Section A6.12.2 _ 02 Annex Point VI.6.9.2	Case report, upper respiratory tract irritation, skin rash and recurrent epistaxis in a hospital employee

		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Case report of a 38-year-old woman using glutaraldehyde for sterilisation of endoscopy equipment. Physical examination and clinical laboratory tests.
5.2	**Results and discussion**	Upper respiratory tract irritation, skin rash and recurrent epistaxis (nose bleeding) in a 38-year-old woman using glutaraldehyde for sterilisation of endoscopy equipment.
5.3	**Conclusion**	Epistaxis has been reported occasionally from vapour exposure.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 14th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	4.1 Clinical Signs. Additionally, there were headaches and eye irritation
Conclusion	Inadequate personal protection had caused epistaxis, headaches, eye and throat irritation, chest tightness and skin rash. The symptoms were resolved when exposure was minimised by personal protective measures.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.2 _ 03 Case report, upper respiratory tract symptoms

Annex Point VI.6.9.2

Official use only

		1 REFERENCE
1.1	**Reference**	Benson WG (1984) Case report exposure to glutaraldehyde. J. Soc. Occup. Med. 34: 63-64 (Published), BPD ID A6.12.2_03
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Substance**	Glutaraldehyde (not further specified)
3.2	**Persons exposed**	1
3.2.1	Sex	Female
3.2.2	Age/weight	No data
3.2.3	Known Diseases	No data
3.2.4	Number of persons	1
3.2.5	Other information	None
3.3	**Exposure**	Inhalation and dermal
3.3.1	Reason of exposure	Occupational
3.3.2	Frequency of exposure	Recurrent
3.3.3	Overall time period of exposure	No data
3.3.4	Duration of single exposure	No data
3.3.5	Exposure concentration/dose	No data
3.3.6	Other information	None
3.4	**Examinations**	Repeated peak-flow measurements on workdays and weekends.
3.5	**Treatment**	No data
3.6	**Remarks**	None
		4 RESULTS
4.1	**Clinical Signs**	Irritant conjunctivitis, increasing breathlessness.
4.2	**Results of examinations**	Drop of peak expiratory flow during workdays with improvement on weekends.
4.3	**Effectivity of medical treatment**	No data
4.4	**Outcome**	Recovered
4.5	**Other**	None

Section A6.12.2 _ 03 Case report, upper respiratory tract symptoms

Annex Point VI.6.9.2

		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Case report of a 38-year-old woman using glutaraldehyde for sterilisation of endoscopy equipment. Physical examination and clinical laboratory tests.	X
5.2	**Results and discussion**	Drop of peak expiratory flow in endoscopy nurse when exposed during workdays to glutaraldehyde.	
5.3	**Conclusion**	Decrease in respiratory function when exposed to glutaraldehyde.	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 14th, 2011
Materials and Methods	5.1 Materials and methods. The age was not specified, and no clinical laboratory tests were performed except for peak-flow measurements.
Results and discussion	The peak-flow was reduced during the working weeks and recovered during weekends. During a glutaraldehyde-free working week there was no reduction in the peak-flow.
Conclusion	Glutaraldehyde exposure caused a reduction in the peak expiratory flow.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.2 _ 04 Case report, upper respiratory tract symptoms

Annex Point VI.6.9.2

			Official use only
		1 REFERENCE	
1.1	**Reference**	Quirce S, Gomez M, Bombin C, Sastre J (1999) Glutaraldehyde-induced asthma. Allergy 54: 1121-1122 (Published), BPD ID A6.12.2_04	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	2 % Glutaraldehyde solution.	
3.2	**Persons exposed**	1	
3.2.1	Sex	Female	
3.2.2	Age/weight	61 year-old nurse	
3.2.3	Known Diseases	No data	
3.2.4	Number of persons	1	
3.2.5	Other information	None	
3.3	**Exposure**	Inhalation and dermal.	
3.3.1	Reason of exposure	Occupational.	
3.3.2	Frequency of exposure	Recurrent.	
3.3.3	Overall time period of exposure	Several years	X
3.3.4	Duration of single exposure	No data	
3.3.5	Exposure concentration/dose	0.064 – 0.081 mg/m3 during simulated specific bronchial challenge test.	
3.3.6	Other information	None	
3.4	**Examinations**	Clinical examination, specific bronchial challenge test with glutaraldehyde.	
3.5	**Treatment**	No data	
3.6	**Remarks**	None	
		4 RESULTS	
4.1	**Clinical Signs**	Symptoms of irritation of the eyes and upper respiratory tract, dyspnoea on exertion, dry cough, and episodic attacks of wheezing.	
4.2	**Results of examinations**	Early asthmatic response during challenge test. Although no late reaction was observed, a recurrent nocturnal asthmatic reaction occurred in the following days after challenge test.	
4.3	**Effectivity of medical treatment**	No data	

Section A6.12.2 _ 04 Case report, upper respiratory tract symptoms

Annex Point VI.6.9.2

4.4	**Outcome**	Recovered
4.5	**Other**	None
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Case report of a 61-year-old nurse using glutaraldehyde for sterilisation of artificial kidney machines. Clinical examination and specific bronchial challenge test with glutaraldehyde.
5.2	**Results and discussion**	Early asthmatic response during challenge test. Although no late reaction was observed, a recurrent nocturnal asthmatic reaction occurred in the following days after challenge test. The same challenge test performed in two unexposed asthmatic patients elicited no response.
5.3	**Conclusion**	The specific challenge test provoked the appearance of non-specific bronchial hyper-responsiveness, which preceded the development of an asthmatic reaction to glutaraldehyde.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 14th, 2011
Materials and Methods	3.3.3 Overall time period of exposure. The exposure occurred for 3-4 years before developing symptoms.
Results and discussion	Agree with applicant's version.
Conclusion	Sensitisation occurred during the 3-4 years after beginning work with glutaraldehyde.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.2 _ 05 Case report, upper respiratory tract symptoms

Annex Point VI.6.9.2

			Official use only
		1 REFERENCE	
1.1	**Reference**	Nicewicz JT, Murphy DMF, Welsh JP, Sirolli H (1986) Occupational asthma caused by glutaraldehyde exposure. Immunology & Allergy Practice 8: 1272 –1278 (Published), BPD ID A6.12.2_05	X
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	2 % Glutaraldehyde solution.	
3.2	**Persons exposed**	1	
3.2.1	Sex	Female	
3.2.2	Age/weight	61 year-old respiratory therapy technician.	X
3.2.3	Known Diseases	No data	
3.2.4	Number of persons	1	
3.2.5	Other information	None	
3.3	**Exposure**	Inhalation and dermal	
3.3.1	Reason of exposure	Occupational	
3.3.2	Frequency of exposure	Recurrent	
3.3.3	Overall time period of exposure	Several years	
3.3.4	Duration of single exposure	For 1 ½ hours per day	
3.3.5	Exposure concentration/dose	No data	X
3.3.6	Other information	None	
3.4	**Examinations**	Clinical examination, specific bronchial challenge test with glutaraldehyde.	
3.5	**Treatment**	Metaproterenol metered dose inhaler, prednisone, oral theophylline.	
3.6	**Remarks**	None	
		4 RESULTS	
4.1	**Clinical Signs**	Chest tightness, wheezing, nasal congestion, and redness as well as weeping of the eyes; upon reexposure status asthmaticus.	
4.2	**Results of examinations**	On lung function test a delayed obstructive response after exposure was shown; serum IgG and IgE levels as well as scratch test performed with 2 % glutaraldehyde were normal; absolute eosinophil count was elevated; upon re-exposure a status asthmaticus developed.	

Section A6.12.2 _ 05 Case report, upper respiratory tract symptoms

Annex Point VI.6.9.2

4.3	**Effectivity of medical treatment**	No data
4.4	**Outcome**	Recovered
4.5	**Other**	None
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Case report of a 25-year-old respiratory therapy technician. Clinical examination and specific bronchial challenge test with glutaraldehyde.
5.2	**Results and discussion**	On lung function test a delayed obstructive response after exposure was shown; serum IgG and IgE levels as well as scratch test performed with 2 % glutaraldehyde were normal; absolute eosinophil count was elevated; upon re-exposure a status asthmaticus developed.
5.3	**Conclusion**	An immunologic mechanism did not appear to be responsible for the respiratory symptoms of the technician.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 14th, 2011
Materials and Methods	1.1 Reference. The correct page numbers are 272-278. 3.2.2 Age/weight. The patient was 25 years old. 3.3.5 Exposure concentration/dose. The patient was exposed to 2 % glutaraldehyde.
Results and discussion	Agree with applicant's version.
Conclusion	Glutaraldehyde exposure resulted in a life-threatening asthmatic condition, while serum IgG and IgE values were normal and absolute eosinophil count was elevated. Further immunological examinations were not performed except for a skin scratch test which was negative.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.2 _ 06 Case reports, health problems in radiographers

Annex Point VI.6.9.2

Official use only

1 REFERENCE

1.1	**Reference**	Hewitt PJ (1993) Occupational health problems in processing of x-ray photographic films. Ann. Occup. Hyg.37: 287–295 (Published), BPD ID A6.12.2_06

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Substance**	Glutaraldehyde solution.
3.2	**Persons exposed**	Radiographers, no further data provided.
3.2.1	Sex	No data
3.2.2	Age/weight	No data
3.2.3	Known Diseases	No data
3.2.4	Number of persons	No data
3.2.5	Other information	None
3.3	**Exposure**	Inhalation and dermal.
3.3.1	Reason of exposure	Occupational.
3.3.2	Frequency of exposure	Recurrent.
3.3.3	Overall time period of exposure	No data
3.3.4	Duration of single exposure	No data
3.3.5	Exposure concentration/dose	No data
3.3.6	Other information	None
3.4	**Examinations**	Clinical examination
3.5	**Treatment**	No data
3.6	**Remarks**	None

4 RESULTS

4.1	**Clinical Signs**	Headache, sore throat, tiredness, eye irritation, chemical taste, nasal secretion catarrh, chest pain, shortness of breath, nausea.
4.2	**Results of examinations**	None
4.3	**Effectivity of medical treatment**	Not of concern

Section A6.12.2 _ 06 Case reports, health problems in radiographers

Annex Point VI.6.9.2

4.4	**Outcome**	Not of concern
4.5	**Other**	None
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Reports of symptoms in radiographers.
5.2	**Results and discussion**	Headache, sore throat, tiredness, eye irritation, chemical taste, nasal secretion catarrh, chest pain, shortness of breath, nausea were reported in radiographers coincident with process changes, in particular the increased addition of glutaraldehyde as a hardening agent in the developer.
5.3	**Conclusion**	Several clinical symptoms coincident with the increased use of glutaraldehyde were reported, however it is unlikely that a single agent is responsible in the specific workplace.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 14th, 2011
Materials and Methods	This is a review article reporting results of other publications.
Results and discussion	This is a review article reporting results of other publications.
Conclusion	No relevant conclusions can be made with respect to glutaraldehyde health effects.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Case reports, health problems in therapeutic application

Section A6.12.2 _ 07

Annex Point VI.6.9.2

Official use only

1 REFERENCE

1.1	**Reference**	Prigent F, Iborra C, Meslay C (1996) Nécrose cutanée secondaire à l'application d'une solution a 20 pour 100 de glutaraldehyde sur une verrue. Ann. Dermatol. Venerol. 123: 644-646 (Published), BPD ID A6.12.2_07

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Substance**	Glutaraldehyde solution 20 %
3.2	**Persons exposed**	
3.2.1	Sex	Male child
3.2.2	Age/weight	7 years old
3.2.3	Known Diseases	No data
3.2.4	Number of persons	1
3.2.5	Other information	None
3.3	**Exposure**	Dermal
3.3.1	Reason of exposure	Therapeutic
3.3.2	Frequency of exposure	Recurrent
3.3.3	Overall time period of exposure	8 weeks, daily
3.3.4	Duration of single exposure	No data
3.3.5	Exposure concentration/dose	20%-solution
3.3.6	Other information	None
3.4	**Examinations**	Clinical examination
3.5	**Treatment**	No data
3.6	**Remarks**	None

4 RESULTS

4.1	**Clinical Signs**	Necrosis of the pulp of the greater toe.
4.2	**Results of examinations**	No data
4.3	**Effectivity of medical treatment**	No data

Case reports, health problems in therapeutic application

Section A6.12.2 _ 07

Annex Point VI.6.9.2

4.4	**Outcome**	Not of concern
4.5	**Other**	Not of concern
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Reports of clinical finding in a child.
5.2	**Results and discussion**	Necrosis of the greater toe in a child treated with glutaraldehyde solution (20 %) for 8 weeks for treatment of plantar warts.
5.3	**Conclusion**	After recurrent prolonged application, glutaraldehyde solution (20 %) may cause caustic lesions.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 14th, 2011
Materials and Methods	Not evaluated.
Results and discussion	Not evaluated.
Conclusion	The publication is in French and has not been evaluated.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.2 _ 08 Case report, Case reports, Odor detection and chemesthesis

Annex Point VI.6.9.2

			Official use only
		1 REFERENCE	
1.1	**Reference**	Cain WS, Schmidt R, Jalowayski AA (2007) Odor and chemesthesis from exposures to glutaraldehyde vapor. Int. Arch. Occup. Environ. Health (In press), BPD ID A6.12.2_08	X
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	Glutaraldehyde	
3.2	**Persons exposed**		
3.2.1	Sex	Female	
3.2.2	Age/weight	18 – 35 years	
3.2.3	Known Diseases	Past history of pulmonary embolism	X
3.2.4	Number of persons	50	
3.2.5	Other information		
3.3	**Exposure**	Nasal and ocular	
3.3.1	Reason of exposure	Experimental	
3.3.2	Frequency of exposure	Recurrent.	
3.3.3	Overall time period of exposure		
3.3.4	Duration of single exposure	Brief (up to 5 sec.) and 15 minutes	
3.3.5	Exposure concentration/dose	0,039 to 4.95 ppb and 229 to 772 ppb (brief) and 35 to 100 ppb (15 min. exposure)	
3.3.6	Other information	---	
3.4	**Examinations**	Subject judgement	
3.5	**Treatment**		
3.6	**Remarks**		
		4 RESULTS	
4.1	**Clinical Signs**	Odor detection and chemesthesis	
4.2	**Results of examinations**		
4.3	**Effectivity of medical treatment**		
4.4	**Outcome**		
4.5	**Other**		

Section A6.12.2 _ 08 **Case report, Case reports, Odor detection and chemesthesis**

Annex Point VI.6.9.2

		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Odor detection and chemesthesis in volunteer subjects	
5.2	**Results and discussion**	After brief exposure detection of odor occurred over a range from about 0,04 ppb to 4 ppb, with a median at 0.3 ppb. Detection of ocular and nasal feel occurred three orders of magnitude higher, with median concentrations of 390 and 470 ppb, respectively. During 15-min exposures some chemesthetic activity was found in the range of 35 to 100 ppb, but failed to follow a concentration-response relationship. The gap between odor detection and chemesthetic detection was also seen in other VOCs.	X
5.3	**Conclusion**	Median odor detection in this study was more than two orders of magnitude lower than previous estimates (0.3 to 40 ppb), whereas the previous estimated chemesthesis threshold agree more or less with the results found here (300 ppb to 390/440 ppb).	

Evaluation by Competent Authorities	
Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 9th, 2011
Materials and Methods	1.1 Reference. The reference is as follows: Cain WS, Schmidt R, Jalowayski AA (2007) Odor and chemesthesis from exposures to glutaraldehyde vapor. Int. Arch. Occup. Environ. Health, 80:8, 721-731. 3.2.3 Known Diseases. The participants were healthy.
Results and discussion	5.2 Results and discussion. The point of 50 % correct odour detection was at 0.3 ppb. The respective values for ocular and nasal chemesthetic detection were 390 and 470 ppb, respectively.
Conclusion	In an experimental setup, glutaraldehyde odour can be detected at 0.3 ppb. The concentration around OEL (35-100 ppb) should be recognisable but not irritating. Irritation will occur at concentrations above the detection levels for ocular (390 ppb) and nasal (470 ppb) feel.
Remarks	The study summary is poorly written and contains very little information.
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.2 _ 09
Annex Point IIA VI.6.9.4

Case report, occupational asthma due to glutaraldehyde exposure in a laboratory technician

Official use only

1 REFERENCE

1.1	**Reference**	Ong TH, Tan KL, Lee HS, Eng P (2004) A case report of occupational asthma due to glutaraldehyde exposure. Ann. Acad. Med. Singapore 33: 275-278, (Published), BPD ID A6.12.2_09

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Test material**	Glutaraldehyde
3.2	**Type of study**	Report of a case of occupational asthma due to glutaraldehyde.
3.3	**Method of data collection**	Description of the clinical course and specific inhalational challenge test.
3.4	**Test Persons / Study Population**	1 female
3.5	**Controls**	None
3.6	**Exposure**	
3.6.1	Exposure Route	Inhalation of glutaraldehyde vapor
3.6.2	Exposure Situation	Inhalation of gutaraldehyde vapor whenever opening the cover of a tray filled with 2.5% glutaraldehyde solution.
3.6.3	Exposure concentration(s)	No data
3.7	**Examinations**	
3.7.1	Type of disease	Asthma

4 RESULTS AND DISCUSSION

4.1	**Diagnosis/Findings**	A 32-year-old laboratory technician presented with adult-onset asthma 2 years after daily exposure to glutaraldehyde which was used to sterilise the mouthpieces used for lung function testing. Specific inhalational challenge test showed a 25% drop in forced expiratory volume in one second after exposure to glutaraldehyde but not after a control substance.
4.2	**Recovery**	Not stated

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Report of a case of occupational asthma due to glutaraldehyde. Specific inhalational challenge test with glutaraldehyde vapor.
5.2	**Results and discussion**	A 32-year-old laboratory technician presented with adult-onset asthma 2 years after daily exposure to glutaraldehyde which was used to sterilise the mouthpieces used for lung function testing. Specific inhalational challenge test showed a 25% drop in forced expiratory volume in one second after exposure to glutaraldehyde but not after a control substance.

X

Section A6.12.2 _ 09 Annex Point IIA VI.6.9.4		Case report, occupational asthma due to glutaraldehyde exposure in a laboratory technician
5.3	**Conclusion**	Inhalation of glutaraldehyde vapor may cause asthma.
5.3.1	Reliability	**2**
5.3.2	Validity	Basic data given, acceptable restrictions
5.3.3	Deficiencies	None
5.4	**Other**	None

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 14th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	5.2 Results and discussion. The drop in forced expiratory volume occurred 2.5 h after exposure to glutaraldehyde.
Conclusion	Glutaraldehyde caused asthmatic symptoms to the technician who had been exposed to glutaraldehyde for 2 years.
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.3_ 01 Surveillance data from health care workers

Annex Point IIA VI.6.9.4

Official use only

1 REFERENCE

1.1 Reference

Pechter E, Davis LK, Tumpowsky C, Flattery J, Harrison R, Reinisch F, Reilly MJ, Rosenman KD, Schill DP, Valiante D, Filios M (2005) Work-related asthma among health care workers: surveillance data from California, Massachusetts, Michigan, and New Jersey, 1993-1997. Am. J. Ind. Med. 47: 265-275, (Published), BPD ID A6.12.3_01

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Test material**	Glutaraldehyde
3.2	**Type of study**	Surveillance data of health care workers.
3.3	**Method of data collection**	Case identified using physician reports and hospital discharge data, as part of four state-based surveillance systems.
3.4	**Test Persons / Study Population**	1,879 cases
3.5	**Controls**	None
3.6	**Exposure**	
3.6.1	Exposure Route	No data
3.6.2	Exposure Situation	No data
3.6.3	Exposure concentration(s)	No data
3.7	**Examinations**	
3.7.1	Type of disease	Asthma

4 RESULTS AND DISCUSSION

4.1	**Diagnosis/Findings**	A number and percentage of work-related asthma cases among health care worker for glutaraldehyde was 27 cases, 9% respectively.
4.2	**Recovery**	Not stated

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Cases identification using physicians reports and hospital discharge data.
5.2	**Results and discussion**	Work-related asthma cases were identified using physician reports and hospital discharge data, as part of four state-based surveillance systems. Structure interviews were used to confirm cases and identify occupations and exposures associated with work-related asthma. Health care workers (N=305) accounted for 16 % of the 1,879 confirmed work-related cases, but only 8 % of the states' workforce. The number and percentage of work-related asthma cases among health care worker for glutaraldehyde was 27 cases, 9% respectively.

