Nasal mucosa in workers exposed to formaldehyde: a pilot study

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Abstract

This study evaluates the histological changes, especially the presence of possible pre-cancerous lesions, in the nasal mucosa of workers exposed to formaldehyde. Nasal biopsies of 37 workers occupationally exposed to formaldehyde for more than five years and 37 age matched referents showed a higher degree of metaplastic alterations in the former group. In addition, three cases of epithelial dysplasia were observed among the exposed. These results indicate that formaldehyde may be potentially carcinogenic to man. Combination of this finding with the inconclusive epidemiological studies suggests that formaldehyde is a weak carcinogen and that occupational exposure to formaldehyde alone is insufficient to induce nasal cancer.

The inhalation of formaldehyde has been shown to induce squamous cell carcinoma in the nasal cavity of rats at exposure levels ranging from 6 to 14.3 ppm^{1,2} and mice at an exposure level of 14.3 ppm.³ Although these findings aroused considerable concern about the possible long term effects in man, epidemiological studies conducted to date have not provided unequivocal evidence that exposure can induce nasal or other types of cancer.^{4,5}

Like most other types of epithelial malignancies, it is reasonable to assume that nasal cancer is preceded by preneoplastic states and that the prevalence of such lesions is considerably higher than that of cancer. Experimental studies have shown that animals exposed to formaldehyde concentrations of 2 ppm or more develop dysplasia and metaplasia of

the nasal mucosa.^{2,3} Nasal epithelial dysplasia has also been described in man and, almost without exception, these lesions have been observed in occupations with a known increased incidence of nasal cancer such as nickel workers⁶⁻⁸ and furniture workers.^{9,10} Considerable evidence exists that these lesions should be considered as preneoplastic.¹¹ Screening for dysplasia of the nasal mucosa therefore seems to be a sensitive method for assessing any possible risk from formaldehyde.

In the present study we have investigated, by means of nasal epithelial biopsies, whether nasal epithelial dysplasia is present in workers occupationally exposed to formaldehyde. Moreover, we have evaluated the significance of rhinoscopic examinations and recorded subjective nasal complaints.

Material and methods

Workers employed at a chemical company, located just outside Oslo, that produces formaldehyde and formaldehyde resins were asked to take part in this study. Since its inception in 1950 the production process has undergone several changes, resulting in a decrease of atmospheric formaldehyde. High exposure concentrations were experienced during the 1950s and 1960s. During the past five years

Table 1 Grading of intensity to formaldehyde exposure

Group	Description of exposure	Airborne concentration of formaldehyde	No of workers exposed
1	Occasional exposure (not daily) up to level of olfactory detection	0.5-2 ppm	0
2	Not daily, but frequent exposure exceeding the level of irritation		12
3	Daily exposure up to level of olfactory detection		17
4	Daily exposure above the level of irritation	> 2 ppm	5
5	Daily exposure inducing discomfort		3

The level of olfactory detection is about 0.05-1.0 ppm formaldehyde. Concentrations of 0.1-3.0 ppm causes irritation of the conjunctiva, nose, and pharynx. Discomfort increases with higher concentrations and few tolerate exposure exceeding 4-5 ppm for more than 10-20 minutes. At concentrations of 10-20 ppm breathing becomes difficult. Exposure above 20 ppm may cause pulmonary oedema.¹²⁻¹⁴

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systematic measurements of atmospheric formaldehyde have been performed in various parts of the workplace. Exposure before 1980 was assessed by the plant health officer according to knowledge of the production process, recent measurements, and previous and present subjective sensations experienced by the workers. The level of exposure to which the workers presumably had been exposed was accordingly divided into five groups (table 1).

SUBJECTS

Thirty seven workers, half the workforce occupationally exposed to formaldehyde, volunteered to take part in the study. The control group consisted of 37 age matched subjects without overt nasal disease or occupations with known or suspected relations to nasal cancer. The controls were selected from the office staff of two chemical industries in Oslo, laboratory personnel at the Norwegian Radium Hospital, and outpatients at the ear, nose, and throat department, National Hospital, Oslo.

