfils the criteria in the CLP regulation for Skin Corr. 1B (responses in 1 of 3 animals are observed following exposure time between 3 min and observations up to 14 days). Under DSD, classification as C; R34 should be assigned if a substance causes full thickness destruction of skin tissue as a result of up to 4 hours exposure. Therefore glutaraldehyde 50% should be classified as C; R34.

4.4.1.4 Conclusions on classification and labelling

Glutaraldehyde is classified in Annex VI, table 3.1 of the CLP Regulation as Skin Corr. 1B, H314 with the following specific concentration limits:

Skin Corr. 1B; H314 : C ≥ 10%
Skin Irrit. 2; H315: 0,5% ≤ C < 10%
Eye Dam. 1; H318: 2% ≤ C < 10%
Eye Irrit. 1; H319: 0,5% ≤ C < 2%
STOT SE 3; H335: C ≥ 0,5%

The current classification according to DSD (Annex VI, table 3.2 of the CLP Regulation) is C; R34 with the following specific concentration limits:

C; R34: C ≥ 10%
Xi; R37/38-41: 2% ≤ C < 10%
Xi; R36/37/38: 0,5% ≤ C < 2%

In conclusion:

CLP: Glutaraldehyde should be classified as **Skin Corr. 1B** on the basis that necrosis resulted already from an exposure of > 3 min ≤ 1 h. Therefore **no change is proposed to the existing classification as Skin Corr 1 B; H314 and the existing SCLs for skin corrosion/irritation should be retained**. However, based on the data on skin corrosion and on respiratory tract irritation (see section 4.4.3), classification as STOT SE 3; H335 is proposed. The existing SCLs for STOT SE 3; H335 is also proposed to be revised (see section 4.4.3)

DSD: Glutaraldehyde meets the criteria for classification as Corrosive (C). The risk phrase R34 should be assigned: Causes burns. Therefore **no change is proposed to the classification** for skin corrosion/irritation and **the existing SCLs for skin corrosion/irritation should be retained.** However, based on the data on skin corrosion and on respiratory tract irritation (see section 4.4.3), classification as Xi; R37 is proposed. The existing SCLs for Xi; R37 is proposed to be revised (see section 4.4.3)

4.4.2 Eye irritation

4.4.2.1 Non-human information

Table 18: Summary table of eye irritation studies

Species	Method	Effects			Reversibility yes/no	Result	Reference
		Cornea	Iris	Conjunctiva			
Rabbit, New Zealand White	(Reportedly EPA FIFRA 81-4) GLP Male and female 3/sex Test substance glutaraldehyde 45 % aq. solution Applied volume: 0.1 ml Rinsing: none	Opacity average score 24, 48, 72 h: 4.0, 4.0, 4.0	Scoring not possible due to severe corneal opacity, swelling, adhesion and/or discharge.	Redness: 1.0, 2.0, 2.0 Chemosis: 4.0, 3.8, 4.0	No	Severely irritating	Myers, R.C. (1987a) Dow A6.1.4(e) Key study
Rabbit, White Vienna	Draize test Male and female 3/sex Test substance glutaraldehyde 50 % aq. solution Applied volume: 0.1 ml Rinsing: none	Opacity, scattered/ diffuse (24 h) to nearly complete (8 d), affected area: 75 to 100 %	Folds above normal, swelling and circum-corneal injection	Redness, swelling with partial eversion of the eyelids, swelling with half-closed lids (seen until day 8), eye discharge	No	Severely irritating Primary irritation index: 58	Grundler, O.J. (1994c) BASF A6.01.4_03 Key study

Glutaraldehyde was severely irritating to rabbit eyes. Glutaraldehyde (45 or 50 %) was administered to rabbit eye in two key studies. Severe corneal injury, iritis and severe conjunctival irritation in each of 6 rabbits were recorderd in the study provided by Dow (Myers, 1987a, Dow A6.1.4(e). Ocular effects included a purulent discharge, conjunctival necrosis, adhesion of the nictitating membrane and cornea and pannus. Corneal opacity and conjunctival swelling were so severe that complete scoring of the cornea and iritis was not possible for most of the observation period. Adhesion of the nictitating membrane to the cornea as well as the purulent discharge further

interfered with the ocular examinations. The effects were not reversible but continued until the end of the observation period of 21 days (Myers, 1987a, Dow A6.1.4(e).

In the study provided by BASF (Grundler, 1994c, BASF A6.01.4_03) administration of 50% glutaraldehyde resulted in increasing opacity of the cornea which was nearly complete at day 8. In the iris, folds above normal were observed as well as swelling and circum-corneal injection. In the conjunctiva redness, swelling with partial eversion of the eyelids, swelling with half-closed lids (seen until day 8), eye discharge were recorded.

4.4.2.2 Summary and discussion of eye irritation

Glutaraldehyde (45 or 50 %) caused severe damage to the rabbit eye.

4.4.2.3 Comparison with criteria

According to the CLP criteria, classification as Eye Dam. 1 should be assigned if a substance produces effects at least in one animal of 3 in cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days; and/or a substance produces a positive response in 2 of 3 tested animals of corneal opacity ≥ 3 and/or iritis ≥ 1.5 calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material. The CLP does not provide criteria for tests using up to 6 rabbits, however in the CLP guidance there is US EPA/UN recommendation on studies with up to 6 rabbits have been used. Since glutaraldehyde (45 or 50 %) produced effects in rabbit eye which fulfil the criteria described above, classification as Eye Dam. 1; H318 (Causes serious eye damage) according to the CLP Regulation is warranted.

According to DSD, a substance should be assigned the risk phrase R41 (Risk of serious damage to eyes) if it causes severe ocular lesions in the eye of the animal (means of the scores: cornea opacity equal to or greater than 3, iris lesion greater than 1.5) which occur within 72 hours after exposure and which persist for at least 24 hours. If using 3 animals then in at least 2 animals the values should be: cornea opacity equal to or greater than 3, iris lesion equal to 2. Therefore, according to the criteria, the risk phrase R41 is warranted.

4.4.2.4 Conclusions on classification and labelling

Glutaraldehyde causes severe damage to rabbit eyes. Therefore glutaraldehyde should be classified as follows:

CLP: Classification as Eye Dam. 1 for irreversible effects on the eye. The corresponding hazard statement (H318) will nevertheless not be proposed because of the **classification as skin corrosive (Skin Corr 1B; H314) which covers the effects on eyes**. **No change to the existing SCLs for eyes is suggested** (see section 4.4.1.4).

DSD: The risk phrase R41 is warranted: Risk of serious damage to eyes. This risk phrase will nevertheless not be proposed because of the **classification as corrosive C; R34 which covers the effects on eye**s. **No change to the existing SCLs for eyes is suggested** (see section 4.4.1.4).

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

Table 19: Summary table of a respiratory tract irritation study

Species	Method	Number of animals, test concentration, exposure	Result	Reference
Mouse ND4 Swiss Webster (♂)	Peripheral sensory irritation test (PSI) No guideline The sensory irritation of the respiratory tract was determined by measuring the decrease of respiratory rate as a function of GA vapour concentration	4 ♂ per group Test concentrations: 1.60, 3.99, 4.65, 5.60, 7.47, 17.7 and 36.7 ppm glutaraldehyde vapour Procedure: 1) 10 min acclimatization period 2) 10 min of head-only air exposure to determine the baseline respiration rate 3) 30 min head-only exposure (test substance) 4) 10 min post-exposure with air (recovery)	RD_{50}: 13.9 ppm There was a direct and linear correlation between the respiratory rate and GA concentration The lowest concentration (1.60 ppm) caused a 26 % decrease in respiratory rate, and the highest concentration (36.7 ppm) a 59 % decrease in respiratory rate The decrease in respiratory rate was almost immediate upon exposure, and did not recover to normal levels during the 10 min post-exposure observation period. No clinical signs were reported during the study.	Werley et al. 1995 BASF A6.01.4_04 Key study

For the purpose of peripheral sensory irritation potential measurement, Swiss Webster male mice were exposed to glutaraldehyde vapour and the respiratory rate was recorded in an open source study (Werley et al. 1995). In rodents, sensory irritation leads to a concentration-dependent reduction in the respiratory rate mediated via the trigeminal nerve reflex, and this can be measured experimentally (non-OECD test, the Alarie assay; ECHA guidance IRSA R.7.a). It can be expected that a substance that is cabable of stimulating the trigeminal nerve in mice will also have this potential in humans (ECHA guidance IRSA R.7.a). Glutaraldehyde vapour exposure resulted in an almost immediate decrease in respiratory rate, which was related to prolongation of the expiratory phase of the respiratory cycle, indicative of peripheral sensory irritation of the respiratory tract. A clear effect-concentration relationship was evident and an RD50 of 13.9 ppm was derived (the exposure concentration that causes a 50 % decrease in respiratory rate). Glutaraldehyde was thus described as a moderately potent peripheral sensory irritant.

4.4.3.2 Human information

With respect to the human evidence on glutaraldehyde-induced respiratory tract irritation the following available open source information on human volunteers and on occupational exposure is presented as summaries.

• Cain S.W. et al., Odour and Chemesthesis from Exposures to Glutaraldehyde Vapour. Int. Arch Occup Environ Health 80(8): 721-31, 2007. Dow 6.12.4(1); BASF 6.12.2_08

Glutaraldehyde odour detection and chemesthetic (sensory irritation) detection by the eye and nose were studied in 50 female volunteers. The threshold of odour detection was around 0.3 ppb. The

study described the odour around 35-100 ppb as discernible green apple odour that was not irritating during 15 min exposure. It was concluded that exposures that start decidedly below irritating (100 ppb and below) seem unlikely to turn irritating over time. However, in briefer exposures (5 s for nose, 25 s for eyes) with concentration range of 229-772 ppb (1.5-fold increments), the chemesthetic thresholds (points of 50% detection) for ocular and nasal detection were determined to be 390 ppb and 470 ppb, respectively. Conclusion: in an experimental setup, glutaraldehyde odour can be detected at 0.3 ppb. Based on this study, irritation is expected to occur at concentrations higher than 390 ppb (eyes) and 470 ppb (nose), with a sharp dependence on the concentration of glutaraldehyde.

• Pisaniello et al.: Glutaraldehyde exposures and symptoms among endoscopy workers in South Australia. Appl. Occup.Environ. Hyg. 12: 171-177, 1997. Dow 6.12.4(4); BASF 6.12.4_3

135 endoscopy nurses exposed to glutaraldehyde and 132 unexposed nurses in the same hospitals were interviewed and their worksites were inspected. Inhalational exposure while using glutaraldehyde was determined and dermal exposure was assessed with skin pads. The measured overall geometric mean inhalational exposure concentration was 32 ppb, the highest mean of 93 ppb being in endoscopy areas with no local exhaust ventilation. Nurses exposed to glutaraldehyde reported more headache, lethargy and symptoms in the skin, eye and throat than the control group. The throat symptoms were mostly itching or tingling (10 vs. 4 % in the control group) and an unpleasant taste (9 vs. 3 %). No information is given on asthma or respiratory sensitization. Conclusion: Headache, lethargy and symptoms in the skin, eye and throat were connected with combined inhalation and dermal exposure to glutaraldehyde.

• Vyas et al.: Survey of symptoms, respiratory function and immunology, and their relation to glutaraldehyde and other occupational exposures among endoscopy nursing staff, Occupational and Environmental Medicine 57: 752-759, 2000

Endoscopy nurses (348 nurses in 59 endoscopy units) in the United Kingdom and 18 ex-employees who had left their job for health reasons were surveyed. Any work-related symptoms were surveyed using questionnaires. Exposure measurements included personal airborne biocide sampling for peak and background concentrations. All ex-employees and 91 % of the current nurses were primarily exposed to glutaraldehyde, while the rest were exposed to a succinaldehyde-formaldehyde composite. Work related contact dermatitis was reported by 44 % of current workers exposed to glutaraldehyde and 44 % of ex-employees. The prevalence of work related symptoms in current glutaraldehyde exposed workers was 14 % for the eyes, 20 % for the nose, and 9 % for the lower respiratory tract, while these were all at least 50 % among the ex-employees. There were 30 current nurses with lower respiratory tract symptoms. For these, peak expiratory flow rates were recorded during one month and analysed using the OASYS-2 analysis program. The program revealed three cases of possible asthma, but re-evaluation of the data by two physicians concluded that none of these showed evidence of bronchial asthma. The mean percentage of the predicted forced expiratory volume in 1 second (FEV1) was 104.5 % for the current workers with no lower respiratory tract symptoms and 99.3 % for those with lower respiratory tract symptoms; for ex-employees it was 93.8 %. Exposures were above the maximum exposure limit of 0.2 mg/m3 (50 ppb) in eight of the units investigated. There was a clear relation between peak glutaraldehyde concentrations and work related chronic bronchitis and nasal symptoms but not to other symptoms. Conclusion: Glutaraldehyde caused clear irritant effects in the skin, eyes, nose and the lower respiratory tract, but asthma was not diagnosed. The results concerning asthma have been questioned in the journal

where the article was published. There were few FEV1 results for the ex-employees but the significantly lower value for this group may be indicative of the reason for leaving the workplace where exposure to glutaraldehyde had occurred.

• Katagiri H. et al., Indoor glutaraldehyde levels in the endoscope disinfecting room and subjective symptoms among workers. Industrial Health 44: 225-229, 2006

Exposure to glutaraldehyde in the air was measured at 6 hospitals in a total of 8 rooms where endoscope washing and disinfection took place. The subjective symptoms of 31 exposed women were compared to those of 101 unexposed control women using a questionnaire. Glutaraldehyde concentrations in the air had geometric means of 1.3 to 19.6 ppb, while personal measurements showed exposure levels of up to 94.2 and 84.9 ppb during the changing of the glutaraldehyde solution in the automatic washers. This high-exposure task is performed every 2 to 4 weeks. The women that were exposed to glutaraldehyde reported a variety of symptoms more frequently than those in the control group. These included asthma (2/31 vs. 0/101 in the control group), cough (9/31 vs. 5/101), pharynx irritation (3/31 vs. 1/101) and pain in the eyes (8/31 vs. 0/101). No attempts were made to clarify or verify the claimed symptoms.

• Nayebzadeh A., The effect of work practices on personal exposure to glutaraldehyde among health care workers, Industrial Health 45: 289-295, 2007

Air samples were taken in 19 locations in five hospitals in the breathing zone by personal sampling to measure exposure to glutaraldehyde during 5 to 15 min. The work practices were monitored and classified as "appropriate", "poor" and "unsafe", and resulted in mean exposure rates of 12, 51 and 80 ppb, and maximum concentrations of around 68, 150 and 150 ppb, respectively. Irritant effects (burning or itchy eyes; itchy nose) and headache were found to correlate with the work practices and consequently with peak exposure to glutaraldehyde. Correlation could not be established between work practices and cough/sneezing/runny nose. Although there was no control group without exposure to glutaraldehyde, it should be noted that even in the group with "appropriate" work practices 14 of the 27 cases reported headache and 11-22 % reported various irritant effects (but it is not mentioned whether e.g. "burning eyes" and "itchy eyes" were mutually exclusive categories). The quantity of glutaraldehyde solution used did not correlate with exposure. Conclusion: Work practices determine the exposure rate to a large extent, while even appropriate practices may result in exposure rates above the OEL of 50 ppb. The quantity of glutaraldehyde solution or the efficiency of general ventilation do not correlate with exposure.

4.4.3.3 Summary and discussion of respiratory tract irritation

In the PSI study on mice (Werley et al. 1995), following glutaraldehyde exposure the breathing rate of the mice decreased in a concentration-dependent manner. The vapour concentration producing a 50 % decrease in the breathing rate (RD50) was determined to be 13.9 ppm. In addition, the breathing rate decreased almost immediately after the exposure commenced. It was concluded that glutaraldehyde is a moderate sensory irritant in mice. An approximate derivation of RD10, albeit with considerable uncertainties, was calculated by the dossier submitter. The derived RD10 value is approximately 0.4 ppm (400 ppb).

In a study on human volunteers the chemesthetic thresholds (points of 50% detection) for ocular and nasal detection were determined to be at 390 ppb and 470 ppb (0.39 ppm and 0.47 ppm),

respectively (Cain et al. 2007). The experimental setup ensured independence of these values from perception of the odour of glutaraldehyde, therefore they represent the sensitivity of sensory irritation. These values are very close to a previous estimate of the chemestetic threshold of 300 ppb for glutaraldehyde (see Ballantyne and Jordan 2001). The difference between the odour detection (0.3 ppb) and the chemesthetic detection of three orders of magnitude in concentration is typical of the pattern of other volatile organic compounds with similar potency. Taken together, this study is a clear demonstration of the sensory irritation potential of glutaraldehyde in humans.

The human occupational exposure evidence on glutaraldehyde-induced respiratory tract irritation included effects in the nose and eyes and in the lower respiratory tract. Symptoms were described as burning and itchy eyes, itchy nose, pain in the eyes, sneezing, runny nose, coughing, pharynx irritation, tingling in the throat etc. There was variation in the effects described and the relationship between exposure concentrations/times and effects could not be established with certainty in most studies. The aforementioned studies could however be considered as supportive information on respiratory tract irritation potential of glutaraldehyde. However it is difficult to draw definite conclusions on the mechanisms of these effects.

The respiratory tract irritation covers two different mechanisms, namely the sensory irritation which is mediated via autonomic nerve receptors on mucosal tissues of eyes and upper respiratory tract, and local cytotoxic effects which are commonly caused by corrosive substances. Glutaraldehyde is a corrosive agent and is classified as Skin Corr 1B according to the CLP Regulation. In the light of the studies presented in this dossier, glutaraldehyde-evoked respiratory irritation may arise via two different mechanisms, namely via the corrosive cytotoxic effects on the respiratory tract and via sensory irritation.

4.4.3.4 Comparison with criteria

According to the CLP Regulation, a substance can be classified as STOT SE 3; H335 (May cause respiratory irritation) if it causes transient effects such as respiratory irritant effects (localized redness, oedema, pruritis and/or pain) that impair function with symptoms such as cough, pain choking and breathing difficulties (data primarily from human studies). Subjective human observations can be supported by objective measurements (such as electrophysiological measurements, markers of inflammation in nasal BAL fluids). There are no validated animal tests that deal specifically with respiratory tract irritation, however useful information may be obtained from other studies and be used as weight of evidence.

The presented human occupational exposure studies describe subjective observations on respiratory tract irritation with various symptoms. However due to lack of clear relationship between exposure and the development of signs of respiratory tract irritation which should be reversible these studies should be regarded as part of weight of evidence. The study on human volunteers using a psychophysical method, however, gave clear evidence of the sensory irritation potential of glutaraldehyde, and tresholds for sensory irritation could be determined (390 ppb for eyes and 470 ppb for nose).

The Alarie test on mice measures the sensory irritation potential of a chemical. Although it is a non-OECD test the data from the test can be used as part of weight of evidence. The test revealed a clear concentration-dependent effect on the breathing rate in exposed mice, with a RD50 value of 13.9 ppm.

In conclusion, glutaraldehyde was described as a moderately potent peripheral sensory irritant in the mouse PSI test (Alarie test). Together with the human data on volunteers, the results imply that glutaraldehyde is a respiratory tract irritant via the sensory irritation mechanism.

As glutaraldehyde is a corrosive substance it can cause respiratory tract irritation via a local cytotoxic mechanism when inhaled below those concentrations which cause respiratory tract corrosion. Therefore, glutaraldehyde can cause respiratory tract irritation via two mechanisms, namely via corrosivity and via sensory irritation.

There are no guidance values for STOT SE 3, therefore if a substance shows clear evidence at any dose level then this could support classification as STOT SE 3 (CLP guidance on criteria).

4.4.3.5 Conclusions on classification and labelling

The current classification of glutaraldehyde as STOT SE 3 at a specific concentration limit of C ≥ 0.5 % obviously stems from the direct translation of R37 (at specific concentration limits) under Directive 67/548/EEC. The mechanism of respiratory tract irritation was corrosivity. However, the presented human and animal data in the current CLH dossier show that glutaraldehyde causes respiratory tract irritation also via a specific mechanism, namely sensory irritation. Therefore, classification as STOT SE 3; H335 is proposed based on two mechanism: corrosivity and sensory irritation in the respiratory tract.

In conclusion, it is proposed to classify glutaraldehyde as follows:

CLP: **STOT SE 3; H335.**

DSD: **Xi; R37.**

SCL: The existing SCL for STOT SE 3; H335 is C ≥ 0,5 %. However, based on the presented data on respiratory tract irritation via the sensory irritation mechanism with the calculated RD10 value of approximately 0.4 ppm for mice and a threshold of 0.39 - 0.47 ppm for the human volunteers, a lower **SCL of 0,00005 %** is proposed under both CLP and DSD.

4.5 Corrosivity

See section 4.4

4.6 Sensitisation

4.6.1 Skin sensitisation

4.6.1.1 Non-human information

Table 20: Summary table of skin sensitisation studies

Species	**Method**	**Number of animals sensitised/total number of animals** **(or description of other results)**	**Result**	**Reference**
Guinea pig Dunkin Hartley Haz:(DH)fBR (10 ♂+ 10 ♀/ GA group)	(Reportedly US EPA OPP Section 798.4100, 1985) Similar to OECD 406 GLP Guinea pig maximisation test intradermal induction 0.1% GA, topical induction 2 % GA	Aqueous GA: • 13/19 (challenge) • 6/19 (re-challenge) Alkalinised GA: • 5/20 (challenge) • 1/20 (re-challenge)	Sensitising	Blaszcak, D.L. (1993) Dow A6.1.5/01 Key study
Mouse BALB/c (4 ♀/group)	LLNA No guideline, no GLP 50 % aqueous GA diluted in acetone to final GA concentrations of 0, 2.5, 5, 12.5 and 25 %	Stimulation indices for 2.5, 5, 12.5 and 25 % GA, as compared to the vehicle control group: 15.5, 23.4, 38.7 and 34.9	Sensitising	Kimber, I. (1994) Dow A6.1.5/02 Key study
Guinea pig, Pirbright White	Open epicutaneous test with guinea pig No guideline, no GLP Test substance: Relugan GT (GA 25 %, water 67 %, methanol 8 %) 25 % GA was used in both induction and challenge	10/10 Induction: thick bloody scabs (10/10) Challenge: distinct spotted erythema (10/10) Negative control: no reactions	Sensitising	Zeller, H. (1975) BASF A6.01.5_01 Supportive
Mouse CBA/Ca (4 ♀/group)	LLNA No guideline, no GLP Test substance: five concentrations of GA in two different vehicles (acetone:olive oil or propylene glycol)	EC3 value 0.07% (in AOO) EC3 value 1.5 % (in PG)	Sensitising	Basketter, D.A. et al 2003 Key study

The skin sensitation potential of glutaraldehyde has been assessed in a guinea pig maximization test (GPMT), in a mouse local lymph node assay (LLNA) and in a guinea pig open epicutaneous test.

In addition, there are a few open source studies available with relevant data on skin sensitation potential of GA.

In a GPMT test according to Magnusson and Kligman and similar to OECD TG 406 (Blaszcak 1993, Dow A6.1.5/01) 20 animals (10 males, 10 females) were exposed to aqueous or alkalinised glutaraldehyde. 2,4-Dinitrochlorobenzene (DCNB; 0.1%) was used as a positive control in 10 animals (5 males, 5 females) and 20 animals served as irritation controls (5 males and 5 females at challenge; 5 males and 5 females at re-challenge). In the main test the treatment regimen involved induction by intradermal injection (0.1 % aqueous or 0.1 % alkalinised GA formulated as 1:20 either in propylene glycol or in Freund's complete adjuvant/water emulsion) in the clipped shoulder region on day 1, induction by topical application (2% aqueous or alkalinised GA) on the clipped shoulder region on day 7 and challenge (0.2% aqueous or alkalinised GA) by topical administration on day 21 and re-challenge (0.2% aqueous or alkalinised GA) on day 28 on the clipped skin of the flanks.

One animal was found dead on day 8 in the aqueous GA group, all other animals survived throughout the study. Necropsy revealed emaciation but no internal abnormalities were found.

Following challenge, all animals (incidence index 100 %, 10/10 animals) treated with the positive control DNCB (0.1 %) gave clear dermal responses with the irritation control animals giving no response at the same concentration. A response was considered positive with a score of 1 or greater. The irritation controls for GA at challenge and re-challenge treated with the same concentrations were negative. The incidence index of sensitation to 0.1% aqueous glutaraldehyde was 68% (13/19 animals) at challenge (reading after 24 h) and 32% (6/19 animals) at re-challenge. The incidence index of sensitation to 0.1 % alkalinized glutaraldehyde was 25% (5/20 animals) at challenge and 5% (1/20) at re-challenge. The scoring scale used in the original study was 0.5-3 giving slightly higher incidence indexes (79% for 0.1% aquaeous GA and 65% for 0.1% alkalinized GA) however for comparison of the results to the CLP classification criteria only the scores 1 and greater have been considered.

The severity index was determined for the response readings by dividing the sum of total grades (scores 0.5-3) in a given group by the number of animals exposed. The positive control (DCNB) severity indices at 24 h and 48 h at challenge were 1.7 and 1.5, respectively. The challenge severity indices for aqueous GA at 24 h and 48 h were 0.8 and 0.5, respectively. At re-challenge the values were 0.5 and 0.1. For alkalinized GA the challenge severity indices at 24 h and 48 h were 0.5 and 0.2, respectively. At re-challenge the values were 0.2 and 0.1.

In conclusion, an intradermal induction dose of 0.1 % aqueous glutaraldehyde exhibited a moderate to strong potential in producing sensitisation whereas intradermal induction dose of 0.1% alkalinized glutaraldehyde exhibited a weak to moderate potential. The reason for the decrease in the incidence of the responses at re-challenge is not clear. However, the presence of responses at both challenge and re-challenge is indicative of sensitisation since the irritation controls were negative.