Section A6.12.3_ 01 Surveillance data from health care workers

Annex Point IIA VI.6.9.4

5.3	**Conclusion**	Health care workers are at risk for work-related asthma due to glutaraldehyde.
5.3.1	Reliability	**2**
5.3.2	Validity	Basic data given, acceptable restrictions
5.3.3	Deficiencies	None
5.4	**Other**	None

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 14th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	Agree with applicant's version.
Conclusion	Glutaraldehyde exposure was associated with 8.9 % of work related asthma among health care workers.
Reliability	2
Acceptability	Acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.4 _ 01
Annex Point IIA VI.6.9.4

Cross-sectional study, survey of symptoms, respiratory function, and immunology

Official use only

1 REFERENCE

1.1	**Reference**	Anees W, Robertson AS, Burge PS (2001) Glutaraldehyde induced asthma in endoscopy nursing staff. Occup. Environ. Med. 58: 544 (Published), BPD ID A6.12.4_01_a Vyas A, Pickering CAC, Oldham LA, Francis HC, Fletcher AM, Merrett T, McL Niven R (2000). Survey of symptoms, respiratory function, and immunology and their relation to glutaraldehyde and other occupational exposures among endoscopy nursing staff. Occup. Environ. Med. 57: 752–759 (Published), BPD ID A6.12.4_01_b Waclawski ER (2001) Glutaraldehyde induced asthma in endoscopy nursing staff. Occup. Environ. Med. 58: 544-545, (Published), BPD ID A6.12.4_01_c

2 GUIDELINES AND QUALITY ASSURANCE

(not applicable)

3 MATERIALS AND METHODS

3.1	**Test material**	Activated alkalised glutaraldehyde solutions (GA) and succinaldehyde-formaldehyde composite (SF).
3.2	**Type of study**	Cross-sectional study.
3.3	**Method of data collection**	Symptoms questionnaires, end of session spirometry, peak flow diaries, skin prick tests (SPTs) to latex and common aeroallergens, and measurements of total immunoglobulin E (IgE) and IgE specific to glutaraldehyde and latex.
3.4	**Test Persons / Study Population**	348 current endoscopy nurses from 59 endoscopy units within the United Kingdom and ex-employees (who had left their job for health reasons (n=18).
3.5	**Controls**	No
3.6	**Exposure**	Occupational
3.6.1	Exposure Route	Not stated
3.6.2	Exposure Situation	Workplace
3.6.3	Exposure concentration(s)	Exposures were above the current maximum exposure limit (MEL) of 0.2 mg/m3 (0,05 ppm) in eight of the units investigated.
3.7	**Examinations**	Spirometry, peak expiratory flow rates started on waking and was performed 2 hourly throughout the day, until sleep, for 1 month, skin prick test and immunoglobulins.
3.7.1	Type of disease	Respiratory and immunological diseases.

Section A6.12.4 _ 01
Annex Point IIA VI.6.9.4

Cross-sectional study, survey of symptoms, respiratory function, and immunology

		4 RESULTS AND DISCUSSION	
4.1	**Exposure**	Occupational exposure to glutaraldehyde and succinaldehyde-formaldehyde composite	
4.1.1	Number of measurements	Personal airborne biocide sampling for peak (during biocide changeover) and background (endoscopy room, excluding biocide changeover) concentrations.	
4.1.2	Average concentrations	Exposures were above the current maximum exposure limit (MEL of 0.2 mg/m3 (0,05 ppm).	X
4.2	**Prevalence**	Work related contact dermatitis was reported by 44 % of current workers exposed to GA, 56.7 % of those exposed to SF, and 44.4 % of ex-employees.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Current endoscopy nurses (n=348) from 59 endoscopy units within the United Kingdom and ex-employees (who had left their job for health reasons (n=18) were surveyed. Symptom questionnaires, end of session spirometry, peak flow diaries, skin prick tests (SPTs) to latex and common aeroallergens, and measurements of total immunoglobulin E (IgE) and IgE specific to GA and latex were performed. Exposure measurements included personal airborne biocide sampling for peak (during biocide changeover) and background (endoscopy room, excluding biocide changeover) concentrations.	
5.2	**Results and discussion**	All 18 ex-employees and 91.4% of the current nurses were primarily exposed to GA, the rest were exposed to a succinaldehyde-formaldehyde (SF) composite. Work related contact dermatitis was reported by 44% of current workers exposed to GA, 56.7% of those exposed to SF composite, and 44.4% of ex-employees. The prevalence of work related symptoms (WRSs) of the eyes, nose, and lower respiratory tract in current workers exposed to GA was 13.5%, 19.8%, and 8.5% respectively and 50%, 61.1%, and 66.6% in the ex-employees. The mean percentage predicted forced expired volume in 1 second (ppFEV(1)) for ex-employees (93.82, 95% confidence interval (95% CI) 88.53 to 99.11) was significantly lower ($p<0.01$) than that of current workers exposed to GA (104.08, 95% CI 102.35 to 105.73). Occupational peak flow diaries completed by current workers with WRSs of the lower respiratory tract showed no evidence of bronchial asthma (<15% variation). Six per cent of the population had positive latex SPTs. Positive indications of one GA specific IgE and 4.1% latex specific IgE occurred. There was no conformity between the latex specific IgE and positive SPTs. Positive SPTs to latex were associated with WRSs of dermatitis and ocular WRSs, but no other WRSs. Exposures were above the current maximum exposure limit (MEL) of 0.2 mg/m(3) (0.05 ppm) in eight of the units investigated. A significant relation existed between peak GA concentrations and work related chronic bronchitis and nasal symptoms (after adjustment for types of local ventilation) but not to other WRSs. Peak GA concentrations were significantly higher in units that used both negative pressure room and decontaminating unit ventilation.	

Section A6.12.4 _ 01 Annex Point IIA VI.6.9.4		Cross-sectional study, survey of symptoms, respiratory function, and immunology
5.3	**Conclusion**	This study documents a significant level of symptoms reported in the absence of objective evidence of the physiological changes associated with asthma.
5.3.1	Reliability	Not applicable
5.3.2	Validity	Not applicable
5.3.3	Deficiencies	Not applicable
5.4	**Other**	None

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 11th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	4.1.2 Average concentrations. Geometric mean concentrations were well below 0.2 mg/m^3 (0.05 ppm). Average background concentration was 0.01 mg/m^3 and average peak concentration 0.06 mg/m^3. Ranges were 0.002-0.1 mg/m3 and < 0.001-1.08 mg/m^3, respectively. 5.2 Results and discussion. • The lack of asthma diagnoses is questionable, and was questioned by commentaries in the scientific journal where the article was published. Briefly, the validity of the PEFR diaries for a negative diagnosis is considered doubtful or the method is seen as non-relevant for the purpose. • The IgE test methodology is unclear. Apparently glutaraldehyde as such was used, which might not be appropriate. Elsewhere, glutaraldehyde-modified proteins have been used in IgE tests, which may be considered more realistic.
Conclusion	Glutaraldehyde caused clear irritant effects in the skin, eyes, nose and the lower respiratory tract. Asthma was not demonstrated, but the methodology and conclusions have been questioned. The RMS considers the negative results on asthma as equivocal.
Reliability	2-3 based on insufficient reporting and doubts on the methodology. An attempt to connect long-term or chronic symptoms with measured peak glutaraldehyde concentrations is questionable.
Acceptability	Acceptable as supportive information.
Remarks	The study summary is poorly written.

Section A6.12.4 _ 01
Annex Point IIA VI.6.9.4

Cross-sectional study, survey of symptoms, respiratory function, and immunology

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

Section A6.12.4 _ 02
Annex Point IIA VI.6.9.4

Epidemiological study, review medical data and mortality analysis among glutaraldehyde workers

Official use only

1 REFERENCE

1.1	**Reference**	Teta MJ, Avashia BH, Cawley TJ, Yamin AT (1995) Absence of sensitizations and cancer increases among glutaraldehyde workers. Toxic Substances Mechanisms 14: 293–305 (Published), BPD ID A6.12.4_02

2 GUIDELINES AND QUALITY ASSURANCE

Not applicable

3 MATERIALS AND METHODS

3.1	**Test material**	Glutaraldehyde (production) not further specified.
3.2	**Type of study**	Review of medical data and mortality analysis.
3.3	**Method of data collection**	Review of plant medical records, work restrictions, and clinic visits for accidental exposure and mortality data.
3.4	**Test Persons / Study Population**	218 workers assigned to glutaraldehyde unit from 1959 to 1992. For mortality analysis 186 males assigned to the glutaraldehyde unit from 1959 to 1978, who were followed through 1988, were included.
3.5	**Controls**	No
3.6	**Exposure**	Occupational
3.6.1	Exposure Route	Not stated
3.6.2	Exposure Situation	Workplace
3.6.3	Exposure concentration(s)	Exposure data were only available from 1977, when routine industry hygiene began. Levels between 1977 and 1988 were well below the permissible exposure limit (PEL) (mean = 0,05 ppm a, 8-h time weighted average) and suggested somewhat higher levels in 1977 and 1978. Prior exposures, particularly in the early years of start-up when the majority or subjects first entered the unit, were probably higher. 1989-1992 time weighted average (TWA) 0.06 ppm (range 0.01 – 0.11).
3.7	**Examinations**	Review of medical data
3.7.1	Type of disease	Respiratory and immunological diseases and cancer

4 RESULTS AND DISCUSSION

4.1	**Exposure**	
4.1.1	Number of measurements	Not specified in detail
4.1.2	Average concentrations	1989-1992 TWA 0.06 ppm (range 0.01 – 0.11); 1977 and 1988 were well below the PEL (mean = 0,05 ppm a, 8-h time weighted average); prior exposures, particularly in the early years of start-up when the majority or subjects first entered the unit, probably higher.

Section A6.12.4 _ 02 Annex Point IIA VI.6.9.4		Epidemiological study, review medical data and mortality analysis among glutaraldehyde workers
4.2	**Prevalence and SMR (standard mortality ratio)**	There was no evidence of sensitisation for 199 (95 %) of the study group and a significant deficit of deaths due to all causes (14 versus 25.4). The rate for total malignancies was less than expected (4 versus 6.1).
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Plant medical records, work restrictions, and clinic visits for accidental exposures were reviewed to determine the incidence of skin sensitisation, respiratory sensitisation, and allergic blepharoconjunctivitis among 218 workers assigned to glutaraldehyde production or drumming from 1959 to 1992. A mortality analysis of males assigned to glutaraldehyde production from its start-up to 1959 through 1988 was also conducted. .
5.2	**Results and discussion**	There was no evidence of sensitisation for 199 (95 %) of the study group; five had documented cases related to chemicals other than glutaraldehyde, and six individuals (3 %) had relevant symptoms that may have signalled a sensitisation but that were not ascribable to a particular chemical. Although based on small numbers, the mortality rate for malignant neoplasms was less than expected, and no indications of glutaraldehyde-induced skin or respiratory sensitisation, allergic blepharoconjunctivitis, or excess cancers in workers exposed at or below 0.2 ppm.
5.3	**Conclusion**	This study did not identify any occurrences of skin or respiratory sensitisation or excess cancers related to glutaraldehyde.
5.3.1	Reliability	Not applicable
5.3.2	Validity	Not applicable
5.3.3	Deficiencies	Not applicable
5.4	**Other**	Not applicable

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 14th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	Agree with applicant's version.
Conclusion	There was no evidence of glutaraldehyde caused sensitization, carcinogenicity or increased mortality in the cohort study.
Reliability	2
Acceptability	Acceptable
Remarks	

Section A6.12.4 _ 02
Annex Point IIA VI.6.9.4

Epidemiological study, review medical data and mortality analysis among glutaraldehyde workers

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

Section A6.12.4 _ 03
Annex Point IIA VI.6.9.4

Cross-sectional study, survey of symptoms, respiratory function, and immunology

Official use only

1 REFERENCE

1.1	**Reference**	Pisaniello DL, Gun RT, Tkaczuk MN, Nitshcke M, Crea J (1997) Glutaraldehyde exposures and symptoms among endoscopy nurses in South Australia. Appl. Occup. Environ. Hyg. 12: 171–177 (Published), BPD ID A6.12.4_03

2 GUIDELINES AND QUALITY ASSURANCE

Not applicable

3 MATERIALS AND METHODS

3.1	**Test material**	Activated alkalised glutaraldehyde solutions.
3.2	**Type of study**	Cross-sectional study.
3.3	**Method of data collection**	Symptoms questionnaires
3.4	**Test Persons / Study Population**	135 endoscopy nurses from 26 South Australian hospitals
3.5	**Controls**	132 unexposed nurses from the same hospitals
3.6	**Exposure**	Occupational
3.6.1	Exposure Route	Inhalation and dermal
3.6.2	Exposure Situation	Workplace
3.6.3	Exposure concentration(s)	Personal inhalation exposures were generally low [overall geometric mean (GM) = 0.032 ppm)]
3.7	**Examinations**	Questionnaire interviews
3.7.1	Type of disease	Skin, eye, and respiratory diseases

4 RESULTS AND DISCUSSION

4.1	**Exposure**	Occupational exposure to glutaraldehyde.
4.1.1	Number of measurements	Personal airborne sampling and area (operating theatres and dedicated endoscopy areas) concentrations.
4.1.2	Average concentrations	Personal inhalation exposures were generally low [overall geometric mean (GM) = 0.032 ppm)]; area measurements were 0.008 ppm GM.
4.2	**Prevalence**	Symptom percentage prevalences are significantly different ($p < 0.05$) for am number of symptoms including skin and eye problems as well as headache and lethargy.

5 APPLICANT'S SUMMARY AND CONCLUSION

Section A6.12.4 _ 03 Annex Point IIA VI.6.9.4		Cross-sectional study, survey of symptoms, respiratory function, and immunology
5.1	**Materials and methods**	A cross-sectional study of exposures among 135 endoscopy nurses in 26 South Australian hospitals was undertaken. Nurses were interviewed with a health/work practice questionnaire, worksite inspections were undertaken, and exposure measurements were conducted. A control group of 132 unexposed nurses in the same hospitals was also interviewed. Inhalation exposure while using glutaraldehyde was determined and dermal exposure was assessed with skin pads. Personal inhalation exposures were measured.
5.2	**Results and discussion**	Personal inhalation exposures were generally low [overall geometric mean (GM) = 0.032 ppm)]. Operating theatres showed significantly lower airborne concentrations than areas dedicated to endoscopy. Both in operating theatres and in endoscopy areas, personal exposures were significantly lower (GM = 0.014 and 0.022 ppm, respectively) where local exhaust ventilation was provided than where was none (GM = 0.034 and 0.093 ppm, respectively). Exposures were also low where nurses were using auto-disinfectors. Nurses exposed to glutaraldehyde were significantly more likely to report headache, lethargy, and skin, eye, and throat symptoms compared with controls. However, the occurrence of skin, eye, and throat symptoms did not appear to correlate with airborne glutaraldehyde levels. Glutaraldehyde-related skin problems are less likely to be related to airborne exposures than to procedural factors, such as placing instruments into solution with ungloved hands. Eighty-six nurses (64 %) had had accidents involving splashes to the skin. It is concluded that local exhaust ventilation should be provided when there is a high turnover of instruments requiring disinfection.
5.3	**Conclusion**	Nurses exposed to glutaraldehyde were more likely to report skin, eye, and throat symptoms; however, the prevalence of skin, eye, and throat symptoms was not correlated with personal glutaraldehyde exposure. There was no evidence for an increased incidence of respiratory effects, including asthmatic symptoms, in the nurses exposed to glutaraldehyde.
5.3.1	Reliability	Not applicable
5.3.2	Validity	Not applicable
5.3.3	Deficiencies	Not applicable
5.4	**Other**	Not applicable

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 11th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	Agree with applicant's version.