Table 2 shows the mean age and range, and duration of exposure. All participants were interviewed using a questionnaire containing detailed information about their occupational history, smoking habits, previous and present nasal complaints, and symptoms suggesting nasal allergy. Workers who had stopped smoking for less than a year before the examination were considered as smokers.

COLLECTION OF SAMPLES

After the application of local anaesthesia (tetracaine 2%, adrenaline 0.1%) to the mucosal surface for about five minutes, biopsy specimens were taken from the anterior curvature of the middle turbinate of the nasal cavity that was judged to have the best air flow.⁶ The specimens were fixed in 4% buffered

Table 2 Mean age and duration of exposure

	No	Age		Years employed	
		Mean	Range	Mean	Range
Exposed	37	51	27-66	20	3-36
Controls	37	49	35-66	—	—

formaldehyde, processed by routine methods, and the sections stained with haematoxylin and eosin.

HISTOLOGICAL EXAMINATION

All sections were examined independently by two of the authors (VA and MB) without access to clinical or occupational information. The histological classification and scoring of the epithelial changes were performed according to previous studies.^{6,7,9} The different types of epithelia are shown in figs 1-5 and the scores given to each type in table 3. Specimens showing more than one type of epithelium were graded according to the highest score.

RHINOSCOPICAL FINDINGS

The rhinoscopic appearance of the nasal mucosa

Table 3 Types of nasal epithelium and histological score

Types of epithelia	Histological score
Pseudostratified columnar epithelium	0
Stratified cuboidal epithelium	1
Mixed stratified cuboidal/stratified squamous epithelium	2
Stratified squamous epithelium, non-keratinising	3
Stratified squamous epithelium, keratinising	4
Dysplasia	5

Figure 1 Pseudostratified epithelium with ciliated cells and goblet cells. (Scale bar = 25 μ m.)

Figure 2 Stratified cuboidal epithelium composed of several layers of cuboidal cells and lacking ciliated cells. (Magnification as in fig 1.)

was scored according to the presence of the following characteristics: no abnormalities: 0, hyperplastic nasal mucosa: 1, and polypoid nasal mucosa: 2.⁹

STATISTICS

The Wilcoxon rank sum test was used to compare the histological findings in the two groups and to evaluate whether smoking, age, and duration and degree of exposure influenced the histological findings. The Chi-squared test was used to compare the rhinoscopic findings and subjective complaints.

Results

The groups did not differ as to environmental

influences, smoking habits, and previous nasal disease. Table 4 shows that the degree of metaplastic alterations was more pronounced among the exposed workers than the controls, giving mean histological scores of 1.9 and 1.4 respectively ($p > 0.05$). Three

Table 4 Distribution of the histological score of exposed and control groups

	No	Histological score						
		0	1	2	3	4	5	Mean
Exposed	37	3	16	5	9	1	3	1.9
Controls	37	5	17	10	5	0	0	1.4

Figure 3 Mixed stratified cuboidal/stratified squamous epithelium consisting of several layers of cuboidal cells covered by a thin layer of flattened cells. (Magnification as in fig 1.)

Figure 4 Stratified squamous epithelium with several layers of squamous cells overlying cells with distinct cell borders. (Magnification as in fig 1.)

cases of epithelial dysplasia, all of the squamous type, were observed in the formaldehyde group. These workers had been exposed daily to formaldehyde at concentrations ranging from 0.5 to 2 ppm (group 3) for more than 22 years. Two of the exposed workers had previously been exposed to wood dust for some years and three were still exposed to some wood dust; none of these had epithelial dysplasia. The histological scores were somewhat higher among smokers than non-smokers, the scores further increased with age, degree, and duration of exposure, but the differences did not reach statistical significance.

Table 5 shows the rhinoscopic findings. The incidence of hyperplastic nasal mucosa was higher in the exposed than in the control group but the

difference was not statistically significant. The incidence of subjective nasal complaints was considerably higher in the exposed subjects ($p < 0.01$) (table 6).

Discussion

Formaldehyde is ubiquitous and the background

Table 5 Rhinoscopic findings in exposed and control groups

	Normal	Hyperplastic nasal mucosa	Polypoid nasal mucosa
Exposed	28	9	0
Controls	33	4	0

Figure 5 Dysplasia of the squamous type with nuclear and cellular pleomorphism and partial loss of polarity. (Magnification as in fig 1.)

