

Skin and respiratory symptoms from exposure to alkaline glutaraldehyde in medical services

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NORBÄCK D. Skin and respiratory symptoms from exposure to alkaline glutaraldehyde in medical services. *Scand J Work Environ Health* 14 (1988) 366—371. The prevalence of certain symptoms (eye, skin and airway symptoms, headache, nausea, and fatigue) were studied among hospital workers with and without exposure to glutaraldehyde during cold sterilization work. The exposure to glutaraldehyde and formaldehyde was quantified by hygienic measurements in the breathing zone of the workers. Aldehydes were measured by a specific method, using sorbent tubes with Amberlite XAD-2 coated with 2,4-dinitrophenylhydrazine (2,4-DNF) and analyzed by liquid chromatography. The exposure measurements revealed that the present exposure to glutaraldehyde was intermittent and well below the Swedish occupational exposure limit. 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 contact allergy to glutaraldehyde was found.

Key terms: airway symptoms, cold sterilization, epidemiologic study, formaldehyde, glutaraldehyde, headache, nasal symptoms, occupational exposure.

Glutaraldehyde (1,5-pentanedial) is a dialdehyde that is slightly acid in its natural state. In a buffered alkaline solution (pH 7.5—8.5) it is a highly effective microbiocidal agent (13, 28, 29). Alkaline glutaraldehyde is widely used in the cold sterilization of medical, surgical, and dental equipment. It is also used as a biocide in contaminated water, cooling towers, and air conditioning plants (8). Besides its use as a biocide, glutaraldehyde is also used as a tanning agent for leather (12), in the treatment of hyperhidrosis (12, 17), as a fixative in histochemistry and electron microscopy (12), and as a cross-linking agent in the preparation of microcapsules (25).

In the United States glutaraldehyde is the most commonly used aldehyde with the exception of formaldehyde, and it has been estimated that approximately 35 000 employees in that country are occupationally exposed to glutaraldehyde (24). Although it has been used for decades in medical services all over the world, the information on exposure levels and the health effects caused by exposure to it is sparse. Glutaraldehyde is a known contact allergen, and case reports on occupational contact dermatitis from glutaraldehyde have earlier been published (4, 9, 12, 14, 15, 16, 21, 30). One case of obstructive airway reaction during cold sterilization with glutaraldehyde has also been described (5). Other than a single exposure measurement during a simulated cold sterilization procedure

(1), no information on the levels of exposure to glutaraldehyde during cold sterilization was found in the literature.

This study was undertaken with the objectives of determining the present levels of exposure to glutaraldehyde during cold sterilization work in medical services and of studying the acute health effects of this exposure.

Materials and methods

Initially, all work areas in which glutaraldehyde was handled during the period of investigation (October 1983—March 1984) in a minor and a major Swedish hospital were identified by an exposure survey. A work area was included in the study if the average consumption of a commercial preparation of a 2 % solution of glutaraldehyde (Cidex[®] or Cidex-longlife[®]) exceeded 1 l/month. Exposure measurements were performed in all seven work areas in which glutaraldehyde was handled. The medical part of the study was restricted to those five work areas where glutaraldehyde was handled manually.

Assessment of symptoms

Prior to the data analysis, the exposed group was defined as those individuals handling glutaraldehyde at least once a month during the period of investigation. The unexposed reference group consisted of individuals handling glutaraldehyde less frequently than once a month.

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All persons working in the five selected areas ($N = 121$) were asked to complete a self-administered questionnaire irrespective of whether they were handling glutaraldehyde or not. There were questions on symptoms which had occurred within the last six months, as well as on smoking habits, atopy, hyper-reactivity, sick leave, work stress, work satisfaction, and the climate of cooperation at work. Occupational stress, well-being, and the climate of cooperation at work were measured with analogue rating scales (7). Information on the frequency of cold sterilization work with glutaraldehyde was also obtained with the questionnaire. In addition, the workers' attitude towards exposure to glutaraldehyde was measured with an analogue rating scale.