Section A6.12.4 _ 03
Annex Point IIA VI.6.9.4

Cross-sectional study, survey of symptoms, respiratory function, and immunology

Conclusion	Headache, lethargy and symptoms in the skin, eye and throat were connected with combined inhalation and dermal exposure to glutaraldehyde. Nasal symptoms were more common in the exposed group than the non-exposed group, but the difference was not reported to be statistically significant.
Reliability	2
Acceptability	Acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.4 _ 04
Annex Point IIA VI.6.9.4

Case series, survey of symptoms, respiratory function, and immunology

			Official use only
		1 REFERENCE	
1.1	**Reference**	Di Stefano F, Siriruttanapruk S, McCoach J, Sherwood Burge P (1999) Glutaraldehyde: an occupational hazard in the hospital setting. Allergy 54: 1105–11109 (Published), BPD ID A6.12.4_04	X
		2 GUIDELINES AND QUALITY ASSURANCE	
		Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Activated alkalised glutaraldehyde solutions	X
3.2	**Type of study**	Case series	
3.3	**Method of data collection**	Symptoms questionnaires, specific bronchial provocation test (SBPT). specific IgE antibodies to glutaraldehyde	
3.4	**Test Persons / Study Population**	24 health-care workers	
3.5	**Controls**	No	
3.6	**Exposure**	Occupational	
3.6.1	Exposure Route	Inhalation and dermal	
3.6.2	Exposure Situation	Workplace	
3.6.3	Exposure concentration(s)	Levels of glutaraldehyde from the air samples collected in the workplace were as follows: personal short-term samples (mean 0.208 mg/m3; median 0.14 mg/m3; range 0.06-0.84 mg/m3), personal long-term samples (mean 0.071 mg/m3; median 0.07 mg/m3; range 0.003-0.28 mg/m3). (1mg/m3 = 0.24 ppm)	
3.7	**Examinations**	Questionnaire interviews	
3.7.1	Type of disease	Skin and respiratory diseases	
		4 RESULTS AND DISCUSSION	
4.1	**Exposure**	Occupational exposure to glutaraldehyde.	
4.1.1	Number of measurements	No data	
4.1.2	Average concentrations	Levels of glutaraldehyde from the air samples collected in the workplace were as follows: personal short-term samples (mean 0.208 mg/m3; median 0.14 mg/m3; range 0.06-0.84 mg/m3), personal long-term samples (mean 0.071 mg/m3; median 0.07 mg/m3; range 0.003-0.28 mg/m3). (1mg/m3 = 0.24 ppm)	
4.2	**Prevalence**	In the eight workers who underwent SBPT, the diagnosis of occupational asthma was confirmed by a positive reaction (late and dual reaction in five and in three subjects, respectively).	
		5 APPLICANT'S SUMMARY AND CONCLUSION	

Section A6.12.4 _ 04 Annex Point IIA VI.6.9.4		Case series, survey of symptoms, respiratory function, and immunology	
5.1	**Materials and methods**	The history of asthmatic symptoms was investigated with peak expiratory flow rate (PEFR) monitoring, and in eight of the subjects, the specific bronchial provocation test (SBPT) was applied as reference standard for diagnosis of occupational asthma. Levels of glutaraldehyde were monitored in the challenge chamber during the SBPT. Work environmental levels of glutaraldehyde were measured from air samples collected at least once during the PEFR monitoring of endoscopy and theatre nurses. Specific IgE antibodies to glutaraldehyde were measured with a series of glutaraldehyde modified proteins.	
5.2	**Results and discussion**	In the eight workers who underwent SBPT, the diagnosis of occupational asthma was confirmed by a positive reaction (late and dual reaction in five and in three subjects, respectively). The mean level of glutaraldehyde observed during the challenge tests was 0.075 mg/m3 (range 0.065-0.084 mg/m3). In 13 out of the 16 remaining workers, the serial PEFR monitoring showed a work-related effect. In three workers, there was no physiological confirmation of occupational asthma. Levels of glutaraldehyde from the air samples collected in the workplace were as follows: personal short-term samples (mean 0.208 mg/m3; median 0.14 mg/m3; range 0.06-0.84 mg/m3), personal long-term samples (mean 0.071 mg/m3; median 0.07 mg/m3; range 0.003-0.28 mg/m3). Measurements of specific IgE antibodies to glutaraldehyde-modified proteins were positive in seven patients (29.1%) according to a cut-off value of 0.88% RAST (radio-allergosorbent test) binding. The presence of atopy to common environmental allergens and smoking was not associated with specific IgE positivity (P>0.05; Fisher's exact test).	
5.3	**Conclusion**	The correlation between specific IgE antibodies and clinical symptoms is poor. Currently, the significance of IgE in the pathogenesis of glutaraldehyde occupational asthma is unclear.	X
5.3.1	Reliability	Not applicable	
5.3.2	Validity	Not applicable	
5.3.3	Deficiencies	Not applicable	
5.4	**Other**	Not applicable	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 9th, 2011
Materials and Methods	1.1 Reference. The correct page numbers are 1105-1109. 3.1 Test material. For specific bronchial challenges, 2 % glutaraldehyde was used. 3.3 Method of data collection. Apart from symptoms questionnaires, the information belongs to *3.7 Examinations* (see correction there). 3.7 Examinations. Additional examinations: specific bronchial provocation test (SBPT), specific IgE antibodies to glutaraldehyde, serial peak expiratory flow rates (PEFR).
Results and discussion	Agree with applicant's version.

Section A6.12.4 _ 04
Annex Point IIA VI.6.9.4

Case series, survey of symptoms, respiratory function, and immunology

Conclusion	RMS disagrees with the applicant's conclusion. 21 out of 24 patients were shown by at least one of the methods to have occupational asthma. Seven patients had glutaraldehyde-specific IgE antibodies, suggesting but not proving that occupational asthma was caused by glutaraldehyde.
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.4 _ 05 Case series, survey of symptoms and respiratory function

Annex Point IIA VI.6.9.4

			Official use only
		1 REFERENCE	
1.1	**Reference**	Gannon PFG, Bright P, Campbell M, O'Hickey SP, Sherwood Burge P (1995) Occupational asthma due to glutaraldehyde and formaldehyde in endoscopy and x-ray departments. Thorax 50: 156– 59 (Published), BPD ID A6.12.4_05	
		2 GUIDELINES AND QUALITY ASSURANCE	
		Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Activated alkalised glutaraldehyde solutions.	X
3.2	**Type of study**	Case series.	
3.3	**Method of data collection**	Symptoms questionnaires, serial measurements of peak expiratory flow (PEF), specific bronchial provocation test (SBPT).	
3.4	**Test Persons / Study Population**	8 health-care workers in endoscopy units and x-ray darkrooms	
3.5	**Controls**	No	
3.6	**Exposure**	Occupational	
3.6.1	Exposure Route	Inhalation and dermal	
3.6.2	Exposure Situation	Workplace	
3.6.3	Exposure concentration(s)	The levels obtained in 13 endoscopy suites and six x-ray darkrooms where median short-term levels were 0.16 mg/m3 during decantation in endoscopy suites and < 0.009 mg/m3 in darkrooms.	
3.7	**Examinations**	Symptoms questionnaires, serial measurements of peak expiratory flow (PEF), specific bronchial provocation test (SBPT).	
3.7.1	Type of disease	Skin and respiratory diseases.	
		4 RESULTS AND DISCUSSION	
4.1	**Exposure**	Occupational exposure to glutaraldehyde.	
4.1.1	Number of measurements	No data	
4.1.2	Average concentrations	The mean level of glutaraldehyde in air during the challenge tests was 0.068 mg/m3, about one tenth of the short-term occupational exposure standard of 0.7 mg/m3. The levels obtained in the challenge chamber were similar to those measured in 13 endoscopy suites and six x-ray darkrooms where median short term levels were 0.16 mg/m3 during decantation in endoscopy suites and < 0.009 mg/m3 in darkrooms.	

Section A6.12.4 _ 05 Annex Point IIA VI.6.9.4		Case series, survey of symptoms and respiratory function	
4.2	**Prevalence**	The diagnosis of occupational asthma was confirmed in seven workers; all of them had PEF records suggestive of occupational asthma and positive specific bronchial challenge tests to glutaraldehyde. Bronchial provocation testing was negative in one worker who was no longer exposed and who had a less clear-cut history of occupational asthma.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Eight workers were referred for investigation of suspected occupational asthma following direct or indirect exposure to glutaraldehyde at work. They were investigated by serial measurements of peak expiratory flow (PEF) and specific bronchial provocation tests. Glutaraldehyde levels were measured using personal and static short- and long-term air samplers during the challenge tests and in 13 endoscopy units and six x-ray darkrooms in the region where concern about glutaraldehyde exposure had been expressed. Three of the workers investigated with occupational asthma came from departments where glutaraldehyde air measurements had been made; the others came from other hospitals or departments.	
5.2	**Results and discussion**	The diagnosis of occupational asthma was confirmed in seven workers; all of them had PEF records suggestive of occupational asthma and positive specific bronchial challenge tests to glutaraldehyde. Bronchial provocation testing was negative in one worker who was no longer exposed and who had a less clear-cut history of occupational asthma. Three workers also had a positive specific bronchial challenge to formaldehyde. The mean level of glutaraldehyde in air during the challenge tests was 0.068 mg/m3, about one tenth of the short-term occupational exposure standard of 0.7 mg/m3. The levels obtained in the challenge chamber were similar to those measured in 13 endoscopy suites and six x-ray darkrooms where median short term levels were 0.16 mg/m3 during decantation in endoscopy suites and < 0.009 mg/m3 in darkrooms.	
5.3	**Conclusion**	Provocation testing confirmed an association between glutaraldehyde and respiratory symptoms in two of four tested subjects. One subject had both an immediate and a late nasal response and the other an isolated late response of the lower airways. The development of the late reaction suggests not only an irritant effect on the airways.	X
5.3.1	Reliability	Not applicable	
5.3.2	Validity	Not applicable	
5.3.3	Deficiencies	Not applicable	
5.4	**Other**	Not applicable	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 8th, 2011

Section A6.12.4 _ 05 **Annex Point IIA VI.6.9.4**	**Case series, survey of symptoms and respiratory function**
Materials and Methods	3.1 Test material. The test material was glutaraldehyde.
Results and discussion	Agree with applicant's version.
Conclusion	Applicant's statement is incorrect: there was a clear association between glutaraldehyde and respiratory symptoms in seven of the eight patients. Glutaraldehyde was not shown to be the causative agent of the asthma, however. Seven workers had occupational asthma whose symptoms were triggered by glutaraldehyde.
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.4 _ 06 Annex Point IIA VI.6.9.4 — Case series, survey of symptoms and respiratory function

Official use only

1 REFERENCE

1.1	**Reference**	Corrado OJ, Osman J, Davies RJ (1986). Asthma and rhinitis after exposure to glutaraldehyde in endoscopy units. Human Toxicol. 5: 325–327 (Published), BPD ID A6.12.4_06

2 GUIDELINES AND QUALITY ASSURANCE

Not applicable

3 MATERIALS AND METHODS

3.1	**Test material**	Activated alkalised glutaraldehyde solutions.
3.2	**Type of study**	Case series
3.3	**Method of data collection**	Symptoms questionnaires, serial measurements of peak expiratory flow (PEF), specific bronchial provocation test (SBPT).
3.4	**Test Persons / Study Population**	4 nurses in endoscopy units.
3.5	**Controls**	No
3.6	**Exposure**	Occupational
3.6.1	Exposure Route	Inhalation and dermal
3.6.2	Exposure Situation	Workplace
3.6.3	Exposure concentration(s)	No data
3.7	**Examinations**	Symptoms questionnaires, serial measurements of peak expiratory flow (PEF), specific bronchial provocation test (SBPT).
3.7.1	Type of disease	Skin and respiratory diseases.

4 RESULTS AND DISCUSSION

4.1	**Exposure**	Occupational exposure to glutaraldehyde.
4.1.1	Number of measurements	No data
4.1.2	Average concentrations	No data
4.2	**Prevalence**	All four nurses complained of respiratory symptoms. A provocation test was positive in two of these.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	4 nurses with complaints of respiratory symptoms were subjected to an open provocation testing with glutaraldehyde (dipping of rubber tubing into an open plastic trough containing glutaraldehyde).
5.2	**Results and discussion**	A provocation test with glutaraldehyde was positive in two of four nurses complaining respiratory symptoms when working in endoscopy units.

Section A6.12.4 _ 06 Annex Point IIA VI.6.9.4		Case series, survey of symptoms and respiratory function
5.3	**Conclusion**	In this series two nurses did not show any evidence of airways hyper responsiveness, one had a delayed nasal response and one had isolated lower airways response.
5.3.1	Reliability	Not applicable
5.3.2	Validity	Not applicable
5.3.3	Deficiencies	Not applicable
5.4	**Other**	Not applicable

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 14th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	Agree with applicant's version.
Conclusion	Two of the four patients gave an asthmatic reaction to glutaraldehyde exposure.
Reliability	2-3
Acceptability	Acceptable as supportive information only Methodology and results are not properly described for independent evaluation of the results.
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.4 _ 07 Experimental study, specific inhalatory challenge test

Annex Point IIA VI.6.9.4

Official use only

		1 REFERENCE
1.1	**Reference**	Palczynski C, Walusiak J, Ruta U, Gorski P (2001) Occupational asthma and rhinitis due to glutaraldehyde: changes in nasal lavage fluid after specific inhalatory challenge test. Allergy 56: 1186–1191 (Published), BPD ID A6.12.4_07
		2 GUIDELINES AND QUALITY ASSURANCE
		Not applicable
		3 MATERIALS AND METHODS
3.1	**Test material**	2 % Glutaraldehyde solution.
3.2	**Type of study**	Single-blind, placebo-controlled study.
3.3	**Method of data collection**	Symptoms score, nasal lavage after inhalatory challenge
3.4	**Test Persons / Study Population**	11 health care workers occupationally exposed to glutaraldehyde with occupational asthma (group A).
3.5	**Controls**	10 atopic patients with perennial asthma and rhinitis (group B) and 10 healthy individuals (group C).
3.6	**Exposure**	Occupational
3.6.1	Exposure Route	Inhalation and dermal
3.6.2	Exposure Situation	Workplace
3.6.3	Exposure concentration(s)	At the challenge test: placebo 0.9 % saline and 2 % glutaraldehyde.
3.7	**Examinations**	Questionnaire interviews, challenge test and nasal fluid analysis
3.7.1	Type of disease	Respiratory diseases
		4 RESULTS AND DISCUSSION
4.1	**Exposure**	Challenge test
4.1.1	Number of measurements	No data
4.1.2	Average concentrations	Mean concentration of glutaraldehyde in the air during tests was 0.32 +- 0.08 mg/m3.
4.2	**Prevalence**	Challenge induced severe symptoms of rhinitis in all subjects from group A. The reaction to glutaraldehyde in groups B and C was slight. Significant increase in eosinophil number and percentage, and albumin, ECP, and tryptase concentrations in nasal lavage fluid in group A compared to controls.
		5 APPLICANT'S SUMMARY AND CONCLUSION

Section A6.12.4 _ 07 Experimental study, specific inhalatory challenge test

Annex Point IIA VI.6.9.4

5.1	**Materials and methods**	Single-blind, placebo-controlled study in 11 health workers with occupational asthma and rhinitis. The control groups comprised 10 atopic subjects with perennial asthma and rhinitis and 10 healthy ones. A "nasal pool" technique was used to evaluate the examined parameters in nasal washing before and 30 min. 4 h, and 24 h after the inhalatory provocation with glutaraldehyde and placebo.	
5.2	**Results and discussion**	There was s significant increase in eosinophil number and percentage, and albumin, eosinophil cationic protein and tryptase concentration in nasal lavage fluid from patients with occupational asthma and rhinitis when compared to controls.	X
5.3	**Conclusion**	The results hint to an immunologic mechanism of asthma in glutaraldehyde exposed subjects.	
5.3.1	Reliability	Not applicable	
5.3.2	Validity	Not applicable	
5.3.3	Deficiencies	Not applicable	
5.4	**Other**	Not applicable	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 14th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	5.2 Results and discussion. Otherwise agree with applicant's version, but the word "albumin" should be deleted. 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 nonexistent. 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.
Reliability	2
Acceptability	Acceptable
Remarks	

Section A6.12.4 _ 07 Experimental study, specific inhalatory challenge test

Annex Point IIA VI.6.9.4

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

Section A6.12.4 _ 08 Annex Point IIA VI.6.9.4

Clinical study, immunologic evaluation of workers exposed to glutaraldehyde

			Official use only
		1 REFERENCE	
1.1	**Reference**	Curran AD, Burge PS, Wiley K (1996) Clinical and immunologic evaluation of workers exposed to glutaraldehyde. Allergy 51: 826–832 (Published), BPD ID A6.12.4_08	
		2 GUIDELINES AND QUALITY ASSURANCE	
		Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	2 % Glutaraldehyde solution.	X
3.2	**Type of study**	Clinical study	
3.3	**Method of data collection**	Immunologic test	
3.4	**Test Persons / Study Population**	20 subjects exposed to glutaraldehyde, 13 of them had occupational asthma diagnosed.	
3.5	**Controls**	21 unexposed workers	
3.6	**Exposure**	Occupational	
3.6.1	Exposure Route	Inhalation and dermal	
3.6.2	Exposure Situation	Workplace	
3.6.3	Exposure concentration(s)	No data	
3.7	**Examinations**	Radio-allergosorbent test (RAST), total serum IgE.	
3.7.1	Type of disease	Respiratory and immunological diseases	
		4 RESULTS AND DISCUSSION	
4.1	**Exposure**		
4.1.1	Number of measurements	No data	
4.1.2	Average concentrations	No data	
4.2	**Prevalence**	A significant difference between exposed and unexposed subjects with serum IgE less than 150 kU/l could be detected for glutaraldehyde-specific IgE antibodies, and 31 % of exposed workers with occupational asthma had antibody levels greater than the unexposed population. False-positive results were obtained with serum from unexposed workers who had total IgE levels greater than 150 kU/l, but this binding was not inhibited by glutaraldehyde-modified proteins.	X
		5 APPLICANT'S SUMMARY AND CONCLUSION	

Section A6.12.4 _ 08 Annex Point IIA VI.6.9.4		Clinical study, immunologic evaluation of workers exposed to glutaraldehyde
5.1	**Materials and methods**	A series of glutaraldehyde-modified proteins was characterized, and used to analyse sera from 20 glutaraldehyde-exposed workers and 21 unexposed workers for IgE antibodies. Inhibition studies were used to determine the specificity of binding. The reaction of glutaraldehyde with albumin in different molar ratios produced a range of modified proteins, which were used to measure specific antibodies.
5.2	**Results and discussion**	A significant difference between exposed and unexposed subjects with serum IgE less than 150 kU/l could be detected for glutaraldehyde-specific IgE antibodies, and 31 % of exposed workers with occupational asthma had antibody levels greater than the unexposed population. False-positive results were obtained with serum from unexposed workers who had total IgE levels greater than 150 kU/l, but this binding was not inhibited by glutaraldehyde-modified proteins.
5.3	**Conclusion**	The study showed some evidence of immunologic sensitisation in some workers exposed to glutaraldehyde. However, specific antibodies can be detected in only a small percentage of exposed workers who report work-related respiratory symptoms.
5.3.1	Reliability	Not applicable
5.3.2	Validity	Not applicable
5.3.3	Deficiencies	Not applicable
5.4	**Other**	Not applicable

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 10th, 2011
Materials and Methods	3.1 Test material. Glutaraldehyde was not tested, only serum samples. The exposure concentrations were not specified.
Results and discussion	4.2 Prevalence. The glutaraldehyde-exposed group had a significantly elevated binding percentage in the RAST analysis ($p = 0.026$), when testing only the sera with less than 150 kU/l (which was considered as a validity limit above which false-positives were seen). The study failed to provide clear evidence of correlation between the specific analytical results and occupational asthma, which 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.
Conclusion	It was shown that a patient may have specific IgE antibodies while this is not evident in IgE testing. The methodology described was shown not to be suitable for demonstrating glutaraldehyde-caused occupational asthma.