Table 6 Subjective nasal complaints

	Total No	Subjects with complaints	Recurrent epistaxis	Nasal stenosis	Irritation
Exposed	37	16*	5	7	5
Controls	37	2	2	0	0

*p < 0.01.

exposure level is about 0.01 ppm.¹³ Unlike most other carcinogens, formaldehyde is also a normal constituent of living cells.¹⁵ It is also a component of cigarette smoke at concentrations as high as 40 ppm.¹⁵ Occupational exposure to formaldehyde exceeding values of 1 ppm has been associated with formaldehyde production, resin and plastic production, clothing manufacture, plywood and particle board production, and wood furniture manufacture. It is also associated with embalming and pathology and biology laboratories.⁵ It is estimated that in the United States about 1.6 m people are occupationally exposed to formaldehyde.⁴ Concern has also been expressed on the possible health effects of formaldehyde emission from products such as plywood panelling and insulation with formaldehyde foam.¹⁶

Many epidemiological studies have been performed in the past years.⁵ Among these, only three case-control studies have suggested an association between exposure to formaldehyde and nasal cancer.¹⁷⁻¹⁹ In two of these studies the subjects had also been exposed to wood dust, a known nasal carcinogen²⁰; in the third a possible association was found in printers. Accordingly, there was no exposure to known or suspected carcinogens and there is no clear evidence of increased frequency of nasal cancer due to exposure to formaldehyde alone.

The fact that epithelial dysplasia has almost exclusively been described in occupational settings with a known increased incidence of nasal carcinoma suggests that it should be interpreted as a preneoplastic lesion.¹¹ This interpretation is supported by morphological similarities with known preneoplastic lesions in the lower respiratory tract.

Assuming that nasal epithelial dysplasia is a preneoplastic lesion and that it has a higher prevalence than carcinoma, its presence in evaluating a possible carcinogenic risk becomes clear. In addition to a higher incidence of squamous metaplasia, we found three cases of nasal epithelial dysplasia of the squamous type among workers with prolonged daily exposure at concentrations between 0.5 and 2 ppm. The study is, however, too small to draw any conclusions as to the significance between the histological findings and the duration or degree of exposure. Metaplastic changes themselves are generally considered as non-specific, being induced by extrinsic factors such as temperature, humidity, dust, and chemicals; they also increased with age and

should not be considered preneoplastic. Metaplasia might, however, be a prerequisite for the development of dysplasia since dysplastic lesions are, as a rule, found within areas of squamous metaplasia.²¹

Only limited areas of the nasal mucosa may be examined with a biopsy. The anterior curvature of the middle turbinate was chosen for several reasons. This region is easily identified and reached with biopsy forceps. Moreover it is believed that tumours favour this region^{8,22} because particles have a tendency to deposit here.²³ In this context it should be noted that in experimental studies the most pronounced degree of epithelial alterations have been seen in the anterior part of the nasal cavity.³ Both in experimental animals and in man exposure to formaldehyde inhibits mucociliary function, which may further enhance its adverse effects.^{24,25}

Since only small areas of the nasal mucosa may be examined histologically the number of dysplastic lesions found in this study cannot be expected to reflect the real prevalence of dysplasia. Based on follow up studies in nickel workers it has been calculated that the real incidence of dysplasia is two to four times that detected in single biopsies.⁶ Accordingly, the biopsy method is of limited value for identifying an individual risk but appears to be useful in identifying and possibly also monitoring groups of people exposed to known or suspected nasal carcinogens.⁶⁻¹⁰ With cytological methods a larger area of the nasal mucosa may be examined. A recent study suggests that a higher incidence of epithelial alterations may be detected with this method than with small biopsies.²⁵ The cytological method may therefore be the method of choice in future screening for nasal epithelial alterations.^{11,26}

The fact that epithelial dysplasia has been observed in formaldehyde workers, as shown by others,^{27,28} supports the concept that formaldehyde might be a carcinogen in man. The inconclusive evidence from epidemiological studies, however, indicates that formaldehyde in the concentrations reached in occupational settings seldom induces nasal cancer. Formaldehyde may, however, interact with other carcinogens or act as a promoter.

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