In a mouse LLNA (Kimber, I. 1994, Dow A6.1.5/02) four female mice per group were exposed to glutaraldehyde concentrations of 0%, 2.5%, 5%, 12.5 % or 25 %. At the time the study was carried the OECD TG 429 was not yet adopted however the test is in principle similar to the TG429. The GA doses were applied on the dorsum of both ears daily for three consecutive days. On day 6 mice were injected with ^{3}H-thymidine and five hours later the mice were sacrificed and the draining auricular lymph nodes were removed and pooled for each dose group. Single cell suspensions were

prepared by mechanical disaggregation through a stainless steel gauge. Pooled cells were washed twice with PBS, and precipitated with 5 % trichloroacetic acid (TCA) for 12 hours, pelleted and resuspended in TCA whereafter the radioactivity was measured by beta-scintillation counting. The results are expressed as DPM-value/dose group divided by DPM-values of the control group (vehicle only, acetone) thus giving the stimulation index (SI) for each dose group. Increasing concentrations of GA elicited SI of 15.5, 23.4, 38.7 and 34.9, respectively, indicating that glutaraldehyde has the potential to induce skin sensitisation. The EC3 -value indicating the estimated concentration required to produce a 3-fold increase in draining lymph-node cell proliferative activity was not calculated.

The EC3-value for glutaraldehyde has been determined in open source studies. In a LLNA study by Basketter et al. (2003) GA was tested using two vehicles, acetone:olive oil (AOO) and propylene glycol (PG). Concentrations of GA used in AOO were 0.039%, 0.052%, 0.13 %, 0.26% and 0.52 % and in PG 0.26%, 0.52%, 1.3 % and 2.6 %. The LLNA was carried out using the standard protocol (Kimber and Basketter 1992). The calculated EC3 values for GA were 0.07% in AOO and 1.5% in PG. In another LLNA study by Basketter et al. (2000) the calculated EC3 for glutaraldehyde was 0.2% in AOO.

In a non-guideline guinea pig open epicutaneous test (Zeller, H. 1975, BASF A6.01.5_01) glutaraldehyde formulation Relugan GT (25 % GA, 8% methanol, 67% water) was tested on female guinea pigs (10 animals). For induction, a skin area of about 25 cm^2 was clipped of each animal on the fore region of each flank. Four hours later the application site (the left flank) was degreased with ether and 25 % glutaraldehyde was applied (3 times) topically using a piece of cotton wool. The application was repeated once daily on five consecutive days per week, over two weeks (total of 10 applications). The shaved right flank remained untreated. Challenge was performed after 11 days following induction. Both flanks of each animal were clipped and after four hours the right flank of each animal was degreased with ether and 25 % glutaraldehyde was applied (single application). Three control animals, which had not been subjected for induction, were treated similarly. The animals were examined for skin reactions 12 hours later.

Following induction the skin of the 10 treated animals showed thick bloody scabs. Following challenge distinct spotted erythrema was reported for all 10 treated animals whereas the control animals showed no skin reaction. In conclusion, the study showed that 25 % glutaraldehyde was sensitising to guinea pig skin.

4.6.1.2 Human information

With respect to the human evidence on glutaraldehyde-induced skin sensitisation potential the following available open source information on human volunteers and on skin patch tests is presented as summaries. In the publication by Shaffer and Belsito (2000) there are references to 13 other case-reports or skin patch tests published before 2000.

• Marzulli F.N. & Maibach H.I., The use of graded concentrations in studying skin sensitizers: Experimental contact sensitization in man. Fd Cosmet. Toxicol. 12: 219-227, 1974.

Two concentrations of glutaraldehyde (0.1 % and 5.0 %) were used for induction and one concentration (0.5 %) for challenge in a Draize test. The subjects were male human volunteers. In inductions, 0.5 g of the test material was applied to the upper lateral portion of the arm and covered with an occlusive patch. This was repeated 10 times over a period of 3.5 weeks. After a 2-week

break in exposures, a challenge of 72 h was performed using a non-irritant concentration of 0.5 % glutaraldehyde. None of the 102 volunteers gave a positive response at the induction concentration of 0.1 % glutaraldehyde, while 7 of 30 reacted at the induction concentration of 5.0 % glutaraldehyde. Conclusion: The NOAEC for sensitization was 0.1 % and LOAEC 5.0 % because of the 50-fold dose spacing.

• Shaffer M.P. & Belsito D.V., Allergic contact dermatitis from glutaraldehyde in health-care workers. Contact Dermatitis 43: 150-156, 2000.

In the University of Kansas dermatology clinics, 516 patients were tested for skin sensitisation to various chemicals in a skin patch test between July 1994 and June 1999. Out of these, 468 were tested for glutaraldehyde and 17 were found positive (3.6 %). There were 51 health care workers and 9 of these were positive (17.6 %), while among the non-health care workers there were 8 positive from 417 (1.9 %). Two of the health care workers gave a positive result to both glutaraldehyde and formaldehyde, and additional 2 were positive to formaldehyde but not glutaraldehyde. Among the non-health care workers, 42 were positive to formaldehyde and 5 of these also to glutaraldehyde. Conclusion: Glutaraldehyde exposure had caused skin sensitisation in nearly one fifth of the tested health care workers, being the most common positive test result among the chemicals tested. Two of the nine glutaraldehyde-positive patients were also positive to formaldehyde.

4.6.1.3 Summary and discussion of skin sensitisation

All animal studies indicate that glutaraldehyde is a potential skin sensitizer. There were unequivocal positive responses in guinea pigs (Blaszcak 1993, Dow A6.1.5/01; Zeller, H. 1975, BASF A6.01.5_01) and in mice (Kimber, I. 1994, Dow A6.1.5/02, Basketter et al 2000,; Basketter et al 2003). Human data confirms the results from animal experiments of glutaraldehyde being a skin sensitizer.

4.6.1.4 Comparison with criteria

Glutaraldehyde is currently classified as Skin Sens. 1. Along with the new criteria in the 2nd ATP of CLP Regulation (286/2011) it is possible to classify sensitisers in sub-categories. The criteria for classification of skin sensitisers to sub-category 1A based on a GPMT study is ≥ 30 % responding ≤ 0.1% intradermal induction dose or ≥ 60% responding at > 0.1 % to < 1% intradermal induction dose. The criteria for sub-category 1B is ≥ 30 % to < 60% responding at > 0.1% to ≤ 1% intradermal induction dose or ≥ 30% responding at > 1% intradermal induction dose. In the described GPMT study (Blaszcak 1993, Dow A6.1.5/01) an intradermal induction dose of 0.1 % aqueous glutaraldehyde evoked skin sensitisation in 68% of the treated animals, therefore it should be classified in sub-category 1A.

The criteria for classification of skin sensitisers based on LLNA study is EC3 value ≤ 2% for sub-category 1A and EC3 value > 2% for sub-category 1B. In the described LLNA study (Kimber, I. 1994, Dow A6.1.5/02) glutaraldehyde was clearly sensitising based on the obtained SI values however the EC3 was not calculated. In two open source studies (Basketter et al. 2000, Basketter et al. 2003) EC3 values of 0.07 and 0.2 % have been obtained therefore glutaraldehyde should be classified in sub-category 1A.

Taken together, the most informative animal data allow and justify classification of glutaraldehyde into sub-category 1A. Other animal studies (Zeller, H. 1975, BASF A6.01.5_01) confirmed the sensitation potential of glutaraldehyde however sub-categorization is not possible due to the non-compliant nature of the study and the high dose used. In addition, the most relevant human data support the results of animal studies as summarised below:

The Draize test data on human volunteers (Marzulli and Maibach, 1974) showed that the topical induction concentration of 5% gave a positive response in 7/30 males (23.3 %) whereas the induction concentration of 0.1 % did not cause any response in 102 males. However it is difficult to draw definite conclusion on the potential of gluraraldehyde since there were only two doses with large spacing (50-fold) and the description of the size of the area of GA application was not given, therefore sub-categorization is not possible.

In a skin patch test (Shaffer and Belsito, 2000), 17 of the 468 tested subjects (3.6 %) were allergic to glutaraldehyde. Moreover, positive reactions were more than eight times likely in the health care workers (17.6 %) than in non-health care workers (1.9%). In all of the health-care workers positive response to glutaraldehyde were found to be currently relevant, in other words they were exposed to or were known to be exposed to products containing glutaraldehyde. On the other hand in non-health care workers current relevance of glutaraldehyde was not found in any. Both of these results point to a high frequency of occurrence of skin sensitisation and could thus allow sub-categorization into 1A. In addition, there are 13 other case-reports mainly on health care workers and skin patch tests on glutaraldehyde referenced in Shaffer and Belsito (2000) that could support the aforementioned conclusion.

4.6.1.5 Conclusions on classification and labelling

Glutaraldehyde is currently classified as Skin Sens. 1 under the CLP Regulation. According to the criteria in the 2nd ATP of CLP (286/2011), classification as **Skin Sens. 1A; H317** is proposed. Under DSD glutaraldehyde is currently classified as R43 and no change is proposed to the existing classification.

In conclusion, it is proposed to classify glutaraldehyde as follows:

CLP: Skin Sens. 1A; H317

DSD: R43

SCL: The classification criteria according to CLP and sub-categorization for the skin sensitisation potency render the current SCL (0.5%) superfluous and thus the SCL is proposed to be removed. The available data justifies the 0.1% GCL for Skin Sens. 1A and there is no need to set a new SCL.

For the classification under DSD there are two options with regard to SCL: either to keep the existing SCL of 0.5 % or adopt a lower SCL of 0.1% to uniform the two classification systems. In the opinion of the DS both options are scientifically justified.

4.6.2 Respiratory sensitisation

4.6.2.1 Non-human information

Table 21: Summary table of a respiratory sensitation study

Species	Method	Number of animals sensitised/total number of animals (or description of other results)	Result	Reference
Mouse, BALB/c (6 ♀/group)	Mouse IgE test No guideline, no GLP 50 % aqueous GA diluted in acetone to final GA concentrations of 0, 2.5, 5 and 12.5 %	Dose-dependent increase in serum IgE, µg/ml, mean ± SE: 0.304 ± 0.024 (acetone only), 0.516 ± 0.038, 0.640 ±0.195 and 1.280 ± 0.193 Negative control (non-respiratory sensitizer DNCB): 0.212 ± 0.042 µg/ml Positive control (trimellitic anhydride): 1.991 ± 0.160 µg/ml	Potential respiratory sensitizer	Kimber, I. (1994) Dow A6.1.5/02

A mouse IgE test was performed to assess the potential for respiratory sensitising (Kimber, 1994, Dow A6.1.5/02). The test is based on measuring the elevation of IgE levels, which do not change in skin sensitisation but rise during respiratory sensitisation. Elevated IgE levels correlate with higher risk of asthma. Groups of six mice were shaved on flanks and dosed dermally with 50 µl of test material. Seven days later 25 µl of the same material at half of the initial concentration was applied to the dorsum of both ears. Fourteen days later the animals were sacrificed and blood was collected and serum prepared. The concentration of serum IgE was determined using ELISA and the results were compared to a positive (25 % trimellitic anhydride) or to a negative (1% DCNB; a known contact sensitizer that does not induce respiratory sensitisation) control. Glutaraldehyde gave a clear dose-dependent positive response indicating that it is a potential respiratory sensitizer.

4.6.2.2 Human information

Table 22: Summary table of relevant information on respiratory sensitisation

Study	Study setup	Result with regard to sensitizing effects	Conclusions on sensitized/non-sensitized population
Teta *et al*., 1995.	218 workers assigned to GA production or drumming 40-80 ppb in air (TWA)	No clear evidence of sensitization to GA 6 cases of possible sensitization not attributable to a particular chemical	**Conclusion: Relatively few people are sensitized at frequent exposures to GA concentrations of 10 to more than 100 ppb (TWA up to 80 ppb).**
BASF A6.12.1_01 Monitoring of manufacturing plant personnel, 2007	Manufacturing plant Up to 8 ppb in air	No sensitization cases reported	**Low GA concentration (≤ 8 ppb) in the manufacturing plant air did not result in verified sensitization.**

Study	Study setup	Result with regard to sensitizing effects	Conclusions on sensitized/non-sensitized population
Pałczyński *et al*., 2001.	A) 11 cases of asthma assumed to be due to GA B) 10 atopic patients with perennial asthma and rhinitis C) 10 healthy individuals No data on exposure	In contrast to groups B and C, GA challenge resulted in strong increases in allergy and asthma markers in group A: • 25-fold increase in the numbers and percentages of eosinophils • 27-fold increase in the numbers and percentages of basophils • 23-fold increase in ECP concentration • Increase in mast cell tryptase concentration (below LOQ before stimulus)	No conclusions can be made with regard to a possible sensitization threshold.
Gannon *et al*., 1995	Eight workers whose asthmatic symptoms improved when away from work **Endoscopy suites**: personal samples, short term median 39 ppb (range 27 to 230 ppb) **Darkrooms**: all short term levels below detection limit of 2.2 ppb	Occupational asthma was confirmed in 7 cases, all of whom had 1) peak expiratory flow (PEF) records suggestive of occupational asthma and 2) gave positive results in specific bronchial challenge tests to GA Exposure data on the sensitized cases: • Three endoscopy nurses had repeated short-term exposure to at least 27 ppb GA • One darkroom technician was exposed to GA-containing developers regularly during 23 years. Static air GA concentrations were less than 2.2 ppb, but no personal measurements were made No exposure data is available for two cases, and one further case (secretary) was reportedly only exposed to newly developed X-ray films.	The endoscopy nurses that became sensitized had experienced repeated short-term exposure to concentrations of at least 27 ppb GA The concentration that the darkroom technician was exposed to is probably lower than this, but the measured level of 2.2 ppb is not a personal measurement and is probably an underestimation. Furthermore, exposure had taken place during 23 years and peak exposure levels have most likely been significantly higher. **Conclusion: Three of the four cases with exposure data had exposure to at least 27 ppb GA. The fourth case is difficult to interpret with regard to the concentration that caused sensitization.**

Study	Study setup	Result with regard to sensitizing effects	Conclusions on sensitized/non-sensitized population
Pisaniello *et al*., 1997	135 endoscopy nurses and 132 unexposed nurses in the same hospitals Highest and lowest geometric mean values: • 93 ppb in endoscopy areas without LEV • 14 ppb in operating theatres with LEV	No information on asthma or respiratory sensitization Wheezing (23 vs. 20.5 %) and cough (17 vs. 13.6 %) were more prevalent in the exposed nurses, but without statistical significance Headache, lethargy and symptoms in the skin, eye and throat were connected with combined inhalation and dermal exposure to GA	No conclusions can be made with regard to a possible sensitization threshold.
Di Stefano *et al*., 1999	24 health care workers with presumed occupational asthma due to GA exposure Mean GA in air: 51 ppb (range 15 to 205 ppb)	8 subjects studied by specific bronchial provocation test (SBPT); all positive 16 studied by serial PEFR monitoring; 13/16 positive 7/24 had GA-specific IgE antibodies	The lowest measured concentration in the short-term samples was 15 ppb and the mean value was 51 ppb "during activities likely to produce peak levels". **Conclusion: The sensitized workers have experienced repeated short-term exposure to concentrations of at least 15 ppb GA.**
Vyas *et al*., 2000	Survey of 348 current and 18 ex-nurses in 59 endoscopy units in UK (ex-nurses having left for health reasons) • Peak concentration range ND to 263 ppb; geometric mean 14.6 ppb • Peak concentrations above 50 ppb in 8/59 units	<u>Lower respiratory tract symptoms:</u> • 27/318 current nurses exposed to GA (altogether 30/348) • 12/18 ex-workers <u>1-month PEFR results:</u> • 17 analysable of those with lower respiratory tract symptoms; 3/17 positive <u>Mean % predicted FEV_1:</u> • Current workers with no lower respiratory tract symptoms: 104.5 • Current workers with lower respiratory tract symptoms: 99.3 • Ex-workers: 93.8	Lower respiratory tract symptoms were not linked to sensitization.

Study	Study setup	Result with regard to sensitizing effects	Conclusions on sensitized/non-sensitized population
Stenton *et al*., 1994	A single endoscopy nurse with symptoms of occupational asthma connected with GA exposure No data on exposure	Initial exposure: entering the workplace; marked asthmatic response After 7 and 8 months of no exposure, double-blind challenges gave inconsistent results in FEV_1 No clear immediate or late asthmatic reactions in the second series	**No conclusions can be made with regard to a possible sensitization threshold.**
Curran *et al*., 1996	20 GA-exposed workers (13 diagnosed with occupational asthma) Control group of 21 unexposed workers No data on exposure	No clear evidence of correlation between IgE levels and occupational asthma 12 of the 20 patients were without GA exposure 6 months prior to testing, allowing IgE decrease	**No conclusion with regard to possible threshold.** **Asthma was associated with GA exposure, but no information on exposure duration/level is available.**
Sutton *et al*., 2007	600 workers in two companies producing bioprosthetic heart valves • Company A: 3 to 100 ppb • Company B: ND to 830 ppb Exposure was > 50 ppb in 23/58 different tasks	2 cases of new-onset work-related asthma associated with GA during the 5-year period (likely to underestimate the true incidence)	Exposure to GA has taken place continuously over each work shift for several years. Exposure has frequently occurred to GA levels above 50 ppb. **Conclusion: Relatively few people are sensitized even at frequent exposures to above 50 ppb GA.**

Study	Study setup	Result with regard to sensitizing effects	Conclusions on sensitized/non-sensitized population
Havics & Bucherl, unpublished/submitted for publication	400 workers in the production area of a company producing bioprosthetic heart valves. Latex gloves were worn but no respiratory protection was used. Some of the workers have almost constant hand (in glove) contact with GA. Personal short-term samples: • Range 1 to 970 ppb • Yearly arithmetic means 29 to 232 ppb • Yearly medians 12 to 85 ppb • 20 % of samples above 80 ppb and 5 % above 325 ppb	1 substantiated case of work aggravated asthma (exposure conditions: 20 % of samples were above 80 ppb; 5 % of samples above 314 ppb) 2 further cases insufficiently described or analysed to make conclusions No new-onset asthma No significant complaints by the workers were reported during 10 years regardless of the high GA concentrations in the air. Only 6 respiratory-related cases were reported during 10 years in a facility of 400 workers with high exposure to GA.	Exposure to high GA concentrations has taken place. This study is not yet published, and overall the results indicate a surprisingly low level of effects regardless of the high exposure levels. **No conclusions can be made with regard to a possible sensitization threshold.** **Note:** Surprisingly few workers are affected and the results may be doubted. In other studies, lower levels of GA have caused symptoms like headache, lethargy, cough, pharynx irritation and pain in the eyes. The lack of any such complaints might suggest a systematic error in the study setup, although this cannot be verified. The healthy survivor effect may be involved. *The RMS received this unpublished work on February 9, 2012. It has apparently not been published by November 8, 2012.*
Waters *et al*., 2003	• 38 nurses exposed to GA • 38 nurses not exposed to GA Various tasks in endoscopy units and operating theatres • Highest reading > 100 ppb in all but one task • Maximum 150 ppb • Detection of aldehydes; not specific to GA	Sensitization or asthma was not considered Modest reductions in cross-shift FEV_1 (mean 30 ml) and FVC (mean 50 ml) in the exposed group. Peak exposure was the only independent predictor of reduction Exposure duration or total dose seemed to have no effect	**Conclusion: the results support the suggestion that avoiding peak exposures may be the key to reducing GA sensitization.** Conversely, low GA concentrations might be less likely to produce sensitization.

Study	Study setup	Result with regard to sensitizing effects	Conclusions on sensitized/non-sensitized population
Arif & Delclos, 2012	Questionnaire sent to 5600 healthcare professionals; 3650 responded No data on exposure	Work-related asthma symptoms: 132/3650 Work-exacerbated asthma: 41/3650 Occupational asthma: 33/3650 Odds ratios for GA and ortho-phthalaldehyde combined; 95 % CI: • Work-related asthma symptoms: 2.18 (1.17 to 4.07) • Work-exacerbated asthma: 1.57 (0.58 to 4.27) • Occupational asthma: 1.03 (0.29 to 3.58)	**No conclusions can be made with regard to a possible sensitization threshold.** Asthma was related to GA exposure, but no information on exposure duration/level is available.
Katagiri *et al*., 2006	31 exposed women; 101 unexposed control women 6 hospitals, 8 rooms with endoscope washing and disinfection Geometric means: 1.3 to 19.6 ppb Personal measurements: up to 94 and 85 ppb	Self-reporting (exposed vs. control): • Asthma (2/31 vs. 0/101) • Cough (9/31 vs. 5/101) • Pharynx irritation (3/31 vs. 1/101) • Pain in the eyes (8/31 vs. 0/101)	The asthma results are based on self-reporting and are not trustworthy. Exposure to up to 94 ppb had taken place. **No conclusions can be made with regard to a possible sensitization threshold.**
Pechter *et al*., 2005	Surveillance data from California, Massachusetts, Michigan, and New Jersey No data on exposure	GA exposure was associated with 8.9 % (27 cases) of work related asthma among health care workers during 1993-1997	**No conclusions can be made with regard to a possible sensitization threshold.**
McDonald *et al*., 2000	SWORD project; UK: occupational physicians reporting voluntarily new cases of occupational asthma No data on exposure	Cases suspected to be due to GA: • 30 (1989-1991) • 128 (1992-1994) • 133 (1995-1997) GA was associated with 291 cases out of the estimated 7387 occupational asthma cases (3.9 %)	**No conclusions can be made with regard to a possible sensitization threshold.**

Study	Study setup	Result with regard to sensitizing effects	Conclusions on sensitized/non-sensitized population
BASF A6.14_04 Monitoring of laboratory personnel, 2007	Pathology laboratory; GA used as fixative Five employees with exposure to GA 0.17 ppb to 3.3 ppb Maximum peak concentration 20 ppb	No adverse health effects related to GA exposure reported during 20 years	**The number of people affected was too low for conclusions with regard to a possible sensitization threshold.**
Diar Bakerly *et al*., 2008	Physicians in West Midlands, UK, reporting newly diagnosed cases of occupational asthma between 1991 and 2005 No data on exposure	1461 occupational asthma cases (85 % verified by confirmatory test; 94 % improved on holidays) Glutaraldehyde associated with 84 cases (6 %) Annual incidence of occupational asthma: 42/1000.000 in working population No consistent time trend	**No conclusion with regard to possible threshold.** Asthma was associated with GA exposure, but no information on exposure duration/level is available.
Liss *et al*., 2011	Retrospective analysis of successful claims filed 1998-2002 and classified as occupational asthma or work-exacerbated asthma in the health care sector No data on exposure	GA was given as the sensitizing agent in 3 of the 5 cases of occupational asthma GA was given as the exposure agent in 1 of the 115 cases of work-exacerbated asthma The record is assumed to be incomplete	**No conclusion with regard to possible threshold.** Asthma was associated with GA exposure, but no information on exposure duration/level is available.
Perdelli *et al*., 2008	GA concentration measurements in hospital rooms where instrument disinfection/washing took place Maximum concentration 8 ppb No personal samplers	-	**No conclusions can be made with regard to a possible sensitization threshold.**
Leinster *et al*., 1993	GA concentration measurements during cold sterilisation and x-ray development in 6 hospitals, 14 locations in South East England Personal samplers: • Mean values 1.2 to 41 ppb • Range 0.73 to 41 ppb	-	**No conclusion with regard to possible threshold.**

Study	Study setup	Result with regard to sensitizing effects	Conclusions on sensitized/non-sensitized population
Nayebzadeh, 2007	Exposure to GA was measured in 19 locations, 5 hospitals Personal sampling during 5 to 15 min Work practices were classified and resulted in: • "appropriate": mean 12 ppb, max 68 ppb • "poor": mean 51 ppb, max 150 ppb • "unsafe": mean 80 ppb, max 150 ppb Quantity of GA used did not correlate with exposure General ventilation systems were inefficient in controlling exposure, even at > 10 air changes/h	Irritant effects (eyes, nose) and headache correlated with work practices. The study concerns exposure levels; sensitization was not studied.	**Conclusion: No conclusions can be made with regard to a possible sensitization threshold.**

In the following short summaries of the studies listed in the table 16 are presented

Manufacturing plant personnel

- **Teta M.J. *et al., Absences of sensitisations and cancer increases among glutaraldehyde workers*. Toxic Substance Mechanisms 14: 293-305, 1995.**

Plant medical records, work restrictions, and clinic visits for accidental exposures between 1959 and 1992 were reviewed to determine the incidence of skin sensitisation, respiratory sensitisation, and allergic blepharoconjunctivitis among 218 workers assigned to glutaraldehyde production or drumming at a Union Carbide plant in the U.S. A mortality analysis of workers assigned to glutaraldehyde production from its start-up to 1959 through 1988 was conducted, and cancer incidences were compared with local population. In addition to glutaraldehyde, the workers handled other chemicals including known sensitizers. Glutaraldehyde concentrations in the air during the measurement years 1977-1992 were consistently below the OELs at the time, time-weighted averages being 40 to 80 ppb (currently the lowest OEL is 50 ppb) and the highest measured concentration 340 ppb in 1990 (not including the data from 1982 where new methodology and measurement problems resulted in figures up to 12.11 ppm). There was no evidence of sensitisation for 199 workers (95 %); five had documented cases related to chemicals other than glutaraldehyde, and six (3 %) had symptoms that may have indicated sensitisation but were not attributable to a particular chemical. These symptoms occurred in the nose (sinus discomfort, irritation,

inflammation, bleeding), the eye (e.g. itching/irritation, conjunctivitis) and on the skin (rash and contact dermatitis). Some of these may have been related to accidental glutaraldehyde exposure. Some of the effects were considered as fungal infections, but the cause-effect relationship is unclear. Mortality and cancer incidence were lower than in the local control population. **Conclusion**: There was no clear evidence of sensitization to glutaraldehyde, and no effect was seen on cancer or mortality.