Assessment of exposure

Automatic cold sterilization machines are gradually replacing the manual handling of glutaraldehyde in many hospitals. Such machines are often bought to reduce the exposure to glutaraldehyde. In the work areas of our study, two automatic sterilization machines were in use. One machine was situated in a large room with proper ventilation (ward A), and the other was situated in a small room with poor ventilation (ward B). Although the medical part of the study was restricted to manual cold sterilization work, short-time exposure measurements were performed for both the manual and automatic cold sterilization work.

The short-time exposure measurements were made during 15-min periods of cold sterilization. In addition, long-term measurements during 3–4 h of exposed work were also made. In order to determine the background level of aldehydes in the studied work areas, long-term exposure measurements were also made for personnel working with tasks other than cold sterilization.

Since there were indications that formaldehyde might evaporate from an activated glutaraldehyde solution, in addition to glutaraldehyde, both these aldehydes were monitored. Personal sampling was done with sorbent tubes containing Amberlite XAD-2 coated with 2,4-dinitrophenylhydrazine (2,4-DNF) in the breathing zone of the workers, the air sampling rate being 0.25 l/min for the half-day samples and 1 l/min

for the short-time samples (15 min). This sampling technique enabled parallel and specific measurement of both formaldehyde (2) and glutaraldehyde (3). The sorbent tubes were analyzed by liquid chromatography at the National Board of Occupational Safety and Health, Umeå, Sweden. The breakthrough of glutaraldehyde under actual sampling conditions was studied through the sampling of a high concentration of glutaraldehyde with two sorbent tubes in series. The room temperature and relative humidity of the work areas were recorded with an Assman psychrometer.

Statistical methods

The analyses of the relationship between the exposure to glutaraldehyde and a certain symptom or individual factors was performed with the aid of the two-tailed chi-square test for fourfold tables or by the two-tailed Student's *t*-test (27). The odds ratio was also calculated (20). As proposed by Leidel et al (19), geometric means and geometric standard deviations of the exposure measurements were used in calculating the average exposure. The dose-response relationship between the frequency of exposure and the number of symptoms was analyzed by linear regression (27).

Results

The nonresponse rate of the study was 12 %. The proportion of smokers, females, or individuals with a history of atopy or nonspecific hyperactivity did not differ significantly between the glutaraldehyde-exposed group and the unexposed group (table 1). Neither did the mean age, the perceived degree of work stress, the attitude towards glutaraldehyde exposure or the climate of cooperation at work differ between the two groups, but the exposed group reported a significantly lower degree of well-being at work than the unexposed group ($P = 0.04$) (table 2).

In the exposed group, the prevalences of certain airway symptoms from the nose and throat were higher than in the unexposed group ($P < 0.05$) (table 3). 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

Table 1. Demographic data for the personnel with and without exposure to glutaraldehyde.

Parameter	Unexposed group ($N = 68$)		Exposed group ($N = 39$)	
	Number with symptoms	Percentage of total number	Number with symptoms	Percentage of total number
Current tobacco smoker	19	28	14	36
Proportion of females	62	91	36	92
Individuals with signs of atopy ^a	16	24	10	26
Nonspecific hyperreactivity ^b	14	21	10	26

^a Asthma, hay fever, or eczema in childhood.

^b Easily irritated eyes or respiratory tract during exposure to nonspecific irritants (tobacco smoke, exhaust gases, organic solvents).

Table 2. Certain demographic and psychological data for the personnel with and without exposure to glutaraldehyde. (NS = not significant)

Parameter	Unexposed group (N = 68)		Exposed group (N = 39)		2-Sided P-value (Student's t-test)
	Mean	SD	Mean	SD	
Age (years)	35	10	35	12	NS
Sick leave during last six months ^a	4	11	4	5	NS ^b
Stress at work ^c	58	24	67	18	NS
Climate of cooperation ^c	83	16	81	18	NS
Job satisfaction ^c	86	12	80	19	0.04
Attitude towards glutaraldehyde ^c	73	21	72	24	NS

^a Sick leave due to respiratory diseases.