Section A6.12.4 _ 08 Clinical study, immunologic evaluation of workers exposed to glutaraldehyde

Annex Point IIA VI.6.9.4

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

Section A6.12.4 _ 09 Prevalence of skin and respiratory symptoms in medical services

Annex Point IIA VI.6.9.4

			Official use only
		1 REFERENCE	
1.1	**Reference**	Norbaeck D (1988). Skin and respiratory symptoms from exposure to alkaline glutaraldehyde in medical services. Scand J Work Environ Health 14: 366–371 (Published), BPD ID A6.12.4_09	
		2 GUIDELINES AND QUALITY ASSURANCE	
		Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Activated 2 % solution of Glutaraldehyde.	
3.2	**Type of study**	Cross-sectional study	
3.3	**Method of data collection**	Standardized questionnaire	
3.4	**Test Persons / Study Population**	39 exposed and 68 non-exposed subjects	
3.5	**Controls**	See 2.4	X
3.6	**Exposure**	Occupational	
3.6.1	Exposure Route	Inhalation and dermal	
3.6.2	Exposure Situation	Workplace	
3.6.3	Exposure concentration(s)	No data	
3.7	**Examinations**		
3.7.1	Type of disease	Skin and respiratory diseases.	
		4 RESULTS AND DISCUSSION	
4.1	**Exposure**	Occupational exposure to glutaraldehyde.	
4.1.1	Number of measurements	16 and 6	X
4.1.2	Average concentrations	Short-time measurements: geometric mean of glutaraldehyde was 0.05 mg/m3 (occupational exposure limit: 0.8 mg/m3); the background level in the work area was below detection limit (0.04 mg/m3).	X
4.2	**Prevalence**	In the exposed group, the prevalences of certain airway symptoms from the nose and throat were higher than in the unexposed ($P < 0.05$). General symptoms such as headache and nausea were also more common in the exposed group ($P < 0.01$), as well as skin symptoms such as eczema and rash on the hands ($P < 0.01$). A dose response effect was found between the frequency of exposure to glutaraldehyde and the number of symptoms ($P < 0.01$).	
		5 APPLICANT'S SUMMARY AND CONCLUSION	

Section A6.12.4 _ 09 Annex Point IIA VI.6.9.4		Prevalence of skin and respiratory symptoms in medical services	
5.1	**Materials and methods**	Prevalence of certain symptoms (eye, skin and airway symptoms, headache, nausea, and fatigue) was studied among hospital workers with and without exposure to glutaraldehyde during cold sterilization work. The exposure to glutaraldehyde was quantified.	
5.2	**Results and discussion**	The exposure measurements revealed an exposure that was intermittent and well below the occupational exposure limit of 0.8 mg/m3. In spite of this low exposure, the exposed group exhibited a significantly increased frequency of skin and airway symptoms, as well as headache, in comparison with the unexposed group. A dose-response relationship between the frequency of exposure and the number of symptoms could also be demonstrated. No case of allergy to glutaraldehyde was found.	X
5.3	**Conclusion**	Irritation airways effects and headache may occur at exposure levels of glutaraldehyde at low concentrations. Irritation skin symptoms are frequently reported among personal who handles activated 2 % glutaraldehyde.	
5.3.1	Reliability	Not applicable	
5.3.2	Validity	Not applicable	
5.3.3	Deficiencies	Not applicable	
5.4	**Other**	Not applicable	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 15th, 2011
Materials and Methods	3.5 Controls. Apparently this refers to 3.4. There were 39 exposed and 68 non-exposed workers, the latter group forming the control group.
Results and discussion	4.1.1 Number of measurements. There were 16 measurements during manual cold sterilization work with 2 % glutaraldehyde, and 6 measurements during automatic cold sterilization. 4.1.2 Average concentrations. Both measurements described above (4.1.1) gave the same geometric mean value of 0.05 mg/m^3 (12 ppb). The highest measured value was 0.57 mg/m^3 (140 ppb). 5.2 Results and discussion. The geometric mean value (12 ppb) was below the lowest current OEL of 50 ppb as well, but individual measurements gave concentrations above this value (up to 140 ppb). The symptoms were associated with the frequency of glutaraldehyde exposure.
Conclusion	Glutaraldehyde exposure caused localised symptoms in the nose, throat and eyes, as well as headache, nausea, tiredness, and eczema and rash on the hands. These symptoms occurred in a working environment where the exposure was generally below the OEL, with occasional higher exposure rates.
Reliability	2
Acceptability	Acceptable
Remarks	

Section A6.12.4 _ 09
Annex Point IIA VI.6.9.4

Prevalence of skin and respiratory symptoms in medical services

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

Section A6.12.4 _ 10 Prevalence of skin and respiratory symptoms in hospital staff

Annex Point IIA VI.6.9.4

			Official use only
		1 REFERENCE	
1.1	**Reference**	Jachuck SJ, Bound CL, Steel J, Blain PG (1989) Occupational hazard in hospital staff exposed to 2 per cent glutaraldehyde in an endoscopy unit. J. Soc. Occup. Med. 39: 69–71 (Published), BPD ID A6.12.4_10	
		2 GUIDELINES AND QUALITY ASSURANCE	
		Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Activated 2 % solution of Glutaraldehyde.	
3.2	**Type of study**	Cross-sectional study	
3.3	**Method of data collection**	Questionnaire and clinical assessment	
3.4	**Test Persons / Study Population**	9 medical and nursing staff (4 male, 5 female).	
3.5	**Controls**	No data	
3.6	**Exposure**	Occupational	
3.6.1	Exposure Route	Inhalation and dermal	
3.6.2	Exposure Situation	Workplace	
3.6.3	Exposure concentration(s)	No data	X
3.7	**Examinations**		
3.7.1	Type of disease	Skin and respiratory diseases.	
		4 RESULTS AND DISCUSSION	
4.1	**Exposure**	Occupational exposure to glutaraldehyde	
4.1.1	Number of measurements	No data	
4.1.2	Average concentrations	0.05 to 0.12 ppm (occupational exposure limit is 0.2 mg/m3 ≙ 0.05 ppm).	X
4.2	**Prevalence**	8 of 9 staff were affected.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Prevalence of certain symptoms (eye, skin and airway symptoms, headache, nausea, and fatigue) was studied among hospital staff exposed to glutaraldehyde in a endoscopy unit. The exposure to glutaraldehyde was quantified.	

Section A6.12.4 _ 10 Annex Point IIA VI.6.9.4		Prevalence of skin and respiratory symptoms in hospital staff
5.2	**Results and discussion**	The exposure measurements revealed an exposure of 0.05 – 0.12 ppm. Eight of nine staff members were affected and the clinical manifestations included watering of the eyes, rhinitis, dermatitis, respiratory difficulties, nausea and headache.
5.3	**Conclusion**	Irritation of airways and skin as well as headache may occur at exposure with glutaraldehyde at low concentrations.
5.3.1	Reliability	Not applicable
5.3.2	Validity	Not applicable
5.3.3	Deficiencies	Not applicable
5.4	**Other**	Not applicable

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 15th, 2011
Materials and Methods	3.6.3 Exposure concentration(s). 2 % glutaraldehyde was used.
Results and discussion	4.1.2 Average concentrations. The concentrations were as follows: • 0.05 ppm - corridor bench, static sample • 0.12 ppm - theatre nurse, personal sample
Conclusion	Exposure to glutaraldehyde vapour around the current OEL of 0.05 ppm caused symptoms in the eyes, nose and skin, and respiratory difficulties, nausea and headache.
Reliability	3
Acceptability	Acceptable as supportive information only. This is a case description with little information. There were only two measurements of the glutaraldehyde in the air, and none of the possibly interfering substances were taken into account.
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.4 _ 11 Surveillance data, reported incidence of occupational asthma

Annex Point IIA VI.6.9.4

Official use only

		1 REFERENCE
1.1	**Reference**	McDonald JC, Keynes HL, Meredith SK (2000) Reported incidence of occupational asthma in the United Kingdom, 1989-97. Occup. Environ. 57: 823–829 (Published), BPD ID A6.12.4_11
		2 GUIDELINES AND QUALITY ASSURANCE
		Not applicable
		3 MATERIALS AND METHODS
3.1	**Test material**	Glutaraldehyde.
3.2	**Type of study**	Surveillance of work related and occupational respiratory diseases.
3.3	**Method of data collection**	Chest and occupational physicians report voluntarily new cases on a monthly or random sampling basis.
3.4	**Test Persons / Study Population**	No data
3.5	**Controls**	No data
3.6	**Exposure**	Occupational
3.6.1	Exposure Route	Inhalation
3.6.2	Exposure Situation	Workplace
3.6.3	Exposure concentration(s)	No data
3.7	**Examinations**	
3.7.1	Type of disease	Respiratory diseases.
		4 RESULTS AND DISCUSSION
4.1	**Exposure**	Occupational exposure to glutaraldehyde.
4.1.1	Number of measurements	No data
4.1.2	Average concentrations	No data
4.2	**Incidence**	In 1989-91 30, in 1992-94 128, and in 1995-97 133 cases of disease after exposure to glutaraldehyde were reported.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Chest and occupational physicians report voluntarily new cases on a monthly or random sampling basis. The number of cases from 1989-97 was presented.
5.2	**Results and discussion**	In 1989-91 30, in 1992-94 128, and in 1995-97 133 cases of disease after exposure to glutaraldehyde were reported.

Section A6.12.4 _ 11 Annex Point IIA VI.6.9.4		Surveillance data, reported incidence of occupational asthma
5.3	**Conclusion**	The diagnostic criteria, which led to registration, are unknown, and there are no results available for the exposure levels. Scientific evidence for sensitising effects on the respiratory tract cannot be derived.
5.3.1	Reliability	Not applicable
5.3.2	Validity	Not applicable
5.3.3	Deficiencies	Not applicable
5.4	**Other**	Not applicable

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 15th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	Agree with applicant's version.
Conclusion	The study gives an indication of the frequency of occupational asthma that is connected with glutaraldehyde exposure, but does not give any evidence of causality.
Reliability	2
Acceptability	Acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.5 _ 01
Annex Point IIA VI.6.9.4

Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available

			Official use only
		1 REFERENCE	
1.1	**Reference**	Anadol D, Özcelik U, Kiper N, Göcmen A (2001) Chemical pneumonia caused by glutaraldehyde. Pediatric International 43:701–702, (Published), BPD ID A6.12.5_01	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Glutaraldehyde (Cidex; Johnson and Johnson, USA)	
3.2	**Type of study**	Case report of an 8-year-old boy who accidentally received glutaraldehyde on his face during an operation of varicocele.	
3.3	**Method of data collection**	Not relevant	
3.4	**Test Persons / Study Population**	8-year-old boy with no respiratory or systemic problems, and totally normal preoperatively chest radiogram	
3.5	**Controls**	none	
3.6	**Exposure**		
3.6.1	Exposure Route	Local (face)	
3.6.2	Exposure Situation	Accidental spillage of on the face during an operation of varicocele Admission in the hospital 24 h after the operation	
3.6.3	Exposure concentration(s)	approximately 100 ml of glutaraldehyde	X
3.7	**Examinations**		
3.7.1	Type of disease	Respiratory distress	

Section A6.12.5 _ 01
Annex Point IIA VI.6.9.4

Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available

4 RESULTS AND DISCUSSION

4.1	**Diagnosis/Findings**	Fever, vomiting, tachypnea and tachycardia 6 h after the operation and inhalation and/or aspiration of the chemical. Cyanosis, subcostal and intecostal retractions with a pulse rate of 140 b.p.m, respiratory rate 48/min, arterial blood pressure 90/60 mmHg and axillary temperature 36.3°C. On auscultation, crackles on the right lung and bronchial sound on the left upper lobe could be heard. Complete blood cell count revealed a hemoglobin of 12.3 g/dL, hematocrit 50.2%, white blood cell count 33.900/mm3 with a predominance of polymorphonuclear leukocytes. The erythrocyte sedimentation rate was 2 mm/h. Chest radiogram revealed infiltration on both lungs with air bronchograms on the right side.
4.2	**Recovery**	Hypoxia continued instead of nasal O2 therapy as well as tachypnea, ortophnea, intercostals retractions and paradoxal breathing. The boy was ventilated with intermittent positive pressure by non-invasive mechanical ventilator (NMV)-bilevel positive airway pressure (BIPAP) with a nasal mask. He was treated with i.v. sulbactam ampicilline and amikacine as bacterial superimposion to chemical pneumonia could not be ruled out, because he had both leukocytosis, infiltration and fever during the follow-up, although his blood and sputum cultures revealed no microorganisms. He was also given digitals and furosemides. He was discharged on the 10th day of the antibiotic therapy. Two weeks after discharge, the boy was clinically stable, had no respiratory symptoms and his chest radiogram was completely normal.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Case report of an 8-year-old boy who accidentally received glutaraldehyde on his face during an operation of varicocele.
5.2	**Results and discussion**	Fever, vomiting, tachypnea and tachycardia 6 h after the operation and inhalation and/or aspiration of the chemical. Cyanosis, subcostal and intecostal retractions with a pulse rate of 140 b.p.m, respiratory rate 48/min, arterial blood pressure 90/60 mmHg, axillary temperature 36.3°C, crackles on the right lung and bronchial sound on the left upper lobe were observed. Complete blood cell count revealed a hemoglobin of 12.3 g/dL, hematocrit 50.2%, white blood cell count 33.900/mm3 with a predominance of polymorphonuclear leukocytes. The erythrocyte sedimentation rate was 2 mm/h. Chest radiogram revealed infiltration on both lungs with air bronchograms on the right side. Treatment consisted of ventilation (intermittent positive pressure) with a nasal mask Intravenous injection of sulbactam ampicilline and amikacine was done as bacterial superimposion to chemical pneumonia could not be ruled out, because the boy had both leukocytosis, infiltration and fever during the follow-up, although his blood and sputum cultures revealed no microorganisms. The boy also given digitals and furosemides. He was discharged on the 10th day of the antibiotic therapy. Two weeks after discharge, the boy was clinically stable, had no respiratory symptoms and his chest radiogram was completely normal.
5.3	**Conclusion**	Accidental spillage of glutaraldehyde on the face can cause chemical pneumonia, as revealed by the presence of vomiting, respiratory distress and chest radiograms revealing infiltration on both lungs.
5.3.1	Reliability	**2**

Section A6.12.5 _ 01 Annex Point IIA VI.6.9.4		Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available
5.3.2	Validity	Basic data given, acceptable restrictions
5.3.3	Deficiencies	None
5.4	**Other**	None

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 15th, 2011
Materials and Methods	3.6.3 Exposure concentration(s). No information is given on the concentration of glutaraldehyde spilled.
Results and discussion	Agree with applicant's version.
Conclusion	Agree with applicant's version.
Reliability	2
Acceptability	Acceptable
Remarks	The same study summary is presented in A6.12.8 _ 01.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.5 _ 02
Annex Point IIA VI.6.9.4

Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available

Official use only

1 REFERENCE

1.1	**Reference**	Murray WJ, Ruddy MP (1985) Toxic eye injury during induction of anesthesia. South. Med. J. 78: 1012-1013 (Published), BPD ID A6.12.5_02

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Test material**	Glutaraldehyde
3.2	**Type of study**	Report of toxic eye injury during induction of anesthesia using a glutaraldehyde-contaminated anesthetic mask.
3.3	**Method of data collection**	
3.4	**Test Persons / Study Population**	1 female
3.5	**Controls**	none
3.6	**Exposure**	
3.6.1	Exposure Route	local
3.6.2	Exposure Situation	Contaminated anesthetic mask fitted to patient's face
3.6.3	Exposure concentration(s)	no data
3.7	**Examinations**	Sodium fluorescein installation in the eyes
3.7.1	Type of disease	Moderate chemical conjunctivitis

4 RESULTS AND DISCUSSION

4.1	**Diagnosis/Findings**	Bilateral bulbar and palpebral conjunctival inflammation was prominent and accompanied by tearing, swelling of the eyelids, burning pain, and photophobia. Therapy included removal of a cataract contact lens from the right eye and application of erythromycin ophthalmic ointment to both eyes every six hours for three days.
4.2	**Recovery**	The inflammation was completely resolved on the third postoperative day and no visual disturbances ensued.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	The authors reported a case of toxic eye injury during induction of anesthesia using a glutaraldehyde-contaminated anesthetic mask.
5.2	**Results and discussion**	Bilateral bulbar and palpebral conjunctival inflammation was prominent and accompanied by tearing, swelling of the eyelids, burning pain, and photophobia. Therapy included removal of a cataract contact lens from the right eye and application of erythromycin ophthalmic ointment to both eyes every six hours for three days. The inflammation was completely resolved on the third postoperative day and no visual disturbances ensued.

Section A6.12.5 _ 02 **Annex Point IIA VI.6.9.4**		**Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available**
5.3	**Conclusion**	In case of accidental inflow of glutaraldehyde in the eye, recovery from injury and disappearance of visual disturbances can be expected and, in case of inflammation, be supported by antibiotic medication..
5.3.1	Reliability	**2**
5.3.2	Validity	Basic data given, acceptable restrictions
5.3.3	Deficiencies	None
5.4	**Other**	None

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 15th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	Agree with applicant's version.
Conclusion	Agree with applicant's version.
Reliability	2
Acceptability	Acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.5 _ 03
Annex Point IIA VI.6.9.4

Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available

Official use only

1 REFERENCE

1.1	**Reference**	Ünal M, Yucel I,Akar Y, Oner A, Altin M (2006) Outbreak of toxic anterior segment syndrome associated with glutaraldehyde after cataract surgery. J Cataract Refract Surg. 32(10):1696-701 (Published), BPD ID A6.12.5_03

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Test material**	Glutaraldehyde
3.2	**Type of study**	Report of a cluster of cases of toxic anterior segment syndrome (TASS) after uneventful phacoemulsification cataract surgery.
3.3	**Method of data collection**	Six eyes of 6 patients developed TASS after uneventful phacoemulsification cataract surgery with implantation of a 3-piece acrylic IOL performed by 2 ophthalmologists on the same day.
3.4	**Test Persons / Study Population**	6 patients
3.5	**Controls**	None
3.6	**Exposure**	
3.6.1	Exposure Route	Via sterilized reusable ocular instruments.
3.6.2	Exposure Situation	Glutaraldehyde 2% solution was used inadvertently by the operating room staff who cleaned and sterilized reusable ocular instruments before autoclaving.
3.6.3	Exposure concentration(s)	Glutaraldehyde 2% solution
3.7	**Examinations**	
3.7.1	Type of disease	Toxic anterior segment syndrome (TASS) in the eye

4 RESULTS AND DISCUSSION

4.1	**Diagnosis/Findings**	Clinical findings included corneal edema, Descemet's membrane folds, anterior chamber reaction, fibrin formation, and irregular, dilated, and unreactive pupils.
4.2	**Recovery**	None of the affected corneas improved.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Glutaraldehyde 2% solution was used inadvertently by the operating room staff who cleaned and sterilized reusable ocular instruments before autoclaving. Six eyes of 6 patients developed TASS after uneventful phacoemulsification cataract surgery with implantation of a 3-piece acrylic IOL.

Section A6.12.5 _ 03 Annex Point IIA VI.6.9.4		Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available
5.2	**Results and discussion**	Clinical findings included corneal edema, Descemet's membrane folds, anterior chamber reaction, fibrin formation, and irregular, dilated, and unreactive pupils. None of the affected corneas improved. Additional surgical procedures were required and included penetrating keratoplasty, trabeculectomy, and glaucoma tube implantation.
5.3	**Conclusion**	Glutaraldehyde in concentrations generally used for cold sterilization is highly toxic to the corneal endothelium.
5.3.1	Reliability	**2**
5.3.2	Validity	Basic data given, acceptable restrictions
5.3.3	Deficiencies	None
5.4	**Other**	None

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 15th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	Agree with applicant's version.
Conclusion	Agree with applicant's version.
Reliability	2
Acceptability	Acceptable
Remarks	The same study summary is presented also in A6.12.8 _ 02.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.5 _ 04
Annex Point IIA VI.6.9.4

Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available

Official use only

1 REFERENCE

1.1	**Reference**	Karpelowsky JS, Maske CP, Sinclair-Smith C, Rode H (2006) Glutaraldehyde-induced bowel injury after laparoscopy. J Pediatr Surg. 2006 Jun;41(6):e23-52, (Published), BPD ID A6.12.5_04

2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)

3 MATERIALS AND METHODS

3.1	**Test material**	Glutaraldehyde
3.2	**Type of study**	Report of a case of sequelae due to inadvertent introduction of glutaraldehyde into the peritoneal cavity.
3.3	**Method of data collection**	Description of the clinical course, progressive histological changes to the bowel at different periods over the course of 1 year.
3.4	**Test Persons / Study Population**	1 3-year-old boy
3.5	**Controls**	None
3.6	**Exposure**	
3.6.1	Exposure Route	Instillation of a few milliliters of 2 % glutaraldehyde solution
3.6.2	Exposure Situation	Instillation during laprascopy
3.6.3	Exposure concentration(s)	No data
3.7	**Examinations**	
3.7.1	Type of disease	Necrosis and fibrosis of the bowel

4 RESULTS AND DISCUSSION

4.1	**Diagnosis/Findings**	A peritonitis with multiple small bowel fistulae, poor bowel healing, fibrosis, and impaired gastrointestinal motility appeared.
4.2	**Recovery**	None; after extensive therapy with lapratomy subsequently the fistulae were resected or closed and a non obstructive transit and function of the bowel was reached. However, the segmental loss of muscularis propria will result in dysfunctional intestinal motility.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1	**Materials and methods**	Report of a case of sequelae due to inadvertent introduction of glutaraldehyde into the peritoneal cavity with progressive changes of the bowel over 1 year. During laprascopy instillation of a few milliliters of a 2 % glutaraldehyde solution into the peritoneal cavity through an insufflation tube happened.

