AN EVALUATION OF THE EXPOSURE OF STUDENTS AND STAFF TO FORMALDEHYDE VAPOUR IN THE HUMAN ANATOMY LABORATORY OF THE FACULTY OF MEDICINE, UNIVERSITY OF NATAL

by

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ABSTRACT

The aims of the study were to review the literature on the currently known adverse health effects of formaldehyde vapour exposure, to measure environmental formaldehyde levels before and after engineering controls were implemented, to measure symptoms of formaldehyde exposure when compared to non - exposed controls and to evaluate the effectiveness of engineering controls in reducing the symptoms associated with formaldehyde vapour exposure in anatomy students at the Faculty of Medicine, University of Natal.

Pre and post intervention environmental monitoring surveys were conducted over the period July 1993 to September 1995 in the aforementioned Human Anatomy Laboratory using passive diffusion badges which were then analyzed by an approved laboratory in Johannesburg. Ambient air temperature, humidity and ventilation rates were measured simultaneously using appropriate instruments. Self-administered questionnaires, relating to the symptoms of exposure to formaldehyde vapours, were obtained from all anatomy students over a two year period before or after as well as during their exposure to the laboratory environment, as well as from all exposed staff members (including their control group). Nasal epithelial scrapings of staff members and a control group were subjected to cytological examination by the Cytology Department of the Provincial Pathology service, at the pre - intervention phase.

The environmental monitoring data of 1993 and 1994 indicated that the ambient levels of formaldehyde vapour exceeded the American (ACGIH) Threshold Limit Value (TLV) and thus posed a potential health risk to students and staff, this was due to inadequate ventilation in the Human Anatomy Laboratory.

An intervention in terms of ventilation controls was implemented and proved to be effective in reducing formaldehyde vapour levels and reported symptoms in the cohorts studied, comparing each group to themselves, however the reported symptom levels did not drop significantly in the group exposed after the intervention compared to the group surveyed at the pre - intervention phase. Whether this reduction is sufficient to prevent long term health effects such as neoplasms and sensitization remains to be established. Hence it is recommended that alternative control methods should be considered.

SUPPORTING SERVICES

1. The South African Bureau of Standards (SABS) approved laboratories of the 3M company in Johannesburg performed the analysis of the formaldehyde vapour samples, collected by passive diffusion badges.

2. The Cytology Department of the Provincial Pathology services in Durban was responsible for the fixation and cytological analysis of the nasal epithelial samples.

3. Statistical planning and analyses were done by the Institute for Biostatistics of the Medical Research Council as well as Mr. Charles Robert.

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PREFACE

This study represents original work by the author and has not been submitted in any form to another University. Where use was made of the work of others it has been duly acknowledged in the text.

The research described in this dissertation was carried out under the auspices of the Department of Community Health, University of Natal and was supervised by Dr. AL Raynal.

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CONTENTS

		PAGE
1.	INTRODUCTION	1
2.	LITERATURE REVIEW	6
2.1	IRRITANT AND GENERAL HEALTH EFFECTS ASSOCIATED WITH FORMALDEHYDE EXPOSURE	6
2.1.1	Animal studies	6
2.1.1.1	Acute	6
2.1.1.2	Low level exposure	7
2.1.2	Human studies	8
2.1.2.1	General effects	8
2.1.2.2	Effects upon the respiratory system	11
2.1.2.3	Carcinogenic potential	17
2.1.2.3.1	Animal studies	19
2.1.2.3.2	Human studies	22
2.2	EFFECT OF FORMALDEHYDE EXPOSURE UPON THE IMMUNE SYSTEM.	36
2.3	FORMATE LEVELS IN URINE AS AN INDICATOR OF FORMALDEHYDE EXPOSURE.	39
2.4	FORMALDEHYDE EXPOSURE IN ANATOMY LABORATORIES AND MORTUARIES.	42
2.5	ENVIRONMENTAL SAMPLING OF FORMALDEHYDE.	49
2.6	BIOLOGICAL MONITORING OF EXPOSURE TO CONTAMINANTS.	52
2.7	ENVIRONMENTAL CONTROL	54
2.7.1	Engineering Control	54
2.7.2	Administrative controls	56
2.7.3	Personal protective equipment	57
2.8	SUMMARY CONCLUSIONS	58
3.	Methods	59
3.1	STUDY DESIGN	59
3.1.2	Study populations	61

3.1.2.1	group 1	61
3.1.2.2	group 2	61
3.1.2.3	group 3	62
3.1.3	Study methods	62
3.1.3.1	Environmental measurements	62
3.1.3.1.1	Ventilation	63
3.1.3.1.2	Formaldehyde vapour sampling	63
3.1.3.1.3	Symptom frequency study	66
3.1.3.1.4	Biological monitoring	67
3.2	REDUCTION OF BIAS	68
4.	RESULTS	70
4.1	DEMOGRAPHIC DATA	70
4.1.1	Group 1	70
4.1.2	Group 2	71
4.1.3	Group 3	72
4.1.4	Comparison of group 2 and group 3	73
4.1.5	Comparison of group 1 and group 2 of 1994	74
4.2	ENVIRONMENTAL MEASUREMENTS	75
4.2.1	Air flow	75
4.2.2	Temperature and relative humidity	76
4.2.3	Formaldehyde vapour concentrations	76
4.3	QUESTIONNAIRE DATA	82
4.4	CYTOLOGICAL EXAMINATION OF NASAL EPITHELIAL SCRAPINGS	91
4.5	SUMMARY OF RESULTS	92

5.	DISCUSSION OF RESULTS	93
5.1	LIMITATIONS OF THE STUDY	93
5.2	SIGNIFICANCE OF RESULTS	94
6.	CONCLUSIONS	100
6.1	RECOMMENDATIONS	100
6.2	RECOMMENDATIONS WHILE FORMALDEHYDE IS USED AS A PRESERVATIVE	101
7.	REFERENCES	102

TABLES

TABLE	TITLE	PAGE
I	Human adverse effects associated with the inhalation of various concentrations of formaldehyde vapour	9
II	Observed and expected deaths for professional and industrial workers exposed to formaldehyde (with 95% confidence limits)	25
III	IARC classification of carcinogenicity	33
IV	Formaldehyde vapour concentrations in an anatomy laboratory	43
V	Relationship of formaldehyde exposure to acute symptoms during exposure, based on analysis of paired samples from 81 subjects	45
VI	Relationship of formaldehyde exposure to persistent symptoms, based on analysis of paired samples from 103 subjects	46
VII	Demographic data of group 1 and controls	70
VIII	Comparison of demographic data of group 2 (1994 - 1995)	71
IX	Comparison of demographic data of group 3 (1994 - 1995)	72
X	Comparison of demographic data between exposed student groups of 1994 and 1995	73
XI	Comparison between exposed students and staff of 1994	74
XII	Air flow velocities measured in the anatomy laboratory before and after the installation of the new ventilation system	75
XIII	Average temperature and relative humidity measured on the days of sampling	76
XIV	Measured formaldehyde concentrations in the anatomy laboratory, prior to intervention	77

XV	Formaldehyde concentrations measured in the anatomy laboratory after intervention	78
XVI	Comparison between pre and post intervention results, measured in the same positions at a similar stage of dissection	80
XVII	Response rate of all study groups	82
XVIII	Symptoms experienced by all student groups	83
XIX	Symptoms for which staff displayed a significant exposure effect when comparing exposed to non-exposed persons, prior to intervention	84
XX	Group 2, students exposed in 1994 and not exposed in 1995 (cessation of exposure)	85
XXI	Group 3, students not exposed in 1994 exposed in 1995 (initiation of exposure)	86
XXII	nasal epithelial scraping score of staff and a matched control group	91

FIGURES

FIGURE	CAPTION	PAGE
1.	Lateral wall of the nasal cavity	23
2.	Study design: cross sectional comparison of groups 1,2 and 3 and a longitudinal cohort study of groups 2 and 3	60
3.	Sampling positions in the Anatomy Laboratory	64
4.	Variation in formaldehyde vapour levels over time	79
5.	Formaldehyde vapour levels before and after intervention	81
6.	Illustration of the increase in symptoms associated with the initiation of exposure and decrease in symptoms associated with the cessation of exposure	88
7.	Comparison of frequency of symptoms experienced by the exposed groups of 1994 and 1995 (effectiveness of intervention)	90

APPENDICES

Summary tables of carcinogenicity studies (WHO 1989)	Appendix A
Laboratory analysis of formaldehyde samples	Appendix B
Symptom questionnaire	Appendix C
Consent form	Appendix D
Information given to subjects	Appendix E

LIST OF ABBREVIATIONS

ACGIH:	American Conference of Governmental Industrial Hygienists
ASHRAE:	American Society of Heating, Refrigeration and Air Conditioning Engineers.
FEV_1:	forced Expiratory Volume in one second
FVC:	forced vital capacity
HCHO:	formaldehyde
HCL:	hydrochloric acid
IARC:	International Agency for Research on Cancer
ILO:	International Labour Organisation
ip;	intra peritoneal
MEF50:	Maximal Expiratory Flow, 50%
NIOSH:	National Institute of Occupational Health and Safety (USA).
NOEL:	no observed adverse effect level.
NRC:	National Research Council (USA)
OSHA:	Occupational Safety and Health Administration
PEFR:	peak expiratory flow rate
PMR:	proportional mortality ratio
ppb:	part per billion
ppm:	part per million
RAST:	radioallergosorbent test
TLV:	threshold limit value
urt:	upper respiratory tract
WHO:	World Health Organisation

CHAPTER 1

INTRODUCTION

Formaldehyde (HCHO) an aliphatic aldehyde was discovered by Butlerov in 1859 (Merk 1983 p. 4115). Formaldehyde is commercially sold as formalin, a methanol - stabilized water solution containing 37,44 or 50 % formaldehyde. This chemical has become a ubiquitous air borne pollutant in our modern environment. It is present at levels of between 0.12 and 0.39 **ppb** in our troposphere. Most people come into contact with this low molecular weight chemical daily. Formaldehyde's wide distribution has caused considerable public health concern and debate over the past several decades. This concern was focused initially on the potential for formaldehyde to cause acute and chronic respiratory hypersensitivity disease (Bardana 1991) and more recently on possible carcinogenicity (ACGIH 1995).

There are many potential sources of formaldehyde exposure in the industrial setting. Most manufactured formaldehyde is used in the production of phenolic, urea, melamine and acetyl resins. In turn these resins are used extensively in the manufacture of textiles, floor covering, plywood, ordinary and some varieties of carbonless paper, particleboard, embalming fluid, fungicides, bactericides, air fresheners, cosmetics and toothpaste. Formaldehyde is also used in the automotive and appliance industries. Outdoor contamination occurs as a result of incomplete combustion of wood, fuels, alcohol and refuse. Aldehydes are among the most abundant of the carbon containing pollutants in urban atmospheres. Mobile sources that contribute to formaldehyde pollution are aircraft, automobiles and trucks. Ambient levels of 0.05 to 0.12 ppm have been measured in the heavily polluted air of the Los Angeles basin (Bardana 1991).

The Occupational Safety and Health Administration (OSHA) of the USA, reviewed 205 articles on formaldehyde during 1992. OSHA estimate that 1.3 million US workers are exposed to this chemical. About 88 % of these workers are exposed to levels below 1 ppm. 8 % to levels between 1 - 3 ppm and about 4 % are exposed to levels higher than 3 ppm. The largest numbers of people who are occupationally exposed according to job type are people in the embalming and funeral service industry. With mean exposures of 0.74 ppm and peak concentrations ranging up to 1.39 ppm (ACGIH 1992).

Formaldehyde vapour is detectable at very low levels, (below 1 ppm). and is responsible for a variety of symptoms such as nose and throat irritation, bronchitis, pulmonary oedema, chemical pneumonitis, irritation, coughing, chest pain, dyspnoea, tissue damage, sensitization and dermatitis. It is also listed as an animal positive, human indefinite carcinogen (Blair et al. 1990, Boysen 1990 and Holstrom and Lund 1992).

In 1992 the ACGIH threshold limit value (TLV) for formaldehyde was 1 ppm, however formaldehyde was placed on the list of intended changes for 1993, with a new proposed ceiling level of 0.3 ppm, which has subsequently been approved. Formaldehyde is also classified as a class A2 substance which means that it has been listed as a suspected human carcinogen. The ACGIH TLV committee focused upon the irritant effect of formaldehyde, the aim of a TLV being to eliminate worker complaints due to irritation, not only significant health or carcinogenic risk (ACGIH 1995). The World Health Organisation (WHO), recommend mean formaldehyde vapour concentration is 0.25 ppm with a permissable peak exposure of 0.8 ppm. The American Society of Heating, Refrigerating and Air Conditioning Engineers (ASHRAE) recommend a level of 0.1 ppm as a ceiling value. Australia have a TLV of 1 ppm, Germany 0.5 ppm, Sweden 0.8 ppm (TWA), with a ceiling value of 1 ppm. All the aforementioned countries / organisation have listed formaldehyde as a potential carcinogen or sensitizer. The British standard is much higher at 2 ppm (ACGIH 1992).

In South Africa the ACGIH standards have generally been in use by Occupational Hygienists as this country, until very recently (September 1995) never had locally determined standards and most professionals used the American TLV's. The Occupational Health and Safety Act (Act 85 of 1993) was adopted in January 1994. In terms of this act, draft regulations pertaining to chemical substances were circulated for comment (Schoeman and Schroder 1994 p. 500). In these regulations formaldehyde had been allocated a proposed TLV value of 1 ppm, however the regulations when published adopted the significantly higher British Standard of 2 ppm.

Students and staff in gross anatomy facilities are all exposed to formaldehyde vapours. Human cadavers used for dissection are traditionally embalmed with solutions containing formaldehyde and phenol. Both these chemicals are toxic agents and are responsible for the pungent and irritating smell experienced in anatomy laboratories. Both chemicals present potential environmental health hazards to anatomy staff and students. Occupational exposure to formaldehyde and phenol may be direct through physical contact or indirect by inhalation of air borne vapours. Exposure levels are determined by a host of interdependent factors, among which are: The volume and concentration of embalming solutions, the region of dissection (body cavities hold higher concentrations than limbs), the quality of the ventilation system, room temperature, number and activity level of students working in the environment, number and location of cadavers relative to room size and ventilation avenues as well as the use of protective clothing, such as gloves or respirators (Winesaki and English 1989). Anatomists are exposed to formaldehyde levels of between 0.02 and 5.87 ppm with peak values as high as 20 ppm (Blair 1992).

The issue of formaldehyde exposures in anatomy laboratories has become increasingly controversial and academic institutions are obliged to evaluate and control formaldehyde levels in their facilities. Conflict may exist between the maintenance of a cadaver's biological hygiene and reducing formaldehyde concentrations to acceptable levels. Ethical and moral considerations do however warrant the control of these vapours (Skisak 1983).

As a result of recommendations made, the University authorities improved the ventilation system of the anatomy hall at the end of the 1994 academic year. Permission was granted to extend the study in 1995. Formaldehyde vapour levels were re - evaluated and the health questionnaire was re - administered in order to measure the effectiveness of the intervention, as well as to measure the initiation and cessation of exposure effect upon students. The previously non - exposed control group (1994) were in their second year of study (1995) and had become the exposed population in the new improved laboratory environment. The initially exposed population on the other hand (1994) had completed anatomy and had again become non - exposed to formaldehyde (1995). The re - administration of the questionnaire to these two groups would therefore measure; The effect of initiation as well as cessation of exposure when compared to themselves (1994 data). In essence the study was changed from a cross sectional to a before and after intervention, with one important variable to consider, ie. the intervention in terms of the improved ventilation.

The effectiveness of the intervention was measured by directly comparing the 1994 and 1995 exposed groups with each other, as well as to repeat the environmental measurements of ventilation and formaldehyde vapour levels.

The main purposes of this study were the following:

i. To critically review the current literature on the adverse human health effects of formaldehyde exposure to establish the potential harm it can cause.

ii. To measure the environmental levels of formaldehyde vapour in the Human Anatomy Laboratory, before and after engineering controls were implemented.

iii. To determine wether students and Staff exposed to the laboratory environment have more symptoms which can be related to their formaldehyde exposure, compared to non-exposed persons.

iv. To assess the impact of an intervention in the form of environmental controls; particularly in reducing exposure symptoms to an acceptable level.

Rationale for the study:

i. The international reduction of legal limits of exposure implies that all users of formaldehyde should evaluate their work environments.

ii. The classification of formaldehyde as a suspected human carcinogen places a moral obligation upon management to reduce exposures.

iii. No publications related to formaldehyde exposures in South African Universities were found.

CHAPTER 2
LITERATURE REVIEW

The evaluation of risk from environmental agents relies heavily on evidence gleaned from epidemiological studies. It is therefore important to emphasize the procedures that should be adopted to assess the value of such investigations with special reference to shortcomings inherent in the epidemiological method. Initially such evaluations require value judgements regarding the quality of the design and execution of the study. Thereafter an assessment is needed of groups of studies to estimate the likelihood or otherwise that the relationship between the exposure and the disease is causal (WHO 1989 pp 150 - 153).