^b Tested by Mann-Whitney's U-test.

^c Expressed as the percentage of the total length of the analogue rating scale.

Table 3. Symptom prevalence among persons with and without exposure to glutaraldehyde. (OR = odds ratio, NS = not significant)

Symptoms	Unexposed group (N = 68)		Exposed group (N = 39)		Odds ratio	2-Sided P-value
	Number with symptoms	Percentage of total number	Number with symptoms	Percentage of total number		
Eye irritation	12	18	11	28	1.8	NS
Swollen eyelids	4	6	4	10	1.8	NS
Nasal catarrh	7	10	10	26	3.0	0.04
Nasal obstruction	8	12	11	28	2.9	0.03
Dryness of the throat	1	16	12	31	2.3	NS
Smarting of the throat	6	9	10	26	3.6	0.02
Irritative cough	5	7	6	15	2.3	NS
Headache	12	18	14	36	2.6	0.04
Abnormal tiredness	18	26	16	41	2.0	NS
Sensation of getting a cold	13	19	14	36	2.4	NS
Nausea	2	3	5	13	4.9	< 0.05
Rashes on the hands	11	16	18	46	4.4	0.0009
Rashes on the face	7	10	2	5	0.5	NS
Itching on the hands	23	34	18	46	1.7	NS
Itching on the face	8	12	3	8	0.6	NS
Eczema	4	6	11	28	6.2	0.002

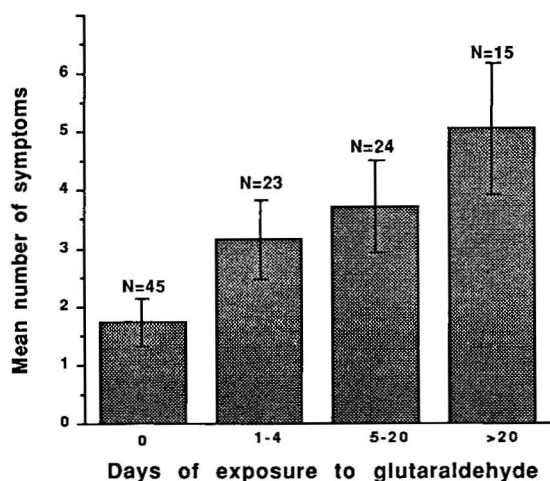


Figure 1. Mean (arithmetic) number of symptoms (range 0–16) experienced by the hospital personnel as a function of the frequency of exposure to glutaraldehyde. The frequency of exposure is expressed as the number of workdays with exposure to glutaraldehyde during the last six months. The vertical bars show the standard errors of the means.

the hands ($P < 0.01$). The prevalence of eye symptoms and facial skin symptoms did not differ between the two groups. A dose-response effect was found between the frequency of exposure to glutaraldehyde and the number of symptoms ($P < 0.01$) (figure 1).

The breakthrough study revealed that, at a glutaraldehyde concentration of 0.28 mg/m^3 , less than 7 % of the glutaraldehyde passed through the sorbent tube. In this test, the sampling conditions were similar to those used in the short-term field measurements (1.0 l of air/minute during 15 min at a temperature of 22°C and a relative humidity of 34 %).

In the short-time measurements during manual cold sterilization work with a 2 % solution of glutaraldehyde, the glutaraldehyde concentration was low in all the samples, and no formaldehyde exposure was detected (table 4). The geometric mean of the 16 glutaraldehyde measurements was 0.05 mg/m^3 with a geometric standard deviation of 3.4. The highest value (0.57 mg/m^3) was measured during the cold sterilization of a gastroscope.