Section A6.12.5 _ 04 Annex Point IIA VI.6.9.4		Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available
5.2	**Results and discussion**	A peritonitis with multiple small bowel fistulae, poor bowel healing, fibrosis, and impaired gastrointestinal motility appeared. After extensive therapy with lapratomy subsequently the fistulae were resected or closed and a non obstructive transit and function of the bowel was reached. However, the segmental loss of muscularis propria will result in dysfunctional intestinal motility.
5.3	**Conclusion**	Instillation of 2 % glutaraldehyde solution into the peritoneal cavity may cause serious bowel damage with sequelae.
5.3.1	Reliability	**2**
5.3.2	Validity	Basic data given, acceptable restrictions
5.3.3	Deficiencies	None
5.4	**Other**	None

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 15th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	Agree with applicant's version.
Conclusion	Agree with applicant's version.
Reliability	2
Acceptability	Acceptable
Remarks	The same study summary is presented also in A6.12.8 _ 03.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.5 _ 05
Annex Point IIA VI.6.9.4

Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available

			Official use only
		1 REFERENCE	
1.1	**Reference**	Caprilli R, Viscido A, Frieri G, Latella G (1998) Acute colitis following colonscopy. Endoscopy 30: 428-431, (Published), BPD ID A6.12.5_05	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Glutaraldehyde	
3.2	**Type of study**	Report of three cases of severe acute self-limited colitis after colonoscopy with glutaraldehyde sterilized endoscopes.	
3.3	**Method of data collection**	Description of the clinical course and endoscopic changes in the bowel.	
3.4	**Test Persons / Study Population**	3 females	
3.5	**Controls**	None	
3.6	**Exposure**		
3.6.1	Exposure Route	Leaking of 2 % glutaraldehyde solution	X
3.6.2	Exposure Situation	Leaking onto the mucosa during endoscopy	
3.6.3	Exposure concentration(s)	No data	
3.7	**Examinations**		
3.7.1	Type of disease	Acute colitis	
		4 RESULTS AND DISCUSSION	
4.1	**Diagnosis/Findings**	Intense abdominal pain, diarrhea with blood and abundant mucus, and systemic events representing an acute-phase response (fever, leukocytosis, neutrophilia, and raised erythrocyte sedimentation rate).	
4.2	**Recovery**	All three patients recovered completely within a few days, one spontaneously and two after treatment with steroids, antibiotics, and mesalazine.	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Three cases of severe acute self-limited colitis after colonoscopy with glutaraldehyde sterilised endocopes were reported. During disinfection some of the 2% glutaraldehyde remained in the endoscope and was then released onto the mucosa during endoscopic maneuvers	
5.2	**Results and discussion**	The clinical presentation was characterized by intense abdominal pain, diarrhea with blood and abundant mucus, and systemic events representing an acute-phase response (fever, leukocytosis, neutrophilia, and raised erythrocyte sedimentation rate). All three patients recovered completely within a few days, one spontaneously and two after treatment with steroids, antibiotics, and mesalazine.	

Section A6.12.5 _ 05 Annex Point IIA VI.6.9.4		Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available
5.3	**Conclusion**	Leaking of 2 % glutaraldehyde solution onto the colon mucus may causes acute colitis.
5.3.1	Reliability	**2**
5.3.2	Validity	Basic data given, acceptable restrictions
5.3.3	Deficiencies	None
5.4	**Other**	None

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 15th, 2011
Materials and Methods	3.6.1 Exposure Route. Instruments used in colonoscopy were contaminated with glutaraldehyde.
Results and discussion	Agree with applicant's version.
Conclusion	Agree with applicant's version.
Reliability	2
Acceptability	Acceptable
Remarks	The same study summary is presented also in A6.12.8_04.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.5 _ 06 Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available

Annex Point IIA VI.6.9.4

Official use only

		1 REFERENCE
1.1	**Reference**	West AB, Kuan S-F, Bennick M, Lagarde S (1995) Gastroenterology 108: 1250-1255, (Published), BPD ID A6.12.5_06
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Test material**	Glutaraldehyde
3.2	**Type of study**	Report of four cases of colitis after colonoscopy with glutaraldehyde sterilized endoscopes.
3.3	**Method of data collection**	Description of the clinical course and histological changes in the bowel.
3.4	**Test Persons / Study Population**	3 females and 1 man
3.5	**Controls**	None
3.6	**Exposure**	
3.6.1	Exposure Route	Leaking of 2 % glutaraldehyde solution
3.6.2	Exposure Situation	Leaking onto the mucosa during endoscopy
3.6.3	Exposure concentration(s)	No data
3.7	**Examinations**	
3.7.1	Type of disease	Acute colitis
		4 RESULTS AND DISCUSSION
4.1	**Diagnosis/Findings**	Colitis similar to ischemic colitis.
4.2	**Recovery**	All four patients recovered after hospital treatment.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Report of four cases of colitis after colonoscopy with glutaraldehyde sterilised endoscopes. During sterilization, some of the 2% glutaraldehyde remained in the endoscope and was then released onto the mucosa during endoscopic maneuvers
5.2	**Results and discussion**	Glutaraldehyde-induced colitis seems similar to ischemic colitis in biopsy specimens. All four patients recovered after hospital treatment.
5.3	**Conclusion**	Leaking of 2 % glutaraldehyde solution onto the colon mucus may cause acute colitis.
5.3.1	Reliability	**2**
5.3.2	Validity	Basic data given, acceptable restrictions
5.3.3	Deficiencies	None

Section A6.12.5 _ 06 Annex Point IIA VI.6.9.4	Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available
5.4 Other	None

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Materials and Methods	3.6.1 Exposure Route. There was no leaking, but the instruments and/or tubing were insufficiently flushed/washed after disinfection using glutaraldehyde.
Results and discussion	Agree with applicant's version.
Conclusion	Agree with applicant's version.
Reliability	2
Acceptability	Acceptable
Remarks	
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.6 _ 01 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

			Official use only
		1 REFERENCE	
1.1	**Reference**	Reifenrath WG, Prystowsky SD, Nonomura JH, Robinson PB (1985) Topical glutaraldehyde-percutaneous penetration and skin irritation. Arch. Dermatol. Res. 277: 242–244 (Published), BPD ID A6.12.6_01	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	Glutaraldehyde solution.	
3.2	**Persons exposed**		
3.2.1	Sex	Male and female	
3.2.2	Age/weight	No data	
3.2.3	Known Diseases	No data	
3.2.4	Number of persons	12	
3.2.5	Other information	Human epidermis and stratum corneum.	X
3.3	**Exposure**	Dermal	
3.3.1	Reason of exposure	Experimental	
3.3.2	Frequency of exposure	Recurrent	
3.3.3	Overall time period of exposure	8 weeks	
3.3.4	Duration of single exposure	No data	
3.3.5	Exposure concentration/dose	10% solution	
3.3.6	Other information	None	
3.4	**Examinations**	Clinical examination, patch testing.	
3.5	**Treatment**	No data	
3.6	**Remarks**	No Data	
		4 RESULTS	
4.1	**Clinical Signs**	Irritation and sensitisation.	
4.2	**Results of examinations**	Not applicable	
4.3	**Effectivity of medical treatment**	Not applicable	
4.4	**Outcome**	Not applicable	

Section A6.12.6 _ 01 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

4.5	**Other**	Not applicable
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	8-week irritancy test applying a 10 % aqueous glutaraldehyde solution to the ankle and heel area of 12 volunteers.
5.2	**Results and discussion**	Irritation and one case of sensitisation resulted from glutaraldehyde application to areas of the thin stratum corneum (anterior ankle) but not from applications to thick stratum corneum (medial, posterior, and lateral heel and posterior ankle) were observed.
5.3	**Conclusion**	Topical application of glutaraldehyde solution (10 %) may result in skin irritation and sensitisation.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Materials and Methods	3.2.5 Other information. The study also concerned *in vitro* dermal absorption using human epidermis and stratum corneum samples. This part of the study is not described in the study summary. The value of the *in vitro* experiment is questionable and the RMS does not request a study summary taking this into account. This does not affect the results of the irritation test. 3.3.4 Duration of single exposure. Test substance was applied daily, 5 days per week, and the test substance was allowed to dry on the skin and was left unwashed.
Results and discussion	4.1 Clinical Signs. During the second week of treatment, 5 out of 12 volunteers had minimal irritation on the application site (anterior ankle; thin stratum corneum) and one became sensitised. There is no data on the sensitisation testing or symptoms. Testing was continued with 11 volunteers (excluding the sensitised one) by applying the test substance daily on areas of thick stratum corneum, where no irritation occurred during the remaining 6 weeks of the study.
Conclusion	Glutaraldehyde (10 %) was irritating on areas of thin stratum corneum but not on thick stratum corneum. One out of 12 volunteers became sensitised.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.6 _ 02 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

			Official use only
		1 REFERENCE	
1.1	**Reference**	Ballantyne B, Berman B (1984) Dermal sensitizing potential of glutaraldehyde: a review and recent observations. J. Toxicol. - Cut. & Ocular Toxicol. 3:251-262 (Published), BPD ID A6.12.6_02	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	Glutaraldehyde water solution.	
3.2	**Persons exposed**		
3.2.1	Sex	Male and female.	
3.2.2	Age/weight	14 to 81-year-old.	
3.2.3	Known Diseases	No disease reported.	
3.2.4	Number of persons	109	
3.2.5	Other information	None	
3.3	**Exposure**		
3.3.1	Reason of exposure	Volunteers	
3.3.2	Frequency of exposure	No data	X
3.3.3	Overall time period of exposure	No data	X
3.3.4	Duration of single exposure	No data	X
3.3.5	Exposure concentration/dose	0.1, 0.2 and 0.5 % glutaraldehyde (w/w)	
3.3.6	Other information	None	
3.4	**Examinations**	Patch-testing	
3.5	**Treatment**	Not applicable	
3.6	**Remarks**	Not applicable	
		4 RESULTS	
4.1	**Clinical Signs**	See 4.2	

Section A6.12.6 _ 02 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

4.2	**Results of examinations**	There was no reaction in any of the 109 subjects during the induction phase, or resulting from the challenge application at 0.1 %. Two subjects gave doubtful reaction, one following the third and the other following the ninth application with 0.2 % test substance. One further subject developed an erythematous reaction following removal of the six induction patches. None of the 109 subjects demonstrated any local skin reaction to the 0.2 % challenge patches. Sixteen of the 109 subjects showed a reaction during the induction phase at 0.5 %. This was doubtful significance in nine, and a definite erythematous reaction in seven. The definite reactions were present after only one of the patches in five subjects, and two successively applied patches in the other two individuals. At challenge, one subject gave a reaction of doubtful significance, and one a local erythema with oedema. Neither of these two subjects had any reaction to the individual patches.
4.3	**Effectivity of medical treatment**	Not applicable
4.4	**Outcome**	Not applicable
4.5	**Other**	Not applicable
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Patch test with glutaraldehyde (0.1, 0.2 and 0.5 % in aq.) in volunteers
5.2	**Results and discussion**	There was no reaction in any of the 109 subjects during the induction phase, or resulting from the challenge application at 0.1 %. Two subjects gave doubtful reaction, one following the third and the other following the ninth application only at 0.2 %. One further subject developed an erythematous reaction following removal of the six induction patches. None of the 109 subjects demonstrated any local skin reaction to the 0.2 % challenge patches. Sixteen of the 109 subjects showed a reaction during the induction phase at 0.5 %. There was doubtful significance in nine, and a definite erythematous reaction in seven. The definite reactions were present after only one of the patches in five subjects, and two successively applied patches in the other two individuals. At challenge, one subject gave a reaction of doubtful significance, and one a local erythema with oedema. Neither of these two subjects had any reaction to the individual patches.
5.3	**Conclusion**	Glutaraldehyde at concentrations of 0.1 and 0.2 % produced no evidence for a sensitisation reaction, but at 0.5 % there was a definite reaction to the challenge patch in one of the 109 subjects. These findings indicate that 0.5 % glutaraldehyde is around the threshold concentration for induction of dermal sensitisation to the test material. While 0.1 and 0.2 % glutaraldehyde were not significantly irritating to the skin, 0.5 % produced mild to moderate local erythema in 6.4 % of the subjects.

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

Section A6.12.6 _ 02 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

Date	February 10th, 2011
Materials and Methods	3.3.2 Frequency of exposure. A total of 10 induction applications were made over a 3-week period. Two weeks after removal of the final induction patch, a challenge patch was applied under occlusive dressing for 48 h to a site not previously used for induction. 3.3.3 Overall time period of exposure. See comment to 3.3.2 above. 3.3.4 Duration of single exposure. Induction 48 to 72 h (occlusive); challenge 48 h (occlusive).
Results and discussion	Agree with applicant's version.
Conclusion	There was no sensitisation using 0.1 or 0.2 % glutaraldehyde, while one out of 109 persons tested gave a sensitising reaction to 0.5 % glutaraldehyde.
Reliability	2
Acceptability	Acceptable as supportive information. The methodology, procedures and the test substance are not described properly. The results should be considered generally valid but cannot be verified.
Remarks	

	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.6 _ 03 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

			Official use only
		1 REFERENCE	
1.1	**Reference**	Fowler JF (1989) Allergic contact dermatitis from glutaraldehyde exposure. J. Occup. Med. 31: 852-853 (Published), BPD ID A6.12.6_03	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	2 % glutaraldehyde in an alcohol-water solution.	
3.2	**Persons exposed**		
3.2.1	Sex	Woman.	
3.2.2	Age/weight	56-year-old.	
3.2.3	Known Diseases	No disease reported.	
3.2.4	Number of persons	1	
3.2.5	Other information	None	
3.3	**Exposure**		
3.3.1	Reason of exposure	Workplace	
3.3.2	Frequency of exposure	Recurrent	
3.3.3	Overall time period of exposure	Seven months	X
3.3.4	Duration of single exposure	No data	
3.3.5	Exposure concentration/dose	No data	
3.3.6	Other information	None	
3.4	**Examinations**	Physical examination, patch testing (1 % glutaraldehyde in aq.).	
3.5	**Treatment**	Topical corticosteroids.	
3.6	**Remarks**	None	
		4 RESULTS	
4.1	**Clinical Signs**	Chronic, dry, erythematous, scaling dermatitis most prominent on the cheeks and right forearm. The neck, left arm, and hands were also mildly involved.	
4.2	**Results of examinations**	Positive patch-test reaction.	
4.3	**Effectivity of medical treatment**	Remained clear of dermatitis after avoiding glutaraldehyde.	

Section A6.12.6 _ 03 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

4.4	**Outcome**	Not applicable
4.5	**Other**	Not applicable
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Patch test with glutaraldehyde (1 % in aq.) in a hospital worker with airborne contact dermatitis.
5.2	**Results and discussion**	Patient showed positive patch-test reaction to glutaraldehyde.
5.3	**Conclusion**	Rare allergic contact dermatitis from glutaraldehyde vapour contact with exposed skin.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Materials and Methods	3.3.3 Overall time period of exposure. The patient had been exposed to glutaraldehyde for several months prior to the onset of dermatitis, but the exact time appears not to be given. 3.3.5 Exposure concentration/dose. Glutaraldehyde solution of 2 % was used.
Results and discussion	Agree with applicant's version.
Conclusion	The technician became sensitised to glutaraldehyde after several months of cleaning and sterilizing work using glutaraldehyde.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.6 _ 04 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

			Official use only
		1 REFERENCE	
1.1	**Reference**	Shaffer MP, Belsito DV (2000) Allergic contact dermatitis from glutaraldehyde in health care workers. Contact Dermatitis 43: 150-156 (Published), BPD ID A6.12.6_04	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	Activated alkalised glutaraldehyde solutions	X
3.2	**Persons exposed**		
3.2.1	Sex	Male and female.	
3.2.2	Age/weight	No data	
1.1.1	Known Diseases	No data	
3.2.3	Number of persons	468 patients	
3.2.4	Other information	Human epidermis and stratum corneum	
3.3	**Exposure**		
3.3.1	Reason of exposure	Occupational	X
3.3.2	Frequency of exposure	Workplace, recurrent	X
3.3.3	Overall time period of exposure	No data	
3.3.4	Duration of single exposure	No data	
3.3.5	Exposure concentration/dose	10% solution	X
3.3.6	Other information	None	
3.4	**Examinations**	Questionnaire and patch test (0.2 % and 1.0 % or 0.5 % and 1.0 % or 1 % glutaraldehyde in petrolatum).	
3.5	**Treatment**	No data	
3.6	**Remarks**	None	
		4 RESULTS	
4.1	**Clinical Signs**	Sensitisation.	
4.2	**Results of examinations**	468 patients were tested against glutaraldehyde. 17 of the 468 subjects were allergic to glutaraldehyde.	X
4.3	**Effectiveness of medical treatment**	Not applicable	

Section A6.12.6 _ 04 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

4.4	**Outcome**	Not applicable
4.5	**Other**	Not applicable
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	In a 5-year study 468 patients were patch-tested to glutaraldehyde (0.2 – 1.0 % in pet.).
5.2	**Results and discussion**	17 of the 468 subjects were allergic to glutaraldehyde. Health care workers were more than 8x likely to be allergic to glutaraldehyde than their non-health care peers.
5.3	**Conclusion**	Allergic contact dermatitis from glutaraldehyde was seen in health care workers.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 11th, 2011
Materials and Methods	3.1 Substance. The test substance was glutaraldehyde in petrolatum. 3.3.1 Reason of exposure. The results concern all allergy tests performed at the site (468 tested for glutaraldehyde), of which 51 were performed on health care workers. 3.3.2 Frequency of exposure. No data is given. See the comment to 3.3.1 above. 3.3.5 Exposure concentration/dose. This information seems to be incorrect. The concentrations to which patients had been exposed to were unknown. Information on the test concentrations is given in 3.4. 3.4 Examinations. The test concentrations in petrolatum were as follows: • 0.2 and 1 % (1994-1996) • 0.5 and 1 % (1996-1998) • 1 % (1998-1999)
Results and discussion	4.2 Results of examinations. Positive results: • 17/468 of all tested (3.6 %) • 9/51 of health care workers (18 %) • 8/417 of non-health care workers 1.9 %)
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.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*