- **BASF report "Monitoring of manufacturing plant personnel", 8 June 2007 (BASF A6.12.1_01).**

In a manufacturing plant of BASF in Germany, no cases of adverse health effects related to glutaraldehyde exposure were reported during 15 years. In regular measurements over 20 years, the highest measured glutaraldehyde concentration in the air was 0.032 mg/m3 (8 ppb). This data is based on the company statement whose reliability the RMS cannot evaluate. Conclusion: The very low exposure concentrations (up to 8 ppb) did not cause any adverse health effects. No further toxicological conclusions can be made due to the low concentrations to which workers have been exposed.

Cohort studies and case reports

- **Pałczyński et al., Occupational asthma and rhinitis due to glutaraldehyde: changes in nasal lavage fluid after specific inhalatory challenge test. Allergy 55: 1186-1191, 2001.**

Three study groups were compared: A) 11 health-care workers with occupational asthma assumed to be due to glutaraldehyde, B) 10 atopic patients with perennial asthma and rhinitis, and C) 10 healthy individuals. In an inhalatory challenge test with glutaraldehyde, subjects in group A were positive, and those in groups B and C negative. Groups B and C had no previous occupational exposure to glutaraldehyde. A "nasal pool" technique was used to evaluate the cellular response and the changes in eosinophil cationic protein (ECP; also known as ribonuclease 3) and mast-cell tryptase concentration in nasal lavage fluid before and after (30 min, 4 h and 24 h) an inhalatory provocation with glutaraldehyde and placebo. Results. In group A, there was a significant increase in the numbers and percentages of eosinophils (25-fold) and basophils (27-fold), and in ECP (23-fold) and mast cell tryptase (below LOQ before stimulus) concentrations. In groups B and C, there was a moderate increase in the basophil percentages (highest in group B, 3.5-fold), eosinophil percentages (highest in group B, 4-fold), while the response with regard to ECP and mast cell tryptase was either minimal or non-existent. Group A did not produce a response to placebo. Other possibly sensitising chemicals were not tested. Conclusion: Using two cellular and two molecular markers for allergy and asthma, the subjects that were assumed to have glutaraldehyde-induced occupational asthma reacted strongly to a glutaraldehyde challenge, while healthy controls and atopic patients with perennial asthma and rhinitis did not.

- **Gannon P.F.G. et al., Occupational asthma due to glutaraldehyde and formaldehyde in endoscopy and x ray departments. Thorax 50: 156-159, 1995. Dow 6.12.2(2); BASF 6.12.4_05**

Eight workers were studied who had a history of asthmatic symptoms that improved when away from work, and had exposure to glutaraldehyde. They were investigated by measuring peak expiratory flow (PEF) with 2-hour intervals during 4 weeks, and using specific bronchial provocation tests using 0.9 % saline, 1 % formaldehyde and 2 % glutaraldehyde in the challenge.

The diagnosis of occupational asthma was confirmed in seven workers, all of whom had PEF records suggestive of occupational asthma and gave positive results in specific bronchial challenge tests to glutaraldehyde. Three of these gave positive results in the specific bronchial challenge to formaldehyde as well, while three others were negative and one was not tested. Two of those positive to formaldehyde used also formaldehyde at work. The mean level of glutaraldehyde in air during the challenge tests was 0.068 mg/m3 (16 ppb), which is lower than the concentrations measured in 13 endoscopy suites but higher than in six x-ray darkrooms. During decantation in endoscopy suites, median short term levels were 0.16 mg/m3 (39 ppb) with a range of 0.11 to 0.94 mg/m3 (27 to 230 ppb). In darkrooms all the short term levels were below the apparent (not mentioned specifically) detection limit of 0.009 mg/m3 (2.2 ppb). The duration of exposure to glutaraldehyde was 6 months to 23 years before the onset of symptoms suggestive of occupational asthma. It should be noted that there was no control group, and of the possible confounding substances used at work, only formaldehyde was tested in addition to glutaraldehyde. Conclusion: Seven workers had occupational asthma whose symptoms were triggered by glutaraldehyde.

- **Pisaniello et al.: Glutaraldehyde exposures and symptoms among endoscopy workers in South Australia. Appl. Occup.Environ. Hyg. 12: 171-177, 1997. Dow 6.12.4(4); BASF 6.12.4_3**

Glutaraldehyde-exposed 135 endoscopy nurses and 132 unexposed nurses in the same hospitals were interviewed and their worksites were inspected. Inhalational exposure while using glutaraldehyde was determined and dermal exposure was assessed with skin pads. The measured overall geometric mean inhalational exposure concentration was 32 ppb, the highest mean of 93 ppb being in endoscopy areas with no local exhaust ventilation. Nurses exposed to glutaraldehyde reported more headache, lethargy and symptoms in the skin, eye and throat than the control group. The throat symptoms were mostly itching or tingling (10 vs. 4 % in the control group) and an unpleasant taste (9 vs. 3 %). No information is given on asthma or respiratory sensitization. Conclusion: Headache, lethargy and symptoms in the skin, eye and throat were connected with combined inhalation and dermal exposure to glutaraldehyde.

- **Di Stefano F. et al.: Glutaraldehyde: an occupational hazard in the hospital setting. Allergy 54:1105-1109, 1999.**

A group of 24 health care workers were identified with respiratory symptoms suggestive of occupational asthma due to glutaraldehyde exposure. Asthmatic symptoms were investigated with peak expiratory flow rate (PEFR) monitoring. During PEFR monitoring the glutaraldehyde concentrations in workplace air were measured by samplers worn by the operator. Short-term measurements gave a mean concentration of 0.21 mg/m3 (51 ppb) and a range of 0.06 to 0.84 mg/m3 (15 to 205 ppb). For eight of the subjects, the specific bronchial provocation test (SBPT) was performed with a mean glutaraldehyde concentration of 0.075 mg/m3 (18 ppb; range 0.065-0.084 mg/m3), and all subjects gave a positive response indicating occupational asthma (late reaction in five and dual reaction in three subjects). In 13 out of the 16 remaining workers, the serial PEFR monitoring showed a work-related effect, while for three workers occupational asthma was not confirmed. Measurements of specific IgE antibodies to glutaraldehyde-modified proteins were positive in seven patients (29 %). The results are suggestive of glutaraldehyde being the causative agent of occupational asthma in the group of health care workers that were identified in a surveillance scheme. There was no control group and a direct cause-effect relationship cannot be demonstrated. Conclusion: Respiratory symptoms were suggestive of occupational asthma caused by glutaraldehyde. Occupational asthma was demonstrated by at least one of the methods in 21 out

of 24 patients. Seven patients had glutaraldehyde-specific IgE antibodies, suggesting but not proving that occupational asthma was caused by glutaraldehyde.

- **Vyas et al.: Survey of symptoms, respiratory function and immunology, and their relation to glutaraldehyde and other occupational exposures among endoscopy nursing staff, Occupational and Environmental Medicine 57: 752-759, 2000**

Endoscopy nurses (348 nurses in 59 endoscopy units) in the United Kingdom and 18 ex-employees who had left their job for health reasons were surveyed. Any work-related symptoms were surveyed using questionnaires. Exposure measurements included personal airborne biocide sampling for peak and background concentrations. All ex-employees and 91 % of the current nurses were primarily exposed to glutaraldehyde, while the rest were exposed to a succinaldehyde-formaldehyde composite. Work related contact dermatitis was reported by 44 % of current workers exposed to glutaraldehyde and 44 % of ex-employees. The prevalence of work related symptoms in current glutaraldehyde exposed workers was 14 % for the eyes, 20 % for the nose, and 9 % for the lower respiratory tract, while these were all at least 50 % among the ex-employees. There were 30 current nurses with lower respiratory tract symptoms. For these, peak expiratory flow rates were recorded during one month and analysed using the OASYS-2 analysis program. The program revealed three cases of possible asthma, but re-evaluation of the data by two physicians concluded that none of these showed evidence of bronchial asthma. The RMS cannot verify these conclusions, which were also questioned in the journal as a response to the publication (BASF A6.12.4_01a). The mean percentage of the predicted FEV1 was 104.5 % for the current workers with no lower respiratory tract symptoms and 99.3 % for those with lower respiratory tract symptoms; for ex-employees it was 93.8 %. Exposures were above the maximum exposure limit of 0.2 mg/m3 (50 ppb) in eight of the units investigated. There was a clear relation between peak glutaraldehyde concentrations and work related chronic bronchitis and nasal symptoms but not to other symptoms. Conclusion: Glutaraldehyde caused clear irritant effects in the skin, eyes, nose and the lower respiratory tract, but asthma was not demonstrated. The results concerning asthma have been questioned in the journal where the article was published. There were few FEV1 results for the ex-employees but the significantly lower value for this group may be indicative of the reason for leaving the workplace where exposure to glutaraldehyde had occurred.

- **Stenton et al., Glutaraldehyde, asthma and work – a cautionary tale. Occup. Med. 44: 95-98, 1994. Dow 6.12.2(1); BASF 6.12.2_01**

A single endoscopy nurse had symptoms of occupational asthma connected with glutaraldehyde exposure. An initial exposure was arranged by entering the workplace, resulting in a marked asthmatic response. Seven and eight months after cessation of glutaraldehyde exposure, two series of double-blind challenges were performed on nine different days each, using various glutaraldehyde concentrations and saline as control. Reactions to glutaraldehyde challenge were inconsistent, as measured from the forced expiratory volume. No clear immediate or late asthmatic reactions were seen in the second series, which was performed due to inconclusiveness of the first series. Conclusion: The initial assumption of glutaraldehyde clearly being the cause of occupational asthma was questioned. Glutaraldehyde was not excluded from being the causative agent, but it was shown that there is no clear evidence of it.

- **Curran A.D. et al., Clinical and immunologic evaluation of workers exposed to glutaraldehyde, Allergy 51: 826-832, 1996. Dow 6.12.2(3); BASF 6.12.4_08**

Sera from 20 glutaraldehyde-exposed workers, 13 of whom had been diagnosed as having occupational asthma, and the control group of 21 unexposed workers were analysed for IgE antibodies in a radioallergosorbent test (RAST). Bovine and human serum albumin were modified by incubating them with glutaraldehyde, and used in RAST. Positive results were defined as the control group mean proportion of binding plus 2.5 × standard deviation (99 % confidence level), and total IgE levels above 150 kU/l. There were however false positives at IgE levels above this limit, and therefore positive results could not be verified using the predefined conditions. When testing only the sera with less than 150 kU/l, the glutaraldehyde-exposed group had a significantly elevated binding percentage in the RAST analysis ($p = 0.026$). The study failed to provide clear evidence of correlation between the specific analytical results and occupational asthma. This could at least partially be explained by the fact that 12 of the 20 patients had not been exposed to glutaraldehyde during at least 6 months prior to testing, which could have allowed the IgE levels to decrease. In further investigation of one of the patients, it was shown in a RAST inhibition assay that both GA-modified bovine and human serum albumin inhibited RAST binding, while there was no inhibition for two control sera. It was concluded that the one patient studied had specific IgE for GA-modified albumin despite the inability to clearly identify the asthma with the criteria on RAST and total IgE. No information is given on the workplace exposure concentrations. Conclusion: It was shown that a patient may have specific IgE antibodies while this is not evident in IgE testing.

- **Sutton P.M. et al., Glutaraldehyde exposures among workers making bioprosthetic heart valves. Journal of Occupational and Environmental Hygiene 4: 311-320, 2007.**

Exposure to glutaraldehyde was measured in two companies by personal air monitoring in a variety of tasks where glutaraldehyde exposure took place. In one company, the range of exposure concentrations in the air was 3 to 100 ppb, and in the other company it was from below the detection limit to 830 ppb. When sorted by different tasks, 40 % of the 58 different tasks involved exposure to more than 50 ppb glutaraldehyde in the air. The workers are reported to be continuously exposed to glutaraldehyde in the air during their work shift. During the 5-year period 1999 to 2003 there were 2 cases of new-onset work-related asthma associated with glutaraldehyde in these two companies, but this is reported to be likely to underestimate the true incidence. The tasks or presumed exposure levels of these two persons are not given. There were a total of 600 workers with potential exposure to glutaraldehyde.

- **Havics A.A. & Bucherl S., An evaluation of asthma risk due to glutaraldehyde at a medical device manufacturing facility. Unpublished/submitted for publication.**

Data was analysed from a company in California that produces bioprosthetic heart valves. Exposure data from years 1996 to 2005 indicated that personal 20-min samples and 240-min samples correlated poorly, as did also personal samples and area samples. The 20-min personal samples were considered more relevant as better representing peak exposures. The methodology of exposure measurements is not described. The values ranged from 1 ppb to 970 ppb, with yearly arithmetic means ranging from 29 to 232 ppb and medians of 12 to around 85 ppb. Altogether, 20 % of the 20-min samples were above 80 ppb and 5 % above 325 ppb. Only one substantiated case of work aggravated asthma was identified among the approximately 400 workers, and two further cases were insufficiently described or analysed to make conclusions (Cases 4 and 5). No cases of new-onset asthma were reported. The authors consider 325 ppb in the air as the threshold for no adverse effects for non-sensitised individuals and between 80 and 314 ppb for sensitized or pre-disposed individuals.

- **Waters A. et al., Symptoms and lung function in health care personnel exposed to glutaraldehyde. American Journal of Industrial Medicine 43: 196-203, 2003.**

Exposure to glutaraldehyde was measured in various tasks in endoscopy units and operating theatres in Australia. Nurses were selected among those who were exposed to glutaraldehyde (38) and those who worked in areas where glutaraldehyde was not used (38). These subjects answered questionnaires concerning symptoms, and their FVC (forced vital capacity) and FEV1 (forced expiratory volume in one second) were measured. Detailed information on glutaraldehyde concentrations in the air is not given. In all but one task the highest reading in the breathing zone exceeded 100 ppb, and the overall maximum was 150 ppb. The measuring system detected aldehydes and was not specific to glutaraldehyde.

There were modest reductions in cross-shift FEV1 (mean reduction 30 ml) and cross-shift FVC (mean reduction 50 ml) in the exposed group. Linear regression modelling suggested the peak exposure to be the only significant independent predictor of the reduction, while other possible factors such as duration of exposure or the total dose did not seem to have an effect. In the questionnaire only skin symptoms were clearly associated with glutaraldehyde exposure, and these were clarified to concern local effects in the hands and forearms. Sensitization or asthma was not considered.

- **Arif A.A. & Delclos T.L., Association between cleaning-related chemicals and work-related asthma and asthma symptoms among healthcare professionals. Occupational & Environmental Medicine 69 (1): 35-40, 2012.**

A questionnaire was sent to 5600 healthcare professionals, and 3650 responded. The information included asthma conditions that were divided into 1) work-related asthma symptoms, 2) work-exacerbated asthma, 3) occupational asthma and 4) none (mutually exclusive categories). The use and use frequencies of various substances as either cleaning agents or instrument disinfectants/sterilants were inquired. Of the 3650 responders, 132 reported work-related asthma symptoms, 41 work-exacerbated asthma and 33 occupational asthma. The odds ratio (OR) for glutaraldehyde and ortho-phthalaldehyde (OPA) combined was 2.18 (95 % confidence interval 1.17 to 4.07) for work-related asthma symptoms, 1.57 (0.58 to 4.27) for work-exacerbated asthma and 1.03 (0.29 to 3.58) for occupational asthma. The large confidence intervals of the latter two are explained by the relatively low numbers of responders reporting work-exacerbated or occupational asthma. The strongest effects were seen for bleach in cleaning (respective ORs of 3.72, 3.13 and 3.22) and chloramines in instrument cleaning/sterilation (3.81, 2.02 and 4.81). The study has obvious shortcomings due to self-reporting and because of an unavoidable healthy worker survival effect which is also seen as the lowest prevalence in the highest age quartile.

- **Katagiri H. et al., Indoor glutaraldehyde levels in the endoscope disinfecting room and subjective symptoms among workers. Industrial Health 44: 225-229, 2006.**

Exposure to glutaraldehyde in the air was measured at 6 hospitals in a total of 8 rooms where endoscope washing and disinfection took place. The subjective symptoms of 31 exposed women were compared to those of 101 unexposed control women using a questionnaire. Glutaraldehyde concentrations in the air had geometric means of 1.3 to 19.6 ppb, while personal measurements showed exposure levels of up to 94.2 and 84.9 ppb during the changing of the glutaraldehyde solution in the automatic washers. This high-exposure task is performed every 2 to 4 weeks. The women that were exposed to glutaraldehyde reported a variety of symptoms more frequently than those in the control group. These included asthma (2/31 vs. 0/101 in the control group), cough (9/31

vs. 5/101), pharynx irritation (3/31 vs. 1/101) and pain in the eyes (8/31 vs. 0/101). No attempts were made to clarify or verify the claimed symptoms.

- **Koda S. et al., Environmental monitoring and assessment of short-term exposures to hazardous chemicals of a sterilization process in hospital working environments. Acta Med Okayama 53 (5): 217-223, 1999.**

Glutaraldehyde concentrations in the air were measured in two hospitals in Japan. The detection limit was 200 ppb, and concentrations higher than this were only recorded in an endoscope unit lacking general ventilation. The two interviewed workers in the endoscope unit complained of headache and irritated eyes, nose and throat.

Surveillance data

- **Pechter E. et al., Work-related asthma among health care workers: surveillance data from California, Massachusetts, Michigan, and New Jersey, 1993-1997. American Journal of Industrial Medicine 47: 265-275, 2005.**

Surveillance data that was collected on a mandatory basis from California, Massachusetts, Michigan, and New Jersey revealed 1879 diagnosed cases of work related asthma, 305 of these being health care workers. Among the health care workers, 27 cases (8.9 %) were reported to be related to glutaraldehyde while 5 % were related to formaldehyde. Glutaraldehyde was the substance most commonly reported after "cleaning products" and "natural rubber latex". There was no information on the tests performed in each case. Conclusion: Glutaraldehyde exposure was associated with 8.9 % of work related asthma among health care workers.

- **McDonald J.C. et al., Reported incidence of occupational asthma in the United Kingdom, 1989-97, Occup. Environ. Med 57: 823-829, 2000.**

In the SWORD (Surveillance of Work Related and Occupational Respiratory Disease) project in the UK, chest and occupational physicians reported voluntarily new cases of occupational asthma. The number of cases suspected to be due to glutaraldehyde were 30 (1989-1991), 128 (1992-1994) and 133 (1995-1997). Reporting was voluntary and was based on the expert opinion of the physician, without any attempts to verify the causes of asthma in the reported cases. Conclusion: This study gives an indication of the frequency of occupational asthma that is connected with glutaraldehyde exposure, but does not give any evidence of causality.

- **BASF report "Monitoring of laboratory personnel", 8 June 2007 (BASF A6.14_04).**

Glutaraldehyde concentrations were measured in a pathology laboratory where glutaraldehyde is routinely used as a fixative. Judging by the data available, the concentrations in the air mostly ranged between 0.0007 and 0.014 mg/m3 (0.17 ppb to 3.3 ppb), with maximum peak concentration of 0.085 mg/m3 (20 ppb). No cases of adverse health effects related to glutaraldehyde exposure were reported during 20 years. Conclusion: The very low exposure concentrations did not cause any adverse health effects. No further toxicological conclusions can be made due to the low concentrations to which workers have been exposed.

- **Diar Bakerly N. et al., Fifteen-year trends in occupational asthma: data from the Shield surveillance scheme. Occupational Medicine 58: 169-174, 2008.**

Physicians in West Midlands, UK, were asked to provide details of newly diagnosed cases of occupational asthma. There were 1461 cases reported between 1991 and 2005, of which 85 % were verified by a confirmatory test and 94 % were reported to improve on holidays. The annual incidence of occupational asthma was 42 per million in the working population, and there was no consistent trend in the incidence over time. Glutaraldehyde was associated with 84 of the cases (6 %).

- **Liss G.M. et al., Work-related asthma in health care in Ontario. American Journal of Industrial Medicine 54: 278-284, 2011.**

A retrospective analysis was made of the successful claims filed between 1998 and 2002 to the Workplace Safety & Insurance Board (WSIB) and classified as occupational asthma or work-exacerbated asthma in the health care sector. There were 5 cases of sensitizer-induced occupational asthma and 115 cases of work-exacerbated asthma. Glutaraldehyde was given as the sensitizing agent for 3 of the 5 occupational asthma cases, one of these classified as 'possible' and two as 'definite'. For work-exacerbated asthma, glutaraldehyde was given as the exposure agent in only one of the 115 cases. The authors mention several reasons why the record might be incomplete: it contains those cases that the claimant has been willing to file, and the requested information and possible examinations have been successfully performed.

Other information

- **Perdelli F. et al., Evaluation of environmental contamination by glutaraldehyde in an outpatient facility for digestive endoscopy in an Italian hospital, International Journal of Environmental Health Research 18(1): 73-78, 2008.**

Glutaraldehyde concentrations in the air were measured in a hospital in static positions in the centre of each room at normal breathing height. Glutaraldehyde was detected in rooms where instrument disinfection and washing took place. These activities resulted in similar concentrations in the air, and the highest concentration measured was 0.0327 mg/m3 (8.0 ppb). This study suffers from the lack of personal samplers and thus localised higher glutaraldehyde concentrations may have occurred. No connection is made between the exposure and any health effects.

- **Leinster P. et al., An assessment of exposure to glutaraldehyde in hospitals: typical exposure levels and recommended control measures, British Journal of Industrial Medicine 50: 107-111, 1993.**

Glutaraldehyde concentrations in the air during cold sterilisation and x-ray development were measured in six hospitals and a total of 14 locations in South East England. Using personal samplers, the mean concentrations were between 0.005 and 0.17 mg/m3 (1.2 and 41 ppb) and the overall range was 0.003 to 0.17 mg/m3 (0.73 to 41 ppb) although the highest value is not available as the range is not given for the activity producing highest air concentrations (cleaning suction bottles). When static monitoring was used, the mean concentrations were at the same range and the maximum concentration was 0.23 mg/m3 (56 ppb). In 9 out of the 14 locations there was no mechanical ventilation, and windows were closed in all 14 locations.

- **Nayebzadeh A., The effect of work practices on personal exposure to glutaraldehyde among health care workers, Industrial Health 45: 289-295, 2007.**

Air samples were taken in 19 locations in five hospitals in the breathing zone by personal sampling to measure exposure to glutaraldehyde during 5 to 15 min. The work practices were monitored and

classified as "appropriate", "poor" and "unsafe", and resulted in mean exposure rates of 12, 51 and 80 ppb, and maximum concentrations of around 68, 150 and 150 ppb, respectively. Irritant effects (burning or itchy eyes; itchy nose) and headache were found to correlate with the work practices and consequently with peak exposure to glutaraldehyde. Correlation could not be established between work practices and cough/sneezing/runny nose. Although there was no control group without exposure to glutaraldehyde, it should be noted that even in the group with "appropriate" work practices 14 of the 27 cases reported headache and 11-22 % reported various irritant effects (but it is not mentioned whether e.g. "burning eyes" and "itchy eyes" were mutually exclusive categories). The quantity of glutaraldehyde solution used did not correlate with exposure. General ventilation systems were inefficient in controlling the exposure rates even when there were more than 10 air changes per hour. Local exhaust ventilation is recommended. Conclusion: Work practices determine the exposure rate to a large extent, while even appropriate practices may result in exposure rates above the OEL of 50 ppb. The quantity of glutaraldehyde solution or the efficiency of general ventilation do not correlate with exposure.

4.6.2.3 Summary and discussion of respiratory sensitisation

Both animal and human evidence imply that glutaraldehyde is respiratory sensitizer. However, despite the abundance of data on respiratory sensitisation potential of glutaraldehyde, a number of uncertainties remain with respect to both the actual concentrations that have caused sensitization and the frequency of sensitization among the exposed populations. In general the data indicates that only a small proportion of the exposed population develop sensitization, and that sensitization seems to occur where relatively high GA concentrations have been detected (see Gannon et al., 1995; Di Stefano et al., 1999; Sutton et al., 2007; Waters et al., 2003). This interpretation is in line with the current understanding that there is a dose-response relationship for respiratory sensitization.

Also one case of sensitization after exposure to a very low GA concentration has been described (Gannon et al., 1995). An X-ray secretary was reportedly exposed to GA only through newly developed X-ray films, and reacted equally to GA and to formaldehyde in a special bronchial provocation test. No GA concentration measurements were made, and the workspace was not described (ventilation, proximity to the darkroom, etc.). Furthermore, it should be noted that respiratory hypersensitivity may also follow from a dermal challenge (see e.g. REACH Guidance on Information Requirements and Chemical Safety Assessment; Chapter R.7a), which might be the case here. Overall there is insufficient information to consider this as an example of a very low GA concentration in the air causing sensitization. In conclusion, no verified sensitization cases have been found where peak GA concentration in the air would have been below around 20-30 ppb.

It is considered likely that sensitization to glutaraldehyde is to a large extent connected to the peak exposure rates. Conversely, exposure to low concentrations of GA will most probably rarely lead to sensitization. The available studies where exposure has been low and no sensitization has occurred (see e.g. BASF A6.12.1_01; BASF A6.14_04) concern few human subjects and do not allow the conclusion that these GA levels were to be considered as safe. Other studies (e.g. Teta et al., 1995) have failed to identify the sensitizing agent, but this does not allow the conclusion that GA was not responsible for any of the cases.

The available evidence supports the general principle that sensitization occurs in workplaces where high exposure rates take place either regularly or as high peak concentrations. The available data seem to suggest that where sensitization has occurred, exposure has occurred to at least 20-30 ppb, and often much higher.

There is also mounting evidence of occupational asthma among health care workers, and this is often connected with glutaraldehyde exposure (e.g. Pechter et al. 2005, McDonald et al. 2000). The studies show that a number of health care workers that have been exposed to glutaraldehyde become asthmatic and the symptoms are triggered by glutaraldehyde (e.g. Gannon et al. 1995, Di Stefano et al. 1999, Pałczyński et al. 2001). There are however also counterarguments and one report (Stenton et al. 1994) describes a single case where initial strong opinion on glutaraldehyde-triggered asthma fails to be demonstrated either correct or incorrect. The question is therefore whether the evidence is sufficient to demonstrate that glutaraldehyde is a causative agent in the cases where asthmatic symptoms are triggered by glutaraldehyde.