The glutaraldehyde exposure levels during automatic cold sterilization are presented in table 5. The highest

exposure was measured in the room with poor general ventilation. The geometric mean of the six glutaraldehyde measurements was 0.05 mg/m³ with a geometric standard deviation of 3.3. No significant difference in airborne glutaraldehyde exposure was found between the automatic and manual sterilization work.

The long-term exposure of the exposed group and the background level in the work areas were below the actual detection limit of glutaraldehyde (<0.04 mg/m³) and formaldehyde (<0.04 mg/m³). Both the short-time and the long-term exposure measurements were performed during the winter, and the temperature of the work areas ranged between 22 and 25°C with a relative humidity of 21–37 %.

Discussion

Selection bias can occur as a result of both a low response rate and incorrect study design. The participation rate was high in our study (88 %) however, and therefore the probability of selection bias due to a loss of individuals from the study group was minimized. The design of the study was cross-sectional, and thus an accumulation of healthy individuals in the exposed group by time could occur. However, if people with symptoms caused by glutaraldehyde exposure leave cold sterilization work, the cross-sectional design will underestimate the true effect of exposure.

Another problem regarding the assessment of the validity is the possible response bias due to the awareness of exposure in the exposed group, as well as to the different attitudes towards exposure in the exposed and unexposed groups. Since many occupational exposures are coupled to work-specific operations known by the workers, it is often impossible to perform a "blind" field study on acute effects of such exposures. However, it is probable that a response bias due to the awareness of exposure would cause a general increase in the frequency of symptoms in the exposed group. In this study, however, an increased frequency was found for only some of the symptoms. In addition, the attitude towards exposure did not differ significantly between the exposed and unexposed groups. In conclusion, it is less probable that the results of our study are due to response bias.

Although the exposure to glutaraldehyde was intermittent and low compared to the Swedish occupational exposure limit, the exposed group reported an increased frequency of symptoms from the nose and the upper respiratory tract. Similar to formaldehyde, glutaraldehyde is highly soluble in water (1), and irritative airway symptoms can thus be expected to occur mainly in the upper respiratory tract (24). Activated glutaraldehyde buffered to a pH of 7.5–8.5 is reported to be a stronger irritant than unactivated glutaraldehyde solutions, which have weak acidity (1, 24). Acute irritation of the eyes, nose, and throat

Table 4. Short-time exposure (15 min) in manual cold sterilization work with an alkaline 2 % solution of glutaraldehyde.

Type of equipment	Glutaraldehyde ^a (mg/m ³)
Catheter	
Sterilization in an open vessel	0.04
Cystoscope	
Sterilization of cystoscope I	0.07
Sterilization of cystoscope II	0.14
Gastroscope	
Background level in the room	<0.01
Filling of glutaraldehyde into U-tube	0.12
Sterilization of gastroscope I	0.12
Sterilization of gastroscope II	0.07
Removal of glutaraldehyde from U-tube	0.02
Fiberscope	
Sterilization of fiberscope I	<0.04
Sterilization of fiberscope II	0.57
Sterilization of fiberscope III	<0.02
Otoscope	
Background level in the room	0.02
Sterilization of otoscope I	0.09
Sterilization of otoscope II	0.06

^a The Swedish occupational exposure limit (15 min) is 0.8 mg/m³ for glutaraldehyde.

Table 5. Short-time (15 min) exposure in automatic cold sterilization work in two hospital wards.

Type of operation/equipment	Glutaraldehyde ^a (mg/m ³)
<i>Ward A (proper ventilation)</i>	
Filling up and starting the machine	0.01
During the sterilization procedure	0.03
At the end of the sterilization procedure	0.02
<i>Ward B (poor ventilation)</i>	
During sterilization procedure I	0.13
During sterilization procedure II	0.13
Preparing and filling the glutaraldehyde	0.18

^a The Swedish occupational exposure limit (15 min) is 0.8 mg/m³ for glutaraldehyde.

has earlier been described in connection with simulated cold sterilization work. In this investigation, the mean glutaraldehyde exposure was measured to be 1.5 mg/m³ during a 12-min period (1). No information has been found in the literature on the acute effects of occupational exposure to glutaraldehyde below the present Swedish short-term occupational exposure limit of 0.8 mg/m³ (23). However, irritative airway symptoms have earlier been described in relation to low-level exposure to other aldehydes such as formaldehyde (6, 11, 18, 22, 26).