Section A6.12.6 _ 04 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

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

Section A6.12.6 _ 05 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

Official use only

		1 REFERENCE
1.1	**Reference**	Kiec-Swierczynska M, Krecisz B (2001) Occupational allergic contact dermatitis in hairdressers due to glutaraldehyde. Contact Dermatitis 44: 185–186 (Published), BPD ID A6.12.6_05
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Substance**	Glutaraldehyde solution
3.2	**Persons exposed**	
3.2.1	Sex	Female
3.2.2	Age/weight	No data
3.2.3	Known Diseases	No data
3.2.4	Number of persons	2 female hairdressers
3.2.5	Other information	None
3.3	**Exposure**	
3.3.1	Reason of exposure	Occupational
3.3.2	Frequency of exposure	Recurrent
3.3.3	Overall time period of exposure	Several years
3.3.4	Duration of single exposure	No data
3.3.5	Exposure concentration/dose	No data
3.3.6	Other information	No data
3.4	**Examinations**	Clinical examination, patch test (0.2 % glutaraldehyde in pet.).
3.5	**Treatment**	No data
3.6	**Remarks**	None
		4 RESULTS
4.1	**Clinical Signs**	Erythema with papules and pruritus on the hands and face and dyspnoea, cough attacks and rhinostenosis.
4.2	**Results of examinations**	Patch test with 0.2 % glutaraldehyde in pet. was positive in both women.
4.3	**Effectivity of medical treatment**	Not applicable

Section A6.12.6 _ 05 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

4.4	**Outcome**	Not applicable
4.5	**Other**	Not applicable
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Case report of 2 female hairdressers with erythema and papules. Patch test with glutaraldehyde (0.2 % in pet.).
5.2	**Results and discussion**	Patch test with 0.2 % glutaraldehyde in pet. was positive in two female hairdressers exposed to glutaraldehyde.
5.3	**Conclusion**	Occupational allergic contact dermatitis may be seen in hairdressers with exposure to glutaraldehyde.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Materials and Methods	3.2.2 Age/weight. The patients were 26 and 46 years old.
Results and discussion	Agree with applicant's version.
Conclusion	Agree with applicant's version.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.6 _ 06 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

			Official use only
		1 REFERENCE	
1.1	**Reference**	Juhlin L, Hansson H (1968) Topical glutaraldehyde for plantar hyperhydrosis. Arch. Dermatol. 97: 327–330 (Published), BPD ID A6.12.6_06	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Substance**	2 and 10 % glutaraldehyde solution	
3.2	**Persons exposed**		
3.2.1	Sex	Male and female	
3.2.2	Age/weight	No data	
3.2.3	Known Diseases	Hyperhydrosis, contact dermatitis	
3.2.4	Number of persons	25 and 160 patients	
3.2.5	Other information	Human epidermis and stratum corneum	X
3.3	**Exposure**	Dermal	
3.3.1	Reason of exposure	Experimental	X
3.3.2	Frequency of exposure	Recurrent	X
3.3.3	Overall time period of exposure	6 weeks	
3.3.4	Duration of single exposure	3 times a week	X
3.3.5	Exposure concentration/dose	10 % solution and 1 % solution	X
3.3.6	Other information	None	
3.4	**Examinations**	Clinical examination, patch test, starch paper-iodine imprint test.	
3.5	**Treatment**	No data	
3.6	**Remarks**	None	
		4 RESULTS	
4.1	**Clinical Signs**	Irritation and sensitisation	X
4.2	**Results of examinations**	Not applicable	
4.3	**Effectivity of medical treatment**	Not applicable	
4.4	**Outcome**	Not applicable	

Section A6.12.6 _ 06 Sensitisation/allergenicity observations

Annex Point VI.6.9.6

4.5	**Other**	Not applicable
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	6-week sweat inhibition test applying a 10 % (2 %) aqueous solution to the feet (palms) of patients with hyperhydrosis. 160 patients routinely tested for contact dermatitis were patch-tested with 1 % glutaraldehyde.
5.2	**Results and discussion**	A good clinical effect was obtained in patients with hyperhydrosis of the soles. Three applications a week of a 10 % solution was sufficient to keep the feet free from excessive sweating. The treatment caused no irritation in the patients. On the palms prolonged treatment was discontinued due to visible discoloration.
5.3	**Conclusion**	Topical application of glutaraldehyde solution (10 %) was used with good effect against hyperhydrosis. Treatment caused irritation.

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	1 EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Materials and Methods	3.2.4 Number of persons. There were 25 patients treated for localised hyperhidrosis of the soles, but the total number treated is not given. Allergy tests were performed on 160 patients. 3.2.5 Other information. It is not clear what is meant by this information. 3.3.1 Reason of exposure. The patients were treated for hyperhidrosis. 3.3.2 Frequency of exposure. The treatment was performed 3 times a week for several weeks. 3.3.4 Duration of single exposure. Apparently glutaraldehyde was allowed to dry on the skin and was left unwashed, but explicit information is not given. 3.3.5 Exposure concentration/dose. Concentrations of 1, 2, 5 and 10 % were used.
Results and discussion	4.1 Clinical Signs. There was no irritation or sensitisation, or any other clinical signs.
Conclusion	Glutaraldehyde was used topically to treat excessive sweating. No irritation or sensitisation was seen in. No allergic cross reactions were seen, as there were 8 patients allergic to formaldehyde, and none of these were allergic to glutaraldehyde.
Remarks	
	2 COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.7 _ 01 **Annex Point 7.1**	**Specific treatment in case of accident or poisoning: first aid measures, antidotes and medical treatment**	
Reference	PAN Pesticides Database – Chemicals (2007)	**1.1**
Specific treatment in case of accident or poisoning: first aid measures, antidotes and medical treatment	Following symptoms of glutaraldehyde poisoning were reported from the International Chemical Safety Cards (ICSC):	

Route of exposure	Symptoms	First Aid
Inhalation	Cough. Headache. Laboured breathing. Nausea. Wheezing	Fresh air rest. Artificial respiration if indicated. Refer to medical attention.
Skin	Redness	Remove contaminated clothes. Rinse and then wash skin with water and soap.
Eye	Redness and pain	First rinse with plenty of water for several minutes (remove contact lenses if easily possible) then take to a doctor.
Ingestion	Abdominal pain. Diarrhoea. Nausea. Vomiting.	Rinse mouth. Give plenty of water to drink. Refer for medical attention.

Additional information:

The applying occupational exposure limit value should not be exceeded during any part of the working exposure. The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential. Anyone who has shown symptoms of asthma due to this substance should never again come into contact with this substance

Undertaking of intended data submission [ ]	Not relevant
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Evaluation of applicant's justification	This is a copy of the information given in the PAN pesticides database. http://www.pesticideinfo.org/
Conclusion	The information is correct.

Section A6.12.7 _ 01 Annex Point 7.1	Specific treatment in case of accident or poisoning: first aid measures, antidotes and medical treatment
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.8 _ 01
Annex Point IIA VI.6.9.4

Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available

Official use only

		1 REFERENCE
1.1	**Reference**	Anadol D, Özcelik U, Kiper N, Göcmen A (2001) Chemical pneumonia caused by glutaraldehyde. Pediatric International 43:701–702, (Published), BPD ID A6.12.5_01
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Test material**	Glutaraldehyde (Cidex; Johnson and Johnson, USA)
3.2	**Type of study**	Case report of an 8-year-old boy who accidentally received glutaraldehyde on his face during an operation of varicocele.
3.3	**Method of data collection**	Not relevant
3.4	**Test Persons / Study Population**	8-year-old boy with no respiratory or systemic problems, and totally normal preoperatively chest radiogram
3.5	**Controls**	none
3.6	**Exposure**	
3.6.1	Exposure Route	Local (face)
3.6.2	Exposure Situation	Accidental spillage of on the face during an operation of varicocele
3.6.3	Exposure concentration(s)	Admission in the hospital 24 h after the operation approximately 100 ml of glutaraldehyde
3.7	**Examinations**	
3.7.1	Type of disease	Respiratory distress

Section A6.12.8 _ 01
Annex Point IIA VI.6.9.4

Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available

4 RESULTS AND DISCUSSION

4.1 Diagnosis/Findings

Fever, vomiting, tachypnea and tachycardia 6 h after the operation and inhalation and/or aspiration of the chemical.
Cyanosis, subcostal and intecostal retractions with a pulse rate of 140 b.p.m, respiratory rate 48/min, arterial blood pressure 90/60 mmHg and axillary temperature 36.3°C. On auscultation, crackles on the right lung and bronchial sound on the left upper lobe could be heard. Complete blood cell count revealed a hemoglobin of 12.3 g/dL, hematocrit 50.2%, white blood cell count 33.900/mm3 with a predominance of polymorphonuclear leukocytes. The erythrocyte sedimentation rate was 2 mm/h. Chest radiogram revealed infiltration on both lungs with air bronchograms on the right side.

4.2 Recovery

Hypoxia continued instead of nasal O2 therapy as well as tachypnea, ortophnea, intercostals retractions and paradoxal breathing. The boy was ventilated with intermittent positive pressure by non-invasive mechanical ventilator (NMV)-bilevel positive airway pressure (BIPAP) with a nasal mask. He was treated with i.v. sulbactam ampicilline and amikacine as bacterial superimposion to chemical pneumonia could not be ruled out, because he had both leukocytosis, infiltration and fever during the follow-up, although his blood and sputum cultures revealed no microorganisms. He was also given digitals and furosemides. He was discharged on the 10th day of the antibiotic therapy. Two weeks after discharge, the boy was clinically stable, had no respiratory symptoms and his chest radiogram was completely normal.

5 APPLICANT'S SUMMARY AND CONCLUSION

5.1 Materials and methods

Case report of an 8-year-old boy who accidentally received glutaraldehyde on his face during an operation of varicocele.

5.2 Results and discussion

Fever, vomiting, tachypnea and tachycardia 6 h after the operation and inhalation and/or aspiration of the chemical.Cyanosis, subcostal and intecostal retractions with a pulse rate of 140 b.p.m, respiratory rate 48/min, arterial blood pressure 90/60 mmHg, axillary temperature 36.3°C, crackles on the right lung and bronchial sound on the left upper lobe were observed. Complete blood cell count revealed a hemoglobin of 12.3 g/dL, hematocrit 50.2%, white blood cell count 33.900/mm3 with a predominance of polymorphonuclear leukocytes. The erythrocyte sedimentation rate was 2 mm/h. Chest radiogram revealed infiltration on both lungs with air bronchograms on the right side.

Treatment consisted of ventilation (intermittent positive pressure) with a nasal mask Intravenous injection of sulbactam ampicilline and amikacine was done as bacterial superimposion to chemical pneumonia could not be ruled out, because the boy had both leukocytosis, infiltration and fever during the follow-up, although his blood and sputum cultures revealed no microorganisms. The boy also given digitals and furosemides. He was discharged on the 10th day of the antibiotic therapy. Two weeks after discharge, the boy was clinically stable, had no respiratory symptoms and his chest radiogram was completely normal.

5.3 Conclusion

Accidental spillage of 100 ml glutaraldehyde on the face can cause chemical pneumonia. Treatment based on ventilation and antibiotic medication as well as medication with digitals and furosemides supported recovery, which was completed after 2 weeks.

Section A6.12.8 _ 01 **Annex Point IIA VI.6.9.4**		**Diagnosis of poisoning including specific signs of poisoning and clinical tests, if available**
5.3.1	Reliability	**2**
5.3.2	Validity	Basic data given, acceptable restrictions
5.3.3	Deficiencies	None
5.4	**Other**	None

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 15th, 2011
Materials and Methods	3.6.3 Exposure concentration(s). No information is given on the concentration of glutaraldehyde spilled.
Results and discussion	Agree with applicant's version.
Conclusion	Agree with applicant's version.
Reliability	2
Acceptability	Acceptable
Remarks	The same study summary is presented in A6.12.5 _ 01.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.8 _ 02 Prognosis following poisoning

Annex Point IIA VI.6.9.4

Official use only

		1 REFERENCE
1.1	**Reference**	Ünal M, Yucel I,Akar Y, Oner A, Altin M (2006) Outbreak of toxic anterior segment syndrome associated with glutaraldehyde after cataract surgery. J Cataract Refract Surg. 32(10):1696-701 (Published), BPD ID A6.12.5_03
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Test material**	Glutaraldehyde
3.2	**Type of study**	Report of a cluster of cases of toxic anterior segment syndrome (TASS) after uneventful phacoemulsification cataract surgery.
3.3	**Method of data collection**	Six eyes of 6 patients developed TASS after uneventful phacoemulsification cataract surgery with implantation of a 3-piece acrylic IOL performed by 2 ophthalmologists on the same day.
3.4	**Test Persons / Study Population**	6 patients
3.5	**Controls**	None
3.6	**Exposure**	
3.6.1	Exposure Route	Via sterilized reusable ocular instruments.
3.6.2	Exposure Situation	Glutaraldehyde 2% solution was used inadvertently by the operating room staff who cleaned and sterilized reusable ocular instruments before autoclaving.
3.6.3	Exposure concentration(s)	Glutaraldehyde 2% solution
3.7	**Examinations**	
3.7.1	Type of disease	Toxic anterior segment syndrome (TASS) in the eye
		4 RESULTS AND DISCUSSION
4.1	**Diagnosis/Findings**	Clinical findings included corneal edema, Descemet's membrane folds, anterior chamber reaction, fibrin formation, and irregular, dilated, and unreactive pupils.
4.2	**Recovery**	None of the affected corneas improved.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Glutaraldehyde 2% solution was used inadvertently by the operating room staff who cleaned and sterilized reusable ocular instruments before autoclaving. Six eyes of 6 patients developed TASS after uneventful phacoemulsification cataract surgery with implantation of a 3-piece acrylic IOL.

Section A6.12.8 _ 02 Prognosis following poisoning

Annex Point IIA VI.6.9.4

5.2	**Results and discussion**	Clinical findings included corneal edema, Descemet's membrane folds, anterior chamber reaction, fibrin formation, and irregular, dilated, and unreactive pupils. None of the affected corneas improved. Additional surgical procedures were required and included penetrating keratoplasty, trabeculectomy, and glaucoma tube implantation.
5.3	**Conclusion**	Glutaraldehyde in concentrations generally used for cold sterilization is highly toxic to the corneal endothelium.
5.3.1	Reliability	**2**
5.3.2	Validity	Basic data given, acceptable restrictions
5.3.3	Deficiencies	None
5.4	**Other**	None

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 15th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	Agree with applicant's version.
Conclusion	Agree with applicant's version.
Reliability	2
Acceptability	Acceptable
Remarks	The same study summary is presented also in A6.12.5 _ 03.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.8 _ 03 Prognosis following poisoning

Annex Point IIA VI.6.9.4

Official use only

		1 REFERENCE
1.1	**Reference**	Karpelowsky JS, Maske CP, Sinclair-Smith C, Rode H (2006) Glutaraldehyde-induced bowel injury after laparoscopy. J Pediatr Surg. 2006 Jun;41(6):e23-52, (Published), BPD ID A6.12.5_04
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Test material**	Glutaraldehyde
3.2	**Type of study**	Report of a case of sequelae due to inadvertent introduction of glutaraldehyde into the peritoneal cavity.
3.3	**Method of data collection**	Description of the clinical course, progressive histological changes to the bowel at different periods over the course of 1 year.
3.4	**Test Persons / Study Population**	1 3-year-old boy
3.5	**Controls**	None
3.6	**Exposure**	
3.6.1	Exposure Route	Instillation of a few milliliters of 2 % glutaraldehyde solution
3.6.2	Exposure Situation	Instillation during laprascopy
3.6.3	Exposure concentration(s)	No data
3.7	**Examinations**	
3.7.1	Type of disease	Necrosis and fibrosis of the bowel
		4 RESULTS AND DISCUSSION
4.1	**Diagnosis/Findings**	A peritonitis with multiple small bowel fistulae, poor bowel healing, fibrosis, and impaired gastrointestinal motility appeared.
4.2	**Recovery**	None; after extensive therapy with lapratomy subsequently the fistulae were resected or closed and a non obstructive transit and function of the bowel was reached. However, the segmental loss of muscularis propria will result in dysfunctional intestinal motility.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Report of a case of sequelae due to inadvertent introduction of glutaraldehyde into the peritoneal cavity with progressive changes of the bowel over 1 year. During laprascopy instillation of a few milliliters of a 2 % glutaraldehyde solution into the peritoneal cavity through an insufflation tube happened.

Section A6.12.8 _ 03 Prognosis following poisoning

Annex Point IIA VI.6.9.4

5.2	**Results and discussion**	A peritonitis with multiple small bowel fistulae, poor bowel healing, fibrosis, and impaired gastrointestinal motility appeared. After extensive therapy with lapratomy subsequently the fistulae were resected or closed and a non obstructive transit and function of the bowel was reached. However, the segmental loss of muscularis propria will result in dysfunctional intestinal motility.
5.3	**Conclusion**	Accidental inflow of small quantities of glutaraldehyde 2% in the peritoneal cavity may cause serious bowel damage with sequelae.
5.3.1	Reliability	**2**
5.3.2	Validity	Basic data given, acceptable restrictions
5.3.3	Deficiencies	None
5.4	**Other**	None

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 15th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	Agree with applicant's version.
Conclusion	Agree with applicant's version.
Reliability	2
Acceptability	Acceptable
Remarks	The same study summary is presented also in A6.12.5_04.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.8 _ 04 Prognosis following poisoning

Annex Point IIA VI.6.9.4

Official use only

		1 REFERENCE
1.1	**Reference**	Caprilli R, Viscido A, Frieri G, Latella G (1998) Acute colitis following colonscopy. Endoscopy 30: 428-431, (Published), BPD ID A6.12.5_05
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)
		3 MATERIALS AND METHODS
3.1	**Test material**	Glutaraldehyde
3.2	**Type of study**	Report of three cases of severe acute self-limited colitis after colonoscopy with glutaraldehyde sterilized endoscopes.
3.3	**Method of data collection**	Description of the clinical course and endoscopic changes in the bowel.
3.4	**Test Persons / Study Population**	3 females
3.5	**Controls**	None
3.6	**Exposure**	
3.6.1	Exposure Route	Leaking of 2 % glutaraldehyde solution
3.6.2	Exposure Situation	Leaking onto the mucosa during endoscopy
3.6.3	Exposure concentration(s)	No data
3.7	**Examinations**	
3.7.1	Type of disease	Acute colitis
		4 RESULTS AND DISCUSSION
4.1	**Diagnosis/Findings**	Intense abdominal pain, diarrhea with blood and abundant mucus, and systemic events representing an acute-phase response (fever, leukocytosis, neutrophilia, and raised erythrocyte sedimentation rate).
4.2	**Recovery**	All three patients recovered completely within a few days, one spontaneously and two after treatment with steroids, antibiotics, and mesalazine.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	Three cases of severe acute self-limited colitis after colonoscopy with glutaraldehyde sterilised endocopes were reported. During disinfection some of the 2% glutaraldehyde remained in the endoscope and was then released onto the mucosa during endoscopic maneuvers
5.2	**Results and discussion**	The clinical presentation was characterized by intense abdominal pain, diarrhea with blood and abundant mucus, and systemic events representing an acute-phase response (fever, leukocytosis, neutrophilia, and raised erythrocyte sedimentation rate). All three patients recovered completely within a few days, one spontaneously and two after treatment with steroids, antibiotics, and mesalazine.