Glutaraldehyde appears to be one of the known substances for which molecular diagnosis of asthma cannot easily be based on specific IgE measurements due to poor correlation with clinical symptoms. One of the studies (Curran et al. 1996) showed that a glutaraldehyde-related asthma patient with IgE levels too low for diagnosis nevertheless had specific IgE to glutaraldehyde-modified proteins. This is however only indicative evidence and firm conclusions cannot be based on this study.

Nasal lavage fluids were analysed for several asthma indicators after glutaraldehyde challenge (Pałczyński et al. 2001). Eosinophils and basophils are granulocytes that respond to parasitic infections, and are also associated with allergy and asthma. Following activation by an immune stimulus, eosinophils degranulate and release cytotoxic proteins, including eosinophil cationic protein (ECP). Increased levels of ECP are associated with inflammation and asthma. Serum ECP measurement is used for assessing asthma severity. Mast cell tryptase is a serine proteinase that is used as a marker of mast cell activation and is involved with allergic response. A significant increase was found in the numbers and percentages of eosinophils and basophils, as well as in the concentrations of ECP and mast cell tryptase. The difference was statistically significant when compared to the reactions of healthy controls and of atopic patients with perennial asthma and rhinitis, and to the study group reactions to placebo. All cellular and molecular indicators for asthma were therefore very clearly elevated as a response to glutaraldehyde challenge, while atopic patients showed a mild reaction.

There could be two explanations to the findings presented above: either glutaraldehyde causes asthma or another substance causes asthma and glutaraldehyde is capable of triggering an asthmatic response once asthma has been induced. Health care workers are exposed to a number of chemicals that might cause sensitisation, and it cannot be excluded that glutaraldehyde might trigger asthmatic symptoms even if asthma was not caused by glutaraldehyde. The DS considers that this explanation is unlikely to explain all the demonstrated cases for the following reasons: 1) glutaraldehyde is associated with a large portion of the asthmatic symptoms among the health care workers (Pechter et al. 2005, McDonald et al. 2000), 2) the most closely related chemical that also produces asthmatic symptoms is formaldehyde, and cross-reactivity appears to exist only in few cases (e.g. Gannon et al. 1995), and 3) none of the ten atopic patients reacted to glutaraldehyde challenge, nor gave a weak response that was not comparable to that of the main test group (Pałczyński et al. 2001). The lack of cross-reactivity between glutaraldehyde and formaldehyde has also been demonstrated in skin sensitisation (Shaffer & Belsito 2000). In conclusion, the DS considers that although it is conceivable that glutaraldehyde could have been a triggerer of symptoms of the asthma patients, it is likely that glutaraldehyde is also a causative agent.

4.6.2.4 Comparison with criteria

According to the CLP Regulation substances shall be classified as respiratory sensitisers in category 1 if there is evidence in humans that the substance can lead to specific respiratory hypersensitivity; and /or if there are positive results from an appropriate animal test. According to the 2nd ATP of the CLP Regulation (286/2011) sub-categorization of the substances in sub-category 1A (strong sensitizers) or in sub-category 1B (other respiratory sensitisers) shall be carried out if there is sufficient data. Substances classified into 1A should show a high frequency of occurrence in humans; or a probability of occurrence of a high sensitisation rate in humans based on animal or other tests. Severity of reaction may also be considered. Substances classified into 1B should show a low to moderate frequency of occurrence in humans; or a probability of occurrence of a low to moderate sensitisation rate in humans based on animal or other tests. Severity of reaction may also be considered. At present there are no recognized and validated animal models for the testing of respiratory hypersensitivity. Under certain circumstances data from animal studies may provide valuable information in a weight of evidence assessment.

According to the draft updated version of the CLP guidance on application of criteria, there is currently no clear way of establishing sub-categories for respiratory sensitisation. However, if there were compelling evidence available such as observations in the workplace it may be possible to determine a sub-category. Furthermore, classification into sub-categories is only allowed if data are sufficient, and care should be taken when classifying substances into category 1B when category 1A cannot be excluded.

DS is of the view that in the light of the presented data, the criteria described above mean that the evidence is sufficient for classification of glutaraldehyde for respiratory sensitisation but not for sub-categorisation. The potential for respiratory sensitisation has not been directly demonstrated, but the overall evidence is based on 1) the mouse IgE test (Dow A6.1.5/02), 2) human data showing asthma in relation to glutaraldehyde exposure and 3) the known skin sensitisation.

Despite the abundance of data on respiratory sensitisation potential of glutaraldehyde, a number of uncertainties remain with respect to both the actual concentrations that have caused sensitization and the frequency of sensitization among the exposed populations. Although the presented human data might be considered pointing towards subcategory 1B, strictly speaking category 1A cannot be excluded and thus sub-categorization is not possible.

4.6.2.5 Conclusions on classification and labelling

Glutaraldehyde is currently classified as Resp Sens. 1; H334 under the CLP Regulation. No change is proposed to the existing classification since classification into sub-categories is not possible. Under DSD glutaraldehyde is currently classified as R42 and no change is proposed to the existing classification.

In conclusion, it is proposed to classify glutaraldehyde as follows:

CLP: Resp. Sens. 1; H334

DSD: R42

4.7 Repeated dose toxicity

Not evaluated in this dossier.

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

Not evaluated in this dossier.

4.9 Germ cell mutagenicity (Mutagenicity)

Not evaluated in this dossier.

4.10 Carcinogenicity

Not evaluated in this dossier.

4.11 Toxicity for reproduction

Not evaluated in this dossier.

4.12 Other effects

Not evaluated in this dossier.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Environmental fate properties and environmental hazard assessment are based on studies and summaries belonging to the assessment of glutaraldehyde under Directive 98/8/EC performed by the Finnish Competent Authority as part of the Review Programme. The Document II-A (Draft, June 15th, 2012) of the Competent Authority Report (CAR), and study summaries (belonging to the Document III-A of the CAR) concerning the most relevant studies in terms of environmental hazard classification, are provided in section 13 of the IUCLID file.

5.1 Degradation

Table 23: Summary of relevant information on degradation

Method	Results	Remarks	Reference
Hydrolysis US EPA FIFRA N 161-1 GLP.	DT_{50} (12 °C) : pH 5 = 1437 d, pH 7 = 288 d, pH 9 = 130d Hydrolytically stable in environmentally relevant conditions		Jalali-Araghi et al. (1992a)
Hydrolysis. US EPA FIFRA N 161-N GLP	DT_{50} (12 °C) pH 5 = 1777 d, pH 7 = 1115 d, pH 9 = 180 d Hydrolytically stable		Levine (1991)
Photolysis US EPA FIFRA 161-2 GLP. Direct phototransformation	DT_{50} 196 d Photolytically stable at pH 5	DT_{50} in dark 355 d	Jalali-Araghi et al. 1992b
Biological degradation OECD guideline 301 A GLP	Readily biodegradable		Schaefer (2000)
Biological degradation OECD guideline 301 A GLP.	Readily biodegradable		Taeger (1993)
Biodegradation in seawater OECD 306 GLP	Potential to biodegrade in the marine environment		Doi (2000)
Biodegradation in seawater ISO 16221 GLP	Potential to biodegrade in the marine environment		Schwarz (2002)
US EPA Pesticide Assessment N 162-4 GLP Water/Sediment Simulation Study. Addition of ^{14}C-glutaraldehyde.	Water: DT_{50} 10.6 h (25 °C) DT_{50} 1.25 d (12 °C) For the whole water-sediment system, degradation DT_{50} was 11 h (25 °C). A part of the added ^{14}C was found in the sediment phase and was counted as glutaraldehyde in the calculation of degradation rate.	Mineralization 67.9% (based on $^{14}CO_2$ production).	Esser (1994a)
US EPA Pesticide Assessment N 162-3 GLP Water/Sediment Simulation Study Addition of ^{14}C-glutaraldehyde.	Water: DT_{50} 7.7 h (25 °C) DT_{50} 0.91 d (12 °C)	Primary biodegradation. Three metabolites identified. CO_2 production was insignificant	Esser (1994b)

Table 24: Summary of biological degradation tests

Guide-li-ne /Test method	Test type	Test para-meter	Inoculum			Addi-tional subs-trate	Test sub-stance conc.	Degradation		Reference
			Type	Conc	Adapt ation			Incuba-tion period	Degree [%]	
OECD 301A GLP	Ready biodegrad-bility	DOC	Activa ted sludge	20.6 mg solids/L (2.21 x 105 CFU/mL)	No	No	15 mg TOC/L	9 d	73%	Schaefer (2000)
OECD 301A GLP	Ready biodegra-dability	DOC	Activa ted sludge	30 mg sus-pended solids/L	No	No	20 mg DOC/L	28 d	90-100%	Taeger (1993)
OECD 306 GLP	Biodegra-dation in seawater	BOD	Sea-water	1.34 x 10^3 CFU/mL	No	No	3 mg /L	28 d	73.4%	Doi (2000)
ISO 16221 GLP	Biodegra-dation in seawater	CO_2	Sea-water	1494 mL sea water/ test vessel	No	No	10 mg TOC/L	70 d	90-100%	Schwarz (2002)
US EPA Pesticid e Assess ment N 162-4	Aerobic water/sedi-ment test	Radio-activit y (added ^{14}C-glutara ldehyd e)	River water/s edime nt	20gdw sediment , 100 ml water	No	No	9.45 µg/l (water phase)	30 d	100% (mainly due to minerali sation)	Esser (1994a)
US EPA Pesticid e Assess ment N 162-3	Anarerobic water/sedi-ment test	Radio-activit y (added ^{14}C-glutar-aldehy de)	River water/s edime nt	20gdw sediment , 100 ml water	No	No	9.45 µg/l (water phase)	123 d	100% (mainly due to primary degradat ion)	Esser (1994b)

5.1.1 Stability

Abiotic degradation

Hydrolysis

References:

Levine AM 1991. Hydrolysis of 14 C-Glutaraldehyde in aqueous solutions buffered at pH 5, 7 and 9. Centre for Hazardous Materials Research, Pittsburgh, Laboratory Project ID 003/0037001/89. GLP, Unpublished.

Jalali-Araghi, K., Ruzo, L.O. and Shepler, K. 1992a. Hydrolysis of [1,5-14C] glutaraldehyde at pH 5, 7 and 9 PRTL West, Inc. K-020301-016

Glutaraldehyde was stable to hydrolysis or hydrolysed slowly at pH 5 and pH 7 at room temperature (DT_{50} 102-628 d at 25°C and 288-1777 d at 12°C). None of the hydrolysis products exceeded 10% of applied radioactivity. Hydrolysis was faster at higher temperature and pH. The hydrolytical half-life of glutaraldehyde was 46-64 d at pH 9 at 25°C (130-180 d at 12°C). One hydrolysis product accounting more than 10% of applied radioactivity was formed in both studies at pH 9. The hydrolysis rate constants and half-lives were calculated assuming pseudo-first order kinetics. The studies are summarized in Table 25.

Conclusion: Glutaraldehyde is hydrolytically stable in the environmentally relevant conditions.

Table 25: Hydrolysis

Guideline / Test method	pH	Tempe-rature [°C]	Initial TS con-centration, C_0	Reaction rate constant, K_h [d]	Half-life, DT_{50} [d] (12°C)	Coefficient of correlation, r^2	Reference
US EPA FIFRA N 161-1 GLP	5	24.5-25.5	0.1 mmol/L (10 mg/L)	4.82×10^{-4}	1437	0.74	Jalali-Araghi et al. (1992a)
	7			2.41×10^{-3}	288	0.78	
	9			5.33×10^{-2}	130	0.84	
US EPA FIFRA N 161-1 GLP	5	25	111.47 ppm	3.90×10^{-4}	1777	0.0966*	Levine (1991)
	7		109.39 ppm	6.22×10^{-4}	1115	0.3222*	
	9		109.09 ppm	3.85×10^{-3}	180	0.9670	

* In the Competent Authority Report according to Directive 98/8/EC, the following footnote is presented: "As the correlation coefficients correlate the change in the dependent variable with a corresponding change in the independent variable, it is not a reliable statistic to use for lines with low slopes. Therefore, this correlation coefficient should not be interpreted to mean the data are unreliable".

Photolysis

Reference:

Jalali-Araghi, K., Ruzo, L.O. and Shepler, K. 1992b. Sunlight photodegradation of [1,5-14C] glutaraldehyde in a buffered aqueous solution at pH 5. PTRL West, Inc. K-020301-014

Glutaraldehyde did not degrade appreciably in a buffer system at pH 5. The half-lives of glutaraldehyde at 25°C were extrapolated for light exposed and dark samples and were 196 days and 355 days, respectively. The study is summarized in Table 26.

Conclusion: Glutaraldehyde is photolytically stable in aqueous solutions in the environmental relevant conditions.

Table 26: Photolysis in water

Guideline / Test method	Initial molar TS concen-tration	Total recovery of test subs-tance [% of appl.a.s.]	Photolysis rate constant (k^c_p)	Direct photolysis sunlight rate cons-tant (k_{pE})	Reaction quantum yield (ϕ^c_E)	Half-life ($t_{1/2E}$)	Reference
US EPA FIFRA 161-2 GLP	0.1 mmol/L (10 mg/L)	94.4±2.8% (overall material balance)	4.09 x 10^{-3}	Not determined	Not determined	Light-exposed samples = 196 days (R^2 = 0.861) Dark samples = 355 days (R^2 = 0.688)	Jalali-Araghi et al. (1992b)

Photo-oxidation in air

If glutaraldehyde is present in ambient air it is expected to exist to a great extent in the vapour phase, based on a vapour pressure of 44 Pa at 20°C (Table 11). Therefore photochemical reactions in air may be important. No experimental information is available for glutaraldehyde on photodegradation in air. The rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals was estimated using the model EPIWIN Version 3.20 including Aopwin (Atmospheric Oxidation Program) Version 1.92 (Environmental Protection Agency). The estimation methods used by the Aopwin are based upon the structure-activity relationship (SAR) methods. The Atkinson calculation method sums up the reactivity towards OH radicals of all structural elements. Using a 24-hours day and a mean daily OH concentration of 5.0 x 10^5 OH/cm³ a half-life of 8.2 hours was assessed (overall OH rate constant: 46.89 E-12 cm³/molecule sec).

The rapid reactivity of glutaraldehyde in the atmosphere indicated by SAR results is also supported by analogy with the homologous dialdehyde glyoxal (photolytic half-life in air: 0.7 d). Glutaraldehyde would be expected to degrade rapidly by photolytic reaction in air. Since the glutaraldehyde absorbs ultraviolet radiation maximally at wavelength of 280 nm this is the most important wavelength area for the direct photolysis of glutaraldehyde in the atmosphere.

Conclusion: Since the photochemical half-life of glutaraldehyde in air is 8.2 hours it is expected to degrade rapidly by photolytic reaction in air.

5.1.2 Biodegradation

5.1.2.1 Biodegradation estimation

Experimental data is available and therefore estimation is not needed.

5.1.2.2 Screening tests

Ready biodegradability of glutaraldehyde was demonstrated in two tests performed according to OECD 301A. This test is considered appropriate as glutaraldehyde is not expected to evaporate from aqueous solution due to its high water solubility (≥ 51.3 g/100 ml) and low Henry's law constant (0.0086 Pa m3 mol-1). OECD 301 guideline (page 5) states: "Unless adsorption of the test substance has been ruled out beforehand, tests which measure biodegradation as the removal of DOC, especially with activated sludge inocula, should include an abiotic control which is inoculated and poisoned". According to the adsorption test (see chapter 5.2.1) glutaraldehyde is mobile in sandy sediment and moderately mobile in soils. One of the two ready biodegradability tests reviewed here included an abiotic control, which is expected to show the potential for adsorption to activated sludge during the experiment.

Test 1:

Reference: Schaefer 2000. Ucarcide 250 Antimicrobial: Ready biodegradability by the dissolved organic carbon die-away test method, Wildlife International Ltd. DR-0222-1070-027

The biodegradability of glutaraldehyde (UCARCIDE® 250 antimicrobial, Batch number IS 782609; 50.9% glutaraldehyde, remainder water, impurities listed in confidential IUCLID) was tested using activated sludge from a municipal wastewater treatment plant as inoculum. Glutaraldehyde was applied at concentration of 15 mgTOC/L (OECD 301 requirement 10-40 mgDOC/l). Sodium benzoate was used as a reference substance at a concentration of 15 mgTOC/L. Inoculum blank test was also conducted and it was used to subtract the DOC concentration due to inoculum alone from those of the test and reference substances. The cell density of bacteria in the inoculum was $3.3 * 10^6$ (CFU/ml) (307 mg solids/L). Abiotic control assay was not performed.

Three test vessels per concentration were used (test volume = 2L). An aqueous mineral salts medium was used for the preparation of test suspensions to provide nutrients and trace elements. Test vessels were not closed. The test batches were stirred/mixed on 15-minute on-off cycles. pH of 7.1-7.2 is reported as test condition; however, it is not mentioned at which time point it was measured and whether pH changed during the experiment. The incubation temperature was 18 – 21 °C. There were small deviations from the test guideline concerning, e.g., pH and temperature, but these were not considered critical. DOC concentration was measured at 0, 1, 2, 3, 4, 5, 6, 9 days using a Shimadzu analyzer or equivalent and, for each sample, the average for duplicate analyses was reported. The percent degradation of test material based on DOC removal was determined.

The results are presented in Figure 2. An average of 13% DOC removal was observed on day 2. The DOC levels in the test material decreased markedly during days 3-5 and remained constant thereafter until the end of experiment (day 9). The biological degradation of glutaraldehyde was 74% after 9 days of incubation. Therefore, the pass level (70% of DOC removal within the 10 day window) was reached.

The reference substance, sodium benzoate, was utilised effectively as there was a 96% DOC removal in less than 9 days, indicating sufficient activity of the inoculum.

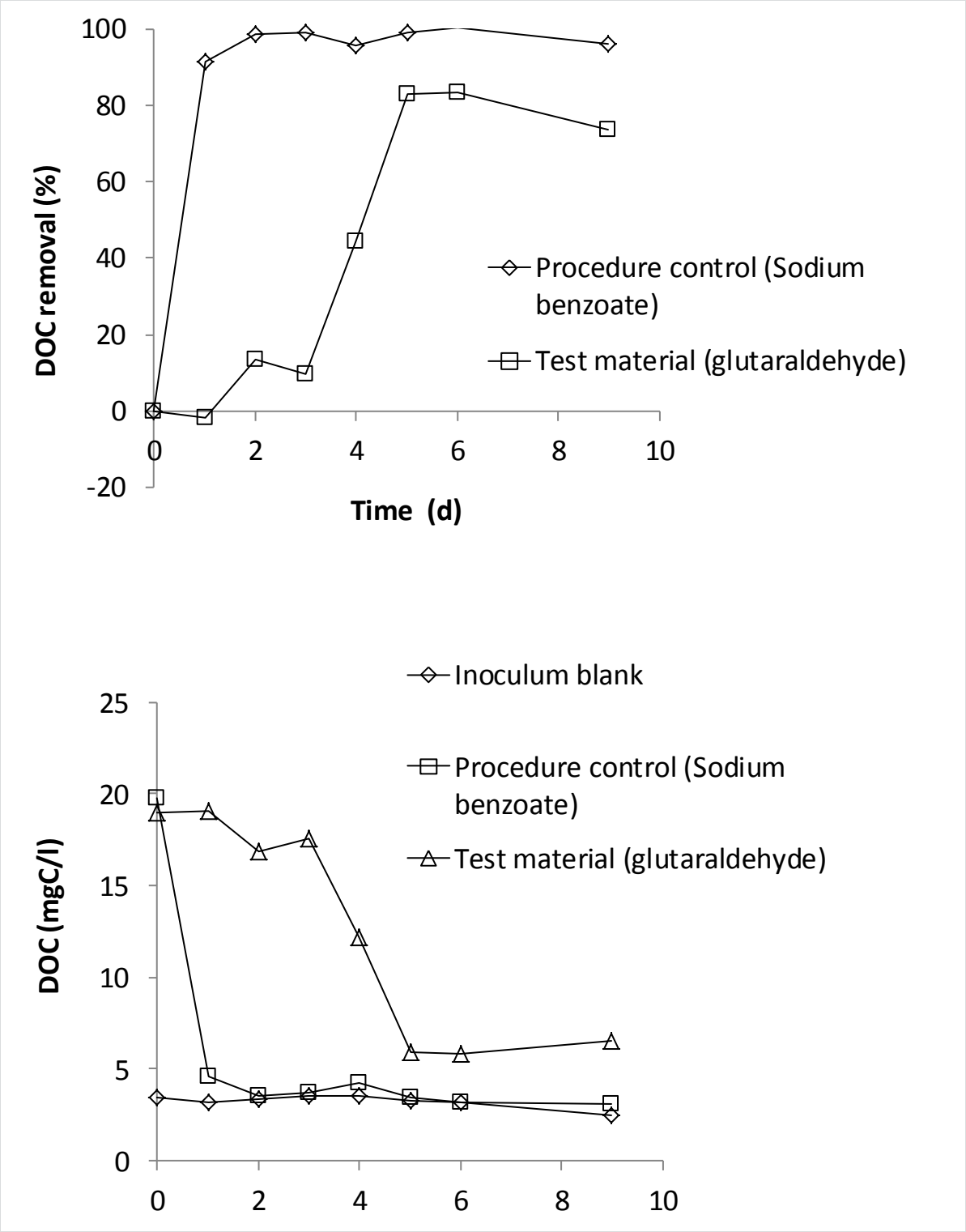


Figure 2: Percentage DOC removal (above) as calculated from the measured DOC levels (below) in ready biodegradability test 1

Test 2

Reference: Taeger K (1993) Determination of the Biodegradability or the Elimination of Protectol GDA in the DOC Die Away (ISO 7827)-Test. BASF AG, Department of Ecology, Ludwigshafen/Rhein, Germany, Report No: 93/0406/21/1 (Unpublished).

The biodegradability of glutaraldehyde (Protectol GDA (1,5-pentandial); batch number not specified, 50% glutaraldehyde; impurities listed in confidential Iuclid) was tested using activated sludge (from laboratory-scale waste water treatment plants fed with municipal and synthetic sewage) as inoculum. Glutaraldehyde was applied at concentration of 20 mgDOC/L (two replicates per concentration. Sodium benzoate was used as a reference substance at a concentration of 20 mgDOC/l. Inoculum blank test was also conducted and it was used to subtract the DOC concentration due to inoculum alone from those of the test and reference substances. The initial concentration of the inoculum was 30 mg suspended solids/l, which is the maximum allowed in OECD 301A instructions. Two replicates per concentration were used (test volume not specified). Abiotic control assay was performed.

Test vessels were not closed. pH was not specified. The incubation temperature was 20 – 25 °C. DOC concentration was measured at 0, 1, 3, 7, 10, 14, 18, 21, 24, 27, and 28 days by a Shimadzu 5000 DOC analyzer according to DIN 38409 Part 3 (1983). For each sample, the average for duplicate analyses was reported. The percent degradation based on DOC removal was determined. It is not mentioned what type or size of flasks were used and whether the flasks were shaken.

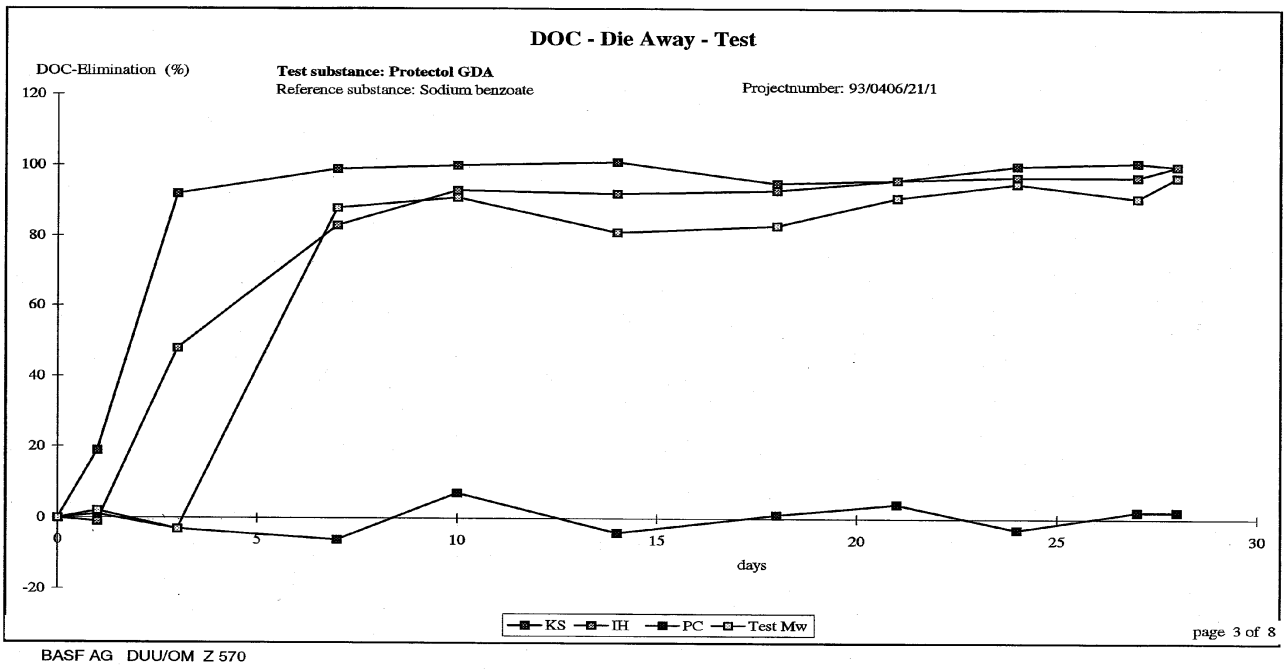


Figure 3: Percentage DOC removal in ready biodegradability test 2. KS = reference substance, IH = toxicity control, PC = abiotic control, MW = test substance (mean value)

The results are presented in Figure 3. The removal of DOC in the glutaraldehyde test started after 3-day lag period and increased to 88% removal by day 7. The DOC removal at the end of the experiment was 97%. Therefore, the pass level (70% DOC removal within the 10 day window) was reached.