In addition to airway symptoms, general symptoms such as headache and nausea were also more common among the group exposed to glutaraldehyde than among the unexposed hospital group. Acute headache in connection with exposure to glutaraldehyde has earlier been described for short-time exposure above

the present occupational exposure limit of 0.8 mg/m³ (1). An increased prevalence of headache has also been described in relation to occupational exposure to low levels of formaldehyde (6, 22, 26).

In the present study, skin symptoms on the hands were more common in the exposed group than in the unexposed group. These skin symptoms could be either of an allergic or nonallergic type. All seven individuals who had consulted a dermatologist for skin symptoms were subjected to patch testing at a clinic of occupational dermatology, but no case of contact allergy to glutaraldehyde or other components in the commercial Cidex[®] solution was found (T Fisher, personal communication). Epicutaneous tests have shown that a 1 % solution of pure nonactivated glutaraldehyde is a nonirritating concentration (10). However, activated glutaraldehyde is a stronger irritant than nonactivated glutaraldehyde (1, 24). In view of this information, it is probable that the greater number of skin symptoms found in this investigation was caused by primary irritative effects of the activated 2 % solution of glutaraldehyde.

The exposure measurements showed that the exposure during both manual and automatic cold sterilization work was low, in all cases below the present Swedish short-term occupational exposure limit of 0.8 mg/m³. No measurable emission of formaldehyde was observed from the activated glutaraldehyde solution. The low degree of exposure could be explained by the low volatility of glutaraldehyde. In the literature, the vapor pressure at 20°C over a 2 % solution of glutaraldehyde is reported to be 0.0012 mm Hg (0.16 Pa) (1), this value corresponds to a saturation concentration of 6.4 mg/m³.

Our investigation has demonstrated that irritative airway effects and headache may occur at exposure levels of glutaraldehyde far below the present Swedish short-term occupational exposure limit. Although contact allergy to glutaraldehyde seems to be relatively uncommon, we have found that irritative skin symptoms are frequently reported among personnel who handle an activated 2 % solution of glutaraldehyde.

The introduction of automatic cold sterilization equipment would lessen the skin contact to glutaraldehyde and thus decrease skin symptoms. However, in order to minimize the airborne exposure to glutaraldehyde also, the automatic sterilization equipment should be placed in a room with good general ventilation. In hospital units where manual cold sterilization is still used, local exhaust ventilation should be installed, and skin contact with the glutaraldehyde should be minimized by the use of suitable protective gloves.