2.1 IRRITANT AND GENERAL HEALTH EFFECTS ASSOCIATED WITH FORMALDEHYDE EXPOSURE

2.1.1 Animal studies

During 1992 the ACGIH were considering changing the TLV value of formaldehyde, this prompted an in depth review by the ACGIH of 205 articles. The review was published in the Applied Occupational Environmental Hygiene Journal (December 1992). The following acute and sub chronic effects were extracted from this review.

2.1.1.1 Acute

Formaldehyde was found to be fatal to cats and mice upon exposure to concentrations of 700 ppm for 8 and 12 hours respectively. Exposure of rats to 0.5 ppm produced sensory irritation of the eyes, nose, throat, and lungs as well as cellular changes in the upper respiratory tract. Mucociliary action was inhibited and this in turn interfered with the nasal cavity's normal function, the draining of secretions of the sinuses and the lacrimal glands (Edling et al. 1985).

Morgan et al. (1986), determined that rats inhaling formaldehyde showed a concentration dependent inhibition of the mucociliary function in the dorsal, lateral and medial maxilloturbinates. Inhibition of mucous flow was more pronounced than inhibition of ciliary action. Morgan and associates identified 0.5 ppm as the "no observed adverse effect level" (NOEL) with regards to irritant action upon the mucosal cilia of the upper respiratory tract.

2.1.1.2 Low level exposure

Rush et al. (1983), conducted tests on monkeys and rats at concentrations of 3 ppm and observed squamous metaplasia in the nasal mucosa of the turbinates. At exposures of 8 ppm decreased body and liver weights were observed as well as nasal irritation and phagocytic activity of the alveolar macrophages.

Beal (1984), reviewed 84 articles on low level exposure to formaldehyde and concluded that there was a qualitative relationship between formaldehyde absorption and hepatotoxicity. These data indicate that exposure to 3 ppm or less for 6 months causes adverse effects upon the liver. The observed effects include decreases in the concentration of DNA. A mottled, discoloured appearance of the organ as well as a significant increase in weight, nuclear polymorphism a profusion of binuclear cells around the triads, focal hyperplasia and dilatation of hepatic veins with some degeneration of liver cells in the centre of the lobules. Beal recommends additional research in order to quantify the potential hepatotoxicity of formaldehyde (ACGIH 1992).

The extrapolation of data gained from animal experimentation at exposure levels that significantly exceed formaldehyde levels and time periods of exposure (dose), that a student or staff member would encounter in the typical anatomy laboratory is problematic and therefore human studies are of more value.

2.1.2 Human studies

2.1.2.1 General effects

The American National Research Council (NRC) concluded that eye irritation is a common complaint of persons exposed to formaldehyde vapour. Human eyes are very sensitive to formaldehyde and are able to detect atmospheric concentrations of 0.01 ppm in some cases. Eye irritation occurs at concentrations in the range of 0.05 - 0.5 ppm.

An ACGIH (1992) review reported effects such as loss of olfactory sense, increased upper respiratory disease, sub atrophic and hypertrophic alterations in the nose and throat, ciliostasis of the nasal mucosa, increased absorptive function of the nasal mucosa, itching eyes, dry and sore throat, disturbed sleep, unusual thirst upon awakening in the morning, tearing of the eye, irritation of the nose and throat, chronic airway obstruction, respiratory tract irritation, small decrease in pulmonary function, menstrual disorders, pregnancy complications and low birth weight among offspring of workers exposed to concentrations of 0.83 to 3.8 ppm formaldehyde.

The following table was extracted by the authors of the ACGIH (1992) review from the (NRC), National Academy of Sciences, Committee on Aldehydes, Board of Toxicology and Environmental Health Hazards: Health Effects of formaldehyde, in Formaldehyde and other Aldehydes, Chap 7. National Academy Press, Washington DC.

Table I. Human adverse health effects associated with the inhalation of various concentrations of formaldehyde vapour

REPORTED HEALTH EFFECTS	FORMALDEHYDE (HCHO) CONCENTRATIONS IN PPM
none reported	0.05
neurophysiologic	0.05 - 1.5
odour threshold	0.05 - 1
eye irritation	0.01 - 2
(urt)* irritation, increased nasal airway resistance	0.1 - 25
lower airway and chronic pulmonary obstruction	5 - 30
pulmonary edema, inflammation, pneumonia	50 - 100
death	100 +

* upper respiratory tract

(ACGIH 1992)

It is important to note that smoking habits, socioeconomic status, pre - existing disease and interaction with other airborne pollutants may modify the reported human responses to formaldehyde.

Low ambient concentrations of formaldehyde will affect the upper airways and eyes and may cause complaints associated with a heightened sense of olfactory awareness. The pathophysiology of annoyance reactions is related to the deposition of formaldehyde on the outer surface of the nasal mucosal blanket, allowing it to reach the periciliary area, stimulating olfactory and trigeminal nerve endings, which causes a burning sensation of the eyes, nasal passages and throat. Lacrimation and reduced flow in mucous secretions of the nose and throat may ensue. These symptoms are transient and abate promptly upon removal from further exposure.

Low ambient formaldehyde levels stimulate the mucociliary function. At high levels, inhibition of mucociliary function might occur with total mucostasis and ciliastasis. Because of it's extraordinary solubility most of the inhaled formaldehyde is retained in the upper respiratory tract and would rarely penetrate the lower airways. Exposure to such low concentrations would not be expected to penetrate the blanket and to reach the periciliary fluid. An exposed individual would be aware of a disagreeable odour, but would not suffer any physiological damage. Certain genetic conditions such as congenital familial dysautonomia and Turner's Syndrome are associated with heightened olfactory awareness. On the other hand, hypothyroidism, sinusitis, polyposis and many rhinoplastic procedures result in anosmia, hyposmia or parosmia. Cigarette smoking, inhalation of cocaine or similar recreational drugs and chronic abuse of nasal decongestants all lead to variable hyposmia.

Nasal hyper - irritability is commonly associated with viral coryzas and symptomatic allergic and non allergic rhinitis. In a murine model, chronic exposure to formaldehyde was usually associated with the development of short term tolerance (Bardana 1991).

2.1.2.2 Effects upon the respiratory system

Reports of occupational asthma attributable to exposure to formaldehyde have appeared since the first reported case of a matchmaker presenting with the symptoms of occupational asthma in 1939. Workers such as embalmers, medical and para medical personnel may all react to formaldehyde in some way. The levels of formaldehyde gas and time periods of exposure necessary to induce asthma are unknown. Inhalation of concentrations in excess of 11 ppm have been reported to cause chemical pneumonitis, pulmonary edema and death (ACGIH 1992).

The Mayo clinic (USA) conducted a study of 13 patients displaying symptoms suggestive of asthma where formaldehyde was suspected as the cause. The patients were subjected to bronchial challenges by exposure to 0.1, 1 and 3 ppm formaldehyde gas and randomly placed placebos. The period of exposure was 20 minutes. Pulmonary function was measured before and for 24 hours after each bronchial challenge. No patient had a significant decrease in FEV1 after exposure to formaldehyde at a concentration of 3 ppm. It was concluded that in no case were the authors able to substantiate that exposure to formaldehyde at 3 ppm or less was indeed causing or aggravating asthmatic symptoms (Frigas et al. 1984).

Although it has not been established how long an exposure period is required to induce asthma, one can assume that the 20 minute period at 3 ppm should have been sufficient to produce symptoms since a rapidly metabolized substance such as formaldehyde does not accumulate in the body. Due to the fact that a formaldehyde bronchial challenge did not provoke asthma in 13 selected patients with symptoms suggestive of asthma and a history of exposure to formaldehyde gas, it is inferred that cases of formaldehyde induced asthma are rare.

Bronchial provocation studies were performed on 15 workers occupationally exposed to formaldehyde who presented symptoms suggestive of occupational asthma by Burge et al. (1985). The results show that formaldehyde exposure can cause asthmatic reactions and suggest that these are sometimes due to hypersensitivity and sometimes as a result of the direct irritant effect. Three workers were found to have classical occupational asthma caused by formaldehyde vapour, which was likely due to hypersensitivity with late asthmatic reactions following formaldehyde exposure.

In Finland a total of 230 workers from across the whole country, who had been exposed to formaldehyde and suffered from asthma like symptoms were referred to the Finnish Institute of Occupational Health over a six and a half year period for examination. All subjects had a bronchial provocation test with formaldehyde.

On the basis of the medical and occupational history of the patients, specific bronchial provocation tests and other test results, 12 of the 230 cases were considered to be caused by specific sensitization to formaldehyde. All the subjects had been exposed occupationally. An exposure period of between 1 month and 9 years preceded the onset of symptoms. Three persons displayed no bronchial hyperactivity as assessed with a histamine or metacholine provocation test. 11 of the 12 reactions were triggered by about 2.5 mg/m^3 and one by 1.2 mg/m^3. 71 of the 218 subjects that did not react when challenged with formaldehyde demonstrated bronchial hyperactivity. The authors concluded that formaldehyde asthma although apparently a rare disease is under reported. Removal from exposure has a favourable effect upon symptoms. Low domestic exposures, however may maintain symptoms in individuals already sensitized (Nordman et al. 1985).

In a study by Schachter (1986) of the respiratory effects of exposure to 2 ppm formaldehyde, 15 non smoking healthy subjects were exposed to 0 and 2 ppm formaldehyde for 40 minutes. Pulmonary function was measured before, during and after exposure. The authors demonstrated that the exposure of healthy subjects to 2 ppm formaldehyde under conditions of rest and exercise did not cause measurable bronchoconstriction. Three subjects were studied for 24 hours and no delayed bronchoconstrictor effects were noted. Additionally, in 6 subjects, airway sensitivity to methacholine was not altered from the baseline study by pre-exposure to formaldehyde. Subjective symptoms noted primarily related to upper airway irritation including unusual odour, taste, sore throat and nasal discharge. Eye irritation was the most frequent non respiratory complaint, symptoms disappeared shortly after exposure.

The authors concluded that short exposures at 2 ppm do not result in acute or subacute changes in lung function among healthy individuals either at rest or with exercise. Subjective complaints following such exposures are confined to irritative phenomena of the upper airways.

Witek et al. (1987) exposed 15 non smoking, mildly asthmatic volunteers in a random, double blind protocol to 20 ppm formaldehyde in a laminar flow environmental chamber. Symptoms of sore throat, eye and nose irritation were common during exposure, however no significant changes in forced vital capacity (FVC), forced expiratory volume in one second (FEV1), peak expiratory flow rate (PEFR), or maximal expiratory flow at 50% of vital capacity (MEF50) were observed. From these data and the results of baseline methacholine inhalation challenge trials the authors concluded that short term formaldehyde exposure in air does not induce bronchoconstriction or other short term airway obstruction but that brief exposures at 2 ppm could alter non-specific airway hyper-responsiveness.

A criticism of both the Schachter and Witek studies is the small sample sizes of the study groups (n = 15) as well as the exclusion of some of the subjects from certain tests performed. If one were to consider that for the Nordman study, workers exposed to formaldehyde suffering from respiratory disease were used as a study population and only 12 out of 230 were considered to have occupational asthma, it is not surprising that the spirometry results obtained in the Witek study were unchanged from the baseline data.

Malaka and Kodama (1990) conducted a study at the PT.NS Plywood Company in Gresik, East Java, Indonesia to evaluate the respiratory health of plywood workers chronically exposed to formaldehyde vapour. The objectives of the study were to evaluate the effect of formaldehyde on chronic obstructive airway disease, acute transitory pulmonary function deficits and the frequency of respiratory symptoms and diseases. The exposed group consisted of a random sample of 100 workers, stratified by smoking habits as well as length of service, (< 5 years or 5 years and more). A control group of 100 unexposed workers, matched for age, ethnicity and smoking habits was selected for the study. Respiratory health was evaluated by spirometric tests, respiratory questionnaires and chest x - rays. Area concentrations of formaldehyde were measured in the work environment and found to range from 0.28 to 3.48 ppm. The average personal exposure was 1.13 ppm. Baseline and across shift spirometric measurements were taken to assess the respiratory health of the subjects studied. Baseline measurements were taken upon return to work after a holiday or on a Monday morning. Across shift measurements were taken half an hour before the end of a work shift. FEV1 and FVC values were calculated. The authors reported that exposure to formaldehyde was associated with "decrements" in the baseline spirometric values and several respiratory symptoms and diseases including cough, phlegm production, asthma, chronic bronchitis and upper respiratory tract infections. The authors concluded that the results of this study support the hypothesis that chronic exposure to formaldehyde induces chronic obstructive lung disease.

It is important to note that in the Malaka and Kodama study, total wood dust concentrations were measured and in some areas the concentration of respirable dust was as high as 1.3 mg/m^3. Research conducted by Gamble et al. (1976). indicates that the presence of a suitable formaldehyde "carrier" such as respirable dust is known to transport formaldehyde deeper into the lungs where it has a more severe biological effect than when deposited in the upper respiratory tract. A high prevalence of chronic upper respiratory tract infections in the study population, was reported and this is considered an additional confounding variable.

In considering the literature related to respiratory effects associated with formaldehyde exposure, it was decided to focus our own study on an evaluation of the symptoms of irritation; not spirometry, as sen - sitisation to formaldehyde and subsequent decrements in baseline lung function and broncho-constriction occur in a very small portion of the population.

2.1.2.3 Carcinogenic potential

Environmental or extrinsic factors are a major cause of human cancers and therefore a great deal of research has been done in order to identify and eliminate such agents. Identification of chemical agents that are potential carcinogens is a long and difficult process. Research is generally conducted on animals for ethical reasons. Epidemiological cohort studies are very complex with many variables and they take place over long periods of time. Early recognition of cancers and their antecedents or precancerous states is sometimes a more viable approach, this of course also has therapeutic value in terms of the control and prognosis of malignant disease (WHO 1989 p 74).

Formaldehyde reacts readily with a variety of cellular nucleophiles, including glutathione, forming adducts of varying stability. The glutathione adduct of formaldehyde is the true substrate of formaldehyde dehydrogenase, which catalyses the oxidation of the adduct to S - formyl - glutathione. Reaction products with DNA, which have been demonstrated in vitro, include adducts and DNA protein cross - links. Investigations in rats exposed to formaldehyde through inhalation have shown that formaldehyde induces the formation of DNA protein cross - links in the nasal respiratory mucosa in vivo. The concentration response curve for DNA protein cross - linking was sublinear below 6 ppm but apparently linear at higher concentrations.

In rats depleted of glutathione, either by simultaneous exposure to acrolein or by intra - peritoneal (ip) injection with phorone a significant increase in the yield of formaldehyde induced DNA protein cross - links was observed, suggesting that the formaldehyde dehydrogenase - catalyzed oxidation of formaldehyde is an important defence mechanism against covalent binding of formaldehyde with nucleic acids in the nasal respiratory mucosa (WHO 1989 pp 77-85).

Increased cell replication occurs as a result of the cytotoxic effects of formaldehyde on the nasal mucosa. Morphological changes such as acute degeneration, swelling, formation of dense bodies and vacuoles in epithelial cells were described in the respiratory epithelium of rats after a single 6 hour exposure to 18 mg/m^3 formaldehyde, upon repetition of the exposure 3 to 5 times, ulceration was observed in the respiratory epithelium. After a nine day exposure reparative hyperplasia and metaplasia were found. At 7.2 mg/m^3 hyperplasia and slight degenerative changes were still detected. In contrast, morphological changes could not be proved at 0.6 and 2.4 mg/m^3. Further research clarified the dependence of cytotoxic effects on the concentration of formaldehyde and on the length of exposure. The results of inhalation studies confirmed that acute exposure to high concentrations rather than the dose is more important in determining the severity of cytotoxic effects of formaldehyde vapour. There was no appreciable difference in the type, degree and incidence of nasal lesions between rats continuously exposed to 10 ppm and those exposed intermittently to the same concentration of formaldehyde, in fact intermittent exposure seemed to produce more severe nasal changes than continuous exposures (WHO 1989 pp. 77 - 85).

2.1.2.3.1 Animal studies

The World Health Organisation (1989) in collaboration with the International Labour Organisation (ILO) reviewed formaldehyde extensively in 1989 in order to make recommendations regarding it's use in industry. In this review animal experimentation studies were critically discussed in an attempt to quantify the human health risk posed by formaldehyde exposure. All routes of absorption were described by the authors however the following extract focuses on "inhalation" studies only. The results of these studies are summarized in tables AI and AII in appendix A.

Several lesions were seen in the nasal cavities of mice exposed to concentrations of 6 or 15 ppm formaldehyde vapour including dysplasia and squamous metaplasia of the respiratory epithelium, purulent or seropurulent rhinitis and atrophy of the olfactory epithelium. Three months after exposure was discontinued the nasal lesions had regressed. In the rats, several lesions occurred in the nasal cavities at the low concentration of 2 ppm. The lesions included dysplasia and squamous metaplasia of the respiratory epithelium, goblet cell hyperplasia and purulent rhinitis. Rats exposed to 25 ppm also exhibited goblet cell metaplasia of the olfactory epithelium, respiratory epithelial hyperplasia, squamous epithelial hyperplasia, squamous atypia and papillary hyperplasia. Dysplasia and squamous metaplasia of the tracheal epithelium were also detected. The incidence of squamous metaplasia in rats exposed to 2 or 5.6 ppm regressed within 3 months of the termination of exposure.