Section A6.12.8 _ 04 Prognosis following poisoning

Annex Point IIA VI.6.9.4

5.3	**Conclusion**	Accidental leaking of glutaraldehyde 2% onto colon mucus during endoscopy may causes acute colitis. However, recovery can be expected and supported by treatment (steroids, antibiotic and anti-inflammatory medication).
5.3.1	Reliability	**2**
5.3.2	Validity	Basic data given, acceptable restrictions
5.3.3	Deficiencies	None
5.4	**Other**	None

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 15th, 2011
Materials and Methods	3.6.1 Exposure Route. Instruments used in colonoscopy were contaminated with glutaraldehyde.
Results and discussion	Agree with applicant's version.
Conclusion	Agree with applicant's version.
Reliability	2
Acceptability	Acceptable
Remarks	The same study summary is presented also in A6.12.5_05.
	COMMENTS FROM ...
Date	*Give date of comments submitted*
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Reliability	*Discuss if deviating from view of rapporteur member state*
Acceptability	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.13 _ 01 Annex Point 7.1	Toxic effects on livestock and pets
	Justification of non submission
Other existing data [ ]	**Technically not feasible [ ]Scientifically unjustified [ ]**
Limited exposure [ ]	**Other justification [X]**
Detailed justification:	The present endpoint is of particular relevance for the use of glutaraldehyde in product type categories 3 (Veterinary hygiene biocidal products) and 4 (Food and feed area disinfectants). When applied as recommended by the use patterns of PT 3, which implies treatment of the areas in the absence of animal, no toxic effects on livestock /pets are expected, as no prolonged continuance of glutaraldehyde residues on treated surfaces is expected, owing to the volatility and rapid photodegradation of glutaraldehyde (vapour pressure 20 hPa at 20 °C, tropospheric half-life 2.738 h; for details see A3.2 and A7.3.1). When applied as recommended to the use patterns of PT 4, which implies no direct application on /contact to food or feedingstuffs, no significant risk of exposure and/or uptake by animals and/or humans is expected, due to (1) the volatility and rapid photodegradation of glutaraldehyde and (2) its chemical reactivity, as glutaraldehyde possesses the ability of reacting with and cross linking proteins (via e.g. free amino groups). The chemical reaction of glutaraldehyde with proteins is fast (minutes to hours), and the cross-linked molecules (oligomers) only slowly penetrate tissues due to their increased size. In case of accidental/unintentional uptake of residual product, no accumulation is expected as glutaraldehyde is rapidly removed from blood, either by macromolecular binding (see above) or by metabolism. No accumulation of glutaraldehyde is expected as the systemically bioavailable glutaraldehyde and/or its metabolites are rapidly distributed (mainly in blood cells, spleen, lung and kidneys), metabolized and eliminated (mainly as exhaled CO_2); in addition, glutaraldehyde and/or its metabolites show no increased affinity to particular organs or tissues.
Undertaking of intended data submission [ ]	Not relevant
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Evaluation of applicant's justification	Agree with the justification.
Conclusion	Justification is acceptable.

Section A6.13 _ 01 **Annex Point 7.1**	**Toxic effects on livestock and pets**
Remarks	
	COMMENTS FROM OTHER MEMBER STATE (specify)
Date	Give date of comments submitted
Evaluation of applicant's justification	Discuss if deviating from view of rapporteur member state
Conclusion	Discuss if deviating from view of rapporteur member state
Remarks	

Section A6.14 _ 01 Other tests related to exposure of humans

Annex Point 7.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2006). Glutaraldehyde release into the air during simulated manual processing of endoscopes. [redacted] (Unpublished) BPD ID A6.14_01	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Glutaraldehyde	
3.2	**Type of study**	Air monitoring	
3.3	**Method of data collection**	Air was drawn into cartridges containing 2,4-dinitrophenylhydrazone (DNPH) coated silica.	
3.4	**Test Persons / Study Population**	None	
3.5	**Controls**	None	
3.6	**Exposure**		
3.6.1	Exposure Route	Air	
3.6.2	Exposure Situation	Glutaraldehyde is released into the air when the lids of disinfection baths are opened to remove or place instruments to be disinfected.	
3.6.3	Exposure concentration(s)	Glutaraldehyde 2.6% solution	
3.7	**Examinations**		
3.7.1	Type of disease	Not applicable	
		4 RESULTS AND DISCUSSION	
4.1	**Diagnosis/Findings**	Glutaraldehyde was detected in the air at 1.2 to 7.4 ppb (15 minute sampling) in the room whilst the lid of the bath was open and shortly after the lids of the baths had been closed. The highest figures were recorded after only 1 air exchange per hour compared to 10 air exchanges per hour.	X
4.2	**Recovery**	Not applicable	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	See above.	
5.2	**Results and discussion**	Air concentrations recorded were well below the lowest workplace exposure levels of 50 ppb established in some countries	
5.3	**Conclusion**	The release of Glutaraldehyde to the air can be controlled to acceptable levels during instrument disinfection.	
5.3.1	Reliability	**2**	
5.3.2	Validity	Basic data given, acceptable restrictions	

Section A6.14 _ 01 Other tests related to exposure of humans

Annex Point 7.1

5.3.3	Deficiencies	None
5.4	**Other**	None

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Materials and Methods	Agree with applicant's version.
Results and discussion	4.1 Diagnosis/Findings. The values above LOD are given correctly, but there were additional measurements below the LOD.
Conclusion	Under the test conditions, glutaraldehyde concentration in the air was well below the lowest current OEL of 50 ppb. It is however not clear whether the test procedure accurately reflected real use situations. Among the affecting conditions are at least: • Glutaraldehyde volume • Room volume • Frequency of sterilization • Time of glutaraldehyde bath remaining without a cover • Volume of glutaraldehyde attached to the equipment and then evaporating Due to these uncertainties, it is difficult to estimate the usefulness of the study.
Reliability	2
Acceptability	Acceptable
Remarks	

Section A6.14 _ 02 Other tests related to exposure of humans

Annex Point 7.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1994). Measurement of glutaraldehyde concentrations in [redacted] Mill on 30.06.1994, BASF (Unpublished) BPD ID A6.14_02	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
Test material		Glutaraldehyde	
Type of study		Air monitoring	
Method of data collection		Air was drawn into cartridges containing 2,4-dinitrophenylhydrazone (DNPH) coated silicagel. Analysis was by LC.	
Test Persons / Study Population		None	
Controls		None	
Exposure			
Exposure Route		Air	
Exposure Situation		Samples were taken immediately after the dosing stage, and then after a further 20, 40, 70 and 100 min.	X
3.1.1	Exposure concentration(s)	Glutaraldehyde content of [redacted]	
3.2	**Examinations**		
3.2.1	Type of disease	Not applicable	
		4 RESULTS AND DISCUSSION	
Diagnosis/Findings		Glutaraldehyde was detected in the air in paper mill 7 at <0.04 mg/m^3.	
		All measurements were below the Ministry of Labour Threshold Limit Values (1993) of 0.1 cm^3/m^3.	X
4.1	**Recovery**	Not applicable	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
Materials and methods		See above.	
Results and discussion		Air concentrations recorded were well below the Threshold Limit Values of 0.1 cm^3/m^3 in place at the time.	
Conclusion		The release of Glutaraldehyde to the air was controlled to acceptable levels during dosing and processing.	
5.1.1	Reliability	**2**	
5.1.2	Validity	Basic data given, acceptable restrictions	
5.1.3	Deficiencies	None	

Section A6.14 _ 02 Other tests related to exposure of humans

Annex Point 7.1

5.2	**Other**	None

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Materials and Methods	Exposure situation. The data is not correct. Measurements were done during the two dosing stages and after them, at various time points.
Results and discussion	Diagnosis/Findings. The concentrations in the air were below 0.02 ppm (v/v).
Conclusion	Agree with applicant's version.
Reliability	2
Acceptability	Acceptable
Remarks	

Section A6.14 _ 03 Other tests related to exposure of humans

Annex Point 7.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (1997). Glutaraldehyde measurements at [redacted] Mill, April 15 1997. BASF (Unpublished) BPD ID A6.14_03	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
Test material		Glutaraldehyde	
Type of study		Air monitoring	
Method of data collection		Air was drawn into cartridges containing 2,4-dinitrophenylhydrazone (DNPH) coated silicagel. Analysis was by LC.	
Test Persons / Study Population		None	
Controls		None	
Exposure			
Exposure Route		Air	
Exposure Situation		Samples were taken immediately after the dosing stage, and then after a further 20, 40, 70 and 100min.	
3.1.1	Exposure concentration(s)	Glutaraldehyde content [redacted]	X
3.2	**Examinations**		
3.2.1	Type of disease	Not applicable	
		4 RESULTS AND DISCUSSION	
Diagnosis/Findings		Glutaraldehyde was detected in the air in paper mill 7 at <0.04 mg/m^3. All measurements were below the Ministry of Labour Threshold Limit Values (1993) of 0.1 cm^3/m^3.	X
4.1	**Recovery**	Not applicable	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
Materials and methods		See above.	
Results and discussion		Air concentrations recorded were well below the Threshold Limit Values of 0.1 cm^3/m^3 in place at the time.	
Conclusion		The release of Glutaraldehyde to the air was controlled to acceptable levels during dosing and processing.	
5.1.1	Reliability	2	
5.1.2	Validity	Basic data given, acceptable restrictions	
5.1.3	Deficiencies	None	
5.2	**Other**	None	

Section A6.14 _ 03 Other tests related to exposure of humans

Annex Point 7.1

	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Materials and Methods	3.1.1 Exposure concentration(s). The substance used was [redacted]
Results and discussion	Diagnosis/Findings. The concentrations in the air are only reported to be below the HTP concentration of 0.42 mg/m^3 (not 0.04). No numerical values are given.
Conclusion	Agree with applicant's version.
Reliability	3
Acceptability	Not acceptable: no data is given, and it is only stated that the concentrations were below the OEL (HTP) values.
Remarks	

Section A6.14 _ 04 Other tests related to exposure of humans

Annex Point 7.1

			Official use only
		1 REFERENCE	
1.1	**Reference**	[redacted] (2007) Monitoring of laboratory personnel. [redacted], (Unpublished), BPD ID A6.14_04	
		2 GUIDELINES AND QUALITY ASSURANCE (NOT APPLICABLE)	
		3 MATERIALS AND METHODS	
3.1	**Test material**	Glutaraldehyde aqueous solutions: 25%, 5%	
3.2	**Type of study**	Monitoring of personnel	
3.3	**Method of data collection**	A validated method in accordance with NIOSH method No. 2532 with personal air sampling which makes use of a silica gel cartridge coated with 2,4,-dinitrophenylhydrazine was applied. Following desorption, glutaraldehyde was quantitatively identified by HPLC. The method meets the German national requirements (German Employer's Liability Insurance Association file 7555) and the competent measurement body [redacted] has been accredited by German authorities	
3.4	**Test Persons / Study Population**	Three female employees	X
3.5	**Controls**	none	
3.6	**Exposure**		
3.6.1	Exposure Route	Air	
3.6.2	Exposure Situation	Laboratory personnel diluting a concentrated glutaraldehyde solution, which is subsequently used for the fixation of rats.	
3.6.3	Exposure concentration(s)	between 0.085 mg/m^3 (0.02 ppm) and a minimum of < 0.00036 mg/m^3	X
3.7	**Examinations**		
3.7.1	Type of disease	not applicable	
		4 RESULTS AND DISCUSSION	
4.1	**Diagnosis/Findings**	No cases of adverse health effects related to glutaraldehyde exposure were reported within a period of 20 years. This is in accordance with regular exposure measurements that have been conducted in the [redacted] laboratory which show that glutaraldehyde concentrations in the air did not exceed the threshold limit value of 0.21 mg/m3 (0.05 ppm) suggested by the MAK-commission and ACGIH	
4.2	**Recovery**	not applicable	
		5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1	**Materials and methods**	Personal air sampling was applied to determine the concentration of glutaraldehyde in the air (8 hour shift median values). Representative data (22 values) measured between 01 Jan 2002 and 16 Apr 2007 revealed a maximum value of 0.085 mg/m^3 (0.02 ppm) and a minimum of < 0.00036 mg/m^3	X

Section A6.14 _ 04 Other tests related to exposure of humans

Annex Point 7.1

5.2	**Results and discussion**	Measurements in a pathology laboratory where glutaraldehyde is routinely used as a fixative for laboratory animals revealed higher values. The following tasks with relevant exposure to glutaraldehyde are routinely performed by one male and three female employees (32, 50, 34, 32 and 49 years of age who have worked in this laboratory for 10, 20, 10, 6 and 10 years, respectively): (1) dilution of a 25% glutaraldehyde solution to a 5% aqueous solution and filling of a 5 L flask under the hood. (2) Fixation of animals with 1 L of the 5% glutaraldehyde solution per animal (20 animals per shift) (3) preparation of a tank with 20 L of a 5% glutaraldehyde solution for the final fixation of animals over night and (4) subsequent pathological examination under a hood or local exhaust system. These tasks are performed during at least 6 hours of an 8 hour shift. The hoods had a minimum volume flow rate of 400 m^3/h. Disposable gloves were the only other safety equipment used during glutaraldehyde exposure. Personal air sampling was applied to determine the concentration of glutaraldehyde in the air (8 hour shift median values). Representative data (22 values) measured between 01 Jan 2002 and 16 Apr 2007 revealed a maximum value of 0.085 mg/m^3 (0.02 ppm) and a minimum of < 0.00036 mg/m^3 with a 95^{th} percentile of 0.081 mg/m^3. Even at theses higher values (compared to values measured at the production plant, see A6.12.1_01), no adverse health effects related to inhalative exposure to glutaraldehyde were reported.	X
5.3	**Conclusion**	In a workplace situation where glutaraldehyde is used for its intended purpose, a concentration of 0.085 mg/m^3 (0.02 ppm), which is a factor of 2.5 below the threshold limit value, did not lead to adverse health effects	
5.3.1	Reliability	**2**	
5.3.2	Validity	Basic data given, acceptable restrictions	
5.3.3	Deficiencies	None	
5.4	**Other**	None	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16^{th}, 2011
Materials and Methods	3.4 Test Persons / Study Population. The report is not consistent: there were 1 male and 3 females, and a total of 5 persons. 3.6.3 Exposure concentration(s). The concentrations of glutaraldehyde were 25 % and 5 %. The figures given are correct but belong to the Results section. 5.1 Materials and methods. The original report is cited correctly, but the measurements were actually between 2004 and 2006.
Results and discussion	5.2 Results and discussion. This is a copy of a chapter in the report, including the inconsistencies mentioned in 3.4 above.
Conclusion	Agree with applicant's version.

Section A6.14 _ 04 Other tests related to exposure of humans

Annex Point 7.1

Reliability	2-3
Acceptability	Data on air concentrations: acceptable. Data on health effects: not acceptable. The only information given is that there were no adverse health effects during 20 years. This information cannot be verified.
Remarks	

Section A6.15 _ 01 **Annex Point 7.1**	**Food and feedingstuffs**
	Justification of non submission
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ] Scientifically unjustified [ ]** **Other justification [X]**
Detailed justification:	When applied as recommended by the use patterns, no prolonged continuance of glutaraldehyde residues on treated surfaces is expected, owing to the volatility and rapid photodegradation of glutaraldehyde. Determination of the vapour pressure at 20.1 °C according to the Pesticide Assessment Guidelines, Subdivision D, "Series 63" revealed that glutaraldehyde is volatile (20 hPa at 20 °C; see section A3.2); the tropospheric half-life of glutaraldehyde (AOPWIN, version 1.91) is 2.738 hours, which indicates rapid degradation of the substance by photochemical processes (see Section A7.3.1). When applied as recommended to the use patterns, no direct contact to food or feedingsstuffs is expected. In case of accidental/unintentional contact to food or feedingsstuffs, no significant risk of exposure and/or uptake by animals and/or humans is expected, due to the chemical properties of glutaraldehyde, which reacts with and cross links proteins via e.g. free amino groups. Glutaraldehyde is a fairly small molecule comprising two reactive aldehyde groups separated by a propyl bridge. The potential for cross-linking is high because it can occur through both -CHO groups and over variable distances. In fact, the -CHO groups are able to react with any protein nitrogens with which they come into contact, which results in cross-linking. The chemical reaction of glutaraldehyde with proteins is fast (minutes to hours), and the cross-linked molecules (oligomers) only slowly penetrate tissues due to their increased size. In case of accidental/unintentional uptake of residual product, no accumulation is expected as glutaraldehyde is rapidly removed from blood, either by macromolecular binding (see above) or by metabolism. No accumulation of glutaraldehyde is expected as the systemically bioavailable glutaraldehyde and/or its metabolites are rapidly distributed (mainly in blood cells, spleen, lung and kidneys), metabolized and eliminated (mainly as exhaled CO_2); in addition, glutaraldehyde and/or its metabolites show no increased affinity to particular organs or tissues.
Undertaking of intended data submission [ ]	Not relevant
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
Date	**EVALUATION BY RAPPORTEUR MEMBER STATE** February 16th, 2011

Section A6.15 _ 01 **Annex Point 7.1**	**Food and feedingstuffs**
Evaluation of applicant's justification	Agree with the justification.
Conclusion	Justification is accepted by the RMS.
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.15.1 _ 01 **Annex Point 7.1**	**Identification of the residues (identity and concentrations), degradation and reaction products and of metabolites of the active substance in contaminated foods or feedingstuffs**
	Justification of non submission
Other existing data [ ] **Limited exposure [ ]**	**Technically not feasible [ ] Scientifically unjustified [ ]** **Other justification [X]**
Detailed justification:	When applied as recommended by the use patterns , neither prolonged remain of glutaraldehyde residues in food or feedingsstuffs nor significant exposure to animal or human is expected ((see A6.15_01). Therefore, no further data of identification of the residues, degradation and reaction products and of metabolites of the active substance in contaminated foods or feedingstuffs are needed.
Undertaking of intended data submission [ ]	Not relevant
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Evaluation of applicant's justification	Agree with the justification.
Conclusion	Justification is accepted by the RMS.
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.15.2 _ 01 **Annex Point 7.1**	**Behaviour of the residues of the active substance, its degradation and reaction products and where relevant, its metabolites on the treated or contaminated food or feedingstuffs including the kinetics of disappearance**
	Justification of non submission
Other existing data [ ]	**Technically not feasible [ ] Scientifically unjustified [ ]**
Limited exposure [ ]	**Other justification [X]**
Detailed justification:	When applied as recommended by the use, neither prolonged remain of glutaraldehyde residues in food or feedingsstuffs nor significant exposure to animal or human is expected (see A6.15_01). Therefore, no further data on residues behaviour, degradation and reaction products and metabolites on the treated or contaminated food or feedingstuffs including kinetics of disappearance are needed.
Undertaking of intended data submission [ ]	Not relevant
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Evaluation of applicant's justification	Agree with the justification.
Conclusion	Justification is accepted by the RMS.
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.15.3 _ 01 **Annex Point 7.1**	**Estimation of potential or actual exposure of the active substance to humans through diet and other means**
	Justification of non submission
Other existing data [ ]	**Technically not feasible [ ] Scientifically unjustified [ ]**
Limited exposure [ ]	**Other justification [X]**
Detailed justification:	When applied as recommended by the use patterns (PT3 & PT 12), neither prolonged remain of glutaraldehyde residues in food or feedingsstuffs nor significant exposure to animal or human is expected (see A6.15_01). Therefore, no considerable potential or actual exposure of glutaraldehyde to humans through diet or other means is expected. Moreover, glutaraldehyde has been evaluated by different organizations including: • The Scientific Committee on Food of the European Commission, Health & Consumer Protection Directorate-General (Opinion on an additional list of monomers and additives for food contact Annex VII to the minutes of the 119th Plenary meeting, 12 December 1999, Published), BPD ID A6.15.3_01_a • The Codex Alimentarius Commission of the Food and Agriculture Organization of the United Nations, WHO (Agenda Item 11(b), CX/RVDF 06/16/13 (Part 1), Report of the working group on residues of veterinary drugs without ADI/MRL, 2005, Published), BPD ID A6.15.3_01_b • The European Medicines Agency (Veterinary Medicines and Inspections, Status if MRL procedures, MRL assessments in the context of Council Regulation (EEC) No 2377/90, 21 March 2007, Published), BPD ID A6.15.3_01_c The evaluation has led to the conclusion that for glutaraldehyde residues, there is no necessity for protection of public health.
Undertaking of intended data submission [ ]	Not relevant
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Evaluation of applicant's justification	Agree with the justification. The cited studies have not been assessed by the RMS.
Conclusion	Justification is accepted by the RMS.
Remarks	