No toxicity was indicated by the toxicity control.

The reference substance, sodium benzoate, was metabolised effectively as there was a 96% DOC removal in less than 9 days, indicating sufficient activity of the inoculum.

Abiotic degradation was in the range of 2-7%. The low DOC removal values (and lack of trend in DOC removal during the experiment) in the abiotic control test showed that abiotic degradation was negligible and that the DOC removal in the glutaraldehyde test was due to biodegradation.

Conclusion on ready biodegradability of glutaraldehyde: According to the CLP criteria glutaraldehyde is considered readily biodegradable. Both tests fulfilled the validity criteria of OECD 301 and the pass level (70% of DOC removal within 10 day window) was reached in both tests.

5.1.2.3 Simulation tests

Aerobic water/sediment test

Reference: Esser, T. (1994a) Aerobic Aquatic Metabolism of ^{14}C- Glutaraldehyde in River Water and Sediment, PTRL West, Inc., The Dow Chemical Company Report No: K-020301-015, GLP, Unpublished, 25 May 1994

The aerobic water/sediment study was carried out under GLP and according to US EPA Pesticide Assessment N 162-4. Glutaraldehyde dissipated with a half-life of 10.6 hours at 25 °C (corresponding to 1.25 d at 12 °C) from the aqueous phase, as estimated using glutaraldehyde concentrations in the aqueous phase and pseudo-first order kinetics. In the aqueous phase, the major metabolites that exceeded 10% were identified as glutaric acid (maximum of 20.2% detected at 12 hours) and carbon dioxide (CO_2) (Table 27). The metabolic pathway proposed is proposed in Figure 4. Glutaraldehyde was detected in the aquatic phase during the first 48 hours but was below detection in the measurements on the day 7 and beyond. It is noted in the report that serious losses of CO_2 occurred in sample treatment in measurements beyond the day 7 and therefore the results of those measurements were not tabulated. It is indicated, however, that CO_2 was the sole metabolite in the water beyond the day 7. At the end of the 30-day experiment 12% of the applied ^{14}C was found in aqueous phase and 14% in sediment phase. The aqueous radiocarbon loss during the experiment was 81.2% (difference between average ^{14}C percentages in water at days 0 and 30; calculated from values in Table 28), corresponding to the sum of the percentages of ^{14}C converted to CO_2 (67.9%; average of replicate values in Table 28) and ^{14}C found in the sediment phase at the end of the experiment (14%). A majority of the radiocarbon in sediment could not be extracted and its identity could not be ascertained (Table 29). The amount of non-extractable radioactivity in sediment at the end of the 30d experiment was 12.6% of applied radioactivity and 90% of the total radioactivity detected in the sediment phase at the same time point (Table 29). Total mean recovery of applied radioactivity was 93.3 ± 9.8% (Table 28).

In conclusion, glutaraldehyde dissipated in the aerobic water/sediment system with the half-life of 1.25 d (12 °C). The corresponding rate constant is 0.555 d^{-1}.

During the assessment of glutaraldehyde under Directive 98/8/EC it was questioned whether it is appropriate to use the dissipation half-life in exposure calculations. It was considered whether it is possible to calculate the degradation half-lives for water, sediment and the whole system according to the FOCUS guidance developed within the plant protection registration framework. It was concluded that it is not possible to derive a degradation rate in the sediment phase because glutaraldehyde is typically not sorbed to sediment but it rather reacts with functional groups and is

incorporated into the organic matter in the sediment. For the entire water-sediment- system, a degradation half-life of 11 hours was obtained; however, this is conservative value based on the assumption that the entire radioactivity extracted from the sediment phase is glutaraldehyde. The actual rate of degradation of glutaraldehyde for the entire system is likely to be higher due to the reactivity of glutaraldehyde. However, because the degradation rate in the entire water-sediment system (corresponding to a half-life of 11 hours) is similar to the dissipation rate in water (half-life 10.6 hours), the water dissipation rate can be used for risk assessment.

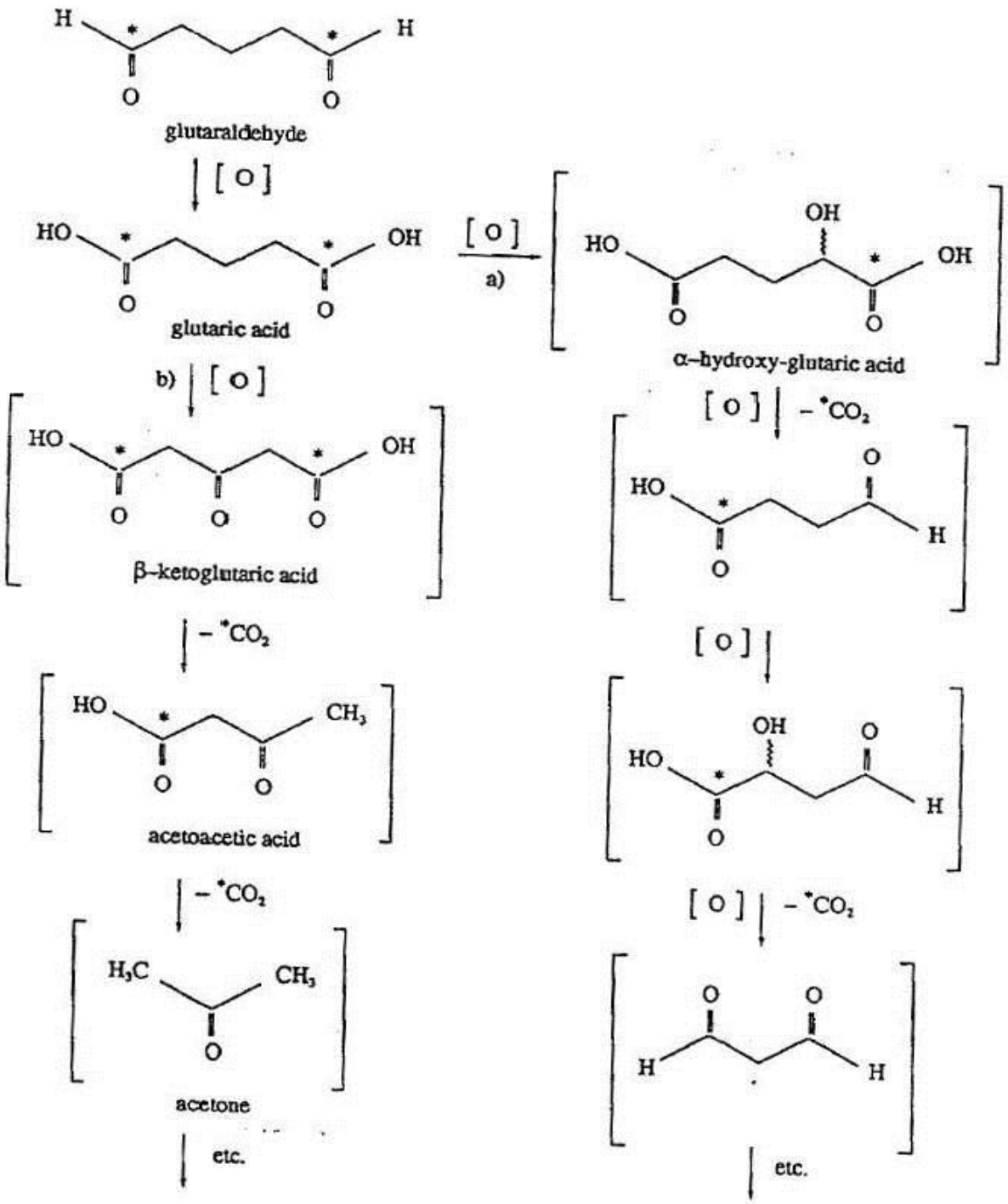


Figure 4: Proposed metabolic pathway for glutaraldehyde under aerobic conditions

Table 27: Composition of aqueous phase under aerobic conditions

Sampling Time & Replicate		Products Detected as Percentage of Applied Radioactivity					
		Glutaraldehyde	Average	Glutaric acid	Average	CO_2	Average
0-hour	A	90.8	88.85	0	0	0	0
	B	86.9		0		0	
4-hour	A	82	75.7	12.9	12.3	0	0
	B	69.4		11.7		0	
12-hour	A	43.4	44.65	21.5	20.2	13	13.7
	B	45.9		18.9		14.4	
24-hour	A	13.9	18.95	11	10.55	32.6	33.8
	B	24		10.1		35	
48-hour	A	0.3	0.15	0	0	52.9	51.35
	B	0		0		49.8	
7-day	A	0	0	0	0	37.1	35.75
	B	0		0		34.4	

Table 28: Radiocarbon material balance (expressed as percent of applied radioactivity) under aerobic conditions

Sampling Time & Replicate		**^{14}C in Sediment**		**^{14}C in Water**		**$^{14}CO_2$**		**Total**
		%	**ppm**	**%**	**ppm**	**%**	**ppm**	**%**
0-hour	A	8.4	0.79	93.4	8.83	-	-	101.8
	B	6.8	0.64	93.7	8.85	-	-	100.5
4-hour	A	9.0	0.85	97.3	9.19	0.1	<0.01	106.4
	B	8.1	0.76	90.6	8.57	0.0	<0.01	98.7
12-hour	A	15.7	1.49	84.1	7.95	0.6	0.06	100.4
	B	17.6	1.67	85.0	8.03	0.4	0.04	103.0
24-hour	A	22.2	2.10	63.3	5.99	0.6	0.06	86.2
	B	18.6	1.75	71.2	6.73	0.4	0.04	90.2
48-hour	A*	-	-	-	-	-	-	-
	B	25.3	2.39	49.8	4.71	10.3	0.97	85.3
7-day	A	20.0	1.89	38.6	3.64	20.4	1.93	78.9
	B	23.7	2.24	26.1	3.32	19.5	1.84	78.3
14-day	A*	-	-	-	-	-	-	-
	B	17.1	1.62	18.6	1.75	48.1	4.54	83.8
30-day	A	11.9	1.12	11.1	1.05	69.4	6.56	92.4
	B	16.1	1.52	13.6	1.29	66.3	6.27	96.0
Average								93.3 $\pm$ 9.8

* Measurements for replicate A are not included. These samples revealed serious losses of radioactive material upon storage probably due to $^{14}CO_2$ formation with only 0 % (48 hr-A) and 2.6 % (14 day-A) recovered.

Table 29: Total, extractable and non-extractable radioactivity in sediment as a percentage of the applied radioactivity under aerobic conditions

Sampling Time & Replicate		Total C-14	Average	Extractable C-14	Average	Not Extractable C-14	Average
0-hour	A	8.4	7.6	3.0	3.0	4.0	4.4
	B	6.8		2.9		4.7	
4-hour	A	9	8.6	3.8	3.8	5.8	5.8
	B	8.1		3.8		5.7	
12-hour	A	15.7	16.7	3.5	3.8	7.9	7.0
	B	17.6		4.1		6.1	
24-hour	A	22.2	20.4	1.2	1.8	2.6	3.4
	B	18.6		2.3		4.3	
48-hour	A	21	23.2	2.6	2.3	11.5	12.1
	B	25.3		2.1		12.8	
7-day	A	20	21.9	1.6	1.8	14.9	19.1
	B	23.7		2.1		23.3	
14-day	A	15.2	16.2	2.1	1.7	19.6	17.7
	B	17.1		1.3		15.8	
30-day	A	11.9	14.0	2.1	1.7	10.4	12.6
	B	16.1		1.4		14.8	

Anaerobic water/sediment test

Reference: Esser, T. (1994b) Anaerobic Aquatic Metabolism of ^{14}C-Glutaraldehyde, PTRL West, Inc., The Dow Chemical Company Report No: K-020301-013, GLP, Unpublished, 2 June 1994

The anaerobic water/sediment study of Dow was carried out under GLP and according to US EPA Pesticide Assessment N 162-3. Under anaerobic conditions only primary biodegradation was observed, with the production of three metabolites that exceeded 10% of applied radioactivity. After 3 days of application only 0.1% of applied radioactivity attributed to glutaraldehyde could be detected in the water phase (Table 30). Concurrently, 3 radioactive metabolic fractions could be detected (Table 30) and were identified as:

-Compound A (2-hydroxy-3,4,4a,7,8,8a-hexahydro-2H-chromene-6-carbaldehyde) (maximum of 17.7% detected at Day 90)
-5-hydroxy-pentanal (5-hydroxyvaleraldehyde) (maximum of 37.0% at Day 1)
-1,5-pentanediol (pentane-1,5,-diol) (maximum of 76.1% detected at Day 14)

Compound A and 1,5-pentanediol are considered persistent because they were present >10% throughout the experiment. Radioactivity assigned to 5-hydroxy-pentanal exceeded 10% only on day 1 and thereafter decreased continuously until day 30. After that it was not detected. Thus, 5-hydroxypentanal is not considered persistent. These three observed metabolites are characterized below. The metabolic pathway is proposed in Figure 5. The production of $^{14}CO_2$ was insignificant. The radioactivity in the water phase remained at a fairly constant level throughout the study being 91.4% at the end of incubation (Day 123). The radioactivity in the sediment reached a maximum of 8.4% of the applied radioactivity at the study termination (Day 123) Table 31). Total mean recovery

of applied radioactivity was 98.7 ± 2.5% (Table 32). The non-extractable radioactivity ranged from 17% (0 hour) to 37% (Day 3) of total radioactivity in sediment (values calculated fromTable 31). This is equivalent to 1.0-2.3% of applied radioactivity as calculated using the total recovered radioactivity percentage (Table 32). A half-life of 7.7 hours at 25 °C (corresponding to 0.91 d at 12 °C) was calculated based on the observed concentration of glutaraldehyde in the aqueous phase using pseudo-first order kinetics.

In conclusion, glutaraldehyde is transformed to two persistent metabolites (Compound A and 1,5-pentanediol) and one intermediate metabolite (5-hydroxy-pentanal) under anaerobic conditions. All three metabolites exceeded 10% of applied radioactivity. The dissipation half-life was 0.91 d (12 °C). The corresponding rate constant is 0.76 d^{-1}.

Significance of the metabolites observed in the anaerobic water/sediment test for classification of glutaraldehyde

Although persistent metabolites were detected in the anaerobic water/sediment tests, these are not considered relevant for classification purposes. In CLP classification, degradation data is required to show whether or not the substance in question is rapidly degradable. In the ECHA Guidance on the application of the CLP criteria (ECHA, 2012) it is stated that "anaerobic degradation tests (OECD 311/ISO 11734 and analogous tests) do not qualify because of the specificity of the anaerobic compartments.". Moreover, in Annex II of the guidance, it is stated that "Data regarding anaerobic degradation cannot be used in relation to deciding whether a substance should be regarded as rapidly degradable, because the aquatic environment is generally regarded as the aerobic compartment where the aquatic organisms, such as those employed for aquatic hazard classification, live.". Therefore, the dossier submitter concludes that anaerobic biodegradation data, including any data concerning the formation of metabolites (whether these fulfill the criteria for classification as hazardous to the aquatic environment or not) in anaerobic conditions must not be considered in the evaluation of fulfillment of the rapid degradability criterion in this case. However, for completeness' sake, the available information relevant for environmental hazard classification of the three degradation products is reviewed below.

Characterisation of the metabolites observed in anaerobic water/sediment test

5-hydroxy-pentanal (5-Hydroxyvaleraldehyde)

In the assessment of glutaraldehyde under Directive 98/8/EC, 5-hydroxy-pentanal (5-hydroxyvaleraldehyde) was identified as a possible metabolite using a skin metabolism simulator and mechanistic profiling indicated potential toxicity (Doc II-A, Chapter 3.1)

5-hydroxy-pentanal is included in the European Chemical Agency's C&L Inventory (5-Hydroxyvaleraldehyde; CAS 4221-03-8) with classification Skin Irrit. 2, Eye Irrit. 2., STOT SE3, while for other hazard categories it is mentioned that data is lacking.

QSAR prediction using BIOWIN models suggests that the substance is readily biodegradable and not persistent (Table 33). The QSAR predicted Log Kow suggests that the substance is not bioaccumulative. The predicted ecotoxicity values suggest that the substance should not be classified for environmental hazards according to CLP (2.ATP) (Table 33).

1,5-pentanediol (pentane-1,5,-diol)

In the Doc II-A under Directive 98/8/EC, 1,5-pentanediol is mentioned only in the context of this anaerobic water/sediment test but not elsewhere in the report.

1,5-pentanediol is included in the European Chemical Agency's C&L Inventory with the name pentane-1,5,-diol (CAS: 111-29-5). The hazard class is "Not classified" in the case of 294 notifiers whereas 3 notifiers have not assigned hazard categories to the substance but have still included the following hazard statement codes: "H302 Harmful if swallowed", "H315 Causes skin irritation", "H319 Causes serious eye irritation", and "H335 May cause respiratory irritation". In addition, one notifier classifies the substance as Acute Tox. 4.

1,5-pentanediol is included in the ECHA database of registered substances (pentane-1,5,-diol; CAS: 111-29-5) with the status "not classified". According to the information available in the database 1,5-pentanediol is readily biodegradable and its ecotoxicity does not warrant a classification for environmental hazards (Table 33). QSAR prediction using BIOWIN models suggests that the substance is readily biodegradable and not persistent (Table 33). According to the registration data, the substance is not bioaccumulative, which is supported by the experimentally determined and QSAR predicted Log Kow values (Table 33).

Compound A (2-hydroxy-3,4,4a,7,8,8a-hexahydro-2H-chromene-6-carbaldehyde)

In the Doc II-A under Directive 98/8/EC, Compound A is mentioned only in the context of this anaerobic water/sediment test but not elsewhere in the report.

Compound A could not be found in any of the European Chemical Agency's databases. No CAS number could be found for this substance. Smiles code C1CC(OC2C1C=C(CC2)C=O)O was obtained from The Pubchem Compound Database (National Center for Biotechnology Information, 2013) (CID 42632221) and this Smiles code was used for QSAR predictions.

QSAR prediction using BIOWIN models suggests that the substance is readily biodegradable and not persistent (Table 33). The QSAR predicted Log Kow suggests that the substance is not bioaccumulative (Table 33). The QSAR predicted ecotoxicity values suggest that the substance should be classified as Aquatic Acute 1 with an M factor of 1 and Aquatic Chronic 2 (no M factor) (Table 33).

Table 30: Composition of aqueous phase under anaerobic conditions

Sampling Time & Replicate		Products Detected as Percent of Dose (ppm)			
		Glutaraldehyde	Compound A	5-Hydroxy-pentanal	1,5-Pentanediol
0-hour	A	78.6	2.89	5.22	0.00
	B	67.6	3.64	9.30	0.00
1-day	A	4.9	10.50	38.97	34.75
	B	4.0	13.24	35.11	34.79
3-day	A	0.0	8.59	7.02	67.16
	B	0.2	14.64	10.58	54.33
7-day	A	0.0	12.46	0.79	69.25
	B	0.0	11.75	2.92	62.98
14-day	A	0.0	12.76	0.38	77.86
	B	0.0	13.33	2.18	74.34
30-day	A	0.0	16.47	0.84	62.17
	B	0.0	11.49	1.46	70.14
60-day	A	0.0	15.14	0.0	71.17
	B	0.0	10.49	0.0	74.78
90-day	A	0.0	22.86	0.0	66.74
	B	0.0	12.62	0.0	75.39
123-day	A	0.0	18.35	0.0	67.51
	B	0.0	14.81	0.0	71.64

Table 31: Total, extractable and not-extractable radioactivity in sediment as a percentage of the applied radioactivity under anaerobic conditions

Sampling Time & Replicate		Total C-14	Average	Extractable	Average	Not-extractable	Average
0-hour	A	5.40	5.70	3.45	3.75	1.14	0.97
	B	6.00		4.06		0.80	
1-day	A	6.10	6.30	5.04	4.77	2.03	1.53
	B	6.50		4.51		1.03	
3-day	A	6.10	6.05	4.54	4.13	2.18	2.24
	B	6.00		3.73		2.30	
7-day	A	7.70	7.05	4.94	4.59	1.59	1.77
	B	6.40		4.24		1.96	
14-day	A	6.90	7.00	4.10	4.40	1.75	1.91
	B	7.10		4.70		2.07	
30-day	A	8.90	8.25	4.44	5.09	3.37	2.58
	B	7.60		5.74		1.79	
60-day	A	7.80	7.20	4.14	4.20	2.96	2.59
	B	6.60		4.26		2.22	
90-day	A	7.40	7.40	3.96	3.79	2.70	2.44
	B	7.40		3.62		2.18	
123-day	A	9.20	8.40	4.96	5.05	2.56	2.64
	B	7.60		5.15		2.72	

Table 32: Radiocarbon material balance (expressed as percent of applied radioactivity) under anaerobic conditions

Sampling Time & Replicate		^{14}C in Sediment		^{14}C in Water		$^{14}CO_2$		Total
		%	ppm	%	ppm	%	ppm	%
0-hour	A	5.4	0.51	92.4	8.73	--	--	97.8
	B	6.0	0.57	91.3	8.63	--	--	97.3
1-day	A	6.1	0.58	95.6	9.03	0.1	0.01	101.8
	B	6.5	0.62	94.5	8.93	0.1	0.01	101.1
3-day	A	6.1	0.58	90.7	857	0.2	0.02	97.0
	B	6.0	0.57	88.5	8.36	0.3	0.03	94.8
7-day	A	7.9	0.75	88.2	8.34	0.0	0.00	96.1
	B	6.4	0.61	89.7	8.48	0.0	0.00	96.1
14-day	A	6.9	0.65	94.0	8.88	0.1	0.01	101.0
	B	7.1	0.67	95.1	8.97	0.1	0.01	102.3
30-day	A	8.9	0.84	86.8	8.20	0.1	0.01	95.8
	B	7.6	0.72	87.1	8.23	0.1	0.01	94.8
60-day	A	7.8	0.74	90.8	8.58	0.2	0.02	98.8
	B	6.6	0.62	92.3	8.72	0.2	0.02	99.1
90-day	A	7.4	0.70	94.3	8.91	0.2	0.02	101.9
	B	7.4	0.70	92.5	8.74	0.3	0.03	100.2
123-day	A	9.2	0.87	91.1	8.61	0.3	0.03	100.6
	B	7.6	0.72	91.7	8.67	0.3	0.03	99.6
Average								98.7 $\pm$ 2.5

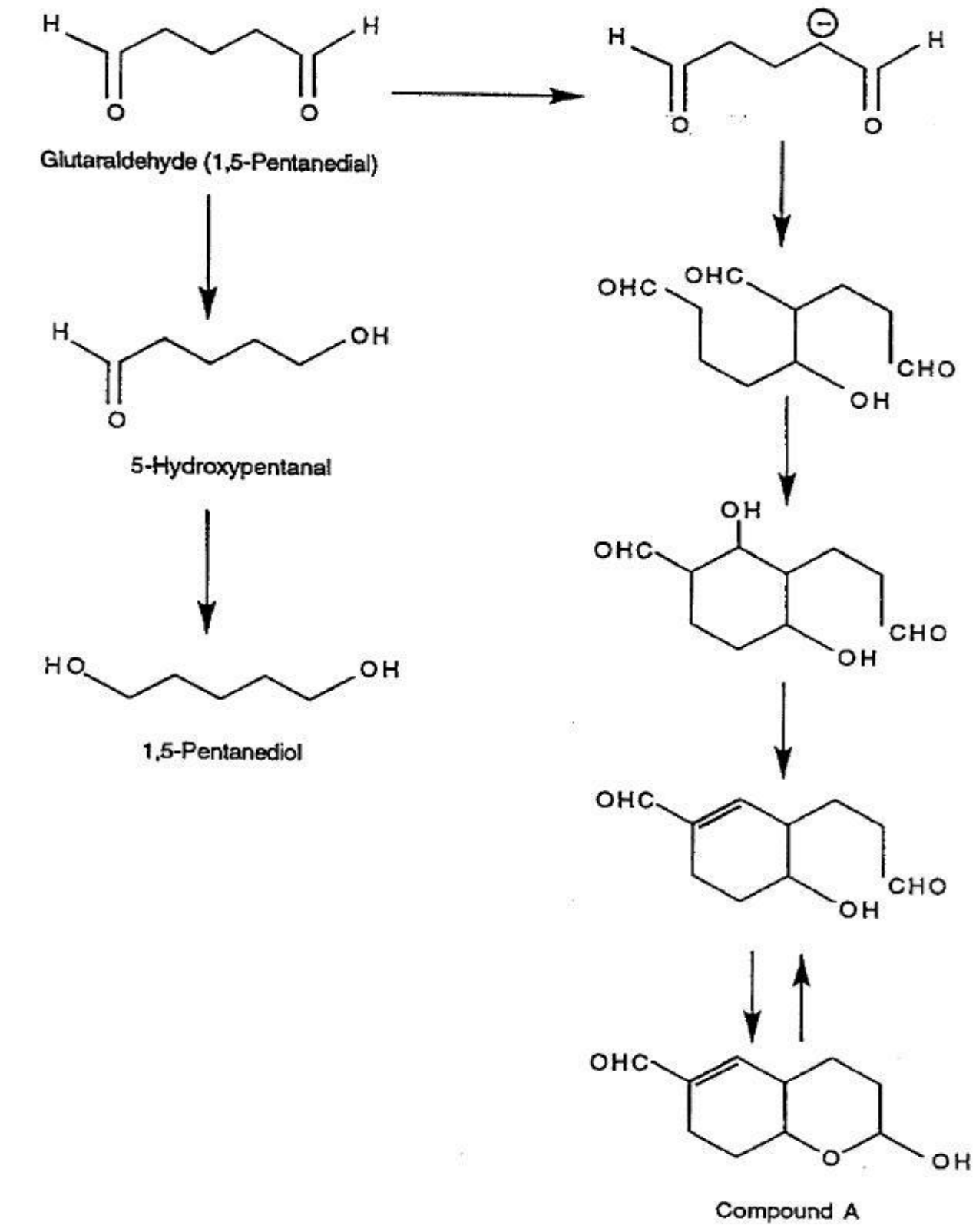


Figure 5: Proposed metabolic pathway for glutaraldehyde under anaerobic conditions

Table 33: Summary of data relevant for the environmental hazard classification of the metabolites detected in the anaerobic water/sediment test.[a]

Substance (CAS No:)	Occurrence in the anaerobic water/sediment test (US EPA Pesticide Assessment N 162-3)	Degradation	Log Kow and bioaccumulation	Aquatic toxicity[b]	Suggested environmental hazard classification according to CLP 2. ATP[c]
5-hydroxy-pentanal (CAS No: 4221-03-8)	Intermediate metabolite	Readily biodegradable[d] (QSAR)	Log Kow: -0.16 (QSAR); low bioaccumulation potential	Acute hazards: 64.7 mg/l (fish, QSAR) Chronic hazards: 5.2 mg/l (fish, QSAR)	**Not classified for environmental hazards**[e]
1,5-pentanediol (CAS No: 111-29-5)	Persistent metabolite	Readily biodegradable (REACH registration data) Readily biodegradable (QSAR)[d]	Log Kow: -0.49 (REACH registration data); low bioaccumulation potential Log Kow: 0.27 (QSAR); low bioaccumulation potential	Acute hazards: >500 mg/l (crustacea and algae), 4640 mg/l (fish), 260 mg/l (algae, QSAR) Chronic hazards: 74.5 mg/l (algae, QSAR), >500 mg/l (algae)	**Not classified for environmental hazards**[e]
2-hydroxy-3,4,4a,7,8,8a-hexahydro-2H-chromene-6-carbaldehyde (Compound A)	Persistent metabolite	Readily biodegradable (QSAR)[d]	Log Kow: 0.10 (QSAR); low bioaccumulation potential	Acute hazards: 0.41 mg/l (fish, QSAR) Chronic hazards: 0.04 mg/l (fish, QSAR)	**Aquatic Acute 1** with an **M factor of 1,** and, (assuming rapid degradability), **Aquatic Chronic 2 with no M factor**

[a] All QSAR predictions were conducted by the dossier submitter (DS) using US EPA Epi Suite vers 4.00. The models used were: ECOSAR Computer program, v1.00 (2009), KOWWIN v1.76a (2008) and BIOWIN v 4.10 (2009).