Male Syrian golden hamsters exposed to 10 ppm formaldehyde for 5 hours per day for 5 days per week for life showed no tumours but 5 % showed hyperplastic and metaplastic areas on the nasal epithelium. Sprague - Dawley rats exposed to formaldehyde concentrations of 14 ppm alone or in combination with hydrochloric acid (HCL), 10 ppm for 6 hours/day, 5 days/week, for life, developed rhinitis, hyperplasia and squamous metaplasia in laryngeal - tracheal segments and nasal mucosa.

Rats exposed to a mixture of gaseous formaldehyde (17.9 mg/m^3) and hydrochloric acid (16.9 mg/m^3) for 6 hours/day, 5 days/week, for life, developed nasal squamous cell carcinomas in 25/99 rats and papillomas in 3/99 rats, squamous metaplasia of the nasal epithelium was found in 64/99 of the exposed rats.

Male f-344 rats exposed for 6 hours/day, 5 days/week, over 28 months to 0.36, 2.4 or 17 mg formaldehyde/m^3 developed rhinitis accompanied by desquamation. In all formaldehyde exposed groups, nasal epithelial hyperplasia and squamous metaplasia with hyperplasia were seen. In the 17 mg/m^3 group, squamous cell carcinoma was recognised in 14 rats and papilloma in 5 of 32 rats exposed. Male rats were exposed to 0, 12 or 24 mg/m^3 formaldehyde for 4, 8 or 13 weeks for 6 hours/day, 5 days/week for 126 weeks. Non neoplastic histopathological changes in the nasal respiratory epithelium (hyper and metaplasia) and olfactory epithelium disarrangement, thinning and metaplasia) and olfactory epithelium (disarrangement, thinning and simple cuboidal or squamous metaplasia) occurred at 24 mg/m^3.

Similar but less pronounced changes of the respiratory epithelium were seen at 12 mg/m^3 and a limited non significant number of nasal tumours occurred at 24 mg/m^3. In an inhalation study performed on male rats with severely damaged or undamaged nasal mucosa, rats were exposed to 0. 0.12, 1.2 or 12 mg formaldehyde/m^3 for 6 hours/day, 5 days/week for either 28 months or 3 months followed by an observation period of 25 months. A significant number of nasal squamous cell carcinomas (17/60) occurred only in rats with a damaged nose exposed to 12 mg/m^3 for a period of 28 months.

C3H mice exposed to 50, 100 or 200 mg formaldehyde/m^3, for 4 hours/day, 3 days/week over 35 weeks, displayed basal cell hyperplasia and / or squamous metaplasia of the tracheo-bronchial epithelium. Atrophic metaplasia was also observed in the highest dose group (WHO 1989, pp 108, 109 and 115).

A criticism of the use of animal experimentation data is the fact that there is a difference in susceptibility to nasal tumours between rats and mice and this makes the extrapolation of these findings to humans even more dubious. The fact that hydrochloric acid (HCL) vapour was mixed with formaldehyde in some of the studies is also not acceptable as formaldehyde reacts with hydrochloric acid to form the potent animal carcinogen bis(chloromethyl) ether (Clayton and Clayton 1981).

2.1.2.3.2 Human studies

Many industrial exposures have been related to an increased risk of sinonasal disease including cancer. A large number of case-control epidemiological studies, clinicopathological studies and experimental studies have shown an association of variable strength between exposure to irritant substances such as formaldehyde and nasal (pre)neoplastic disease. This is not surprising if one considers that the nose is the first part of the respiratory system to be exposed to airborne environmental agents. Due to the highly soluble nature of formaldehyde it is easily absorbed by the mucous lining of the upper respiratory tract, in particular the nasal cavity (cavum nasi).

Formaldehyde has been implicated as the toxic agent responsible for squamous metaplasia of the nasal epithelium in humans and to a lesser degree dysplastic changes of the metaplastic squamous epithelium. It is reasonable to assume that in most cases nasal squamous carcinoma is preceded by a precancerous dysplastic lesion such as carcinoma - in - situ or severe dysplasia (Hellquist 1990 pp. 49 - 50).

Due to the fusion of bones that comprise the nose it is a difficult organ to describe. There are however three important components of nasal anatomy, these are the nasal septum, the maxilla and the lateral wall. The lateral wall being most important as this is the region where pathological processes due to exposure to formaldehyde have been demonstrated in experimental animals, see figure 1.

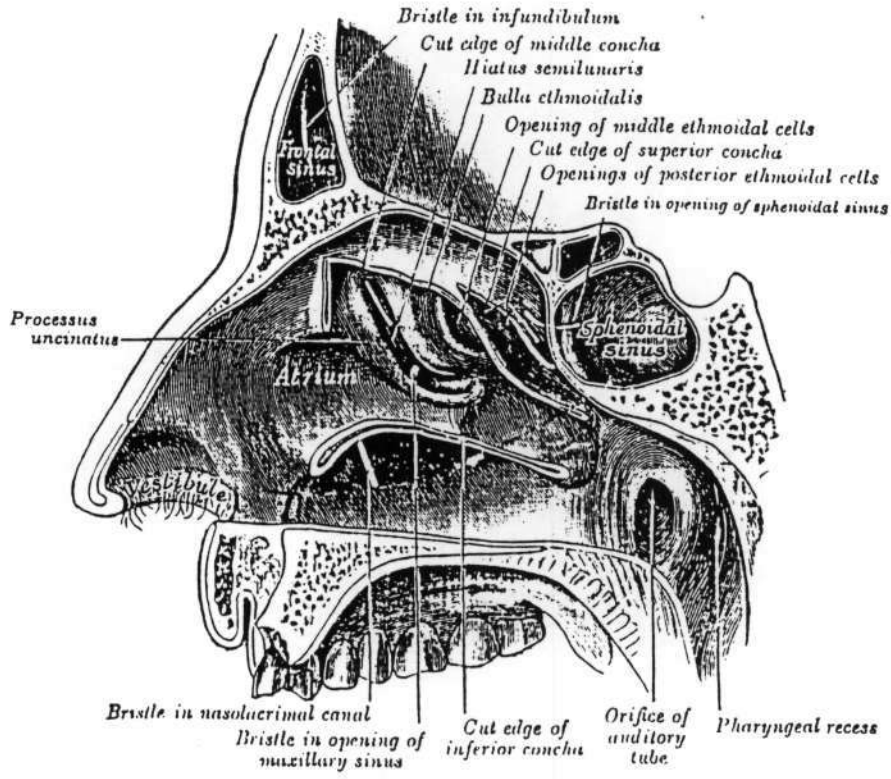

Figure 1. Lateral wall of the nasal cavity
(Gray's Anatomy, Gray H, 1959 p. 1171)

The most anterior part of the vestibule is lined with a keratinized stratified squamous epithelium which is a continuation of the skin of the nose. There are also some stiff hairs in this area, which assist in filtering dust particles from inspired air. The nasal epithelium is covered by a mucous blanket that is renewed every 10 - 20 minutes. This mucous blanket forms a protective layer or barrier over the underlying mucosa and also retains particles from inhaled air. The mucus consists of 95% water (Hellquist 1990 pp. 6 - 8).

Due to the highly soluble nature of formaldehyde, normal conditions of exposure encountered in the anatomy environment will not be sufficient to penetrate this protective "blanket".

The authors of the WHO review on formaldehyde produced the following summary tables to describe the carcinogenic potential of occupational exposures to formaldehyde.

Table II is a summary of observed and expected deaths for professionals and industrial workers exposed to formaldehyde. The professionals used formaldehyde in the preservation of biological tissues (embalmers, anatomists, pathologists and zoologists). The industrial workers were involved in the production and use of formaldehyde. The pattern and intensity of exposure to formaldehyde differed for both groups.

Table II. Observed and expected deaths for professional and industrial workers exposed to formaldehyde (with 95% confidence limits)

Cause	Professional observed/ expected	Professional confidence limits	Industrial observed/ expected	Industrial confidence limits
CANCER	**obs/ exp**	**95%**	**obs/exp**	**95%**
Nasal	0 /1.7	0 -2.17	0 /1.3	0 -2.84
Mouth	20 /23.8	0.51-1.3	12/9.2	0.67-2.28
Brain	40 /22.6	**1.26-2.41**	6 /13.2	0.17-0.99
Lymphatic and haematopoietic	80 /64	0.98-1.53	25/30.6	0.53-1.21
Leukaemia	40 /27.2	**1.05-2**	9 /11.4	0.36-1.5
Other lymphatic and haematopoietic	40 /36.8	0.78-1.48	16/19.2	0.48-1.35
Lung	175/244	0.62-0.83	214/227	0.82-1.08
Prostate	61 /51.6	0.9 -1.52	2 /0.6	0.4-12.04
Skin	12 /11.4	0.54-1.84	0 /0.4	0 -9.22
Bladder	23 /24.3	0.6 -1.42	1 /0.3	0.18-18.6
Kidney	21 /18.6	0.7 -1.73	1 /0.4	0.06-13.9
Digestive system	211/245	0.74-0.98	8 /10.4	0.33-1.52
OTHER CAUSES				
Liver cirrhosis	83 /59.3	**1.11-1.74**	10 /9	0.53-2.04
non neoplastic				
respiratory disease	109/164	0.55-0.8	243/241	0.88-1.14

statistically significant findings in bold.
(WHO 1989 table 36 pp. 152).

As can be seen from the data presented in table II professionals such as anatomists are at a higher risk of brain, liver, lymphatic and haematopoietic cancers as well as leukaemia. Industrial workers seem less likely in general to contract cancers and the incidence of mouth and prostate cancers are slightly increased.

The authors of the WHO publication did not postulate any hypothesis regarding the data presented, however embalming fluid does contain a large percentage of alcohol and it may be the alcohol not the formaldehyde that is responsible for the excess in liver cirrhosis. The differences in brain cancer incidence between the two groups may be attributed to differences in social class. It is interesting to note that no nasal cancers were detected in either group.

Appendix A, tables AIII, AIV and AV are a (WHO) summary of epidemiological studies of persons exposed to formaldehyde. An excess of several forms of cancer, ie., Hodgkin's disease, leukaemia, cancers of the buccal cavity and pharynx, lung, nose, prostate, bladder, brain, colon, skin and kidney is seen in more than one of the studies summarised. Some of these excesses could be due to random variation and others may depend upon factors other than formaldehyde exposure. Some of the studies involved the same populations and therefore do not provide completely independent information.

In view of the high solubility and rapid metabolism of formaldehyde it seems more likely that upper respiratory tract cancers would be causally related to formaldehyde exposure than other forms of cancer. Confounding factors that need further investigation include controlling for smoking, differences in occupational exposure patterns and possible synergistic effects such as wood dust.

Excess of nasal or nasopharyngeal cancer in relation to formaldehyde exposure was reported in six of the case control studies summarised in table AI. In two other case control studies, the question of a relationship with formaldehyde was addressed either by primary design or by reporting formaldehyde exposure for either cases or controls, but no excess risk was demonstrated. None of the cohort or proportional mortality ratio (PMR) studies listed in tables AIII and AV had adequate power to detect even a considerably increased risk.

Cancers of the buccal cavity and pharynx have either not been included in studies or in some case control studies the risk has appeared to be normal. There was no excess in the largest cohort, though an excess appeared in other studies involving small numbers, these are not considered statistically significant.

An excess of respiratory cancer appeared in 3 case - control studies in comparison with low exposures in general or comparable unexposed workers and between physicians in surgery and internal medicine, though these findings were based on small numbers. Two other studies were not positive.

Three cohort and (PMR) studies, had adequate power and were designed to elucidate the risk of respiratory cancer from formaldehyde, these studies showed an excess. One study showed some excess in laryngeal cancer (table AV). Seven studies with reasonable power were negative or not positive with regard to respiratory cancer. Deviations in both directions from the expected in these studies are explainable by the lack of control for smoking and the "healthy worker effect", which means that the study population is not comparable with the general population.

Leukaemia incidence was high in all the studies involving reasonable numbers of cases and even significantly high in one study. Three of these studies involved either embalmers or anatomists, which might suggest some alternative or contributing etiological factor (such as alcohol) operating.

Similarly, brain cancer, which was found in significant excess in some studies, a confounding factor regarding the relationship between brain cancer and social class is suspected.

An excess of colon cancer among embalmers may perhaps be explained by an association between sedentary work and colon cancer. Cancers of the skin, bladder, kidney and prostate as well as Hodgkins disease are represented by small numbers of excesses (WHO 1989 pp 170 - 177).

Klein-Szanto et al. (1989), obtained cells from the nasal epithelium of young adults during autopsy, which were amplified in primary cultures, and inoculated into de-epithelialized rat tracheas. These tracheas were sealed and transplanted subcutaneously into irradiated nude mice. Four weeks after this xenotransplantation procedure, when the tracheal lumina were covered by normal respiratory epithelium, the transplants were exposed to slow releasing silastic devices containing 0, 0.5 or 1 mg paraformaldehyde. Histological examination supplemented with autoradiographies revealed that the aldehyde produced both involutional changes such as erosion and atrophic epithelium and proliferative reactions such as hyperplastic; metaplastic lesions. These epithelial changes were characterized by a higher labelling index that in some focal areas reached values 10 to 20 times higher than normal.

These effects were noted 2 weeks after exposure to formaldehyde and in an attenuated form could also be seen at 8 weeks. This response pattern is very similar to that of the xenotransplanted human tracheobronchial epithelium and also of the rat nasal and tracheobronchial epithelia, in which formaldehyde proved to be an effective carcinogen.

In an attempt to quantify the nasal cancer risk of humans exposed to formaldehyde vapour, Boysen et al. (1990) evaluated histological changes in the nasal mucosa of workers exposed to formaldehyde. Nasal biopsies of 37 workers occupationally exposed to formaldehyde for more than five years showed a higher degree of metaplastic alterations than a control group of age matched persons. In addition three cases of epithelial dysplasia were observed among the exposed population. In view of the inconclusive epidemiological studies done to date the authors suggested that formaldehyde is a weak carcinogen.

Blair et al. (1990) performed a historical cohort study of 26 561 workers employed in ten different industries, in order to evaluate the cancer risks associated with exposure to formaldehyde. Historical exposures to formaldehyde by job, work area and calender time were estimated using monitoring data available, comments from long term workers and company officials. Slightly positive but nonsignificant exposure response associations between lung cancer and levels of formaldehyde occurred in only a few out of a large number of comparisons. Mortality from lung cancer was more strongly associated with exposure to other substances including phenol, melamine, urea and wood dust than with exposure to formaldehyde alone.

It is suggested that the association between formaldehyde and phenol should be further evaluated. Phenol is an important ingredient of most embalming solutions and it interferes with the monitoring of formaldehyde. The possible synergistic effect of a mixture of these two chemicals is unknown.

Phenol vapour was measured in this study, the levels were found to below the level of detection of the instrument used and therefore, well below the TLV and within acceptable ranges for the use of the 3M formaldehyde monitors.

In 1990 Blair et al. reported on more than 30 epidemiological studies that had evaluated cancer risks associated with formaldehyde exposure. Excesses were reported for several sites, leukaemia and cancers of the nasal cavities, nasopharynx, lung, and brain generating the greatest interest. The excesses of leukaemia and brain and colon cancer found among professionals may not be related to formaldehyde exposure, since similar excesses were not observed among industrial workers. Inconsistencies among and within studies impede assigning formaldehyde a convincing causal role for the excesses of lung cancer found among industrial workers. A causal role for formaldehyde is the most probable for cancers of the nasopharynx and, to a lesser extent, the nasal cavities. Evidence of exposure response relationships, the fact that direct contact with formaldehyde may occur at these upper respiratory sites, and the consistency of these findings with experimental studies make this assumption highly probable.

Following on from their study in 1989 Klein-Szanto et al. (1992) performed a series of studies using a laboratory animal model that permits the exposure of xenotransplanted human respiratory epithelium to formaldehyde to study the effects of formaldehyde alone or in combination with the ultimate carcinogenic metabolite of benzo[a]pyrene, diol epoxide. These studies show that formaldehyde, although toxic at higher doses, is able to elicit at lower doses a proliferative response of the human infant tracheobronchial epithelium that is not preceded by a massive toxic effect.

The frequency of micronuclei and cytology of respiratory nasal mucosa cells were evaluated in 15 non smokers exposed to formaldehyde in a plywood factory. Each subject was paired with a control matched for age and sex. Mean levels of exposure to formaldehyde ranged from 0.1 mg/m^3 to 0.39 mg/m^3. It must be noted that in this study there was a contemporary exposure to low levels of wood dust. Nasal respiratory cell samples were collected by an otorhinolasryngologist near the inner turbinate using a brush for endocervical cytology. After staining, about 6000 cells were screened for micronuclei and scored in parallel for cytology according to a histopathological scale. A higher frequency of micronucleated cells was observed in the exposed group. Cytological examinations indicated chronic phlogosis in the nasal respiratory mucosa of plywood factory workers, with a high frequency of squamous cells (Balarin et al. 1992).

