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Occupational formaldehyde exposure and the nasal mucosa

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SUMMARY

This study was undertaken to evaluate the possible cytotoxic effect of formaldehyde on the nasal mucosa in man. 38 men with an average age of 38 years and average exposure time of 10.5 years were studied. They were exposed to formaldehyde when processing laminae. All men passed a medical examination and a nasal biopsy. The histological findings were scored, 0–8, according to a system proposed by Torjussen. The findings were compared with a non-exposed reference group of 25 men (mean age 35 years). 35% of the exposed were smokers compared to 48% of the non-exposed. The average histological score was 2.8 for the exposed versus 1.8 for the non-exposed ($p < 0.05$, Wilcoxon). The more common findings in the exposed were loss of cilia, goblet cell hyperplasia and squamous metaplasia. In four cases (11%) there was a mild dysplasia. Smoking had a slight modifying effect on the histological picture. The results indicate that the suspected precancerous findings in animal studies after exposure to formaldehyde might also be present in workers exposed to formaldehyde at relatively low levels.

Formaldehyde is a widely used chemical, with a world production of about 5 billion ton per year. It is used in the production of specific resins and in a variety of other industries and professions, including hospitals and dentistry (Siegel et al., 1983; Lewis and Chestner, 1981). Formaldehyde is a colourless, water soluble gas and highly reactive, with well known acute toxic effects, i.e. irritation of mucous membranes and allergic sensitation of the skin. Following long-term exposure, mutagenic effects have been demonstrated in vitro (Temcharon and Thilly, 1983) and carcinogenic effects in experimental animals (Swenberg et al., 1980; Albert et al., 1982). During the last years, there has been a growing concern about the possible human cancer risk posed by exposure to formaldehyde.
In some epidemiologic studies of persons exposed to formaldehyde an increased risk of cancer (including cancer of the nasal cavity and paranasal sinuses) has

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been observed, whereas other studies have not demonstrated an association between formaldehyde exposure and cancer (c.f. Levine et al., 1984; Hayes et al., 1986).

Most authors consider cancer caused by formaldehyde exposure unlikely in sites other than those in direct contact with the agent. The nose is such a contact organ for formaldehyde and is also easily explored and investigated. Studies (Swenberg et al., 1980; Albert et al., 1982) showing an increase of nasal carcinoma among rodents also revealed a dose dependent and reversible change of the nasal mucosa e.g. rhinitis, epithelial dysplasia and squamous metaplasia. Some of these irritative effects might be regarded as precancerous lesions and could be an early sign of exposure to a carcinogen (Boysen et al., 1984).

The aim of this study was to evaluate if occupational exposure to formaldehyde causes similar changes of the nasal mucosa in man, and whether there is a difference between smokers and never-smokers in this respect.

SUBJECT AND METHODS

Workers at a plant processing laminae and with occupational exposure to formaldehyde were invited to take part in a health examination. Those accepting underwent a medical examination, including a nasal biopsy.

The participants were interviewed according to a questionnaire and asked about exposure time, smoking habits, earlier diseases, duration and intensity of different symptoms from the respiratory tract, and their relation to work-place exposure. In a clinical examination of the nose and nasopharynx changes from normal were noted.

After application of local anesthesia biopsies with a diameter off 2 mm were taken by a small forceps 1 cm behind the anterior edge of the inferior turbinate. The specimens were fixed in 10% neutral buffered formalin and embedded in paraffin, cut at various levels and stained with haematoxylin and eosin. The sections, with covered labels, were examined twice by the pathologist with an interval of three weeks and without access to clinical or occupational information. The morphological grading was performed according to the scoring system proposed by Torjussen et al. (1979) (Table 1).

The histological findings were compared with a referent group of 25 men, selected with regard to age and smoking habits but without any known nasal disease or industrial exposure.

Difference in histological score between the groups was tested by the Wilcoxon non-parametric test.

The working places were normally ventilated and the workers used no personal protections. Hygienic measurements from 1975 and onwards had revealed levels (TWA) of formaldehyde in air in the range of 0.5–1.1 mg/m^3.