[b]For all three metabolites, the Chronic Values (ChV) obtained from the ECOSAR QSAR models have been used here similarly as NOEC for comparison with the classification criteria. In the ECOSAR documentation, ChV is defined as the geometric mean of the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC). This can be mathematically represented as: ChV = 10^([log(LOEC x NOEC)]/2) (Methodology Document for the ECOlogical Structure-Activity Relationship Model (Ecosar). EPA, 2012)

5-hydroxy-pentanal: Ecosar QSAR results for class "Aldehydes (Mono)": the lowest EC/LC value is 64.7 mg/l (fish (SW), 96-hr LC50)), and the lowest ChV value is 5.2 mg/l (fish (SW))[f]. Ecosar QSAR results for class "neutral organics": the lowest EC/LC value is 416.4 mg/l (green algae, 96-hr LC50) and the lowest ChV value is 101.6 mg/l (green algae).

1,5-pentanediol: In the ECHA database of registered substances, short-term aquatic toxicity data for fish, invertebrates, algae and bacteria is presented. The reported EC/LC values relevant for classification are:

>500 mg/l (*Daphnia magna*, 48-hr EC50, nominal) (highest tested concentration 500 mg/l)

>500 mg/l (green algae *Scenedesmus subspicatus* (new name: *Desmodesmus subspicatus),* 72-hr EC50) (highest tested concentration 500 mg/l)

4640 mg/l (fish (*Leuciscus idus*), 96-hr LC50, nominal)

One experimental long-term aquatic toxicity value is available (the same test result is also used for the short-term toxicity above): green algae *S. subspicatus* (>500 mg/l, 72-hr EC50, highest tested concentration 500 mg/l). Ecosar QSAR results for class "neutral organics": lowest EC/LC value is 260 mg/l (green algae, 96-hr EC50). The lowest ChV value is 74.5 mg/l (green algae).

2-hydroxy-3,4,4a,7,8,8a-hexahydro-2H-chromene-6-carbaldehyde:

Ecosar QSAR results for class ""Vinyl /Allyl Aldehydes": lowest acute toxicity concentration is 0.41 mg/l (fish, 96-hr LC50) and the lowest ChV value is 0.04 mg/l (fish, ChV)[f]. For the class "neutral organics the lowest EC/LC value is 519.3 mg/l (green algae, 96-hr EC50) and the lowest ChV value is 132.7 mg/l (green algae).

[c]This is a tentative environmental hazard classification as evaluated by the dossier submitter based on the available data (physical and health hazard classification was not evaluated). There are no harmonized classifications for these substances within the EU.

[d]On the basis of BIOWIN results the substance is not likely to fulfill the persistence screening criteria in ECHA guidance R.11 ("Table R11-2 Screening criteria for P and vP". Guidance for information requirements and chemical safety assessment. Chapter R.11: PBT Assessment. ECHA. May 2008 (page 14)) and is likely to fulfill the ready biodegradability criteria mentioned in ECHA guidance R.7b ("Ready biodegradability prediction: yes or no". Guidance for information requirements and chemical safety assessment. Chapter R.7b: Endpoint specific guidance. ECHA. May 2008 (version 1.1). (pp. 170-171)). It is noted, however, that BIOWIN 2 and BIOWIN 3 results should be used cautiously because the compounds contain one or more fragments that are not included in the training sets of the models BIOWIN 2 and BIOWIN 3. Therefore, the structure is only partially taken into account in the prediction.

[e]The predicted effect concentrations are above the classification criteria for acute aquatic category 1 (≤1 mg/l) or chronic aquatic category 3 (≤1 mg/l for substances which are rapidly degradable and not bioaccumulative).

[f]The Ecosar output included a note "The toxicity value was determined from a predicted SAR using established acute-to-chronic ratios and ECOSAR regression techniques which are documented in the supporting Technical Reference Manual. When possible, this toxicity value should be considered in a weight of evidence approach".

Biodegradation in seawater

Test 1:

Reference: Doi, J. (2000) Biodegradability in Seawater Study- Closed Bottle Method, Amended Final Report Including Page 3a, Aqua Survey, Inc., The Dow Chemical Company, Report No: 0222-100-028, Unpublished, 28 March 2000.

This seawater biodegradation test was performed according to the closed bottle method described in OECD306, with no deviations from the guideline stated in the report or protocol. The tested glutaraldehyde product was Ucarcide® 250 Antimicrobial (Lot and/or Batch number IS 782609; purity 50.9% glutaraldehyde). No additional inoculum other than those microorganisms already in the natural seawater was added to the treatment bottles. The extent of biodegradation was determined as biological oxygen demand (BOD) as a percentage of theoretical oxygen demand (%ThOD). BOD of test substance was calculated from dissolved oxygen concentrations; oxygen consumption due to seawater alone was measured separately and subtracted from oxygen consumption of test substance and seawater to obtain BOD due to test substance. The initial concentration of test substance in test solution was 3.0 mg/l. Sodium benzoate was used as the reference control at 2.0 mg/L. The dissolved oxygen was determined in the BOD bottles on days 0, 1, 3, 5, 8, 11, 15, 19, 23, and 28.

The test showed that after five days lag period 73% biodegradation was attained by the 28 d, thus fulfilling the level of 60% defined in the OECD 306 guideline. Therefore, glutaraldehyde has a potential to biodegrade in the marine environment.

Validity of test: The validity criteria listed in the OECD 306 were fulfilled. According to the OECD 306 the test substance can be considered inhibitory to bacteria as the BOD of the toxicity control was less than the sum of BOD from test and procedure control. However, it was noted that the extent of degradation in the toxicity controls could not be reliably quantified because the dissolved oxygen concentrations in the toxicity controls decreased to below 1 mg/L within 11 days. The decrease in dissolved oxygen was attributed to the large quantity of carbon added to the reaction mixtures in the toxicity control assay. Due to extensive degradation observed in both test and procedural control treatments, inhibition of the microbial inoculum by glutaraldehyde in the test is considered negligible and therefore the validity criteria are considered to be met despite the low biodegradation in the toxicity control.

Test 2:

Reference: Schwarz, H. (2002) Protectol GA (50% glutaraldehyde), Determination of the Biodegradability in the marine CO2-Evolution Test. BASF AG, Department of Experimental Toxicology and Ecology, Ludwigshafen/Rhein, Germany, Report No: 01/0411/32/1 (Unpublished).

This seawater biodegradation test was performed according to ISO 16221-2001, with GLP. The extent of biodegradation was determined as carbon dioxide (CO_2) evolution as a percentage of theoretical CO_2 evolution. Test substance was Protectol GA (1,5-Pentanedial), batch Nr. 50-4402, substance Nr. 01/0411-1, date of production 16 Feb 1999, product Nr. 004181, purity 50.3% (water 46%, impurities listed in confidential IUCLID).

The biodegradation of Protectol GA was evaluated at a concentration of 32 mg test substance/l (corresponding to 10 mg/l TOC). A blank control (seawater and inorganic medium without test substance), a reference substance (aniline) and a toxicity control (reference and test substances) were considered in this test. Evolved CO_2 was trapped in NaOH absorber flasks. CO_2 was determined 17 times during the 71-day experiment). The relation of the determined CO_2 evolution to the calculated theoretical CO_2 value is the measure for the marine biodegradation of Protectol GA. 100 mg TS/l showed a decreased level of degradation in the toxicity control assay (with initial concentrations of 100 mg TS/l test substance and 100 mgTS/l reference substance) therefore only the measurements of the lowest test substance concentration were used for biodegradability estimation.

The percentage of degradation of Protectol GA at 10 mg/l TOC was determined to be 90-100% at the end of incubation (71 days). At a test concentration of about 100 mg/l (equivalent to 30 mg TOC/l) biodegradation was decreased (30% degradation), apparently due to toxic effects as indicated by the toxicity control. Biodegradation of the reference substance was > 60% on day 6 and > 90 % after 50 days. Since there were no indications for abiotic elimination processes Protectol GA can be regarded as biodegradable in this test system.

Glutaraldehyde degraded steadily achieving the 95% degree of degradation after 70 d. After 30 d the degree of degradation was 41%.

Validity of test: Validity criteria can be considered fulfilled. It was noted, however, that until day 17 the replicates deviated from each other more than 20% (22-55%), after that day the deviation was less than 10%. No plateau could be identified.

Conclusions on biodegradation in seawater:

According to both of the two tests, glutaraldehyde has a potential to biodegrade in the marine environment.

5.1.3 Summary and discussion of degradation

Glutaraldehyde is readily biodegradable. In the ready biodegrability tests, the pass level (70% of DOC within the 10 day window) was reached.

Glutaraldehyde has the potential to biodegrade in the marine environment. An OECD 306 test showed that after five days lag period 73% biodegradation was attained after 28 d, thus fulfilling the level of 60% defined in the guideline. In an ISO 16221-2001 test, glutaraldehyde degraded steadily achieving the 95% degree of degradation after 70 d.

In aerobic water/sediment simulation test, glutaraldehyde dissipated from the aqueous phase with a half-life of 1.25 d (12°C). Major metabolites were glutaric acid and carbon dioxide (CO_2). A majority of glutaraldehyde was mineralized as indicated by the 67.9% of radiocarbon recovered as CO_2. At the end of the 30-d experiment, glutaraldehyde was not detected and 12% of the applied ^{14}C was found in aqueous phase and 14% in sediment phase.

In anaerobic water/sediment simulation test, glutaraldehyde dissipated from the aqueous phase with a half-life of 0.91 d at 12°C, with three metabolites identified, two of which (1,5-pentanediol and 2-hydroxy-3,4,4a,7,8,8a-hexahydro-2H-chromene-6-carbaldehyde; the latter is referred in this report as Compound A)) were persistent and one (5-hydroxy-pentanal) non-persistent. Production of $^{14}CO_2$ was insignificant. A maximum of 9.4% of radioactivity was detected in the sediment and >90% of ^{14}C remained in the aqueous phase throughout the experiment. In this case the metabolites formed in anaerobic water/sediment simulation tests are not relevant for classification as explained in chapter 5.1.2.3. However, a brief characterisation of the properties of these metabolites was presented.

Glutaraldehyde can be considered hydrolytically and photolytically stable in the aquatic environment. In the atmosphere, glutaraldehyde is likely to be photochemically degraded with an estimated half-life of 8.2 hours.

5.2 Environmental distribution

5.2.1 Adsorption/Desorption

Soil adsorption study

Reference: Skinner, W., Shepler, K. and Estigoy, L. (1994), Soil adsorption/desorption of [14C] glutaraldehyde by the batch equilibrium method, PTRL West, Inc., The Dow Chemical Company Report No: K-020301-081, Unpublished, 29 March 1994.

This adsorption/desorption study was carried out in accordance with US EPA Guideline 163-1. Freundlich K values for adsorption ranged from 0.59 (sediment with 24.9% of total radioactivity adsorbed) to 4.94 (silty clay loam with 43.1% of total radioactivity adsorbed). Freundlich K values for desorption were not calculated, this was due to rapid degradation of glutaraldehyde which could not be measured in the desorption supernatants. Further details of the test are provided in Table 34.

Conclusion: Glutaraldehyde is mobile in sandy sediment and moderately mobile in the four studied soils.

Table 34: Adsorption/desorption in four soils and one sediment

Guideline /Test method	Soil	Adsorbed a.s. [%]	K_a [1]	K_{aOC} [2]	K_d [3] K_{dOC} [4] K_a/K_d [5]	Degradation products Name	Degradation products [%] of a.s.	Reference
US EPA FIFRA 163-1 GLP	Soil 1 Sandy loam	38.4	2.06	210	NR*	Glutaric acid (8 other trans-formation products but these were not identified as they formed less than 10% of applied radioactivity)	0 - 4.8%	Skinner et al. (1994)
	Soil 2 Silty clay loam	43.1	4.94	500				
	Soil 3 Silt loam	42.7	4.83	340				
	Soil 4 Loamy sand	40.2	1.10	460				
	Sediment Sand	24.9	0.59	120				

[1] K_a = Adsorption coefficient
[2] K_{aOC} = Adsorption coefficient based on organic carbon content
[3] K_d = Desorption coefficient
[4] K_{dOC} = Desorption coefficient based on organic carbon content
[5] K_a / K_d = Adsorption / Desorption distribution coefficient
NR* = Not required. Due to the rapid degradation of glutaraldehyde desorption isotherms could not be determined.

5.2.2 Volatilisation

Glutaraldehyde is a volatile substance, with vapour pressure of 44 Pa at 20 °C (Table 11). Therefore, photochemical reactions in air may be important (see 5.1.1). However, based on the Henry's constant (0.0086 Pa×m^3/mol), glutaraldehyde is not very volatile from a water solution.

5.2.3 Distribution modelling

Not relevant for this dossier.

5.3 Aquatic Bioaccumulation

5.3.1.1 Bioaccumulation estimation

The estimation of bioaccumulation of glutaraldehyde was done on the basis of n-octanol/water partition coefficient, log Kow (Table 35). Glutaraldehyde has a low potential for bioaccumulation, as indicated by measured and calculated log Kow values. Glutaraldehyde is highly hydrophilic and lipophobic and therefore would not be expected to bioaccumulate. Log Kow values are -0.33 in one test (pH not reported) and -0.41 (pH 5), -0.36 (pH 7) and -0.80 (pH 9) in another. A calculation with the EPISUITE program is also available. The calculation method supported low bioaccumulation potential of glutaraldehyde. The calculated log K_{ow} value is -0.18 (SRC KOWWIN v1.67).

Table 35: Partition coefficient of glutaraldehyde

pH	Temperature	result (log K_{ow})	Reference
5	23 ± 1 °C	-0.41	Sametschek 2002
7	23 ± 1 °C	-0.36	
9	23 ± 1 °C	-0.80	
not reported	25°C	-0.33	Shepler 1996

5.3.1.2 Measured bioaccumulation data

No experimental bioaccumalation data is available.

5.3.2 Summary and discussion of aquatic bioaccumulation

Glutaraldehyde is not expected to bioaccumulate in aquatic organisms.

5.4 Aquatic toxicity

The aquatic toxicity studies show that the concentration of glutaraldehyde in test water does usually not remain in range of 80 to 120 % of the nominal concentration. In some available ecotoxicity tests no analytical measurements were performed. In these cases deviation of more than 20% from the nominal concentration cannot be excluded because glutaraldehyde is known to be readily biodegradable and relatively reactive. Glutaraldehyde has the ability to react with proteins and as a result of this “chemisorption,” glutaraldehyde is likely bound by covalent chemical bonds to proteinaceous material and loses its identity as glutaraldehyde. Consequently studies without any analytical monitoring of test substance concentrations were considered as invalid and were not used for this report.

In most studies with measured concentrations glutaraldehyde was demonstrated to be very unstable during the test. This was considered to be related to the instability of the test substance in aqueous

media and/or adsorption of the test material in the test system (algal cells, *Daphnia*, glassware surfaces etc.). In addition, it was thought that yeast might have reacted with glutaraldehyde and further reduced glutaraldehyde concentrations. The oxidation sensitivity of the test substance was also speculated to be in relation to the reduction of the test concentrations.

In those studies where concentrations of glutaraldehyde did not remain 80-120% of nominal, the effect concentrations were expressed relative to geometric mean or arithmetic mean concentrations depending on the test conditions (static/semi-static/flow-through) as instructed in the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD, 2000).

All ecotoxicological studies have been performed with an aqueous solution of glutaraldehyde (appr. 50 %). To the best of knowledge the results are considered as 100 % glutaraldehyde for this report.

Table 36: Summary of relevant information on aquatic toxicity

Method	Results	Remarks	Reference
Short-term toxicity to fish US EPA FIFRA 72-3 GLP	LC_{50} 32 mg active substance (a.s.)/L	Marine species	Machado, M.W. 1993a
Long-term toxicity to fish ASTM method, Non-GLP	NOEC 1.0 mg a.s./L		Sano et al. 2005
Short-term toxicity to aquatic invertebrates UK Proposal to ISO TC147/SC5/W92, GLP	**LC_{50} 0.07 mg a.s./L**	Marine species Results based on the geometric mean of the measured concentrations.	Wetton and Bartlett 1997
Long-term toxicity to aquatic invertebrates OECD 211, GLP	NOEC 0.26 mg a.s./L	Results based on the arithmetic mean.	Migchielsen, M.H.J. 2003
Growth inhibition on algae 92/69/EEC C.3, GLP	**NOECr 0.025 mg a.s./L** ErC_{50} 0.6 mg a.s./L	Results based on the geometric mean of the measured concentrations.	Maisch, R. 1997

5.4.1 Fish

5.4.1.1 Short-term toxicity to fish

Only one 96-h acute fish test with measured concentration is available. It was carried out with the marine fish species Sheepshead Minnow giving LC_{50} value of 32 mg active ingredient (a.i.) /l for acute fish toxicity indicating Glutaraldehyde to be harmful to marine fish (Sheepshead Minnow).

Test 1

Reference: Machado, M. W., 1993a Glutarladehyde - Acute Toxicity to Sheepshead Minnow (Cyprinodon variegatus) Under Flow-Through Conditions, Springborn Laboratories Inc., The Dow Chemical Company Report No: K-020301-010, Unpublished, 13 April 1993

The acute toxicity of glutaraldehyde (purity 51%, remainder water, batch number 566756) to the marine species Sheepshead minnow (*Cyprinodon variegatus*) was determined under flow-through conditions for 96 hours. The test was carried out in compliance with GLP and according to US EPA FIFRA 72-3 guideline. Fish were acclimated to test conditions for a minimum of 14 days. Immature individuals with mean wet weight of 0.31 (0.14-0.51) g and mean length of 24 (19-28) mm were used in the test. All treatment levels and the controls were maintained in duplicate and 10 fish/vessel were used. Mean analytical concentrations based on analyses in the beginning and at the end of the test were 2.9, 4.9, 9.2, 14, 24 and 41 mg a.i./L (averaging 99 % of nominal dose). Dissolved oxygen varied 5.8-7.1 mg/L (81-100 %) in vessels. Test temperature ranged 21-23 °C and pH 7.9-8.2. LC_{50} 96 h was determined to be 32 mg a.i./l based on the mean measured concentrations (95 % confidence interval 24-52 mg a.i./L).

Table 37: Acute toxicity to fish

Guideline Test method	Species	Endpoint	Exposure		Results mg a.s./L			Remarks	Study owner Reference
			design	duration	LC_0	LC_{50}	LC_{100}		
US EPA FIFRA 72-3 GLP	Sheepshead minnow *Cyprinodon variegatus*	Mortality	Flow-through	96 h	24	32	41	Key study Meas. conc. Marine spec	Machado, M.W. 1993a

5.4.1.2 Long-term toxicity to fish

Effects on reproduction and growth rate in fish

Three long-term studies are available in fish, all carried out with freshwater species. NOEC values derived from the three studies are close to each other, ranging from 1.0 to 1.6 mg a.s./L. The study with the lowest test result is chosen as the key study giving NOEC value of 1.0 a.i. mg /l indicating glutaraldehyde to be slightly toxic to fish (*Oncorhynhus mykiss*) in long-term. The studies are summarized in Table 38.

Test 1

Reference: Sano, L.L., Krueger, A.M. and Landrum, P.F. (2005) Chronic toxicity of glutaraldehyde: different sensitivity of three freshwater organisms, Aquatic Toxicity, 71:283-296

Long-term toxicity of glutaraldehyde (purity 50 %, remainder water) to the early-life stages of Rainbow trout (*Oncorhynchus mykiss*) was investigated under semi-static conditions according to ASTM (1998c) method. The experiment lasted 62 days and it was not carried out in compliance with GLP. Initial nominal test concentrations of test substance were 0, 0.6, 1.3, 2.5, 5.1, 13.6 mg/l and the actual concentrations were measured both prior to and after renewing test solution which was done daily (24-hour weighted averages -0.1, 0.6, 1.3, 2.5, 5.1 and 13.6 mg/l). Four vessels per

concentration were used and 30 embryos were placed in each vessel. Dissolved oxygen concentration was not specified and the water temperature ranged 9-13°C and therefore the temperature range was higher than the maximum range (±1.5 °C) recommended in the guideline. Daily observations were made on embryo condition (alive/dead/deformed) and hatching time. Glutaraldehyde concentrations fluctuated substantially both over the 24-h period between solution renewals and over the 62-day exposure period. For the embryonic period (through hatch-out, day 34) the initial renewing solution was close to the nominal concentration but by the end of the 24-h period, most concentrations had decreased by an average of 20 %. After day 35, test solutions declined on an average of 65 % over the 24-h period between renewals. In addition, the concentration in the renewed solution was often much lower than the nominal value (usually about 50 % less). The results are separated out by the two different exposure periods, pre-hatch (embryonic) and post-hatch (sac-fry and larval). Survival rates of embryos, up until day 25, were comparable for all concentrations tested including the controls. Although most of the embryos survived the initial embryonic period, the majority of organisms at the 2.5 mg/l treatment level and higher were not able to hatch from the embryo stage into the sac-fry stage. After the 10-day post-hatch period (up to day 35), only 3 % of the surviving embryos treated at 2.5 mg/l had successfully emerged from the chorion and none of the embryos at the higher concentrations had survived. Even at concentrations as low as 1.3 mg/l embryos had difficulty emerging from the chorion. The survival rates were estimated separately due to the large effect of glutaraldehyde exposure on hatching success and due to differences in measured glutaraldehyde concentrations over the experimental period. Larval fish were followed for 27 days after hatching, through the alevin and the fry stages. At the end of this period, there was no significant difference between survival in the controls and the two remaining treatments (0.4 and 1.0 mg/l). The overall estimated NOEC for this experiment (embryo to fry stage) was 1.0 mg/l, and the LOEC was 2.5 mg/l.

Test 2

Reference: Roberts, C.A., Drottar, K.R., Swigert, J.P. and Krueger, H.O. (1999) Ucarcide® 250 Antimicrobial: An early life-stage toxicity test with the Fathead minnow (*Pimephales promelas*), Wildlife International Ltd., Unpublished, 22 January 1999

Effects of glutaraldehyde (purity 50.9%, remainder water, batch number IS-720843) on early life-stage of Fathead minnow was studied according to FIFRA 72-4 and OECD 210 during 32 days. The test was conducted under flow-through conditions and in compliance with GLP. Two replicates were used per concentration and 40 embryos per replicate were placed (80 totals per dose level). Initial nominal concentrations of test substance were 0.38, 0.77, 1.5, 3.0 and 6.0 mg/l. The mean measured concentrations were 81-98% of the nominal concentrations except in the lowest test concentration where the mean measured concentration was 76% of the nominal concentration. The temperature ranged during the test from 24.5°C to 26.0°C. Effects parameters were time to hatch, hatching success, survival and growth. There were no significant differences in time of hatching or hatching success between the control and any treatment groups. The survival was the most sensitive parameter. It was statistically reduced at the level of 2.9 and 5.9 mg a.i./l. Post-hatch growth was also reduced in the same groups when compared to the negative controls. NOEC of glutaraldehyde to Fathead minnow was determined to be 1.4 mg a.i./l (survival and growth) based on the measured concentrations.

Test 3

Reference: Zok, S. (2000) Protectol GDA (50 % Glutaraldehyde) - Early Life-Stage toxicity test on the Rainbow trout (*Oncorhynchus mykiss*). BASF AG, Department of Product Safety, Ludwigshafen/Rhein, Germany, Report No: 52F0447/975114 (Unpublished).