It was decided to adopt this method of cell collection from the nasal epithelium in our study in preference to biopsy due to the fact that this technique is not as invasive.

An ACGIH (1992) review describes a study conducted by Colizzo et al., wherein the authors described the following changes in ciliated respiratory epithelium upon exposure to formaldehyde.

a) Reduced extraction of surface accessible membrane components.

b) Increased retention of internal soluble proteins within the cilia, subsequently released into the membrane matrix fraction.

c) Increased retention of surface accessible components with internal axonemes.

Together these points confirm that components accessible at the epithelial surface were altered to varying degrees by exposure to formaldehyde, possibly through internal molecular stabilization. Such alterations if not reversed may result in other secondary responses leading to loss of cilia and to cell injury and death, which have been observed at higher formaldehyde concentrations or longer exposure periods.

The ACGIH (1992) review also refers to an article by Edling et al. where the authors conducted a biopsy evaluation of the inferior turbinate of the nasal mucosa of 20 men, who had been exposed to 0.1 - 1.1 ppm formaldehyde in a particle board processing plant, for an average of 7 years. The histopathological findings were compared to those of a reference group of 25 men with no occupational exposure to irritating agents. Five of the men in the formaldehyde group had swollen or dry changes or both of the nasal mucosa. Microscopic examination revealed a loss of cilia and goblet cells, squamous metaplasia and in some cases mild dysplasia.

Fisher et al. (1994) published an article on Environmental and occupational risks health care workers are exposed to, formaldehyde being one of the chemicals reviewed. The report refers to the mutagenic effects of formaldehyde upon micro-organisms and insects which may be regarded as an important step in the development of carcinogeneses. In humans however the evidence appears to be inconclusive.

A study of chromosome aberrations and sister chromatid exchange in the lymphocytes of staff in pathology departments showed no differences in these markers of genetic damage between exposed and unexposed individuals. Studies of pathologists and medical laboratory technicians in Britain have suggested that this group may have an above average incidence of deaths from lymphatic and haemopoietic neoplasms and brain cancers. There was no rise above the expected occurrence of cancers of the lung, nose or nasal sinuses as animal evidence had suggested might be the case.

The International Agency for Research on Cancer (IARC) devised the following method of classification of potentially carcinogenic agents.

Table III IARC classification of carcinogenicity

CLASS	DESCRIPTION OF CARCINOGENIC POTENTIAL
1	Agent is carcinogenic to man
2A	Agent is probably carcinogenic to man
2B	Agent is possibly carcinogenic to man
3	Not classified as to carcinogenicity in humans
4	probably not carcinogenic in humans

(Molhave et al. 1995)

According to this classification method the (IARC) concluded that the body of data suggests sufficient evidence to implicate formaldehyde as a carcinogen in animals (benign and malignant neoplasms in two or more species carried out at different times) but that there was limited evidence for its carcinogenicity in humans; the agency classified the chemical as a class 2A carcinogen. Evidence indicates that acute formaldehyde exposure may be more important for the occurrence of nasal tumours than the accumulated dose. These cancers are apparently caused by a chain of effects related to exposure, ranging from cellular damage to tissue damage, cell proliferation and finally development of cancer. A risk evaluation based on a multi-stage model was developed by the WHO in 1987. This evaluation was based on the investigations of squamous cell carcinomas among rats exposed to three formaldehyde concentrations in air. The upper confidence limit (95%) associated with exposures in the range of 1 ppm to 0.1 ppm was 7.4 to 7.7 ug/m^3 at a lifetime risk of 10^{-5} (Molhave et al. 1995).

Conclusions cannot be drawn with confidence from published mortality studies of occupationally exposed adults whether or not formaldehyde is a human carcinogen. Most studies have inherent design problems such as lack of reliable and complete information on exposure and outcomes for groups of potentially exposed individuals, insufficient latency time between initial exposures and ascertainment of cases, insufficient sample size, inadequate characterization of historical exposures to formaldehyde and other potential carcinogens; use of mortality data, rather than cases, inadequate follow up of workers in cases of job migration and weak statistical power to detect a true excess of cancer in an exposed population.

In view of the evidence of nasal epithelial carcinoma in experimental rats and mice it was decided to include samples of nasal epithelial scrapings obtained with the aid of endocervical brushes, according to the method of Balarin (1992) in this study.

2.2 EFFECT OF FORMALDEHYDE EXPOSURE UPON THE IMMUNE SYSTEM

Many low molecular weight chemicals have been described that can combine with human self protein to form antigenic conjugates capable of inducing hypersensitivity reactions.

In a study done as early as 1934 it was shown that the inhalation of formaldehyde gas still produced cutaneous reactions when the possibility of local contact had been ruled out. In certain circumstances formaldehyde may even produce an IgE mediated type 1 reaction in the nose, but this is rare.

Maurice et al. (1986) reported the development of anaphylactic shock secondary to formaldehyde exposure in a 20 year old female undergoing chronic haemodialysis. This patient had a history of formaldehyde contact sensitivity, before dialysis associated formaldehyde exposure. The evaluation included a positive epicutaneous test with 0.1 and 1 % formaldehyde. Similar tests were negative in 30 atopic and 30 non-atopic control individuals. Patch testing with a 1 % solution was also strongly positive and produced anaphylaxis 26 hours after application. Contact urticaria was not observed. Elevated levels of IgE specific antibody to a formaldehyde conjugate were noted. This case was consistent with formaldehyde induced anaphylaxis mediated by an IgE mechanism. Participation by other class specific antibodies of cellular mechanisms cannot be excluded. A similar systemic anaphylactoid reaction to a patch test with 1 % formaldehyde was reported in a woman with laryngospasm and bronchospasm after accidental inhalation of formaldehyde (Bardana 1991).

Data are lacking to determine a threshold value for inhaled formaldehyde as an allergen. A case cited in a review (ACGIH 1992), refers to a young male neurology resident who spent 2 hours in autopsy of formaldehyde preserved human brains. He experienced conjunctival and nasal irritation while working; however, over the next 15 hours after cessation of exposure, he developed progressive dyspnea and chest tightness. Early edema indicative of pneumonitis was visible on X - ray, and after treatment with aminophylline, hydrocortisone and oxygen (nasal prong at 4 l/min.), he gradually improved over the following two days. He continued to need prednisone (20 mg every other day for 2 weeks) and he had fully recovered 5 weeks after the onset of his hypersensitivity reaction to formaldehyde. Asthmatic attacks, may be due specifically to formaldehyde sensitization or allergy (ACGIH 1992).

Wilhelmsson and Holstrom (1992) studied a population of 66 workers occupationally exposed to formaldehyde who experienced nasal discomfort through hyper-reactivity. The level of exposure of the workers monitored was between 0.05 and 0.6 $mg/^3$ (mean 0.26). The conclusion of the study was that formaldehyde in moderate doses can provoke nasal hyper-reactivity in 50 % of a population subjected to long - term exposure (significant nasal discomfort, mainly obstruction) in an environment in which not all exposed people feel annoying symptoms when allergic mechanisms can be ruled out. Atopic and non-atopics run the same risk of suffering from nasal hyper-reactivity. A further finding was that many of the formaldehyde exposed workers with dermatological problems also had airway symptoms. Two of the workers with a history of long term inhalation exposure to formaldehyde presented with a positive Radioallergosorbent (RAST) test.

Salkie (1994) presented data concerning the prevalence and relationship of atopy and hypersensitivity among pathologists in active practice indicating that 46% of the study group had problems related to formaldehyde. There was no tendency for atopic subjects to be more sensitive to formaldehyde and no subjects had detectable circulating formaldehyde - specific IgE.

Formaldehyde is able to evoke an immune response in persons chronically exposed to relatively high levels of the vapour, however the periods of time and concentrations of formaldehyde exposure of medical students appears to be too low to evoke such a response and therefore this study did not include testing for an immune response in the exposed population.

2.3 FORMATE LEVELS IN URINE AS AN INDICATOR OF FORMALDEHYDE EXPOSURE

The possible use of formate levels in urine as a biological indicator of formaldehyde exposure was investigated.

Distribution studies in rats have shown that inhalation of radiolabeled formaldehyde is followed by rapid elimination in expired air (apx. 40 %), urine (17 %), faeces (5 %) with the remainder deposited in the tissues (35 %).

Formate, a sodium salt (HCOONa), one of the simplest endogenous forms of carbon in man is the intermediate in many anabolic and catabolic reactions. Formaldehyde has been shown to be involved in single carbon transfers from many essential amino acids including glycine, histidine, tryptophan and serine and in the synthesis of purines, pyrimidines methionine and choline. The tetrahydrofolic acid (THF) pathway is the primary means through which the above metabolism occurs. Once formate has entered into the one carbon unit pool, numerous reactions can occur that direct formate to various other pathways including the citric acid pathway where it can be utilized for energy needs, releasing carbon dioxide (CO_2) and water. In addition to the major THF pathway, there is evidence that formate may be converted to CO_2 and water by reactions with peroxide or catalase. The presence of a small amount of endogenously derived formate in human urine is normal; however formate derived from the metabolism of formaldehyde and several other industrial compounds may elevate the urine concentration above normally expected values, this presents the opportunity of using formate levels to evaluate exposure to formaldehyde. There are however certain important variables that have to be considered, they include : dietary intake, nutritional status and exposure to cigarette smoke.
Formate arises from many sources, there always appears to be a certain amount of it in the blood. Excess formate that is not utilized metabolically will be eliminated in the urine.

The average urine formate concentration in non - exposed individuals, as reported in the literature during the past two decades, ranges from 11.7 to 18 mg/l. One of the disadvantages of using urinary formate levels as an indicator of formaldehyde exposure is the fact that differences in diet and nutritional status are factors that account for broad individual day to day fluctuations of formate levels in urine. Examples of foodstuffs that increase the formate output in the urine are carbohydrate and protein rich food. In addition certain foods such as red meat, poultry, fish, some fruits, smoked meats, some soft drinks and beer contain formaldehyde. The ethanol found in alcoholic beverages may elevate the serum formate concentration after consumption. In addition to nutritional variables, cigarette smoke contains apx. 0.82 mg of formaldehyde per pack. The smoke also contains additional compounds that may be metabolised to formate (Boeniger 1987).

In a study of urine formate levels, anatomy students were exposed to formaldehyde vapour concentrations of 0.26 - 0.92 ppm for 3 hours. Urine was obtained from 12 students and pooled directly after exposure. A second sample was obtained 21 hours after exposure. The urine formaldehyde concentration was higher in the second sample (2.5 mg/l) as opposed to the first (1 mg/l). Formic acid levels for the second sample were also elevated compared to the first (52 + or - 20 mg/l as opposed to 35 + or - 11 mg/l) These results were statistically different using a t - test ($p < \text{or} = 0.05$) Boeniger (1987). If the researcher had collected a baseline concentration before exposure and had not pooled the sample, the study would have been more valuable.

In the same study, urine samples were collected from four factory workers exposed to an average of 1 ppm formaldehyde. During the day of exposure a urine sample was collected. Workers were removed from the formaldehyde environment and another urine sample was collected six days after exposure. On the day of exposure the concentration was 152 mg/l and 6 days later it was 24 mg/l.

This difference is statistically significant ($p < 0.01$). It was determined that the students excreted approximately 7.5 M of formic acid for every mole of exposure to formaldehyde. This means that the formate excretion mass for workers was approximately 8 times higher than their exposure. Perhaps the excess elimination could be explained by concomitant dermal penetration of formaldehyde (Boeniger 1987).

In a review by Bardana (1991), the author states that "exogenous formaldehyde is rapidly cleared from the human plasma with a biological half life of one to one and a half minutes. Urinary formate or formic acid levels do not reflect environmental exposure to formaldehyde.

In view of the great variability in human urinary formate levels and the above statement by Bardana, it was decided to exclude urinary formate as a measure of formaldehyde exposure in this study.

2.4 FORMALDEHYDE EXPOSURE IN ANATOMY LABORATORIES AND MORTUARIES

The tissue hardening properties of formaldehyde were discovered in 1893. Since that time, formaldehyde's efficacy as a preserving and embalming agent has been realized, which has led to its widespread use as a constituent of embalming fluids. The use of formaldehyde eliminated the health hazards associated with the previously used metal based (arsenic, lead, mercury or zinc) solutions (Perkins et al. 1985).

Human cadavers used for dissection are traditionally embalmed with solutions containing formaldehyde. Occupational exposure to formaldehyde may be direct (physical contact) or indirect (air borne vapours). Exposure levels are determined by a host of interdependent factors, among which are: volume and concentration of solutions, region of dissection (body cavities hold higher concentrations than limbs), quality of room ventilation, room temperature, number and activity level of students working in the environment, number and location of cadavers relative to room size and ventilation avenues as well as the use of protective clothing (Winesaki and English 1989).

Various studies dating back to the 1970's were conducted in funeral parlours and anatomy laboratories. Kerfoot and Mooney (1975), completed an extensive study of six funeral homes in the Detroit area, collecting 187 air samples under a variety of conditions. The formaldehyde vapour concentration ranges varied between 0.09 to 5.26 ppm with the overall average concentration 0.74 ppm, prior to intervention.

Skisak (1983), evaluated formaldehyde exposures in a leading American State University. A total of 52 cadavers were present in the laboratory. Formaldehyde samples were collected from 8 similar laboratories All laboratories were under negative pressure and there was no recirculation of air. There were 17.5 air changes per hour and each laboratory had six or seven dissecting tables. The table tops remained closed when class was not in session. 44 % of all the breathing zone samples collected exceeded 1 ppm. Half of the detected exposures were in the 0.6 - 1 ppm range. The lowest value obtained was 0.3 and the highest 2.63 ppm. The majority 62 % of daily mean exposures detected were between 1 and 2 ppm. Nine out of ten ambient air samples were below 1 ppm (Skisak 1983).

A study of the exposures of medical students and staff to formaldehyde in an anatomy laboratory was conducted by Perkins et al. (1985). Laboratory periods were scheduled Monday through Friday for three hours each day. At any one time 8 - 10 instructors and 150 students were exposed to formaldehyde. The laboratory consisted of a rectangular room without windows. General Ventilation (100 % make up) was provided by four wall vents located in the corners of the room near the floor. Exhaust vents were located around fluorescent lights in the ceiling. Approximately 11 room - air changes occurred each hour. The design of the ventilation system described in the Perkins study is poor as formaldehyde is heavier than air and should therefore be exhausted at floor level. The results obtained in this study were summarized as follows :

Table IV. Formaldehyde vapour concentrations in an anatomy laboratory

SAMPLE TYPE	RANGE (PPM)	MEAN (PPM)	NUMBER OF SAMPLES
INSTRUCTOR	0.24 - 5.87	1.69	36
STUDENT	0.31 - 6.77	1.53	32
STATIC AREA	0.18 - 1.29	0.50	15

(Perkins et al. 1985)

A prospective study of respiratory effects of formaldehyde among healthy and asthmatic medical students was conducted by Uba et al. (1989). Lung function and respiratory symptoms among 103 medical students exposed to formaldehyde over a 7 month period was monitored in order to determine the incidence of bronchoconstriction and respiratory symptoms in response to exposure. The following summary of results was reported (tables V and VI).

Table V Relationship of formaldehyde exposure to acute symptoms during exposure, based on analysis of paired samples from 81 subjects

SYMPTOM	NUMBER OF SUBJECTS WHO REPORTED SYMPTOMS			
SYMPTOM	ONLY DURING EXPOSURE (A)	ONLY DURING CONTROL LAB. EXPOSURE (B)	ODDS RATIO (A/B)	p VALUE (2-SIDED)
Itchy eyes	33	1	33.0	<.001
Watery eyes	36	3	12.0	<.001
Burning eyes	47	0	infinite	<.001
Burning nose	19	0	infinite	<.001
Sore throat	21	4	5.3	<.01
Sneezing	10	1	10.0	<.01
Rhinorrhea	13	3	4.3	.01
Chest tightness	4	0	infinite	.05
Cough	5	4	1.3	NS
Wheezing	2	0	infinite	NS
Dyspnea	2	0	infinite	NS

(Uba et al. 1989)

Table VI Relationship of formaldehyde exposure to persistent symptoms, based on analysis of paired samples from 103 subjects

SYMPTOM	NUMBER OF SUBJECTS WHO REPORTED SYMPTOM			
SYMPTOM	ONLY AT BEGINNING OF EXPOSURE PERIOD (A)	ONLY AT END OF EXPOSURE PERIOD (B)	ODDS RATIO (B/A)	p VALUE 2 - SIDED
Cough	1	8	8.0	.02
Phlegm	4	9	2.3	NS
Chronic bronchitis	4	2	0.5	NS
Chest illness	9	0	0	<.001
Wheezing	37	1	0.03	<.001
Wheezing with dyspnea	4	0	0	.05
Dyspnea on exertion	0	0	-	-

(Uba et al. 1989)

Wheezing both with and without dyspnea were reported more frequently at the beginning of exposure, when formaldehyde levels were also higher. Time weighted average formaldehyde exposures were generally less than 1 ppm and peak exposures were less than 5 ppm. Average formaldehyde levels declined with time over the seven month period, these findings being consistent with Perkins (1985). Acute symptoms of eye and upper respiratory irritation were significantly associated with exposure to formaldehyde. There was no pattern of bronchoconstriction in response to exposure after either 2 weeks or 7 months of exposure. Twelve subjects had a history of asthma, they were no more likely to have symptoms of respiratory irritation or changes in pulmonary function than those without such a history.