Table 1. Histological characteristics and scores used for grading the nasal mucosa.

histologic characteristics	point score
normal respiratory epithelium	0
loss of cilia	1
mixed cuboid/squamous epithelium, metaplasia	2
stratified squamous epithelium	3
keratosis	4
"budding" of epithelium	add 1
mild or moderate dysplasia	6
severe dysplasia	7
carcinoma	8

RESULTS

The exposed group comprised 38 men whose mean age at the time of examination was 38 (range 21–62). The period of exposure ranged from one to 30 with a mean of 10.5 years (range 1–30). Fifteen (39%) were smokers, 1 (2%) ex-smoker (stopped smoking ten years before examination) and 22 (59%) had never smoked (Table 2). In the referent group of 25 men whose mean age was 35 (range 25–60), there were 12 (48%) smokers, 4 (10%) ex-smokers and 9 (36%) never-smokers. Subjective complaints disclosed a high frequency of symptoms from the nose and eyes (Table 3). Nasal symptoms, mainly a running nose and crusting, related to the exposure to formaldehyde, were at hand in 50% of the subjects whereas 66% complained of running eyes when exposed to formaldehyde.

Table 2. Number of examined men, age, exposure time and smoking habits.

	exposed	referents
number	38	25
age (years) mean	38	35
range	21–62	25–60
exposure time (years) mean	10.5	-
range	1–30	
smokers	15	12
ex-smokers	1	4
never-smokers	22	9

Table 3. Frequency of exposure related symptoms from the eyes and upper airways of the exposed.

symptoms	%
running eyes	66
running nose	50
sore throat	53

The rhinoscopial findings were a grossly normal nasal mucosa in 74% of the cases, whilst 36% of the exposed workers had swollen and/or dry changes of the nasal mucosa.

The histological evaluation of the exposed is presented in Table 4. In only 3 (8%) of the cases there was a normal, ciliated pseudostratified epithelium. Four (11%) men had a loss of cilia and goblet cell hyperplasia, 27 (71%) had squamous metaplasia and in four cases (11%) there was a mild dysplasia.

The mean histological score was 2.8 for the exposed, significantly higher than the 1.8 for the unexposed, $p<0.05$ (Table 5). The histological score was about the same regardless of duration of exposure. Exposed smokers had a higher score than never-smokers, although this did not attain statistical significance (Table 6). There was no difference in exposure time to formaldehyde between smokers and never-smokers.

DISCUSSION

The results of the present study indicate that similar dysplastic changes as observed in animal studies after exposure to formaldehyde may be present

Table 4. Distribution of the histological score of the exposed.

point score	no	%
0	3	8
1	4	11
2	12	31
3	8	21
4	7	18
5	0	0
6	4	11
7	0	0
8	0	0

Table 5. Average histological score in exposed and referent groups.

	average score
exposed	2.8
referents	1.8

$p<0.05$

Table 6. Number of men, age, exposure time and average histological score for the exposed, smokers and never-smokers.

	smokers	never-smokers
number	15	22
age (years) mean	38	37
exposure time (years) mean	9	9
score	3.3	2.4

among workers with occupational exposure to formaldehyde in the range of 0.5–1.0 mg/m^3 (to be compared to the Swedish TLV of 1.0 mg/m^3). A non-carcinogenic response at low levels of exposure is in accordance with the animal experiments (Albert et al., 1982) where nasal cancer in rats and mice were induced after inhalation of 14 ppm formaldehyde for 6h/day, 5 days/week for two years whereas dose-dependent and reversible changes of metaplasia and dysplasia were found at an exposure level of 2 ppm.

The design of the study is cross-sectional and 92% of the invited took part. Since the participation was volontarily it might be possible that only people with symptoms from the upper airways took part, i.e., a selection bias could be at hand. On the other hand if people with symptoms caused by the workplace exposure leave the plant, the cross-sectional design will underestimate the true effect of exposure.

Another explanation for the findings could be that the unexposed reference group was too healthy and had an unusually low score. However, the average score of 1.8 is higher than that of 1.3 found in the non-industrial reference group of 45 persons used by Torjussen et al. (1979). This indicates that our reference group is representative of the non industrially exposed population.