Section A6.15.3 _ 01 **Annex Point 7.1**	**Estimation of potential or actual exposure of the active substance to humans through diet and other means**
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.15.04 _ 01 Annex Point 7.1	Proposed acceptable residues and the justification of their acceptability
	Justification of non submission
Other existing data [ ]	**Technically not feasible [ ] Scientifically unjustified [ ]**
Limited exposure [ ]	**Other justification [X]**
Detailed justification:	As reported in A6.15_01, when applied as recommended by the use patterns, no prolonged remain of glutaraldehyde residues on the treated surfaces and no direct contact to food or feedingsstuffs is expected. In case of accidental/unintentional contact to food or feedingsstuffs, no significant risk of exposure and/or uptake by animals and/or human is expected, due to the mechanistic properties of glutaraldehyde, which reacts with and cross-link proteins. In case of accidental/unintentional uptake of residual product, no accumulation is expected as glutaraldehyde is rapidly removed from blood, either by macromolecular binding (see above) or by metabolism. Systematically available residues of glutaraldehyde are rapidly distributed (mainly in blood cells, spleen, lung and kidneys), metabolized and eliminated (mainly as exhaled CO_2); in addition, glutaraldehyde and/or its metabolites show no increased affinity to particular organs or tissues. Moreover, glutaraldehyde has been evaluated by different organizations including: • The Scientific Committee on Food of the European Commission, Health & Consumer Protection Directorate-General (Opinion on an additional list of monomers and additives for food contact Annex VII to the minutes of the 119th Plenary meeting, 12 December 1999, Published), BPD ID A6.15.3_01_a • The Codex Alimentarius Commission of the Food and Agriculture Organization of the United Nations, WHO (Agenda Item 11(b), CX/RVDF 06/16/13 (Part 1), Report of the working group on residues of veterinary drugs without ADI/MRL, 2005, Published), BPD ID A6.15.3_01_b • The European Medicines Agency (Veterinary Medicines and Inspections, Status if MRL procedures, MRL assessments in the context of Council Regulation (EEC) No 2377/90, 21 March 2007, Published), BPD ID A6.15.3_01_c The evaluation has led to the conclusion that for glutaraldehyde residues, there is no necessity to establish a maximum residue limit for the protection of public health.
Undertaking of intended data submission [ ]	Not relevant
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE

Section A6.15.04 _ 01 **Annex Point 7.1**	**Proposed acceptable residues and the justification of their acceptability**
Date	February 16th, 2011
Evaluation of applicant's justification	Agree with the justification. The cited studies have not been assessed by the RMS.
Conclusion	Justification is accepted by the RMS.
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.15.5 _ 01 Annex Point 7.1	Any other available information that is relevant
	Justification of non submission
Other existing data [ ]	**Technically not feasible** [ ] **Scientifically unjustified** [ ]
Limited exposure [ ]	**Other justification** [X]
Detailed justification:	The Scientific Committee on Food (SCF) of the European Commission (Health & Consumer Protection Directorate-General (1999) Opinion on an additional list of monomers and additives for food contact materials. Annex VII to the minutes of the 119th Plenary meeting, 12/12/1999, page 3 of 7, Published, BPD ID A6.15.3_01_a) has (re)evaluated a number of monomers and additives for food contact materials, including glutaraldehyde. Glutaraldehyde was evaluated and classified in the SCF List 7, which was defined as list of substances for which some toxicological data exist, but for which an ADI or a TDI could not be established yet. Moreover, the SCF reported that no data on migration in foodstuffs or in the residual quantity in finished products were available, so that migration data according to SCF guidelines (RIVM/TNO SDS, June 1999 = CS/PM/3283 REV. II/55660) (Adopted at the 119th SCF meeting) (2 December 1999) still were needed. The Codex Alimentarius Commission of the Food and Agriculture Organization of the United Nations, WHO (Agenda Item 11(b), CX/RVDF 06/16/13 (Part 1), Report of the working group on residues of veterinary drugs without ADI/MRL, 2005, Published, BPD ID A6.15.3_01_b) has classified glutaraldehyde in the Annex I list of veterinary drugs used in food producing animals, as permitted (EU, Korea) and not subjected to maximum residue limits. The European Medicines Agency, Veterinary Medicines and Inspections, Status if MRL procedures, MRL assessments in the context of Council Regulation (EEC) No 2377/90, 21 March 2007 (Published, BPD ID A6.15.3_01_c)) has classified Glutaraldehyde in Annex II (Regulation amending Annex of Regulation 2377/90, Reg. 2796/95). The classification in Annex II indicates that based on the evaluation of glutaraldehyde, there is no necessity to establish MRL for protection of public health.
Undertaking of intended data submission [ ]	Not relevant
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Evaluation of applicant's justification	Agree with the justification. Glutaraldehyde has been included on Annex II of Regulation 2377/90 among "Substances generally recognised as safe" and therefore a MRL is not necessary.

Section A6.15.5 _ 01 **Annex Point 7.1**	**Any other available information that is relevant**
Conclusion	Justification is accepted by the RMS.
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.15.6 _ 01 Annex Point 7.1	Summary and evaluation of data submitted under point 6.15
	Summary
	When applied as recommended by the use patterns, no prolonged continuance of glutaraldehyde residues on treated surfaces is expected, owing to the volatility and rapid photodegradation of glutaraldehyde; furthermore, no direct contact to food or feedingsstuffs is expected. In case of accidental/unintentional contact to food or feedingsstuffs, no significant risk of exposure and/or uptake by animals and/or humans is expected, due to the chemical properties of glutaraldehyde, which reacts with and cross links proteins via e.g. free amino groups. The chemical reaction of glutaraldehyde with proteins is fast (minutes to hours), and the cross-linked molecules only slowly penetrate tissues due to their increased size. In case of accidental/unintentional uptake of residual product, no accumulation is expected as glutaraldehyde is rapidly removed from blood, either by macromolecular binding (see above) or by metabolism. No accumulation of glutaraldehyde is expected as the systemically bioavailable glutaraldehyde and/or its metabolites are rapidly distributed (mainly in blood cells, spleen, lung and kidneys), metabolized and eliminated (mainly as exhaled CO_2); in addition, glutaraldehyde and/or its metabolites show no increased affinity to particular organs or tissues. Conclusion: When applied as recommended by the use patterns, no considerable potential or actual exposure of glutaraldehyde to animals and /or humans through diet or other means is expected.
Undertaking of intended data submission [ ]	Not relevant
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Evaluation of applicant's justification	Agree with the justification.
Conclusion	Justification is accepted by the RMS
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*

Section A6.15.6 _ 01 Annex Point 7.1	Summary and evaluation of data submitted under point 6.15
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.16 _ 01 **Annex Point 7.1**	**Any other tests related to the exposure of the active substance to humans, in its proposed biocidal products, that are considered necessary may be required**
	Justification of non submission
Other existing data [ ]	**Technically not feasible [ ]Scientifically unjustified [ ]**
Limited exposure [ ]	**Other justification [X]**
Detailed justification:	For human, the primary routes of exposure to glutaraldehyde include inhalation, eye contact, skin contact and ingestion, which all were considered and documented. As the biocidal product is identical to the active ingredient glutaraldehyde 50%, no other test related to the exposure of the active ingredient to humans in its proposed biocidal products are therefore necessary.
Undertaking of intended data submission [ ]	Not relevant
	Evaluation by Competent Authorities
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	February 16th, 2011
Evaluation of applicant's justification	Agree with the justification.
Conclusion	Justification is accepted by the RMS.
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A 6.17 _ 01 Annex Point VI.6	Assessment of toxic effects of metabolites from treated plants	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [X]**	
Detailed justification:	No data is presented, as glutaraldehyde is not used in products for action against plants.	
Undertaking of intended data submission [ ]	Not relevant	
	Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	February 16th, 2011	
Evaluation of applicant's justification	Agree with the justification.	
Conclusion	Justification is accepted by the RMS.	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.1.1 Annex Point IIA, VI.6.1.1 IUCLID 5.1.1/01		Acute Toxicity Acute peroral toxicity study in the rat	
		1 REFERENCE	Official use only
1.1	**Reference**	[redacted] (1992) [redacted]: Acute peroral toxicity study in the rat, [redacted] (Unpublished), 9 January 1992	
1.2	**Data protection**	Yes	
1.2.1	Data owner	The Dow Chemical Company	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	Yes, OECD 401	X
2.2	**GLP**	Yes	
2.3	**Deviations**	No analyses of the stability of the test substance or its dilutions in distilled water were performed by the testing facility. Concentrations of the test substance in distilled water were documented on the basis of weight and volume. No further chemical analyses were performed by the testing facility. The study director had no knowledge of the procedures used for feed and water analyses, or whether these procedures conformed to GLP.	
		3 MATERIALS AND METHODS	
3.1	**Test material**	[redacted] (50% Aqueous Glutaraldehyde)	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	Not given	
3.1.2.1	Description	Transparent, colorless liquid	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Stable under normal storage conditions	
3.2	**Test Animals**		
3.2.1	Species	Rat	
3.2.2	Strain	[redacted]	
3.2.3	Source	[redacted]	
3.2.4	Sex	Male and Female	
3.2.5	Age/weight at study initiation	7-9 weeks old Weight range 166 – 267 grams	
3.2.6	Number of animals per group	5/sex/dose	

Section A6.1.1 Annex Point IIA, VI.6.1.1 IUCLID 5.1.1/01		Acute Toxicity Acute peroral toxicity study in the rat	
3.2.7	Control animals	No	
3.3	**Administration/ Exposure**		
3.3.1	Postexposure period	14-day observation period. After 14 days all survivors were sacrificed.	
3.3.2	Type	Peroral intubation	
3.3.3	Concentration	Doses were varied through changes in concentration. Males-200, 100, 50 mg a.i./kg b.w. Females-100, 71, 50 mg a.i./kg b.w.	
3.3.4	Vehicle	None	X
3.3.5	Concentration in vehicle	Not applicable	X
3.3.6	Total volume applied	1 mL of dose per 100 grams of rat body weight.	
3.3.7	Controls	No	
3.4	**Examinations**	Dose rats were observed frequently for signs of toxic effect on the first day of the test and twice daily thereafter. Weights were recorded on the day of dosing and at 7 and 14 days after dosing, at death. After 14 days, all survivors were sacrificed. Necropsies were performed on all animals.	
3.5	**Method of determination of LD_{50}**	Separate LD_{50}'s were determined for males, females, and both sexes combined based on the 14-day observation period. They were calculated by the Moving Average Method. Estimates of the slope were made by the formula developed by C.S. Weil.	
3.6	**Further remarks**	Not applicable	
		RESULTS AND DISCUSSION	
3.7	**Clinical signs**	Signs of toxicity included sluggishness, lacrimation, piloerection, diarrhea, and a trace amount of blood in the urine of 2 animals. Red, perinasal soiling and perineal soiling was also noted. Deaths occurred at 1-2 days post-dosing. Survivors recovered within 4-5 days.	
3.8	**Pathology**	Necropsy findings of victims revealed red, mottled lungs, red stomachs (some hemhorrhaged, 1 full of red liquid), discolored intestines, and dark red kidneys. Necropsy revealed no remarkable gross lesions on examination of survivors.	
3.9	**Other**	Not applicable	
3.10	**LD_{50}**	LD_{50} (males) = 123 mgAI/kg bw LD_{50} (females) = 77 mgAI/kg bw Combined LD_{50} = 100 mgAI/kg bw	
		4 APPLICANT'S SUMMARY AND CONCLUSION	

Section A6.1.1 **Annex Point IIA, VI.6.1.1** **IUCLID 5.1.1/01**	**Acute Toxicity** **Acute peroral toxicity study in the rat**	
4.1 Materials and methods	Male and Female [redacted] rats were obtained from a commercial supplier. Upon arrival at the testing facility, animals were evaluated by technicians for general health status. Animals were separated by sex and housed up to 5 animals per cage in rooms designed to maintain adequate environmental conditions for the species, and were acclimated to the laboratory for at least 5 days prior to dosing. They were offered food and water *ad libitum* with the exception of feed being removed for approximately 18 hours prior to dose administration. Post-dose administration feed was provided *ad libitum*. Doses were varied through changes in concentration. Five males per dose level (200, 100, 50 mg AI./kg b.w.) and five females per dose level (100, 71, 50 mg AI/kg b.w.) were administered the test material by a single Peroral intubation through a 16 gauge ball-end stainless-steel needle attached to a disposable syringe. The exact amounts of sample and mixture given to each rat were recorded. The dose volume was adjusted according to the body weight to give 1 mL of dose per 100 grams of rat body weight. Dose rats were observed frequently for signs of toxic effect on the first day of the test, and twice daily thereafter. Weights were recorded on the day of dosing and at 7 and 14 days after dosing, and at any unscheduled death. After 14 days, all survivors were sacrificed. Necropsies were performed on all animals.	
4.2 Results and discussion	Signs of toxicity included sluggishness, lacrimation, piloerection, diarrhea, and a trace amount of blood in the urine of 2 animals. Red, perinasal soiling and perineal soiling was also noted. Deaths occurred at 1-2 days post-dosing. Necropsy findings in spontaneously-dying animals revealed red, mottled lungs, red stomachs (some hemorrhaged, 1 full of red liquid), discolored intestines, and dark red kidneys. Necropsy revealed no remarkable gross lesions on examination of survivors.	
4.3 Conclusion	Male LD_{50} 123 mg a.i./kg bw Female LD_{50} 77 mg a.i./kg bw Combined LD_{50} 100 mg a.i./kg bw	
4.3.1 Reliability	1	
4.3.2 Deficiencies	None	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	May 4th, 2010	
Materials and Methods	**1.1.1. Vehicle; 1.1.2. Concentration in vehicle.** The test substance was [redacted] which contains 50 % a.i. in water. The doses are given correctly for the a.i. Otherwise agree with Applicant's version.	
Results and discussion	Agree with Applicant's version.	

Section A6.1.1 **Annex Point IIA, VI.6.1.1** **IUCLID 5.1.1/01**	**Acute Toxicity** **Acute peroral toxicity study in the rat**	
Conclusion	Agree with Applicant's version. Conclusions for the test substance (50 % glutaraldehyde in water): • LD_{50} male 246 mg/kg bw • LD_{50} female 154 mg/kg bw • LD_{50} combined 200 mg/kg bw • The risk phrase R25 "Toxic if swallowed" is warranted. • CLP: Classification in Category 3 for Acute toxicity is warranted. Conclusions for glutaraldehyde, as calculated from the above: • LD_{50} male 123 mg/kg bw • LD_{50} female 77 mg/kg bw • LD_{50} combined 100 mg/kg bw • The risk phrase R25 "Toxic if swallowed" is warranted. • CLP: Classification in Category 3 for Acute toxicity is warranted.	
Reliability	1	
Acceptability	Acceptable	
Remarks	Key study. **2.1 Guideline study**. The method used was in compliance with OECD 401. This method (OECD 401) is however not mentioned, but instead it "*... was based on 1984 EPA Pesticide Assessment Guidelines, 40 CFR Part 158, and EPA Health Effects Test Guidelines, 40 CFR Part 798*".	
	COMMENTS FROM ...	
Date	*Give date of comments submitted*	
Materials and Methods	*Discuss additional relevant discrepancies referring to the (sub)heading numbers and to applicant's summary and conclusion.* *Discuss if deviating from view of rapporteur member state*	
Results and discussion	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Reliability	*Discuss if deviating from view of rapporteur member state*	
Acceptability	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Table A6.1.1/01-1 Table for Acute Toxicity – Oral

Dose [mg a.i./kg]	Number of dead / number of investigated	Time of death (range)	Observations

Section A6.1.1 Annex Point IIA, VI.6.1.1 IUCLID 5.1.1/01	Acute Toxicity Acute peroral toxicity study in the rat		
50	Males 0/5 Females 0/5	Not Applicable	Males- None noted. Females- Sluggishness in 1, trace amount of blood in urine of 2 (positive by HEMASTIX® Reagent Strips) at day 1. Recovery at 4 days.
71	Females 2/5	Day 1	None noted except for deaths.
100	Males 1/5 Females 4/5	Male-Day 2 Female- Day 1 & 2	Males- Sluggishness in 2 at 2.5 hr to day 1. Piloerection and lacrimation in 1 at day 1. Red crust on perinasal fur of 5 at day 1. Brown stain on perineal fur of 1 at day 4. Survivors recovered at 4 to 5 days. Females- Sluggishness in 5 at 2.5 hr. Piloerection in 2, red crust on perinasal fur of 3 at day 1. Survivor recovered at 4 days.
200	Males 5/5	Day 1	Sluggishness in 5 at 2.5 hr, lacrimation in 5, diarrhoea in 3 at 2.5 hr.
LD_{50} value	Male 123 mg a.i./kg bw Female 77 mg a.i./kg bw Combined 100 mg a.i./kg bw		

Section A6.1.2 **Annex Point IIA, VI.6.1.2** **IUCLID 5.1.3/01**		**Acute Toxicity** **Percutaneous toxicity**	
		1 REFERENCE	**Official use only**
1.1	**Reference**	[redacted] (1981) Glutaraldehyde dilutions: Percutaneous toxicity and eye irritation studies, [redacted], Not GLP, Unpublished, 01 June 1981	
1.2	**Data protection**	Yes	
1.2.1	Data owner	The Dow Chemical Company	
1.2.2	Companies with letter of access	[redacted]	
1.2.3	Criteria for data protection	Data submitted to the MS after 13 May 2000 on existing a.s. for the purpose of its entry into Annex I	
		2 GUIDELINES AND QUALITY ASSURANCE	
2.1	**Guideline study**	No	
2.2	**GLP**	No	
2.3	**Deviations**	Not applicable	
		3 MATERIALS AND METHODS	
3.1	**Test material**	50% Glutaraldehyde	
3.1.1	Lot/Batch number	[redacted]	
3.1.2	Specification	Not given	
3.1.2.1	Description	Clear, watery, colourless, liquids	
3.1.2.2	Purity	[redacted]	
3.1.2.3	Stability	Assumed to be stable under normal storage conditions	
3.2	**Test Animals**		
3.2.1	Species	Rabbit	
3.2.2	Strain	[redacted]	
3.2.3	Source	Not Reported	
3.2.4	Sex	Male	
3.2.5	Age/weight at study initiation	3 to 5 months of age Weights not reported.	
3.2.6	Number of animals per group	4	
3.2.7	Control animals	No	
		Dermal	
3.2.8	Area covered	% of surface area not specified. The material was applied to the clipped, intact skin of the trunk of the rabbit.	