The toxicity of glutaraldehyde (purity 48.15 %, remainder water, batch number 40-2699) to early life-stage of Rainbow trout was assessed in a 97 days study under flow-through conditions. The test was run according to FIFRA 72-4 and OECD 210 (1992) and it was done in compliance with GLP. Initial nominal test concentrations were 0, 0.32, 1.0, 3.2 and 10 mg/, mean analytically determined test concentrations were 0.28 (0.1-0.44), 0.79 (0.3-1.27), 3.41 (2.8-4.0) and 10.58 (9.4-12.5) mg/l. Four replicates for each test concentration and control were used (25 fertilized eggs in each test vessel) and two replicates as viable control for the first 14 days. For monitoring test substance concentration samples were taken on day zero and then generally at weekly intervals and generally alternating from all test aquaria generally before the replacement of the stock solutions. The lower concentrations were near the analytical detection limit. A reliable analytical determination was therefore difficult. The dilution system was checked regularly and no technical problems occurred which could explain the deviation from the theoretical concentration values. The relevant concentrations for the determination of the effect concentrations were within the range of ± 20% of the nominal concentrations, with the only exception: in one week values of 125% of the nominal concentrations were determined. Dissolved oxygen was maintained in a range between 8.3 and 11.3 mg/l, corresponding to 70-100% of the saturation at the test temperature. Test temperature maintained at the 10 ±1 °C throughout the study in all aquaria. Survival, time to hatch and swim-up, toxic signs and abnormalities, body weight and length were evaluated. NOAEC and LOAEC for survival was determined to be 1.6 mg a.i./l and 5 mg a.i./l, respectively based on the measured concentrations.

Table 38: Long-term toxicity to fish

Guideline / Test method	Species	Endpoint / Type of test	Exposure		Results mg a.s./L	Remarks	Study owner Reference
			design	duration	NOEC		
ASTM method Non-GLP	Rainbow trout (*Oncorhynchus mykiss*)	Embryo larval survival and growth	Semi-static	62 d	1.0	Key study Meas. conc.	Sano et al. 2005
FIFRA 72-4/ OECD 210 GLP	Fathead minnow (*Pimephales promelas*)	Time to hatch, hatching success, survival and growth	Flow-through	32 d	1.4	Meas. conc.	Roberts et al. 1999
OECD 210 GLP	Rainbow trout (*Oncorhynchus mykiss*)	Time to hatch, hatching success, survival and growth	Flow-through	97 d	1.6	Meas. conc.	Zok S. 2000

5.4.2 Aquatic invertebrates

5.4.2.1 Short-term toxicity to aquatic invertebrates

In total five acute tests on invertebrates with measured concentrations are available. All of them were performed on marine species. The most sensitive species was a marine copepod, *Acartia tonsa*, with LC_{50} of 0.07 mg a.s./L. The toxicity value for *Acartia tonsa* was an order of magnitude lower than that for the next most sensitive species, the Eastern oyster. For other species, the test result exceeded 1 mg/L. This test was chosen as the key study. The result indicated glutaraldehyde to be acutely very toxic to marine copepod *Acartia tonsa*. All tests are summarized in Table 39.

Test 1

Reference: Wetton, P.M. and Bartlett, A.J. (1997) Ucarcide Antimicrobial 250: Acute Toxicity to *Acartia Tonsa*, Safepharm Laboratories Limited, The Dow Chemical Company Report No: DR-0222-1070-033, Unpublished, 24 April 1997

Acute toxicity of glutaraldehyde (purity 50.9, remainder water) to a marine crustacean, *Acartia tonsa*, was investigated in a 48 hours test under static condition. Test was indicated to be GLP compliant and done according to UK proposal to ISO TC147/SC5/WG92. Potassium dichromate was used as a reference substance, and an additional control group was maintained under identical conditions but not exposed to the test material. Four replicates per each test concentration were used and five copepods at least 14 days old were placed per test vessel. Initial nominal concentrations were 0.01, 0.018, 0.032, 0.056, 0.1, 0.18, 0.32, 0.56 and 1.0 mg/l. Actual concentrations were analysed for nominal concentration of 0.01, 0.032, 0.1, 0.32 and 1.0 at the initial of the test giving a mean average recovery of 99,6 %. At the termination of the test (48 h) analyses were conducted for all exposure levels. Measured concentrations were ranging then from 8-33 % of the nominal and measured initial test concentrations. Pre-study analysis of the test material (Ucarcide Antimicrobial 250) had showed it to be stable over the exposure period; hence the marked decline in glutaraldehyde concentrations during the experiment was thought to be result from biodegradation in the seawater. The water temperature was maintained at 20-22 °C. Dissolved oxygen (ranging from 7.8 to 8.5 mg/l) and pH (ranging from 8.1 to 8.2) were recorded at the start and end of the test. Test parameters were mortality and sublethal effects. Because of the substantial decline of test substance concentrations, LC_{50} (48 h) value was calculated based on the geometric mean of the measured concentrations, resulting LC_{50} to be of 0.07 mg a.i./l with confidence limits of 0.058-0.084 mg a.i./L.

Test 2

Reference: Dionne, E. (1993) Glutaraldehyde - Acute Toxicity to Eastern oysters (*Crassostrea virginica*) Under Flow-Through Conditions, Springborn Laboratories, Inc., The Dow chemical Company, Report No: K-020301-011, Unpublished, 7 September 1993

Acute toxicity of glutaraldehyde to *Crassostrea virginica* was studied in a 96 h test under flow-through conditions. Test was carried out in compliance with GLP and according to US EPA FIFRA 72-3 with minor deviations. Two vessels per concentrations were used in the test and 20 animals were placed per vessel after 14-day acclimation. Nominal concentrations were 0.12, 0.19, 0.32, 0.54 and 0.90 mg a.i./l. Measured concentrations were consistent between replicate samples but decreased by an average of 35 % between 0 and 96 hours of exposure. Measured concentrations obtained at 96-hours for the lowest treatment level tested were below the established limit of quantification. This decrease was attributed to adsorption of the test material to the high concentration of organisms present in unfiltered salt water, combined with high density of algal cells added as food which accumulated over the exposure period. Based on the mean measured concentrations, the concentrations of glutaraldehyde tested were defined as 0.71, 0.33, 0.16, 0.11 and 0.068 mg/l, which averaged 61 % of the nominal. The water temperature varied 18-22 °C. Test parameters were shell growth and sublethal effects, The 96 hour EC_{50} for *Crassostrea virginica* was 0.78 mg a.i./L based on mean measured concentrations and biological responses. The NOEC was determined to be 0.16 mg a.i./l.

Test 3

Reference: Sousa, J.V. (1995) Glutaraldehyde - Acute toxicity to Mysids (*Mysidopsis bahia*) under flow-through conditions. Springborn Laboratories Inc., Environmental Sciences Division, Wareham, Massachusetts, SLI Report No. 94-12-5603 (Unpublished)

Acute toxicity of glutaraldehyde (purity 50.2 %, remainder water) to marine invertebrates *Mysidopsis bahia* was investigated under flow-through conditions during 96 hours. The study was GLP compliant and was run according to FIFRA Guideline No: 72-3. US EPA (1985). Nominal concentration were 0.62, 1.0, 1.7, 2.9, 4.8 and 8.0 mg a.i./l. Mean measured concentrations over the test period (measured at the test initiation and ending) were 0.38, 0.71, 1.1, 2.4, 4.5 and 76 mg a.i./l corresponding to 62-95% percentages of nominal concentrations. Two replicates were used per test concentration and 10 mysids were placed per chamber. Test temperature was maintained at 25 ±1 °C. Dissolved oxygen was >3 mg/l in all test vessels ranging between 89 - 102 % of saturation and pH varied between 7.75 and 7.9. Test parameters were mortality and biological observations (absence of mobility or response to gentle prodding). At the 4.5 mg a.i./l 10 % mortality was recorded after 72 hours. At the highest test concentrations of 7.6 mg a.i./l, mortality was 45 % after 48 hours and reached 100 % after 96 h. From 1.1 mg a.i./l sublethal effects were seen. LC_{50} value (96h) was determined to be 5.5 mg a.i./l (95 % confidence limits 4.5-7.6 mg/l) based on the measured concentrations and NOEC was 0.71 mg a.i./l.

Test 4

Reference: Machado, M.W. (1993b) Glutaraldehyde - Acute Toxicity to Mysid Shrimp (*Mysidopsis bahia*) Under Flow-Through Conditions, Springborn Laboratories, Inc., The Dow chemical Company, Report No: K-020301-018, Unpublished, 7 September 1993

Acute toxicity of glutaraldehyde to Mysid Shrimp (*Mysidopsis bahia*) was studied during 96 hours under flow-through conditions and according to US EPA FIFRA 72-3 with minor deviations. Two vessels were used at each of the five test concentrations and control and ten animals were placed per aquarium. Nominal concentrations were 0.78, 1.3, 2.2, 3.6, 6.0, 10 mg a.i./l and mean measured concentrations were 0.78, 1.5, 2.5, 3.9, 6.8 and 12 mg a.i./l, averaging 112 % of nominal concentrations. Dissolved oxygen ranged during the study from 6.9 to 7.3 mg/l and temperature varied between 25 and 26 °C. Mortality and sublethal effects were observed at the initiation of the test and at every 24 hour interval during the exposure period. LC_{50} was established at 7.1 mg a.i./l with 95 % confidence interval 6.0-8.6 mg a.i./l and the NOEC was 0.78 mg a.i./l based on the mean measured concentrations.

Test 5

Reference: Caferella, M.A. (2006): Glutaraldehyde - Acute Toxicity to White Shrimp (*Penaeus vannamei*) Under Flow-Through Conditions, Springborn Smithers Laboratories, The Dow Chemical Company Report No: K-020301-114, Unpublished, 27 February 2006

Acute toxicity of glutaraldehyde to White Shrimp (*Penaeus vannamei*) was investigated under flow-through conditions for 96 hours. Test was carried out according to EPA OPPTS 850.1045 and was indicated to be GLP compliant. Initial test concentrations were 0, 3.8, 7.5, 15, 30, 60 and 120 mg a.i./l. Actual mean measured concentrations were 0, 4.4, 6.2, 18, 31, 61, and 120 mg a.i. /l). Two vessels were used at each test concentration including control and ten juvenile shrimps were placed in each vessel. Acclimatization for at least 14 days was reported. Oxygen content was 7.3-7.9 mg/l (96-104 % of saturation). Temperature maintained at 23 °C throughout the study and pH was at 8.0. Test parameters mortality and sublethal effects were observed at 0, 3, 6, 12, 24, 48, 72 and 96

hours. LC_{50} 96 h was 68 mg a.i./l based on the mean measured concentrations with 95 % confidence interval 52-96 mg a.i./l.

Table 39: Acute toxicity to invertebrates

Guideline / Test method	Species	End-point	Exposure		Results mg a.s./L			Remarks	Study owner Reference
			design	duration	E/LC_0	E/LC_{50}	E/LC_{100}		
UK Proposal to ISO TC147/SC5/ W92 GLP	*Acartia tonsa*	Mortality	Static	48 h		0.07	>0.18	Key study Meas. conc. Marine spec. Results based on the geometric mean of the measured concentrations	Wetton and Bartlett 1997
US EPA FIFRA 72-2 GLP	Eastern oyster *Crassos-trea virgi-nica*	Growth	Flow-through	96 h	0.16	0.78		Meas. conc. Marine spec.	Dionne, E. 1993
FIFRA Guideline No: 72-3 GLP	Mysid shrimp *Mysido p-sis bahia*	Mortality	Flow-through	96 h	~4.5	5.5	7.6	Meas. conc. Marine spec.	Sousa, JV. 1995
US EPA FIFRA 72-3 GLP	Mysid shrimp *Mysido p-sis bahia*	Mortality	Flow-through	96 h	0.78	7.1	>12	Meas. conc. Marine spec.	Machado, M.W. 1993b
EPA OPPTS 850.1045 GLP	White shrimp *Penaeus vannamei*	Mortality	Flow-through	96 h	18	68	>120	Marine spec. Meas. conc.	Caferella, M.A. 2006

5.4.2.2 Long-term toxicity to aquatic invertebrates

Effects on reproduction and growth rate in invertebrates

One reproduction tests on *Daphnia magna* and a reproduction test on *Ceriodaphnia dubia* were available. The study with the lowest NOEC of 0.12 mg a.s./L was chosen as the key study which indicated glutaraldehyde to be toxic to *Daphnia magna* in long-term. The studies are summarized in

Table 40.

Test 1

Reference: Migchielsen, M.H.J. (2003) *Daphnia magna*, Reproduction Test with Glutaraldehyde 50 % (flow-through), Notox Safety Environmental Recearch, The Dow Chemical company Report No: K-020301-115, Unpublished, 10 April 2003

The effects of glutaraldehyde 50% on reproduction and growth of *Daphnia magna* was tested under flow-through conditions for 21 days. Test was run according to OECD 211 guideline and was indicated to be GLP compliant. For each test concentration including control there was one stainless steel vessel (1.5 l) with 4 mesh containers of stainless steel. Ten daphnids (<24 hours old) were placed in each mesh container. Nominal concentrations were 0.9, 1.3, 2.1, 3.3, 4.5 mg a.i./l. Measured concentrations were 88-106 % of target concentrations at the initiation of the test but dropped significantly on sampling days 7, 14 and 21, ranging from 7 to 25 % of nominal concentrations. Temperature ranged from 19.6 C° to 22.2 C° and pH was 7.4-8.1. The dissolved oxygen was reported to be 6.9-8.9. As instructed in the OECD Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (ENV/JM/MONO(2000)6) the effects concentrations used are based on the arithmetic mean concentrations resulting to the NOEC for reproduction is 0.26 mg/l.

Test 2

Reference: Jatzek H-J (1993) Determination of the chronic toxicity of Protectol GDA to *Daphnia magna*. BASF AG, Department of Ecology, Ludwigshafen/Rhein, Germany, Report No: 93/0406/51/2 (Unpublished)

The chronic toxicity of glutaraldehyde 50% (remainder water) to *Daphnia magna* was tested under semi-static conditions for 21 days. Ten daphnids (2-24 hours old) were used per concentration and one animal was placed individually per test vessel (ten vessels per concentrations). Test solutions were changed 2 times a week. Nominal test concentrations were 0, 0.039, 0.078, 0.156, 0.313, 0.625, 1.25, 2.5, 5, 10 and 20 mg/l. Analytical monitoring was performed for nominal concentrations of 0, 0.156, 1.25, 20 and 100 (stock solution) mg/l each week. For each concentration, the freshly prepared test solution and the corresponding 48 h or 72 h old test solution (with or without *Daphnia*) were analysed. For smaller concentrations (0.156, 1.25 mg/l) measured concentrations were significantly below the expected values but the actual values were not demonstrated. This reduction was speculated to be in relation to the oxidation sensitivity of the test substance. For the higher concentrations (20 and 100 mg/l), the measured concentrations were as expected (95-100% of the nominal values). Daphnids were examined daily for mortality and reproduction. No significant effects were observed on reproduction or offspring at the low concentrations, and no parental mortality was observed. In the 20 mg/l group 100% mortality was reached after 2 days. Temperature varied between 18.7-21.2 °C during the test. Oxygen content was in the range of 7.1 to 9.2 mg/l and pH 7.5-8.5. NOEC (21 d) was 5 mg/l based on the nominal concentrations.

Table 40: Long-term toxicity to invertebrates

Guideline / Test method	Species	Endpoint /Type of test	Exposure		Results (mg a.s./L)	Remarks	Study owner Reference
			design	duration	NOEC		
OECD 211 GLP	*Daphnia magna*	Survival, growth and repro-duction	Flow-Through	21 d	0.13	Key study Meas. conc. Result based on arithmetic mean concentrations	Migchielsen, M.H.J. 2003
Directive XI/681/86 Draft 4 GLP	*Daphnia magna*	Survival, growth and repro-duction	Semi-static	21 d	5	Result based on nominal concentrations	Jatzek, H-J. 1993

5.4.3 Algae and aquatic plants

Growth inhibition on algae

Two algae studies on freshwater species and one test on marine species are available. The three algal studies showed approximately equal toxicity to algae. The study with the green alga *Scenedesmus subspicatus* was chosen as a key study with the ErC50 of 0.6 mg a.s./L and NOEC of 0.025 mg a.s./L. The results indicated glutaraldehyde to be very toxic to green alga (*Scenedesmus subspicatus*). The results of available studies in algae with Glutaraldehyde are summarised in Table 41.

Test 1

Reference: Maisch, R. (1997): Determination of the inhibitory effect of Basolon GDA 50 on cell multiplication of unicellular green algae. BASF AG, Department of Ecology, Ludwigshafen/Rhein, Germany, Report No: 97/0329/60/1 (Unpublished)

The effect of Basolon GDA 50 (glutaraldehyde 50%, remainder water) on the growth of green alga *Scenedesmus subspicatus* was determined in a 72 h test under static condition. Test was carried out according to Directive 92/69/EEC, C.3 (1992) and in compliance with GLP. Initial nominal test concentrations were 0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, and 12.8 mg/l. The analytical monitoring was performed to nominal concentrations of 0, 0.1, 1.6 and 12.8 mg/ which indicated a recovery rate > 80 % and therefore the effect concentrations were based on the nominal values. The initial cell density of *Scenedesmus subspicatus* was 104 cell/ml. Temperature during the test was 23 ±2 °C and pH in the range of 7.8-9.4. Fluorescence measurements were performed after 0, 24, 48 and 72 hours. NOECr was determined to be 0.025 mg a.i./l and ErC_{50} 0.6 mg a.i. /l.

Test 2

Reference: Mead, C. and Bartlett, A.J. (1997) Ucarcide Antimicrobial 250: Marine Algal inhibition Test, Safepharm Laboratories Limited, The Dow Chemical Company Report No: DR-0222-1070-032, Unpublished, 30 April 1997

The effect of glutaraldehyde, 50% (purity 50.9%, remainder water) on the growth of marine algae *Skeletonema costatum* was investigated in a 72 h test under static conditions according to ISO/DIS 10253 and in compliance with GLP. Target test concentrations were 0.625, 1.25, 2.5, 5.0 and 10 mg/l. The actual initial test concentrations were 0.607, 1.28, 2.54, 5.12 and 9.8 mg/l. At the end of

the test (72 h) the actual concentrations were not detectable at the two lowest nominal concentrations of 0.625 and 1.25 mg/l. The remaining values were quantified at 0.935, 2.53 and 7.94 mg/l corresponding 37, 51 and 79 % of the nominal concentration, indicating that the test substance concentrations did not remain at > 80 % of initial concentrations during the test. Test temperature was 24 ±1 °C and pH was measured at the start of the test (ranging from 7.8 to 8.0) and at the end (ranging from 8.1 to 10.4). Results based on the geometric mean of the measured concentrations were: ErC_{50} 0.61 mg a.i./l (72 h) with 95 % confidence limit 0.21-1.0 mg a.i./l and NOEC 0.071 mg a.i./l (72 h).

Test 3

Reference: Migchielsen, M.H.J. (2001) Fresh water algae growth inhibition test with glutaraldehyde 50 %, NOTOX Safety and Environmental Research The Dow Chemical Company Report No: K-020301-095, unpublished, 19 June 2001

The inhibitory effect of glutaraldehyde 50 % (remainder water, Batch number 12863) on the growth of fresh water green algae *Selenastrum capricornutum* was studied in a 72 h test under static condition. Test was conducted to OECD 201 and indicated to be GLP compliant. Algal cell density was 104 cell/ml in the beginning of the test. Three replicates were used in each test concentration. Initial nominal test concentrations were 0.025, 0.05, 0.11, 0.24, 0.52, 1.14 and 2.5 mg a.i./l. Only four highest test concentrations (0.24, 0.52, 1.13 and 2.5 mg/l) were detectable at 0, 24, 48 and 72 hours. Mean measured concentrations were 0.054, 0.23, 0.69 and 1.81 mg/l, respectively. Temperature ranged between 22.0 and 23.5 °C during the test. pH increased towards the end of the study (at the start 7.6-7.8 and at the end 8.0-10.3). ErC_{50} was determined to be 0.82 mg a.i./l with confidence limits 0.76-0.88 mg/l and NOEC was 0.108 mg a.i./. The results are based on the geometric mean concentrations of measurements in test concentrations 0.24, 0.52, 1.14 and 2.5 mg/l.

Table 41: Growth inhibition on algae

Guideline Test method	Species	Endpoint	Exposure		Results mg a.s./L			Remarks	Study owner Reference
			design	duration	NOE_rC	E_bC_{50}[1]	E_rC_{50}[2]		
92/69/EEC C.3 GLP	*Scenedesmus subspicatus*	Growth inhibition	Static	72 h	0.025	0.38	0.6	Key study Meas. conc, Results based on nominal	Maisch R. 1997
ISO/DIS 10253 GLP	*Skeletonema costatum*	Growth inhibition	Static	72 h	0.071	0.19	0.61	Meas. conc. geometric mean. Marine spec.	Mead and Bartlett 1997
OECD 201 GLP	*Selenastrum capricornutum*	Growth inhibition	Static	72 h	0.108	0.52	0.82	Meas. conc; geometric mean.	Migchielsen, M.H.J. 2001

[1] calculated from the area under the growth curve
[2] calculated from growth rate

5.4.4 Other aquatic organisms (including sediment)

Not evaluated in this dossier.

5.5 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

CLP (2nd ATP) criteria

Glutaraldehyde is rapidly degradable in the environment as shown by ready biodegradability tests. Glutaraldehyde does not have a tendency to bioaccumulate, as shown by Log Kow values. Based on aquatic acute toxicity tests, glutaraldehyde is classified as "Aquatic Acute 1" and M factor of 10 must be used for classification of mixtures on the basis of acute toxicity. Based on aquatic chronic toxicity tests, glutaraldehyde is classified as "Aquatic chronic 2".

DSD criteria

Glutaraldehyde is readily degradable in the environment as shown by ready biodegradability tests. Glutaraldehyde does not have a tendency to bioaccumulate, as shown by Log Kow values. Based on aquatic acute toxicity tests, glutaraldehyde is classified as "Dangerous for the environment; Very toxic to aquatic organisms".

Table 42: Comparison of glutaraldehyde data with criteria for environmental hazards

Endpoint	Results	Comparison with classification criteria
Degradation	Glutaraldehyde is **hydrolytically stable** at environmentally relevant conditions. Glutaraldehyde is **readily biodegradable** under test conditions, as indicated by the DOC removals of 74 and 88% reached during 7-9 days from the start of the experiments.	According to CLP and DSD criteria, **Glutaraldehyde is readily/rapidly degradable in the environment**, based on ready biodegradation. According to both regulations, a substance is regarded as readily/rapidly degradable if DOC removal of 70% is reached fulfilling the 10-day window.
Bioaccumulation	Log K_{ow} -0.80 to -0.36 (pH 5-9, 25°C)	The measured log Kow values are below the two classification criteria: Log $K_{ow} < 4$ (CLP) and Log $K_{ow} < 3$ (DSD). Therefore, according to CLP and DSD criteria, **Glutaraldehyde does not have a tendency to bioaccumulate.**
Acute aquatic toxicity	*Acartia tonsa* EC_{50} = 0.07 mg/L	Glutaraldehyde fulfills the criteria for **N; R50** classification according to Directive 67/548/EEC (DSD) and the criteria for the proposed classification as **H400** according to Regulation EC 1272/2008 (CLP) (namely L(E)C50 ≤ 1 mg/l). In the case of the H400 classification according to CLP, an **M-factor of 10** is applicable based on 0.01 < L(E)C50 ≤ 0.1 mg/l. In the case of DSD classification, a specific concentration limit of C ≥2.5% shall be applied with the **N; R50** classification. It should be noted that N; R50-53 classification, however, is not applicable to glutaraldehyde, due to the ready biodegradability and the absence of bioccumalation tendency.
Chronic aquatic toxicity	*Scenedesmus subspicatus* NOECr (72 h) = 0.025 mg/l *Skelatonema costatum* NOEC(72 h) =0.071 mg/l	According to CLP (2nd ATP), in the case of rapidly degradable substances, **H411** classification is applicable based on 0.01 <NOEC ≤0.1 mg/l. Therefore, glutaraldehyde fulfills the criteria for H411 according to Regulation EC 1272/2008.

5.6 Conclusions on classification and labelling for environmental hazards (sections 5.1 – 5.4)

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

Glutaraldehyde should be classified Dangerous for the Environment with the following risk and safety phrases:

N Dangerous for the Environment

R50 Very toxic to aquatic organisms

S61 Avoid release to the environment. Refer to special instructions/safety data sheet

Specific concentration limit C ≥2.5% shall be applied with the N; R50 classification.