Other reports have suggested that similar pathological changes of the nasal mucosa might be due to age, smoking and occupational exposures e.g. wood dust, nickel, oil mist, solvents and dicumylperoxide (Boysen et al., 1984; Torjussen et al., 1979; Irander et al., 1980; Hellquist et al., 1983; Hansson and Petruson, 1986). In the present study the influence of age and smoking was controlled by the similarity between the exposed and referents in this respect and other occupational factors than formaldehyde could be ruled out. We thus interpret the histopathological changes as due to exposure to formaldehyde and reflecting the current exposure situation. However, smoking might have a modyfying and aggravating effect on the histological picture, reflected in a higher mean histological score for smokers despite the same length of exposure to formaldehyde as the never-smokers.

Milder changes in the nasal mucosa lead to more or less severe symptoms but no serious illness, while higher degrees of alterations in the mucosa, i.e. dysplasia should be considered a precancerous lesion (Boysen et al., 1984). We found a mild dysplasia in four of the exposed workers of whom two were smokers and two never-smokers. The average exposure time for the four men was six years, with a range of one to eleven years. Although there seems to be no dose-response relationship, the present findings of dysplasia could be an effect of exposure to formaldehyde since it is reported in the animal experiments that exposure to high concentrations of formaldehyde for a few hours are likely to cause greater damage to the mucosa than longer exposures at lower concentrations. It might well be

that those four men with dysplasia had had a different and higher exposure than the other men, with more peak exposures to formaldehyde. Unfortunately it was not possible to estimate the individual exposure of each man.

In conclusion, this study indicates that exposure to low levels of formaldehyde, i.e. levels usually found in industry, causes a high frequency of symptoms from the eyes and upper airways, metaplastic changes of the nasal mucosa, probably as an irritant response and dysplastic changes of the nasal mucosa, regarded as a suspected precancerous lesion. Smoking seems to have a synergistic effect.

The experiences from this and our other studies (Hellquist et al., 1983; Irander et al., 1980) are that the examination and biopsies are easily performed at the industrial plant, with a minimum of loss in time (or blood) for the examined workers. Histological examination of the nasal mucosa might therefore be an useful screening instrument in occupational groups with exposure to a suspected nasal carcinogen.

ZUSAMMENFASSUNG

Diese Untersuchung wurde unternommen um eventuelle cytotoxische Veränderungen von Formaldehyde an dem Nasenschleimhaut zu bewerten. 38 Männer im Durchschnittsalter von 38 Jahren und durchschnittlicher Expositionszeit von 10,5 Jahren waren beobachtet. Sie wurden von Formaldehyde exponiert während der Herstellung von Holzspanplatten. An der Männern wurde eine medizinische Untersuchung und eine Nasenbiopsy vorgenommen. Die histologischen Werte wurden von 0 bis 8 gesetzt nach einem von Torjussen vorgeschlagenem System. Die Werte wurden mit einer nicht-exponierten Referenzgruppe von 25 Männer im Durchschnittsalter von 35 Jahren verglichen. 35% der exponierten Gruppe waren Raucher im Vergleich zu 48% der nicht exponierten Referenzgruppe. Die durchschnittlichen histologischen Werte der exponierten Gruppe waren 2.8 gegen 1.8 für die nicht-exponierte Referenzgruppe ($p<0.05$, Wilcoxon). In der exponierten Gruppe wurde allgemeiner Mangel an Cilia, Bechercell Hyperplasia und schuppiges Metaplasia festgestellt. In vier Fälle (11%) wurden eine leichte Dysplasia gefunden. Die histologischen Befunde deuten darauf, dass das Rauchen nur einen unbedeutenden Einfluss hat. Die Resultate deuten darauf hin, dass die verdächtigen prekancerogenen Befunde in Tierstudien nach Exposition von Formaldehyde auch bei Arbeitern, die einem relativ niedrigem Niveau von Formaldehyde exponiert sind, vorkommen kann.

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