The effect of low level exposure to formaldehyde on oral, nasal, and lymphocyte biological markers was studied prospectively in a group of 29 mortuary science students who were about to take a course in embalming. During the 85 day study period, the subjects performed an average of 6.9 embalmings and an average air concentration of 1.4 ppm was measured during embalming. Epithelial cells from the buccal area of the mouth showed a 12 fold increase in micronucleus frequency during the study period, from 0.046 +/- 0.17/1000 cells preexposure to 0.60 +/- 1.27/1000 cells at the end of the course ($P < 0.05$). Nasal epithelial micronuclei increased 22%, from 0.41 +/- 0.52/1000 cells to 0.50 +/- 0.67/1000 cells ($P = 0.26$). In blood cells, the frequency of micronucleated lymphocytes increased by 28%, from 4.95 +/- 1.72/1000 cells to 6.36 +/- 2.03/1000 cells ($P < 0.05$), while sister chromatid exchanges decreased 7.5% ($P < 0.05$). A dose response relationship was observed between cumulative exposure to formaldehyde and increases in buccal micronuclei in the 22 male subjects but not in the 7 female subjects. The authors concluded that low level exposure to formaldehyde is associated with cytogenetic changes in epithelial cells of the mouth and in blood lymphocytes. These cytogenetic effects may be useful as markers of biologically effective dose (Suruda 1993).

The increase in micronucleus frequency is consistent with the findings of Balarin et al. (1992) and Klein-Szanto et al. (1992) and may be associated with a defence mechanism of the epithelium upon exposure to low levels of formaldehyde.

Akbar Khanzadeh et al. (1994) performed a study of the exposure of students in gross anatomy laboratories. The specific objectives being to explore the degree of exposure, acute subjective symptoms and short term decrements in pulmonary function during one day (pre and post exposure) at various stages of the dissection process. Time weighted average (TWA) exposure to formaldehyde ranged from 0.07 - 2.94 parts per million (ppm) during dissecting operations.

More than 94% of the sample population were exposed to formaldehyde levels in excess of the ceiling value of 0.3 ppm. The study was conducted over a five week period after students had been exposed for six weeks. A weakness of the study is the fact that the sample population was very small (34 exposed and 12 controls). Furthermore, ambient levels of formaldehyde and reported symptoms are likely to decrease over time and the sampling was only initiated after six weeks of dissection. Reported symptoms included irritation of eye (88%), nose (74%), throat (29%), and airways (21%).

Each gross anatomy facility is a unique environment and a considerable variation will exist in laboratory design and institutional practices. Sources of variation include embalming techniques, number and spacing of dissecting tables, location of air supply diffusers and exhaust vents, air exchange rates and the utilization of retaining solutions. The substantial number of exposures greater than the TLV places a moral obligation upon academic institutions to evaluate and control formaldehyde levels in their facilities (Skisak 1983).

2.5 ENVIRONMENTAL SAMPLING OF FORMALDEHYDE

Several methods are available for determining the level of formaldehyde (HCHO) vapour in air. Selecting the appropriate sampling and analytical method is critical and must be consistent with the type of environment and the anticipated concentration levels to be sampled. The sampling method chosen should be critically evaluated for compatibility with the sampling strategy as well as for adequate sensitivity and precision. The specificity of the analytical method should be considered, including the potential for interference by phenols and other chemicals that may be present in the environment to be evaluated. Strict adherence to the manufacturers directions is essential to obtain valid results.

If epidemiological evaluations are being conducted, data relating to the demographic characteristics and health status of the exposed occupants and a suitable comparison group must be obtained. The health status must be specified by the use of standardized questionnaires which include queries regarding medical risk factors, occupational and lifestyle exposure, chronic symptoms and the temporal and spatial occurrence and nature of acute complaints (Bernstein et al. 1984).

The stability of an environmental hygiene sample is often neglected but yet it is extremely important in evaluating the overall effectiveness of an air monitoring method. It is therefore deemed necessary to consult sample stability studies before selecting a sampling method. Pure water should not be used as a collection medium for formaldehyde as the sample degrades rapidly. Various alternatives are available such as an aqueous solution of 1 % sodium bisulphite (Daggett and Stock 1985).

Until fairly recently the standard impinger collection method used to be the most common sampling method used. Room air is drawn through a derivatizing agent in solution at a calibrated flow rate with a sampling pump. The resulting solution is then analyzed by spectrophotometry. This method is suitable for short term area samples with a sensitivity range of apx. 0.1 ppm (lower limit), with a 25 litre sample of air. An advantage of this sampling method is that an integrated result over a period of time is obtained, the disadvantages, however, outweigh the advantages. The sampling "train" when set up is very cumbersome and difficult to attach near the breathing zone. The person wearing the sampler is severely restricted in his movements and can not bend over as he normally would during dissection, as the liquid in the impinger may spill. The transportation of the liquid based sample is difficult. Battery operated pumps are needed and these have to be calibrated properly. Problems are often experienced with pumps that are not able to maintain a constant flow rate over an extended sampling period.

An alternative method of sampling is the use of detector tubes A small quantity of air is drawn through a glass tube with a hand held pump. The tube contains a substance that will react with a specific air contaminant to produce a colour change. The length of the colour stain is indicative of the concentration.

Detector tubes are cheap but they lack sensitivity and are therefore used primarily as a qualitative tool. A sample taken in this manner gives an indication of the concentration at a specific point in time and is classified as a grab sample.

Passive diffusive sampling devices are gaining in popularity due to their small size and weight and the fact that no pump is required and they do not hamper the worker in any way. The badges consist of a liquid filled chamber, bound at the front by a permeable membrane which allows for the passage of gas or vapour but retains the liquid in the chamber.

A diffusion barrier 3 mm thick made from an inert material is mounted in front of the membrane. Sampling takes place through the barrier by diffusion followed by permutation through the membrane into the sampling medium. The sample is then analyzed by any of the normal methods used for the analysis of liquid samples (Ellwood et al. 1990).

After careful consideration Drager tubes were selected for the sampling of phenol and 3 M passive diffusion monitors for the sampling of formaldehyde.

2.6 BIOLOGICAL MONITORING OF EXPOSURE TO FORMALDEHYDE.

Biological monitoring is a rapidly emerging science that is finding increasing use. It is often used in conjunction with environmental monitoring to describe more completely exposures and absorption of chemicals found in the workplace. Specifically, biological monitoring includes the measurement of the absorption of an environmental chemical in a worker. In order to determine this effect, biological specimens are analyzed for the chemical agent, it's metabolite or some specific effect on the worker. In a broader sense it may include behavioral and performance testing and medical procedures.

Biological monitoring, unlike environmental monitoring, should be considered a medical procedure since, by definition, the specimen comes directly from a human, informed consent and medical - legal ethics are important issues that have to be considered by the researcher. Considerable advance planning is necessary in order to select the most appropriate test and to ensure that data is obtained that will be meaningful in assessing worker exposure. Factors such as the types of exposure (acute / chronic / intermittent) and routes of exposure as well as other chemicals in the environment are to be considered. Biological monitoring has been called the ultimate personal sampler because, when properly used, it can assess worker exposure to industrial chemicals by all routes including skin absorption and ingestion.

A limitation of biological monitoring is the lack of detailed information on the fate of industrial chemicals in humans. Most of the data available is obtained from animal studies and these can not always be applied to humans. Another concern is the apparent wide variability seen in the majority of biological monitoring data. Research is under way to develop more definitive methods and to better define dose - response relationships and suggested limit values. Proper collection, preservation and shipment of samples is essential (NIOSH 1985).

Animal experimentation has established the carcinogenic potential of formaldehyde upon the nasal epithelium, yet there is no recognised biological screening or sampling method to measure personal exposure to formaldehyde vapour. The nose is the contact organ for inhaled air contaminants and formaldehyde is readily solubilised by the mucous membrane where it has an irritant effect. The hypothesis that exposure to formaldehyde will exhibit an effect upon the nasal epithelium is therefore considered to be plausible.

After reviewing the literature ACGIH (1992), Balarin et al. (1992), Klein-Szanto et al. (1992) and Suruda (1993), it was decided to collect nasal epithelial cells according to the methodology of Balarin et al. (1992), in order to ascertain whether cytological examination of the nasal epithelium could be used as a biological screening method for formaldehyde exposure.

2.7 ENVIRONMENTAL CONTROL

Environmental hazards in a workplace have to be controlled in order to render an environment safe for humans to work in without undue discomfort or risk to their health.

Hazards in a work environment such as the Anatomy Laboratory can be controlled in various ways.

2.7.1 Engineering Control

Engineering control refers to the design of the facility and applies the principles of substitution, isolation and ventilation. Engineering controls are more costly initially but they are also more effective.

i. Substitution :

If one were to apply this principle it would mean discontinuing the use of formaldehyde in the embalming and preservation process, while ensuring that the substance used as a substitute is in fact safer to use and easier to control. This may not seem to be a feasible option as formaldehyde was used for cadaver preservation because it was found to be safer than some of the previously used embalming preparations such as mercury. Since substitution would however be the best option in any environmental control programme it does warrant further investigation. The questions raised are :

ia. Do undergraduate medical students need to dissect a cadaver or could one make use of alternative methods to teach anatomy, this would suggest an evaluation of the current curriculum and an investigation into alternative methods and techniques of teaching the subject matter.

ib. Do all medical students need to dissect a cadaver or only some (for example those wishing to specialise in a surgical discipline) as this would significantly reduce the exposed population and the number of cadavers needed. This is also a curriculum related matter.

ic. Can the method of preservation / embalming be changed? Literature does suggest that there are different embalming techniques available that significantly reduce the levels of irritating and health threatening chemicals in the dissection room. One of the alternatives suggested is phenoxyethanol (Wineski and English 1989).

Thiel (1992) in Germany has developed a new low odour embalming technique and reports that the colour, consistency and transparency of the cadaver is well preserved without releasing harmful substances into the environment.

Plastination may an alternative, where a number of cadavers may be dissected and once treated would not emit any vapours. Plastination is an expensive technique and the capital outlay to prepare cadavers in this way would be very high.

Computer aided education through virtual reality is also becoming a feasible alternative as such programmes are being developed in the USA.

ii. Isolation :

Isolation implies interposing a barrier between the source of contamination and the individual (USA 1973 p.517). In this instance isolation is not a practical control measure, however the use of glove boxes may be of value.

iii. Ventilation :

Ventilation is the most common engineering control measure used. General ventilation dilutes the contaminants in the air to such an extent that the concentration of the contaminant is kept below levels hazardous for most human beings. The following criteria should be used to ascertain whether one can make use of general (dilution) ventilation:

iii a. small quantities of contaminant released at a uniform rate.

iii b. sufficient air movement to dilute the contaminant before it reaches the breathing zone

iii c. low toxicity of the contaminant

iii d. no need to filter the air discharged to the atmosphere (Plog 1988 p.507).

2.7.2 Administrative controls

Administrative controls do not apply in this instance as this method deals mainly with controlling exposure levels by rotating staff to reduce individual exposure time.

2.7.3 Personal protective equipment (PPE)

PPE should be a "last resort" interim control measure. Any ppe programme needs to be supported by proper advice in terms of the selection of equipment, supervision to ensure the correct use and maintenance of equipment as well as on going monitoring of the contaminants to ensure compliance with legislation.

2.8 SUMMARY CONCLUSIONS

From the review of literature the following can be concluded.

i. Formaldehyde should be considered a mild or weak human carcinogen of the nasal epithelium, IARC classification 2A.

ii. Formaldehyde may cause sensitisation of the skin, upper respiratory tract and lung in some individuals.

iii. Formaldehyde will cause discomfort and irritation in exposed persons at very low levels in some instances below 0.3 ppm.

iv. High levels of exposure to formaldehyde have been recorded in anatomy laboratories overseas, no data on South African exposures was found.

v. Formate levels in urine or blood and lung function parameters are not considered to be accurate indicators of formaldehyde exposure.

vi. The nasal epithelium is considered to be the most likely objective biological indicator of exposure to formaldehyde.

vii. It is likely that at the levels of exposure measured in anatomy laboratories the exposed population at Natal University would suffer from irritational symptoms.

viii. Monitoring of formaldehyde by means of passive diffusion personal samplers is currently the preferred method of sampling.

CHAPTER 3

METHODS

3.1 STUDY DESIGN

In order to evaluate the potential health risk associated with formaldehyde vapour exposure in the Human Anatomy laboratory of the Faculty of Medicine, University of Natal, a study was designed to collect and analyze data related to:

i. demographic composition of the various formaldehyde exposed groups.

ii. air flow patterns and velocities as well as formaldehyde vapour concentrations in the laboratory environment.

iii. frequency of formaldehyde related symptoms experienced by the exposed groups.

iv. cytological examination of scrapings of the nasal epithelium of exposed staff members and a matched control group.

A cross sectional descriptive study was conducted during the period, July 1993 to June 1994. Upon implementation of our environmental control recommendations, made to the safety committee of the University, the study design was changed to a longitudinal cohort (follow up study). The frequency of formaldehyde related symptoms in the exposed groups as well as environmental parameters were re - evaluated in 1995, following the installation of a new ventilation system in the Anatomy Laboratory (intervention).

Permission to conduct the study was obtained from the Dean of the Faculty of Medicine, the acting Head of the Department of Anatomy, the Higher Degrees Committee and all persons who participated in the study (appendix B).

The study design of the symptom prevalence survey is illustrated in figure 2.

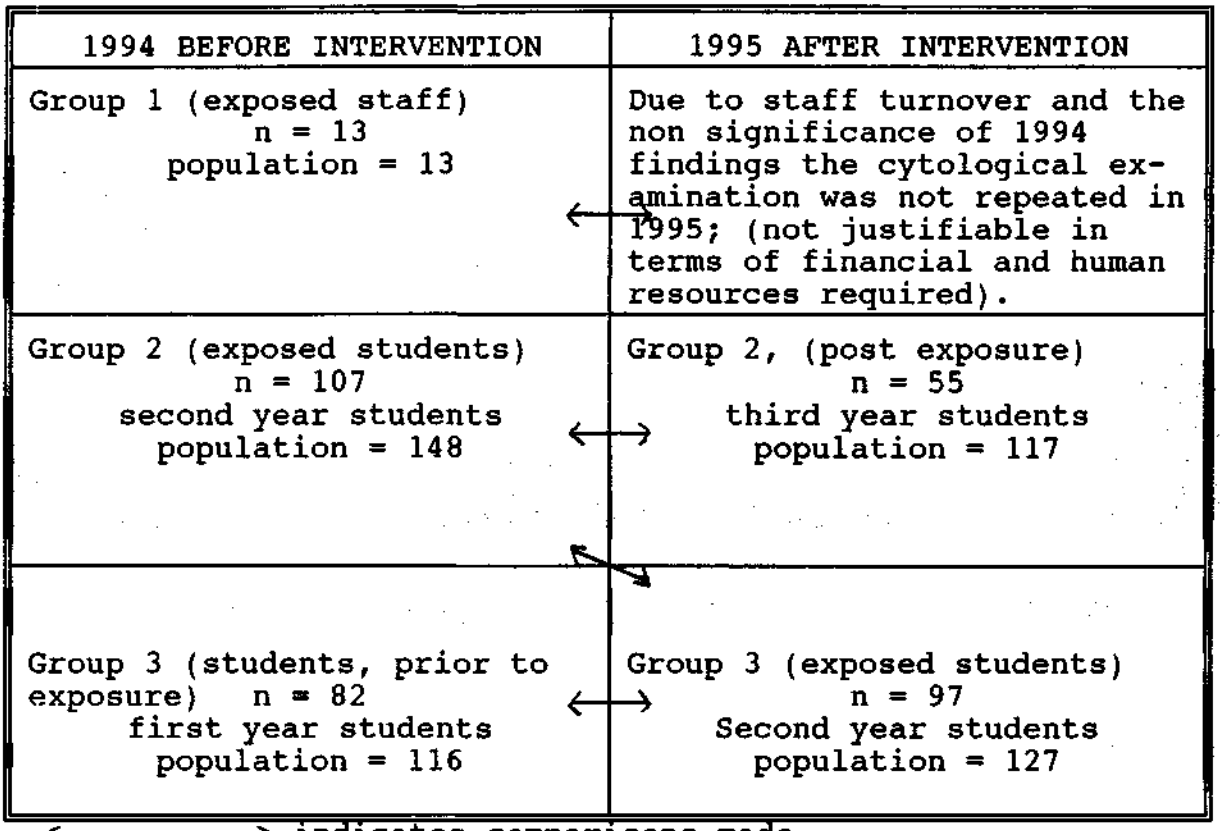

Figure 2 Study design: Cross sectional comparison of groups 1,2 and 3 and a longitudinal cohort study of groups 2 and 3.