Conclusion of environmental classification according to Regulation EC 286/2011 (2nd ATP to EC 1272/2008)

Based on the CLP Regulation, Glutaraldehyde should be classified as:

Classification categories	aquatic **acute category 1, M factor 10**	
	aquatic **chronic category 2**	
Hazard Statement	**H400**	'Very toxic to aquatic life',
	H411	'Toxic to aquatic life with long lasting effects'

In the labelling H400 and H411 are combined resulting to Hazard Statement H410 'Very toxic to aquatic life with long lasting effects'

6 REFERENCES

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Anonymous	1995	Dampfdruck von Glutardialdehyd, wässerig. BASF AG, Ludwigshafen/Rhein, Germany, Report BRU 95.311, Unpublished	Yes	BASF	A3.1.2_02
Arif A,A., and Delclos G.L.	2012	Association between cleaning-related chemicals and work-related asthma and asthma symptoms among healthcare professionals Occupational and environmental medicine 69, 35-40	No	Public	
Ballantyne, and Jordan	2001	Toxicological, medical and industrial hygiene aspects of glutaraldehyde with particular reference to its biocidal use in cold sterilization procedures Journal of Applied Toxicology 21, 131-151	No	Public	Ballantyne and Jordan (2001)
Basketter, D.A., Blaikie, L., Dearman, R.J., Kimber, I., Ryan, C.A., Gerberick, G.F., Harvey, P., Evans, P., White, I.R. and Rycroft, R.J.G.	2000	Use of the local lymph node assay for the estimation of relative contact allergenic potency Contact dermatitis 42, 344-348	No	Public	

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Beauchamp, R.O et al.	1992	A critical review of the toxicology of glutaraldehyde Critical Reviews in Toxicology, 22:143-174	No	Public	
Beimborn, D.B., Leibold, E.	2004	Report on 14C-GDA - Study of the biokinetics in rats. BASF AG, Department of Product Safety, Ludwigshafen/Rhein, Germany, Report No: 02B0310/036005, Unpublished	Yes	BASF	A6.02_01
Beimborn, D.B. and Liebold, E.	2004	^{14}C-GDA- Study of the Biokinetics in Rats BASF AG K-020301-063	Yes	Dow	A6_2/01
Blaszcak, D.L.	1993	Guinea pig maximisation test with glutaraldehyde Pharmaco LSR Inc. K-020301-009	Yes	Dow	A6_1_5/01
Brunner, E.	1993	Dampfdruck von Protectol GDA, and Translation of the Report (1994). BASF AG, Ludwigshafen/Rhein, Germany, Report 93L00012, Unpublished	Yes	BASF	A3.2_02
Cafarella, M.A.	2006	Glutaraldehyde- Acute Toxicity to White Shrimp (Penaeus vannamei) Under Flow-Through Conditions. Springborn Smithers Laboratories K-020301-114	Yes	Dow	A7_4_1_2/01

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Cain, W.S., Schmidt, R. and Jalowayski, A.A.	2007	Odor and chemestesis from exposures to glutaraldehyde vapour International archives of occupational and environmental health, 80: 721-731	No	Public	6.12.4(1); Dow 6.12.2_08; BASF
Curran, A.D., Burge, P.S. and Wiley, K.	1996	Clinical and immunologic evaluation of workers exposed to glutaraldehyde. Allergy 51, 826-832	No	Public	
Diar Bakerly N.., Moore V.C., Vellore A.D., Jaakkola M.S., Robertson A.S. and Burge P.S.	2008	Fifteen-year trends in occupational asthma: data from the Shield surveillance scheme Occupational Medicine 58, 169-174	No	Public	
Dionne, E.	1993	Glutaraldehyde - Acute Toxicity to Eastern Oysters (*Crassostrea virginica*) Under Flow-Through Conditions. Springborn Laboratories, Inc K-020301-011	Yes	Dow	A7_4_1_2/03
Di Stefano F., Siriruttanapruk S., McCoach J. and Sherwood Burge P.	1999	Glutaraldehyde: an occupational hazard in the hospital setting Allergy 54, 1105-1109	No	Public	
Doi, J.	2000	Biodegradability in Seawater Study- Closed Bottle Method Aqua Survey, Inc. DR-0222-100-028	Yes	Dow	A7_1_1_2_3
Drögemüller A.	2002	Water Solubility of "Protectol GA (50% Glutaraldehyde)". BASF AG, Ludwigshafen/Rhein, Germany, Study 01L00614, Unpublished	Yes	BASF	A3.5_01

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ECHA	2012	Guidance on information requirements and chemical safety assessment Chapter R.7a: Endpoint specific guidance Version 2.0; November 2012	No	Public	
Esser, T.	1994a	Aerobic Aquatic Metabolism of ^{14}C- Glutaraldehyde in River Water and Sediment PTRL West, Inc. K-020301-015	Yes	Dow	A7_1_2_2_2/01
Esser, T.	1994b	Anaerobic Aquatic Metabolism of ^{14}C-Glutaraldehyde PTRL West, Inc. K-020301-013	Yes	Dow	A7_1_2_2_2/02
Finking, R. and Eisenbarth, P.	2007	Monitoring of manufacturing plant personnel. BASF AG, Department of Product Safety, Ludwigshafen/Rhein, Germany Non GLP, Unpublished	Yes	BASF	A6.12.1_01
Finking, R. and Eisenbarth, P.	2007	Monitoring of laboratory personnel. BASF AG, Department of Product Safety, Ludwigshafen/Rhein, Germany, Non GLP, Unpublished	Yes	BASF	A6.14_04
Fowler, T.	2009	Flash Point of UCARcide The Dow Chemical Company AL-2009-003663	Yes	Dow	A3_12
Frantz S.W., Beskitt J.L. and Tallant, M.J.	1993	Glutaraldehyde: Species comparisons of in vitro skin penetration. Cutaneous and Ocular Toxicology, 1993, 4:349-361 Published	No	Public	A6.02_06

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Gannon P.F.G., Bright P., Campbell M., O'Hickey S.P. and Sherwood Burge P.	1995	Occupational asthma due to glutaraldehyde and formaldehyde in endoscopy and x ray departments Thorax 50, 156-159	No	Public	
Gödde, M.	2004	Evaluation of physical and chemical properties according to Directive 92/69/EC: Annex A.9-A.17. BASF AG, Ludwigshafen/Rhein, Germany, Laboratory Study Code: SIK-Nr. 04/2080, Unpublished	Yes	BASF	A3.10_01
Gonsior, S.J., Stock, M.K., and Rivard, M.A.	2001	Determination of the Adsorption of Glutaraldehyde to Activated Sludge Using the ISO/CD 18749 Batch Adsorption Test The Dow Chemical Company K-020301-002	Yes	Dow	A7_1_3
Greenspan, B.J., Longo, L.C., and Eisler, D.L.	1982	Glutaraldehyde Four-Hour LC50 Inhalation Study on Rats Bushy Run Research Centre, Union Carbide 44-96	Yes	Dow	A6_1_3
Grundler O.J.	1994a	Study on the irritation to the intact dorsal skin of the albino rabbit (short-term test). BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, Report No: 80/265, (original report in German dated 22 Dec 1981), Non GLP, Unpublished	Yes	BASF	A6.01.4_01
Grundler O.J.	1994b	Study on the irritation to the intact dorsal skin of the albino rabbit (short-term test). BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, Report No: 80/265, (original German report dated 22 Dec 1981), Non GLP, Unpublished	Yes	BASF	A6.01.4_02

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Grundler O.J.	1994c	Report on the study of the irritation to the eye of white rabbits based on Draize. BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, Report No: 80/265, (original German report dated 22 Dec 1981), Non GLP, Unpublished	Yes	BASF	A6.01.4_03
Hansen, S.C., Clark, A. J., McClymont, E. L. and Staley, J. L.	2007	Glutaraldehyde: Pharmacokinetics Of Drinking Water Administered Glutaraldehyde In Crl:Wl(Han) Rats Toxicology & Environmental Research and Consulting 51125	Yes	Dow	A6_2/03
Hansen S.C., Clark, A.J., McClymont, E.L. and Staley, J.L.	2007	Glutaraldehyde: Pharmacokinetics Of Drinking Water Administered Glutaraldehyde In Crl:Wl(Han) Rats Toxicology & Environmental Research and Consulting Unpublished	Yes	BASF	A6.02_09
Havics, A. and Bucherl, S.		An evaluation of asthma risk due to glutaraldehyde at a medical device manufacturing facility Pending publication	No	Public	
Jaeckh, R.	1994a	Report on the study of the acute oral toxicity 80/265; rat/oral. BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, Report No: 80/265, (original report in German dated 1981), Unpublished	Yes	BASF	A6.01.1_01
Jalali-Araghi, K., Ruzo, L.O. and Shepler, K.	1992a	Hydrolysis of [1,5-14C] glutaraldehyde at pH 5, 7 and 9 PRTL West, Inc. K-020301-016	Yes	Dow	A7_1_1_1_1

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Jalali-Araghi, K., Ruzo, L.O. and Shepler, K.	1992b	Sunlight photodegradation of [1,5-14C] glutaraldehyde in a buffered aqueous solution at pH 5 PTRL West, Inc. K-020301-014	Yes	Dow	A7_1_1_1_2
Jatzek, H-J.	1993	Determination of the chronic toxicity of Protectol GDA to Daphnia magna. BASF AG, Department of Ecology, Ludwigshafen/Rhein, Germany, Report No: 93/0406/51/2, Unpublished	Yes	BASF	A7.4.3.4_01
Jaeckh R.	1994a	Report on the study of the acute oral toxicity 80/265; rat/oral. BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, Report No: 80/265, (original report in German dated 1981), Non GLP, Unpublished	Yes	BASF	A6.01.1_01
Jaeckh R.	1994b	Report on the study of the acute dermal toxicity of "Glutaraldehyde" in the rat. BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, Report No: 80/265, (original report in German dated 1981), Non GLP, Unpublished	Yes	BASF	A6.01.2_02
Katagiri, H., Suzuki, T., Aizawa, Y. and Kadowaki, T.	2006	Indoor glutaraldehyde levels in the endocope disinfecting room and subjective symptoms among workers Industrial Health, 44: 225-229	No	Public	
Kimber, I.	1994	Mouse Lymph Node Assay and Mouse IgE Test on Glutaraldehyde Zeneca K-020301-007	Yes	Dow	A6_1_5/02

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Kiplinger, G.R.	1995	Acute dermal toxicity study of glutaraldehyde in albino rabbits. WIL Research Laboratories Inc., Ashland, OH, Report No: WIL-234002, (sponsor: BASF Corporation; BASF Reg Doc No: #95/5102), GLP, Unpublished	Yes	BASF	A6.01.2_01
Klimisch, H-J.	1994	Acute inhalation toxicity LC50 4 hours (rat) of "glutaraldehyde, approx. 50% solution, poor in methanol", liquid aerosol study (test substance No. 80/265). BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, Report No: 80/265, (original report in German dated 1982), Unpublished	Yes	BASF	A6.01.3_01
Klimisch, H-J.	2001	Acute inhalation toxicity LC50 4 hours (rat) of "glutaraldehyde, 50% solution" (test substance No. 83/59), liquid aerosol study. BASF AG, Department of Product Safety, Ludwigshafen/Rhein, Germany, Report No: 83/59, (original report in German dated 1985), Unpublished	Yes	BASF	A6.01.3_02
Koda S., Kumagai S. and Ohara H.	1999	Environmental monitoring and assessment of short-term exposuresto hazardous chemicals of a sterilization process in hospital working environments Acta Med Okayama 53, 217-223	No	Public	
Leder, J.	1989	End-use Product Chemistry UCARCIDE 250 Antimicrobial Union Carbide Corporation The Dow Chemical Company -	Yes	Dow	A3_11

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Leinster, P., Baum, J.M. and Baxter, P.J.	1993	An assessment of exposure to glutaraldehyde in hospitals: typical exposure levels and recommended control measures British Journal of Industrial Medicine 50, 107-111	No	Public	
Levine, A.M.	1991	Hydrolysis of 14 C-Glutaraldehyde in aqueous solutions buffered at pH 5, 7 and 9. Centre for Hazardous Materials Research, Pittsburgh, Laboratory Project ID 003/0037001/89 Unpublished	Yes	BASF	A7.1.1.1.1_01
Liss G.M., Buyantseva L., Luce C.E., Ribeiro M., Manno M. and Tarlo S.M.	2011	Work-related asthma in healthcare in Ontario American Journal of Industrial Medicine 54, 278-284	No	Public	
Machado, M.W.	1993a	Glutaraldehyde - Acute Toxicity to Sheepshead Minnow (Cyprinodon variegatus) Under Flow-Through Conditions Springborn Laboratories Inc. K-020301-010	Yes	Dow	A7_4_1_1/01
Machado, M.W.	1993b	Glutaraldehyde - Acute Toxicity to Mysid Shrimp (*Mysidopsis bahia*) Under Flow-Through Conditions. Springborn Laboratories, Inc. K-020103-018	Yes	Dow	A7_4_1_2/02
Maisch, R.	1997	Determination of the inhibitory effect of Basolon GDA 50 on cell multiplication of unicellular green algae. BASF AG, Department of Ecology, Ludwigshafen/Rhein, Germany, Report No: 97/0329/60/1, Unpublished	Yes	BASF	A7.4.1.3_01

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Marzulli, F.N. and Maibach, H.I.	1974	The use of graded concentrations in studying skin sensitizers: experimental contact sensitization in man Food and cosmetics toxicology 12, 219-227	No	Public	
McDonald, J.C., Keynes, H.L. and Meredith, S.K.	2000	Reported incidence of occupational asthma in the United Kingdom, 1989-97 Occupational and Environmental Medicine 57, 823-829	No	Public	
McKelvey J.A., Anuszkiewicz C. M. and Tallant M.J.	1985	Skin Penetration and Pharmacokinetics of Glutaraldehyde in Rats and Rabbits, Union Carbide Corporation, The Dow Chemical Company Report no. 47-197	Yes	Dow	Dow A6.02/6
McKemie, T.H.	2000a	Freezing point/melting point of UCARCIDE 250 Antimicrobial PTRL West, Inc. DR-0222-1070-040	Yes	Dow	A3__1/01
McKemie, T.H.	2000b	Boiling Point of UCARCIDE 250 Antimicrobial PTRL West, Inc. DR-0222-1070-039	Yes	Dow	A3_1_2/01
McKemie, T.H.	2000c	Density of UCARCIDE 250 Antimicrobial PTRL West, Inc. DR-0222-1070-038	Yes	Dow	A3_1_3/01
McKemie, T.H.	2000e	Surface Tension of UCARCIDE 250 Antimicrobial PTRL West, Inc. DR-0222-1070-041	Yes	Dow	A3_13/01
McKemie, T.H.	2000f	Viscosity of UCARCIDE 250 Antimicrobial PTRL West, Inc. DR-0222-1070-037	Yes	Dow	A3_14/01
Mead, C. and Bartlett, A.J.	1997	Ucarcide Antimicrobial 250: Marine Algal Inhibition Test Safepharm Laboratories Limited DR-0222-1070-032	Yes	Dow	A7_4_1_3/02

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Mendrala, A.L., Clark, A.J. and Sushynski, J.M.	2004	Glutaraldehyde: pharmacokinetics in Fischer 344 rats following oral gavage or dermal application. The Dow Chemical Company, Department of Toxicology and Environmental Research and Consulting, Midland, Michigan 48674, USA, Report No: 021134, (sponsor: The Dow Chemical Company and BASF AG), BPD ID A6.02_02 Unpublished	Yes	BASF	A6.02_02_a A6.02_02_b A6.02_02_c
Mendrala, A.L., Clark, A.J. and Sushynski, J.M.	2004	Glutaraldehyde: Pharmacokinetics in Fischer 344 Rats Following Oral Gavage or Dermal Application The Dow Chemical Company K-020301-003	Yes	Dow	A6_2/02
Migchielsen M.H.J.	2001	Fresh water algal growth inhibition test with glutaraldehyde 50%. NOTOX Safety and Environmental Research K-020301-095	Yes	Dow	A7_4_1_3/01
Migchielsen M.H.J.	2003	Daphnia magna, Reproduction Test with Glutaraldehyde 50% (flow-through) Notox Safety and Environmental Research K-020301-115	Yes	Dow	A7_4_3_4/01
Myers, R.C.	1981	Glutaraldehyde dilutions: Percutaneous toxicity and eye irritation studies Bushy Run Research Centre, Union Carbide 44-65	Yes	Dow	A6_1_2
Myers, R.C.	1987	50% aqueous glutaraldehyde samples, Primary eye irritancy studies in the rabbit Bushy Run Research Centre, Union Carbide 50-104	Yes	Dow	A6_1_4(e)
Myers, R.C	1988	50% aqueous glutaraldehyde samples, Primary dermal irritancy studies in the rabbit Bushy Run Research Centre, Union Carbide 51-14	Yes	Dow	A6_1_4(s)

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Myers, R.C. and Christopher, S.M.	1992	Ucarcide Antimicrobial 250: Acute peroral toxicity study in the rat Bushy Run Research Centre, Union Carbide DR-0222-1070-013	Yes	Dow	A6_1_1
National Center for Biotechnology Information n.	2013	PubChem Compound Database; CID=42632221, http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=42632221 (accessed Apr. 10, 2013)	No	Public	
Nayebzadeh, A.	2007	The effect of work practices on personal exposure to glutaraldehyde among health care workers Industrial Health, 45: 289-295	No	Public	
Norris J.C., and Kintigh W.J.	1995	Glutaraldehyde: Acute Vapour Inhalation Toxicity Study in Rats, Union Carbide Corporation, The Dow Chemical Company Report No: K-020301-089	Yes	Dow	A6_1_3/02
OECD	2000	Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures OECD Series on Testing and Assessment, Number 23 / ENV/JM/MONO(2000)6	No	Public domain	
Olson, J.D.	1998	The vapour pressure of pure and aqueous glutaraldehyde. Fluid Phase Equilibria 150-151: 713-720, Published	No	Public	A3.2_03
Olson, J.D.	1998	The Vapor Pressure of Pure and Aqueous Glutaraldehyde Fluid Phase Equilibria Vol. 150, p 713-720	Yes	Dow	Olson, J.D. (1998)
Palczynski, C., Walusiak, J., Ruta, U. and Gorski, P.	2001	Occupational asthma and rhinitis due to glutaraldeyhde: changes in nasal lavage fluid after specific inhalatory test. Allergy 56: 1186-1191,	No	Public	

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Pechter, E., Davis, L.K., Tumpowsky , C., Flattery J., Harrison, R., Reinisch, F., Reilly, M.J., Rosenman, K.D., Schill, D.P., Valiante, D. and Filios, M.	2005	Work-related asthma among health care workers: surveillance data from California, Massachusetts, Michigan, and New Jersey, 1993-1997 American Journal of Industrial Medicine 47, 265-275	No	Public	
Perdelli, F., Ottria, G., Cristina, M.L., Lombardi, R., Sartini, M., Spagnolo, A.M., Dallera, M. and Orlando, P.	2008	Evaluation of environmental contamination by glutaraldehyde in an outpatient facility for digestive endoscopy in an Italian hospital International Journal of Environmetal Health Research 18, 73-78	No	Public	
Pisaniello, D.L, Gun, R.T., Tkaczuk, M.N., Nitschke, M. and Crea, J.	1997	Glutaraldehyde exposures and symptoms among endoscopy nurses in South Australia Applied Occupational and Environmental Hygiene, 12: 171-177	No	Public	6.12.4(4); Dow 6.12.4_3; BASF
Rick, D.L. and West, R.J.	2006	A Critical Evaluation of Vapor Pressure Measurements for Aqueous Glutaraldehyde Formulations The Dow Chemical Company Toxicology and Environmental Research and Consulting K-020301-122	Yes	Dow	A3_2
Roberts, C.A., Drottar, K.R., Swigert, J.P. and Krueger, H.O.	1999	Ucarcide Antimicrobial: An early life-stage toxicity test with the fathead minnow (*Pimephales promelas*) Wildlife International Ltd. DR-0222-1070-011	Yes	Dow	A7_4_3_2/01

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Salway, J. G.	1994	Metabolism at a glance, Blackwell Scientific Publications	No	Public	Salway J. G. (1994)
Sametschek, E.	2002	Partition Coefficient n-Octanol/Water (log Pow) of "Protectol GA (50% Glutaraldehyde)". BASF AG, Ludwigshafen/Rhein, Germany, Study 01L00615, Unpublished	Yes	BASF	A3.9_01
Sametschek, E.	2004	Physico-chemical Properties of "Protectol GA 50" for the Notification in the Netherlands. BASF AG, Ludwigshafen/Rhein, Germany, Study 04L00165, Unpublished	Yes	BASF	A3.13_01
Sano, L.L., Krueger, A.M., and Landrum, P.F.	2005	Chronic toxicity of glutaraldehyde: differential sensitivity of three freshwater organisms. Aquatic Toxicology 71:283-296	No	Public domain	A7_4_3_2/02
Schaefer, E.C.	2000	Ucarcide 250 Antimicrobial: Ready biodegradability by the dissolved organic carbon die-away test method Wildlife International Ltd. DR-0222-1070-027	Yes	Dow	A7_1_1_2_1
Schmidt, P.	2002	Determination of the Melting Temperature of "Protectol GA (50% Glutaraldehyde)". BASF AG, Ludwigshafen/Rhein, Germany, Study 02L00155, Unpublished	Yes	BASF	A3.1.1_01
Schwarz, H.	2002	Protectol GA (50% Glutaraldehyde), Determination of the Biodegradability in the marine CO2-Evolution Test. BASF AG, Department of Experimental Toxicology and Ecology, Ludwigshafen/Rhein, Germany, Report No: 01/0411/32/1 Unpublished	Yes	BASF	A7.1.1.2.3_01

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Shaffer, M.P. and Belsito, D.V.	2000	Allergic contact dermatitis from glutaraldehyde in health-care workers Contact dermatitis 43, 150-156	No	Public	
Shepler, K.	1996	Partition coefficient (n-octanol/deionized water) of [14C]glutaraldehyde PTRL West, Inc. 96U1629	Yes	Dow	A3_9/01
Siemann, L.	1999	Product Chemistry for Glutaraldehyde (50% Solution), Series 63 - Physical and Chemical Characteristics. Midwest Research Institute, Laboratory Project ID: 4217-F(02), BASF MicroCheck Ltd., Nottingham, UK, BASF No. BM99006, Unpublished	Yes	BASF	A3.1.2_01
Simms, R.	2006	Protectol GA 50 - Thermal Decomposition. BASF AG, Nottingham, UK, Statement, Unpublished	Yes	BASF	A3.10_02
Skinner, W., Shepler, K. and Estigoy, L.	1994	Soil adsorption/desorption of [^{14}C] glutaraldehyde by the batch equilibrium method PTRL West, Inc. K-020301-081	Yes	Dow	A7_2_3_1/01
Sousa, J.V.	1995	Glutaraldehyde - Acute toxicity to Mysids (Mysidopsis bahia) under flow-through conditions. Springborn Laboratories Inc. , Environmental Sciences Division, Wareham, Massachusetts, SLI Report No: 94-12-5603, Unpublished	Yes	BASF	A7.4.1.2_04

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Stenton, S.C., Beach, J.R., Dennis, J.H., Keaney, N.P., Hendrick, D.J.	1994	Glutaraldehyde, asthma and work - a cautionary tale. Occupational Medicine 44, 95-98	No	Public	
Sutton, P.M., Quint J., Prudhomme J., Flattey J., Materna B. and Harrison, R.	2007	Glutaraldehyde exposure among workers making bioprosthetic heart valves. Journal of Occupational and Environmental Hygiene 4, 311-320	No	Public	
Taeger, K.	1993	Determination of the Biodegradability or the Elimination of Protectol GDA in the DOC Die Away (ISO 7827)-Test. BASF AG, Department of Ecology, Ludwigshafen/Rhein, Germany, Report No: 93/0406/21/1 Unpublished	Yes	BASF	A7.1.1.2.1_01
Tallant, M.J., Beskitt, J.L., and Frantz, S.W.	1991	Glutaraldehyde: Species Comparisons of *In Vitro* Skin Penetration Following a Single Application to the Excised Skin of Humans, Fischer 344 Rats, CD-1 Mice, Hartley Guinea pigs, and New Zealand white rabbits Union Carbide Corporation 53-15	Yes	Dow	A6_2/04
Teta J.M., Avashia B. H., Cawley T.J. and Yamin A.T.	1995	Absences of sensitizations and cancer increases among glutaraldehyde workers Toxic Substance Mechanisms 14, 293-305	No	Public	

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Vyas, A., Pickering, C.A.C, Oldham, L., Francis, H.C., Fletcher, A.M., Merret, T. and Niven, R. McL	2000	Survey of symptoms, respiratory function, and immunology and their relation to glutaraldehyde and other occupational exposures among endoscopy nursing staff Occupational and Environmental Medicine, 57: 752-759	No	Public	
Water A., Beach J. and Abramson M.	2003	Symptoms and lung function in health care personnel exposed to glutaraldehyde American Journal of Industrial Medicine 43, 196-203	No	Public	
Wells, D.F	1994a	Ucarcide 250 Antimicrobial-Determination of the Solubility in Water and Selected Solvents Springborn Laboratories, Inc. DR-0222-1070-001	Yes	Dow	A3_5/01
Werley, M.S., Burleigh-Flayer, H.D. and Ballantyne, B.	1995	Respiratory peripheral sensory irritation and hypersensitivity studies with glutaraldehyde vapour Toxicology and Industrial Health, 11: 489-501	No	Public	A6.01.4_04; BASF
Wetton, P.M. and Bartlett, A.J.	1997	Ucarcide Antimicrobial 250: Acute Toxicity to *Acartia Tonsa* Safepharm Laboratories Limited DR-0222-1070-033	Yes	Dow	A7_4_1_2/04
Wittmer, E.	2012	Summary Report; Protectol GA 50 - Technical trail 12I0674/05I015	Yes	BASF	A6.01.3_01a
Zeller H	1975	Bericht ueber die Pruefung von Methoxidihydropyran im Vergleich zu Methoxidihydropyran, roh und Relugan GT auf etwaige hautsensibilisierende Wirkung. BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, Report No: XXIII/115, (German report), Non GLP, Unpublished	Yes	BASF	A6.01.5_01

Author(s)	Year	Title. Source (where different from company) Company, Report No. (Un)Published	Data Protection Claimed (Yes/No)	Owner	BPD ID Section No / Reference No
Zhang, F., Hansen, S. C. and Clark, A.J.	2007	Glutaraldehyde: Identification of Metabolites in the Wistar Rat, The Dow Chemical Company, Study ID 0410321	Yes	Dow	Dow A6.02/05
Zhang, F., Hansen, S.C. and Clark, A.J.	2007	Glutaraldehyde: Identification of metabolites in the Wistar-rat. The Dow Chemical Company, Toxicology and Environmental Research and Consulting (TERC), Midland, Michigan 48674, USA, Report No: 041032 Unpublished	Yes	BASF	A6.02_05
Zok, S.	2000	Protectol GDA (50% Glutaraldehyde) - Early Life-Stage toxicity test on the Rainbow trout (Oncorhynchus mykiss). BASF AG, Department of Product Safety, Ludwigshafen/Rhein, Germany, Report No: 52F0447/975114, Unpublished	Yes	BASF	A7.4.3.2_01

7 ANNEXES