References

1. American Conference of Governmental Industrial Hygienists. Documentation of the threshold limit values. Fourth edition. Cincinnati, OH 1980, pp 204–205.
2. Andersson K, Hallgren C, Levin J-O, Nilsson C-A. Chemosorbent sampling and analysis of formaldehyde in air: Influence on recovery during the simultaneous sampling of formaldehyde, phenol, furfural and furfuryl alcohol. *Scand J Work Environ Health* 7 (1981) 282–289.
3. Andersson K, Hallgren C, Levin J-O, Nilsson C-A. Solid chemosorbent for sampling sub-ppm levels of acrolein and glutaraldehyde in air. *Chemosphere* 10 (1981) 275–280.
4. Bardazzi F, Melino M, Alagna G, Veronesi S. Glutaraldehyde dermatitis in nurses. *Contact Dermatitis* 14 (1986) 319–320.
5. Benson W. Exposure to glutaraldehyde. *J Soc Occup Med* 34 (1984) 63–64.
6. Bernstein RS, Stayner LS, Elliot LR, Kimbrough R, Falk H, Blade L. Inhalation exposure to formaldehyde: An overview of its toxicology, epidemiology, monitoring and control. *Am Ind Hyg Assoc J* 45 (1984) 778–785.
7. Bond A, Lader M. The use of analogue rating scales in rating subjective feelings. *Br J Med Psychol* 47 (1974) 211–218.
8. Clark EG. Risk of isothiazolinones. *J Soc Occup Med* 37 (1987) 30–31.
9. Cronin E. Clinical patterns of hand eczema in women. *Contact Dermatitis* 13 (1985) 153–161.
10. Fregert S. Manual of contact dermatitis. Second edition. Munksgaard, Copenhagen 1981.
11. Gamble J. Effects of formaldehyde on the respiratory system. In: Gibson JE, ed. *Formaldehyde toxicity*. Hemisphere Publishing, Washington, DC 1983, pp 175–197.
12. Goncalo S, Brandao M, Pecegueiro M, Moreno A, Sousa I. Occupational contact dermatitis to glutaraldehyde. *Contact Dermatitis* 10 (1984) 183–184.
13. Gorman SP, Scott EM, Russell AD. A review: Antimicrobial activity, uses and mechanism of action of glutaraldehyde. *J Appl Bacteriol* 48 (1980) 161–190.
14. Hansen K. Glutaraldehyde occupational dermatitis. *Contact Dermatitis* 9 (1983) 81–82.
15. Hansen K. Occupational dermatoses in hospital cleaning women. *Contact Dermatitis* 9 (1983) 343–351.
16. Jordan W, Dahl M, Albert H. Contact dermatitis from glutaraldehyde. *Arch Dermatol* 105 (1972) 94–95.
17. Juhlin L, Hansson H. Topical glutaraldehyde for planar hyperhidrosis. *Arch Dermatol* 97 (1968) 327–330.
18. Kilburn KH, Seidman BC, Warshaw R. Neurobehavioral and respiratory symptoms of formaldehyde and xylene exposure in histology technicians. *Arch Environ Health* 40 (1985) 229–233.
19. Leidel NA, Busch KA, Lynch JR. Occupational exposure sampling strategy manual. Department of Health Education and Welfare, Cincinnati, OH 1977. [DHEW Publ (NIOSH) 77–173].
20. Lilienfeld AM, Lilienfeld DE. Foundations of epidemiology. Second edition. Oxford University Press, New York, Oxford 1980.
21. Maibach H. Glutaraldehyde: Cross-reactions to formaldehyde? *Contact Dermatitis* 1 (1975) 326.
22. Main DM, Hogan TJ. Health effects of low-level exposure to formaldehyde. *J Occup Med* 25 (1983) 896–900.
23. National Board of Occupational Safety and Health. Code of statutes. Stockholm 1987. (AFS 1987: 12).
24. National Research Council Committee on Aldehydes. Formaldehyde and other aldehydes. National Academy of Sciences Press, Washington, DC 1981.
25. Norbäck D. Emission av kemikalier från självkopierande papper [Emission of chemicals from carbonless copy papers]. Arbets- och hälsöversikt, Stockholm 1983, pp 51–62. (Arbete och hälsa 1983: 37).
26. Olsen JH, Dössing M. Formaldehyde induced symptoms in day care centers. *Am Ind Hyg Assoc J* 43 (1982) 366–370.
27. Owen DB. Handbook of statistical tables. Pergamon

- Press, London 1962.
28. Snyder RW, Cheatele EL. Alkaline glutaraldehyde an effective disinfectant. *Am J Hosp Pharm* 22 (1965) 321—327.
29. Stonehill AA, Krop S, Borick PM. Buffered glutaraldehyde: A new chemical sterilizing solution. *Am J Hosp Pharm* 20 (1963) 458—465.
30. Weaver J, Maibach H. Dose response relationships in allergic contact dermatitis: Glutaraldehyde-containing liquid fabric softener. *Contact Dermatitis* 3 (1977) 65—68.

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