3.1.2 Study populations

The study population consisted of all staff members in the Anatomy Department who were exposed to formaldehyde during 1994, (academic and technical staff) as well as all second year (anatomy) students of 1994 and 1995. All students present in class at the time of sampling were included in the study. The following three study groups were distinguished.

3.1.2.1 Group 1

This group consisted of all the exposed staff members in the Anatomy Department during 1994 (n = 13). All staff members were males aged between 25 and 57 years, 11 staff members were Indian and two African.

A control group (n = 12) which consisted of volunteers from the Durban City Health Department, with no prior occupational exposure to formaldehyde and which was matched for age, race, sex, smoking habits and socio - economic factors was selected, this group consisted of 10 Indians and two African males between the ages of 25 and 57.

Group 1 and their controls completed the questionnaire and samples of their nasal epithelium were taken.

3.1.2.2 Group 2

This group consisted of all the second year (anatomy) students present in class on the day of the study. These students were exposed to the laboratory environment during 1994 (n = 107) and were followed through to their third year of study in 1995 (n = 55), where they were no longer exposed.

The high dropout rate in this group can be attributed to the fact that permission for the continuation of the study was obtained very late in the year and students were requested to complete the questionnaire after their last lecture of the term. Many students were absent from the lecture and others did not stay after the lecture to complete the questionnaire.

3.1.2.3 Group 3

This group consisted of all the 1994 first year students present in class on the day of the study. These students were not exposed to formaldehyde during 1994, (n = 82) and the group was followed through to 1995 where they became the exposed group (n = 97). Students were requested to complete the questionnaire in 1995 after their last Anatomy lecture of the term and there were more students present on this day than during the 1994 study.

3.1.3 Study methods

3.1.3.1 Environmental measurements

At the time of sampling two rows of dissecting tables were arranged across the length of the rectangular anatomy laboratory, 17 on one side and 18 on the other (35 in total). The tables were approximately 1 metre apart with a passage of approximately 2 metres wide down the centre of the hall. The anatomy laboratory is 9.30 M X 30.8 M and 2.85 M in height. All windows are closed and ventilation is mechanical.

3.1.3.1.1 Ventilation

Smoke tubes were used to visualise air flow patterns in the laboratory in order to subjectively evaluate the effectiveness of contaminant capture by the exhaust air system.

The efficiency of the ventilation system was measured before and after the intervention (new ventilation system) with the aid of a metrosonics hot wire anemometer, as well as a calibrated wet and dry bulb thermometer with psychometric chart and smoke tubes.

3.1.3.1.2 Formaldehyde vapour sampling

Formaldehyde samples were collected by passive diffusion with the aid of 3M monitors. The monitors were used as personal samplers and were clipped onto the collars of individuals as close to the breathing zone as possible. Formaldehyde was measured at various stages of the dissection process during 1993, 1994 and 1995. These data were related to activities taking place in the laboratory at the time of the survey as well as the ventilation system in use at the time. Time periods of formaldehyde sampling in each case was for the full duration of a laboratory session (3 hours). The 35 cadavers are considered to be the principle sources of formaldehyde contamination of the air. Bodies were laid out in a near perfect grid, providing for a homogenous distribution of the contaminant in the sampling environment. Sampling positions were selected from the grid in order to evenly distribute the samples throughout the anatomy laboratory as illustrated in figure 3.

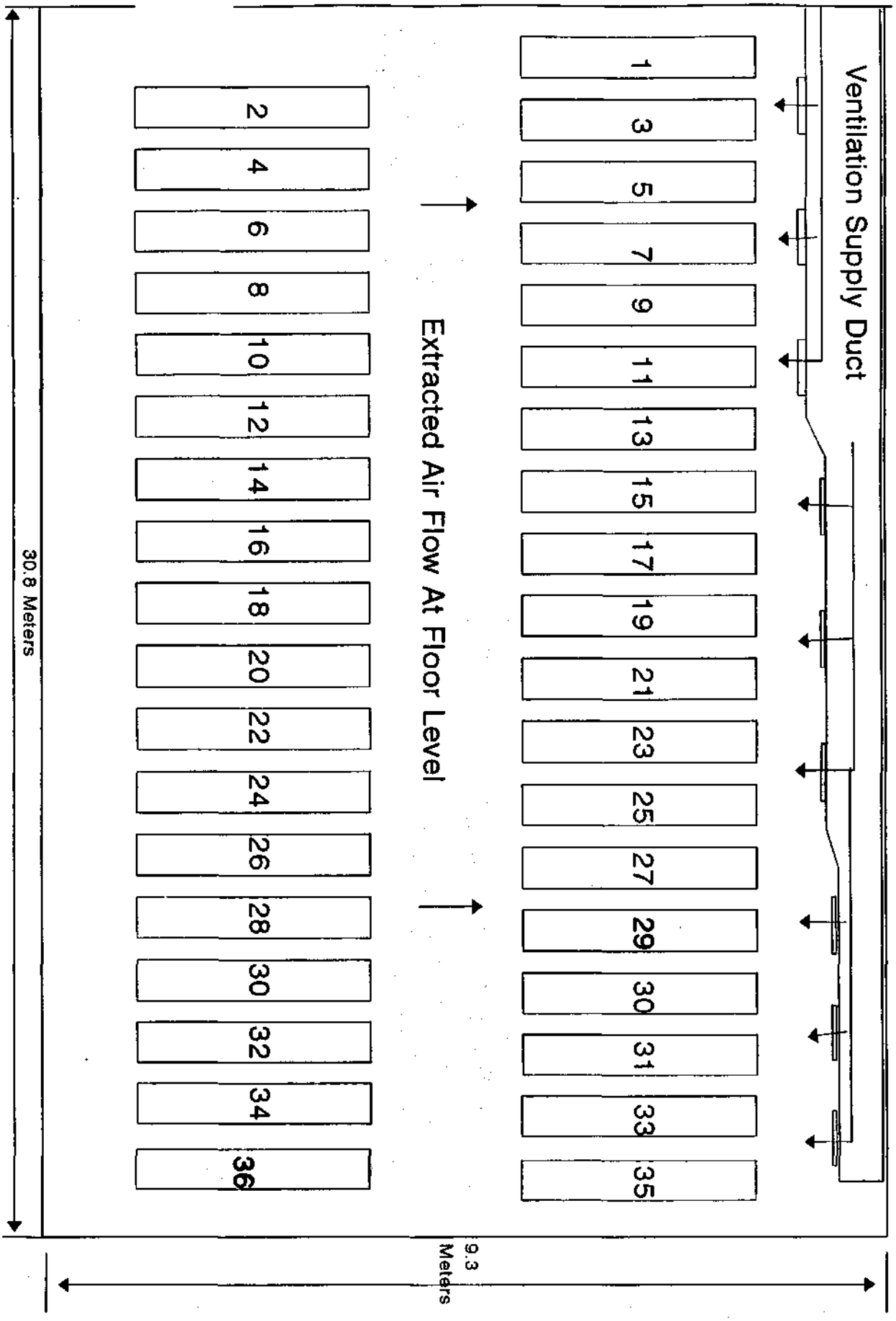

Figure 3: Sampling positions in the Anatomy Laboratory

All chemical samples were taken and analyzed in accordance with 3 M analytical Method 4D (1985), this being the prescribed method for 3M monitor # 3720 or # 3721, by an independent SABS approved laboratory in Johannesburg. A control monitor or "field blank" was subjected to the same environmental conditions as the other formaldehyde monitors by placing an unopened monitor in the laboratory environment. The blanks were sent together with the batches of samples to the 3 M laboratory in Johannesburg where they were analyzed according to 3M method 4D (1985), as specified by the manufacturer, (Appendix B).

Humidity, atmospheric pressure and phenol levels were taken into consideration during the analysis of the samples but the use of correction factors was not necessary as the acceptable parameters were not exceeded.

After implementation of the environmental controls in the form of a new ventilation system, the sampling regimen of 16 July 1993 was repeated on 29 September 1995. The reasoning being that cadavers were at the same stage of dissection, as they were during the 16 July 1993 sampling period. By taking formaldehyde samples and ventilation measurements in exactly the same positions as in 1993 (prior to intervention), one could therefore hypothesise that a comparison of these formaldehyde vapour results would be a measure of the effectiveness of the ventilation intervention. Ventilation was not measured during 1994 as installation of the new ventilation system had not been completed.

3.1.3.1.3 Symptom frequency study

Data relating to symptoms associated with formaldehyde vapour exposure were obtained from the respective study populations during July 1994 and September 1995 with the aid of self administered, standardised questionnaires (Appendix C). This questionnaire was developed by Sherwood Burge et al. (1987), who showed a 96% repeatability in symptoms reported in building populations when measured one year apart.

On 28 June 1994, group 1 (Anatomy staff), as well as a control group of health officers from Durban City Health Department, (matched for age, race, gender and smoking habits) and with no previous occupational exposure to formaldehyde, were also requested to complete the questionnaire. On 14 July 1994 group 2 which consisted of the exposed anatomy students (second years) were requested to complete the same health questionnaire. First year medical students with no known exposure to formaldehyde vapour (group 3), completed the questionnaire on 25 July 1994.

Just over a year later group 3 and group 2, were requested to repeat the questionnaire survey on 29 September and 6 October 1995 respectively, in order to measure the effectiveness of the intervention, as well as the effect of initiation and cessation of exposure.

Due to the refusal of most students to provide their names on the questionnaire, personal levels of exposure could not be related to symptom frequency. Data was used in group data format only.

The data obtained from the health questionnaires were analyzed by the Medical Research Council (Institute of Biostatistics 1994) and Mr. C Robert (1995), using SAS version 6.08. Various statistical tests such as CHI Square, hypothesis testing for the difference between two population proportions and logistic regression were used for hypothesis testing in relation to the effects of exposure to formaldehyde on the health of students and staff. Identified confounders such as age, smoking habits, gender, race and whether the person lived in an industrial area, were controlled for in the analysis.

3.1.3.1.4 Biological monitoring

After due consideration of the literature, cost factors and compliance of the subjects, it was decided to use nasal scrapings of the formaldehyde exposed staff members and their controls as a potential biological indicator of formaldehyde exposure. Samples were collected by means of endo - cervical brushes as performed by Balarin (1992) to obtain objective data in respect of the cytological effect of formaldehyde vapour exposure upon the nasal epithelium.

Permission for this form of sampling was obtained from the higher degrees and ethics committees as well as from all members of the sample group and their controls. All members were requested to complete a consent form; (appendix D) and were properly informed of the procedures that were to be carried out upon them (appendix E).

On 28 July 1994, a registered Medical Practitioner obtained samples of the nasal epithelium of both the sample group and control group with the aid of endo cervical brushes. Cells were fixed on glass slides by Cytotechnicians from the Cytology Department of the Provincial Pathology laboratory services in Durban. The slides were transported to the pathology laboratory where they were analyzed by a medical technologist for epithelial changes. Logistic regression was used by the Medical Research Council (Institute of Biostatistics) to analyze the data and to determine the relationship between the number of columnar cells, squamous cells and metaplastic cells and exposure to formaldehyde. This study was not repeated in 1995.

3.2 REDUCTION OF BIAS

i. All instruments used were calibrated and SABS approved.

ii. All formaldehyde samples were taken and analyzed according to the instructions of the manufacture. Control samples (field blanks) were exposed to the exact conditions encountered during sampling and the formaldehyde absorbance of the controls was subtracted from the measured results.

iii. The formaldehyde sampling method selected has a cross sensitivity for phenol, airborne phenol vapour concentrations in the air were therefore measured to determine if a correction factor calculation would be necessary in determining the formaldehyde concentration.

Three grab samples of phenol (one on either side of the laboratory and one in the centre), were obtained and evaluated with drager tubes in accordance with the instructions of the manufacturer. All three samples were below the level of detection of the instrument. Correction for temperature was not required, no cross sensitivities were observed and the pump was flushed after each operation.

iv. Personal sampling positions were spread throughout the laboratory environment in a "sampling grid" and monitors were suspended as close to the breathing zone of the subject as possible.

v. A validated indoor air quality questionnaire designed by Burge et al. (1987), was adapted and used to obtain data relating to symptoms associated with formaldehyde exposure, from all exposed individuals.

vi. Scrapings of the nasal epithelium were obtained from all exposed staff members and controls matched for age, race, smoking habits and gender, the latter had no known occupational exposure to formaldehyde.

vii. Environmental samples were obtained on 16 July 1993, 24 January 1994, 18 March 1994, 26 July 1994 and 29 September 1995, in order to obtain data at various stages of dissection of the cadavers as well as to measure the effectiveness of the new ventilation system (intervention).

CHAPTER 4

RESULTS

The following results were obtained:

4.1 DEMOGRAPHIC DATA

4.1.1 Group 1

The characteristics of the group and their matched controls is summarised in table VII. The table shows that there was no significant demographic difference between the groups, except for the variable measured (exposure to formaldehyde).

Table VII Demographic data of group 1 and controls

VARIABLE	EXPOSED GROUP (n = 13)	CONTROL GROUP (n = 12)	P-Value
RACE	69.23 % Indian 30.77 % Black	91.67 % Indian 8.33 % Black	0.81
AGE	mean 37.62 sd = 11.072	mean 38.08 sd = 12.508	0.808
SEX	100 % male	100 % male	-
% CURRENT OR EX -SMOKERS	38.46%	33.33%	0.881
YEARS EXPOSED TO FORMALDEHYDE	mean 12.77 sd = 9.4	0	-

sd (standard deviation)

P values were calculated from Chi squared testing of the difference between two population proportions.

4.1.2 Group 2

Table VIII shows that the students who participated in group 2 were comparable in terms of age and sex, however there was a significant difference in racial composition as well as a statistically non significant increase in the number of smoking students. Since cigarette smoke contains 0.82 mg of formaldehyde per pack, further statistical analyses (logistic regression) was performed in order to test whether race and smoking were confounding variables. The results proved negative, race, r = 0.16 (p = 0.24) and smoking, r = 0.22 (p = 0.15).

Table VIII Comparison of demographic data of group 2 (1994 - 1995)

VARIABLE	1994 (n = 107) EXPOSED	1995 (n = 55) POST - EXPOSURE	P - Value
RACE	58 % Black 42 % Indian	38 % Black 62 % Indian	**0.033**
AGE	mean 18.641 sd = 3.712	mean 19.731 sd = 3.920	0,383
SEX	46 % female 54 % male	42.31 % female 57.69 % male	0,768
% CURRENT AND EX - SMOKERS	11.43 %	16.36 %	0.59
PERIOD OF EXPOSURE TO FORMALDEHYDE IN PREVIOUS 6 MONTHS	6 months	0	

sd (standard deviation)

P values were calculated from Chi squared testing of the difference between two population proportions.

4.1.3 Group 3

The characteristics of group 3 over the study period are summarised in table IX. The table shows that there was no significant demographic difference between the groups, except for the variable measured (exposure to formaldehyde). There was a statistically non significant increase in the number of smoking students.

Table IX Comparison of demographic data of group 3 (1994 - 1995)

VARIABLE	1994 (n = 82) PRE - EXPOSURE	1995 (n = 97) EXPOSED	P - Value
RACE	39.51 % Black 60.49 % Indian	50.55 % Black 49.45 % Indian	0.924
AGE	mean 18.073 sd = 0.663	mean 20.73 sd = 1.324	0.883
SEX	53.66 % female 46 34 % male	50 % female 50 % male	0.739
% CURRENT AND EX - SMOKERS	6.1 %	12.4 %	0.233
PERIOD EXPOSED TO FORMALDEHYDE	0	8 months	

sd (standard deviation)

P values were calculated from Chi squared testing of the difference between two population proportions.

4.1.4 Comparison of group 2 and group 3

During the analysis of data a comparison was made between the exposed student groups of 1994 and 1995 (table X). The demographic data of these groups was compared and there were no significant differences between the groups except for the fact that the 1995 group had an exposure period of 8 months as opposed to the 6 months of the 1994 group.

Table X Comparison of demographic data between exposed student groups of 1994 and 1995

VARIABLE	1994 (n = 107) EXPOSED	1995 (n = 97) EXPOSED	P - Value
RACE	58 % Black 42 % Indian	50.55 % Black 49.45 % Indian	0.375
AGE	mean 18.641 sd = 3.712	mean 20.73 sd = 1,324	0.543
SEX	46 % female 54 % male	50 % female 50 % male	0.696
% CURRENT AND EX-SMOKERS	11.43 %	12.4 %	0.987
YEARS EXPOSED TO FORMALDEHYDE	6 months at mean of 0.63 ppm	8 months at mean of 0.05 ppm	-

sd (standard deviation)

P values were calculated from Chi squared testing of the difference between two population proportions.

4.1.5 Comparison of group 1 and group 2 of 1992

In an attempt to ascertain long term versus short term exposure symptoms, the exposed student group of 1994 were compared to the exposed staff group of 1994. These demographic data are presented in table XI. It was felt that there were such large differences between these two groups that a comparison of the two study populations would not be valid.

Table XI Comparison between exposed students and staff of 1994

VARIABLE	1994 (n = 107) EXPOSED STUDENTS	1994 (n = 12) EXPOSED STAFF	P - Value
RACE	58 % Black 42 % Indian	30.77 % Black 69.23 % Indian	0.119
AGE	mean 18.641 sd = 3.712	mean 37.62 sd = 11.072	**0.000**
SEX	46 % female 54 % male	100 % male	**0.006**
% CURRENT AND EX-SMOKERS	11.43 %	38.46 %	**0.028**
YEARS EXPOSED TO FORMALDEHYDE	6 months	mean 12.77 sd = 9.4	**0.000**

sd (standard deviation)

P values were calculated from Chi squared testing of the difference between two population proportions.

4.2 ENVIRONMENTAL MEASUREMENTS

4.2.1 Air flow

The results of the air flow velocity measurements at the various work stations, before and after the intervention are shown in table XII.

Table XII Air flow velocities measured in the Anatomy laboratory before and after installation of the new ventilation system

SAMPLE NUMBER	DISSECTION TABLE	AIR FLOW ms^{-1} 16/7/1993	AIR FLOW ms^{-1} 29/9/1995
1	6	0.1	0.2
2	14	0	0.2
3	22	0.1	0.2
4	32	0	0.5
5	27	0	0.2
6	21	0	0.1
7	15	0	0.1
8	9	0.1	0.2
9	23	0.1	0.5

A Wilcoxon test for matched pairs was performed and a significant increase in airflow for 1995, (post intervention) was shown (significance level = 0.01).

4.2.2 Temperature and relative humidity

Temperature and relative humidity were measured in order to ensure that the acceptable parameters of the sampling instrument were not exceeded. All readings taken were within acceptable limits as specified by the manufacturers for the use of both the formaldehyde and phenol sampling equipment and therefore no correction factor calculations were required.

Table XIII Average temperature and relative humidity measured on the days of sampling

DATE	temperature in °C	Relative humidity
16 July 1993	22.3	43%
24 January 1994	24.4	67%
18 March 1994	23	65%
26 July 1994	22.6	54%
29 September 1995	22.2	64%

4.2.3 Formaldehyde Vapour Concentrations

Results of formaldehyde concentrations measured during July 1993 as well as January, March and July 1994, are presented in Table XIV. In 12 out of 19 samples the American ACGIH standards were exceeded. However in all cases except one (during brain dissection in July 1994) levels were within the UK and South African limits. The data also demonstrates a decline in formaldehyde levels over time as the year progresses, however a peak in formaldehyde vapour levels was experienced when brain dissection was performed. An unusually high reading was obtained from sample 8, position 23 on 16 July 1993, this could not be explained and the possibility that the monitor was faulty or was tampered with can not be excluded. Since the mean levels measured for this period are however still within the South African limits the reading was not excluded from the results.

Table XIV Measured formaldehyde concentrations in the Anatomy Laboratory, prior to intervention

DATE	SAMPLE NO	POSITION SEE FIG.2	MEASURED CONC (PPM)
16/07/1993 LOWER LIMB	1	6	0.3
"	2	14	0.29
"	3	22	0.19
"	4	32	0.19
"	5	21	0.26
"	6	15	0.23
"	7	9	0.26
"	8	23	0.83
24/01/1994 DAY 1 OF DISSECTION	1	27	0.29
"	2	3	0.80
"	3	34	0.84
"	4	29	0.40
18/03/1994 ABDOMEN OPEN	1	36	0.46
"	2	4	1.10
"	3	17	0.48
"	4	13	0.63
26/07/1994 BRAIN DISSECTION	1	19	1.25
"	2	34	2.29
"	3	11	0.91

After the University authorities installed the new ventilation system the formaldehyde concentrations were measured again. Table XV shows that there was a significant decline in formaldehyde levels. All measurements were well within the most stringent (ACGIH) limits.

Table XV Formaldehyde concentrations measured in the Anatomy Laboratory after intervention

DATE	SAMPLE NO.	POSITION SEE FIG.2	MEASURED CONCENTRATION (PPM)
29/09/95	1	6	< 0.03
"	2	14	0.04
"	3	22	0.08
"	4	32	0.08
"	5	21	< 0.03
"	6	15	0.04
"	7	9	< 0.03
"	8	23	0.06
"	9	27	< 0.08

Figure 4. illustrates the decline of formaldehyde vapour levels with time as well as the peak experienced during brain dissection and the effectiveness of the ventilation intervention (1995 results).

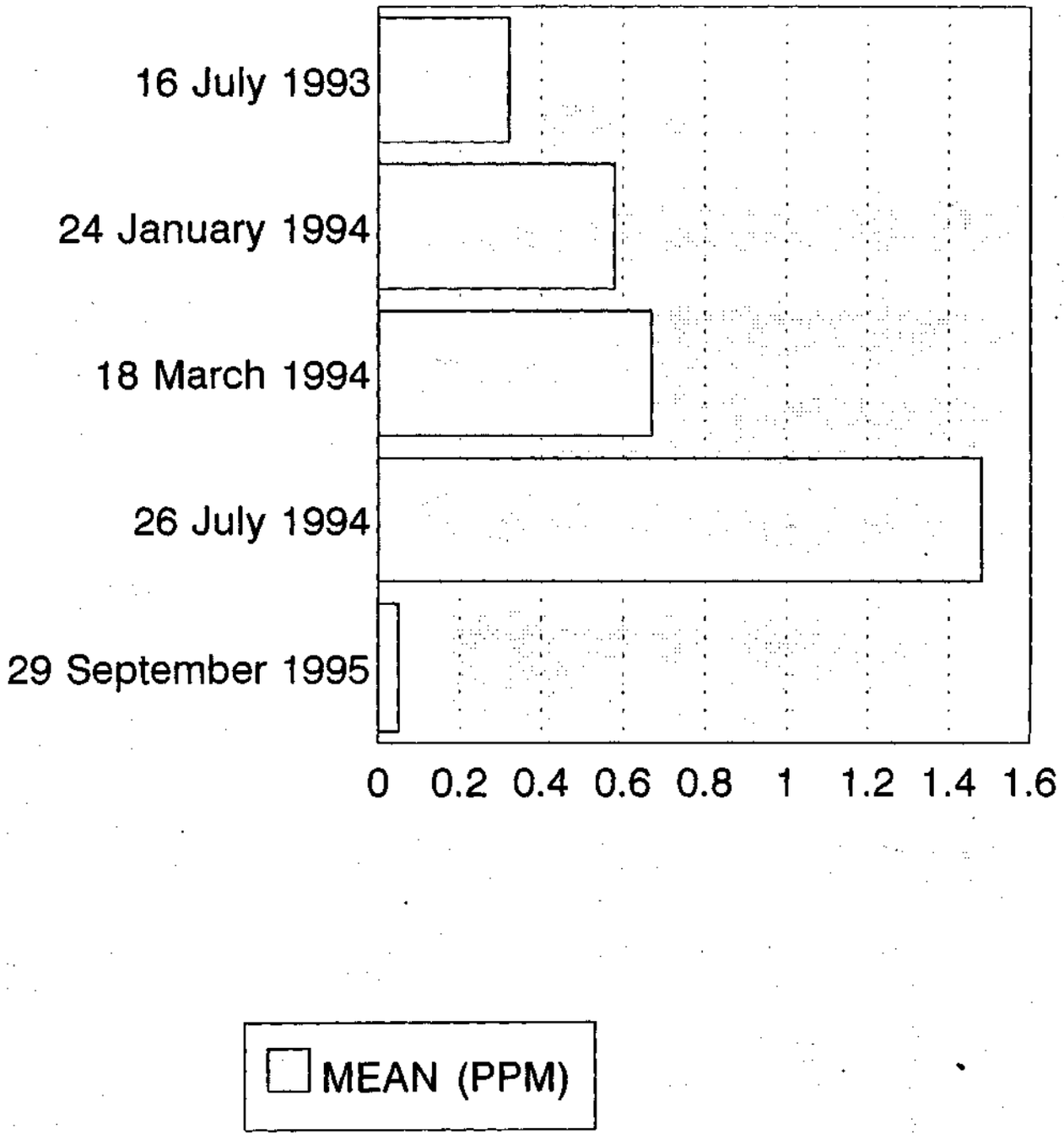

Figure 4 Variation in formaldehyde vapour levels over time

Based upon the assumption of a normal distribution of data, a (t - test) was performed by comparing the two data sets in table XVI and a significant drop in formaldehyde levels was demonstrated (t = 0.0085). In addition a Wilcoxon test for matched pairs (non - parametric statistics) was performed and this test also demonstrated a significant decrease in formaldehyde levels at a 1 % level of significance. P values were calculated from Chi squared testing of the difference between two population proportions. A significant improvement in the laboratory ventilation was demonstrated after intervention (P = 0.000).

Table XVI Comparison between pre and post intervention results, measured in the same positions at a similar stage of dissection

SAMPLE NO	POSITION IN LAB.	FORMALDEHYDE CONCENTRATION IN (PPM) **BEFORE (PRE) INTER-VENTION, 1993**	FORMALDEHYDE CONCENTRATION IN (PPM) **AFTER (POST) INTER-VENTION, 1995**
1	6	0.3	< 0.03
2	14	0.29	0.04
3	22	0.19	0.08
4	32	0.19	0.08
5	21	0.26	< 0.03
6	15	0.23	0.04
7	9	0.26	< 0.03
8	23	0.83	0.06
9	27	sample damaged	< 0.03

The significantly reduced formaldehyde in air levels at all sampling sites after the introduction of engineering controls is illustrated in ppm. (figure 5).
figure 5.

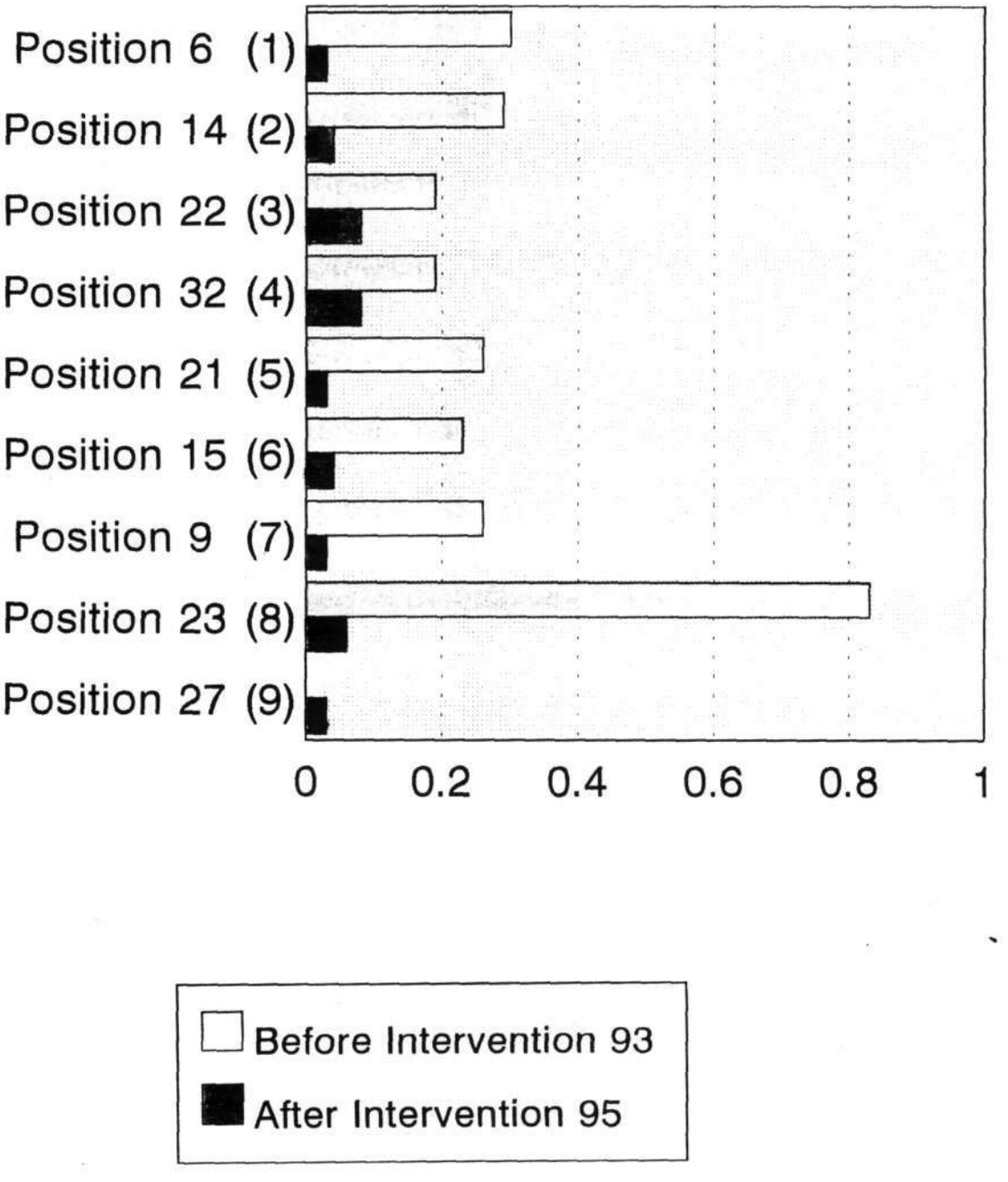

Figure 5: Formaldehyde vapour levels before and after intervention

4.3 QUESTIONNAIRE DATA

Table XVII represents a summary of the response rate of all three study groups. The overall response rate of all groups was very good (83.35 % - 100 %) and the analysis of the data is therefore acceptable.

Table XVII Response rate of all study groups

SYMPTOM	% MISSING RESPONSES FOR GROUP 1 1994 n = 12	% MISSING RESPONSES FOR GROUP 2 1994 + 1995 n = 162	% MISSING RESPONSES FOR GROUP 3 1994 + 1995 n = 179
HEADACHE	0 %	11.7 %	4.47 %
EYE IRRIT.	O %	2.47 %	2.79 %
LACRIMATION	0 %	3.08 %	1.12 %
BLOCKED NOSE	8.34 %	4.32 %	22.9 %
RUNNY NOSE	16.67	2.47 %	0.56 %
THROAT IRRIT.	0 %	3.09 %	0.06 %
DRY THROAT	8.34 %	3.09 %	0.06 %
COUGHING	8.34 %	3.09 %	0.06 %
PHLEGM	0 %	2.47 %	1.12 %
CHEST TIGHT	16.67 %	3.09 %	2.79 %
LOSS SMELL	25 %	3.7 %	1.12 %
DRY SKIN	0 %	3.70 %	0.06 %
DISTURB SLEEP	0 %	3.09 %	0.06 %
DEPRESSION	0 %	3.7 %	0.06 %
THIRST/AWAKE	0 %	4.32 %	0.06 %
MENSTRUAL DIS	all male	3.09 % of females	3.02 % of females
TIME OFF	0 %	8.64 %	7.27 %
SEX	0 %	6.8 %	1.68 %
RACE	0 %	6.8 %	2.8 %
AGE	0 %	2.47 %	0 %

Table XVIII presents a summary of the symptoms experienced by all student groups measured.

Table XVIII Symptoms experienced by all student groups

SYMPTOM	PRE EXP. FIRST YRS GROUP 3 1994 (n=82)	EXPOSED SECOND YRS GROUP 3 1995 (n=97)	EXPOSED SECOND YRS GROUP 2 1994 (n=107)	POST EXP. THIRD YRS GROUP 2 1995 (n=55)
HEADACHE	55.6 %	80.2 %	74.5 %	64.2 %
EYE IRRIT.	22.8 %	**52.6 %**	**62.3 %**	44.2 %
LACRIMATION	19.8 %	**62.5 %**	**64.5 %**	34.0 %
BLOCK NOSE	48.8 %	60.0 %	61.0 %	60.0 %
RUNNY NOSE	46.3 %	51.0 %	62.6 %	52.9 %
THROAT IR.	30.5 %	50.0 %	58.5 %	47.1 %
DRY THROAT	17.1 %	26.0 %	33.0 %	19.6 %
COUGH	41.5 %	42.7 %	45.8 %	30.0 %
PHLEGM	15.9 %	22.9 %	24.3 %	20.0 %
TIGHT CHEST	12.2 %	18.8 %	26.2 %	14.0 %
LOSS SMELL	4.90 %	11.6 %	17.9 %	14.0 %
DRY SKIN	29.3 %	**35.4 %**	**50.0 %**	26.0 %
DIST. SLEEP	34.1 %	**35.4 %**	**50.5 %**	32.0 %
DEPRESS.	36.6 %	**50.0 %**	**57.5 %**	22.0 %
THIRST/AWAKE	12.2 %	26.0 %	27.6 %	16.0 %
MENST. DIS	19.6 %	**21.6 %**	**26.3 %**	6.10 %
TIME OFF	6.30 %	27.6 %	16.7 %	15.2 %

Symptoms highlighted in bold are significantly associated with exposure to the laboratory environment when comparing students during and (after / prior to) exposure ($p < 0.05$). P values were calculated from Chi squared testing of the difference between two population proportions.

Table XIX demonstrates symptoms that are frequently experienced by exposed staff members when compared to controls. This was most significant for eye irritation, throat irritation, phlegm, lacrimation, dry throat and sick leave.

Table XIX Symptoms for which staff displayed a significant exposure effect when comparing exposed to non - exposed persons, prior to intervention

SYMPTOM	ODDS RATIO	P - VALUE
EYE IRRITATION	**48.98**	**0.0012 ***
LACRIMATION	**52.97**	**0.0024 ***
THROAT IRRITATION	**26.72**	**0.0013 ***
DEPRESSION	**6.09**	**0.0308 ***
BLOCKED NOSE	**2.59**	**0.0333 ***
COUGH	**2.84**	**0.0164 ***
PHLEGM	**5.26**	**0.0016 ***
DRY THROAT	**3.86**	**0.0041 ***
WHEEZING	**2.74**	**0.0186 ***
LOSS OF SMELL	5.38	0.0667
SICK LEAVE	**3.35**	**0.004 ***

*** indicates significant results**

P values were calculated from Chi squared testing of the difference between two population proportions.

Table XX demonstrates that group 2, while exposed to formaldehyde, suffered significantly from depression, lacrimation, dry skin, disturbed sleep, eye irritation and menstrual irregularities when compared to themselves after their removal from exposure for a period of 1 year.

Table XX Group 2, students exposed in 1994 and not exposed in 1995 (cessation of exposure)

SYMPTOM	**EXPOSED** 1994, EXPRESSED AS % OF THE POPULATION AFFECTED (n = 107)	**AFTER (POST) EXPOSURE** 1995, EXPRESSED AS % OF THE POPULATION AFFECTED (n = 55)	P-VALUE
HEADACHE	74.5 %	64.2 %	0.173712
EYE IRRIT.	**62.3 %**	**44.2 %**	**0.031751 ***
LACRIMATION	**64.5 %**	**34 %**	**0.000349 ***
BLOCKED NOSE	61 %	60 %	0.909669
RUNNY NOSE	62.6 %	52.9 %	0.24673
THROAT IRRIT.	58.5 %	47.1 %	0.177726
DRY THROAT	33 %	19.6 %	0.081799
COUGHING	45.8 %	30 %	0.060617
PHLEGM	24.3 %	20 %	0.550523
CHEST TIGHT	26.2 %	14 %	0.08789
LOSS OF SMELL	17.9 %	14 %	0.539345
DRY SKIN	**50 %**	**26 %**	**0.004633 ***
DISTRUB SLEEP	**50.5 %**	**32 %**	**0.030097 ***
DEPRESSION	**57.5 %**	**22 %**	**0.0000324 ***
THIRST AWAKE	27.6 %	16 %	0.112681
MENSTRUAL DIS	**26.3 %**	**6.1 %**	**0.037**
TIME OFF	16.7 %	15.2 %	0.824794

*** Signifies significant results**

P values were calculated from Chi squared testing of the difference between two population proportions.

Table XXI shows that in spite of the fact that they were exposed to a much lower mean formaldehyde level (0,05 ppm), group 3 suffered from lacrimation, eye irritation, headache, throat irritation and thirst upon awakening when exposed to the anatomy environment for the first time.

Table XXI Group 3, students not exposed in 1994, exposed in 1995 (initiation of exposure)

SYMPTOM	**BEFORE (PRE) EXPOSURE** 1994 EXPRESSED AS % OF POPULATION AFFECTED (n = 82)	**EXPOSED** 1995, EXPRESSED AS % OF POPULATION AFFECTED (n = 97)	P-VALUE
HEADACHE	**55.6 %**	**80.2 %**	**0.000414 ***
EYE IRRIT.	**22.8 %**	**52.6 %**	**0.0000589 ***
LACRIMATION	**19.8 %**	**62.5 %**	**0.00000104 ***
BLOCKED NOSE	48.8 %	60 %	0.134773
RUNNY NOSE	46.3 %	51 %	0.531774
THROAT IRRIT.	**30.5 %**	**50 %**	**0.008336 ***
DRY THROAT	17.1 %	26 %	0.149333
COUGHING	41 %	42.7 %	0.866846
PHLEGM	15.9 %	22.9 %	0.237289
CHEST TIGHT	12.2 %	18.8 %	0.231201
LOSS SMELL	4.9 %	11.6 %	0.110446
DRY SKIN	29.3 %	35.4 %	0.382998
DISTURB SLEEP	34.1 %	35.4 %	0.859262
DEPRESSION	36.6 %	50 %	0.072181
THIRST/AWAKE	**12.2 %**	**26 %**	**0.020514 ***
MENSTRUAL DIS	19.6 %	21.6 %	0.806552
TIME OFF	6.3 %	27.6 %	0.000315

*** Signifies significant results**

P values were calculated from Chi squared testing of the difference between two population proportions.

In an attempt to differentiate between the symptoms experienced upon initiation and cessation of exposure the data from tables XX and XXI were superimposed as illustrated in figure 6. It was found that there was a significant increase in the frequency of eye irritation and lacrimation in both groups.

In addition to eye irritation and lacrimation, students suffered from an increase in the frequency of headache, throat irritation, thirst upon awakening and time off for sickness, upon the initiation of their exposure.

In addition to the improvement in symptoms of eye irritation and lacrimation, students also experienced an improvement in the frequency of dry skin, disturbed sleep, depression and menstrual irregularity, upon removal from exposure.

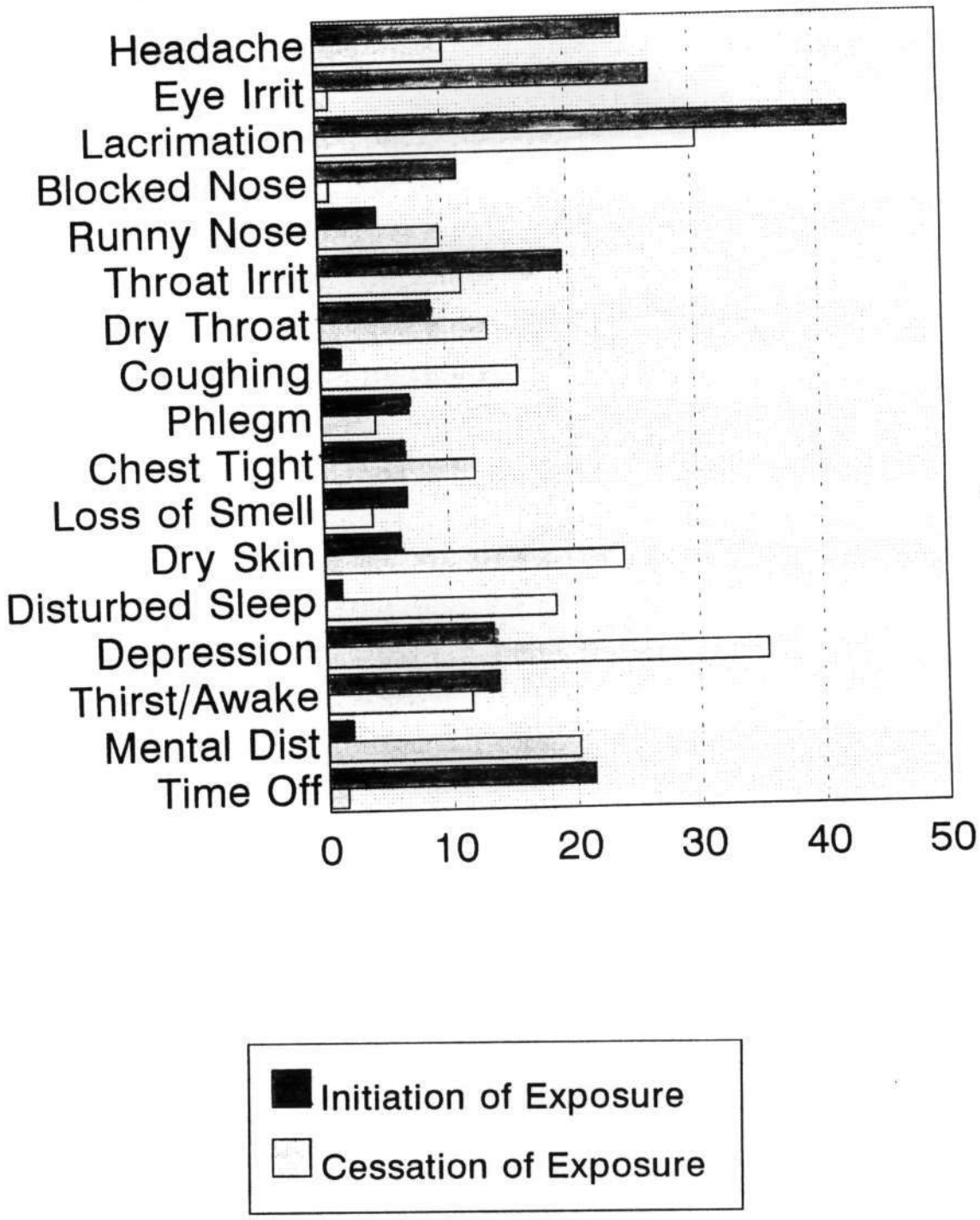

Figure 6. Illustration of the increase in symptoms associated with the initiation of exposure and decrease in symptoms associated with the cessation of exposure.

The effectiveness of the intervention (ventilation system) in terms of relieving the symptoms of formaldehyde vapour exposure was evaluated by comparing symptom frequency in the two student groups. Hypothesis testing of the difference between two population proportions for large samples ($n1 + n2 > 30$) was done, the null hypothesis (H0) in each case being that no difference in symptom frequency existed. In each case it was not possible to reject H0 at a 5 % significance level, however there was some reduction (not statistically significant) in symptom frequency of eye irritation, lacrimation, blocked and runny nose as well as menstrual disorders, as illustrated in figure 7.

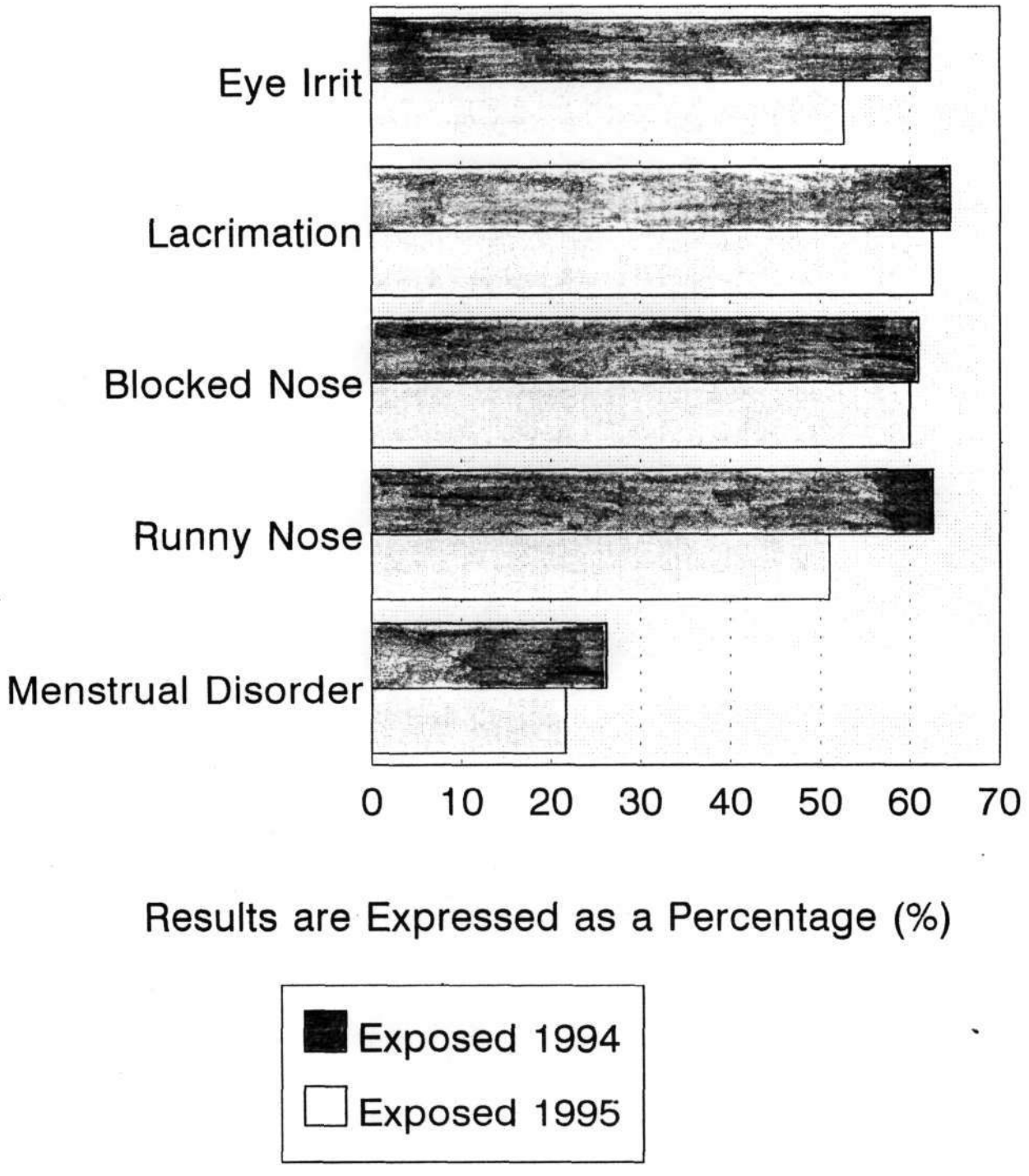

Figure 7 Comparison of frequency of symptoms experienced by the exposed groups of 1994 and 1995 (effectiveness of intervention)

4.4 CYTOLOGICAL EXAMINATION OF NASAL EPITHELIAL SCRAPINGS

The results obtained from the cytological analysis of nasal epithelial scrapings of group 1 are presented in table XXII. Staff members had a reduced number of nasal epithelial columnar cells and contrary to expectations control members had more metaplasia than exposed staff members, although this finding was not statistically significant.

Table XXII Nasal epithelial scrapings score of staff and a matched control group

VARIABLE	EXPOSED GROUP (STAFF) (n=13)		MATCHED UN-EXPOSED CONTROL GROUP (n=12)		P Value
	mean score	sd	mean score	sd	
squamous cells	1.3	0.48	1.75	1.06	0.143
columnar cells	**1.69**	**0.95**	**3.17**	**1.03**	**0.023**
metaplastic cells	0.85	0.37	1	0	0.497
years exposed	12.77	9.4	0	0	-

NOTE; EACH (+) = 1 AND (-) = 0
sd = standard deviation
P values were calculated from Chi squared testing of the difference between two population proportions.

4.5 SUMMARY OF RESULTS:

i. Ventilation in the Anatomy laboratory prior to intervention was poor. After the new ventilation system was installed air flow patterns and velocity were adequate.

ii. Formaldehyde vapour levels in the Anatomy laboratory prior to intervention were generally within the South African limits of permissible exposure, however they exceeded more stringent international levels. After the intervention, formaldehyde levels were greatly reduced and currently levels comply with the international TLV's.

iii. Both formaldehyde exposed students and staff showed a significant increase in the frequency of irritational symptoms (lacrimation, eye irritation, headache, throat irritation, thirst upon awakening, depression, dry skin, disturbed sleep and menstrual irregularities), when compared to themselves or in the case of staff members a non - exposed control group.

iv. The intervention did not have a statistically significant effect on the frequency of reported symptoms, however there was a reduction in the frequency of eye irritation, lacrimation, blocked nose, runny nose, menstrual disorders, depression and dry skin.

v. The cytological evaluation of the nasal epithelium showed that formaldehyde exposed staff members have fewer columnar cells than a matched control group.

CHAPTER 5

DISCUSSION OF RESULTS

5.1. LIMITATIONS OF THE STUDY

In any study there are certain limitation that can be identified and these need to be highlighted and brought to the attention of the reader as they may influence the validity of the findings. The following limiting factors were identified in this study.

i. The ideal formaldehyde sampling instrument would be capable of measuring formaldehyde vapour levels continuously for the whole study period (two years) and have the capacity to capture peak exposures which will influence symptoms. This could not be done due to the prohibitive purchase and maintenance costs of such equipment.

   The sampling method ultimately selected was still deemed to be also relatively expensive and only a limited number of formaldehyde samples could be taken (20) of which one was damaged and only 19 could be used. It is possible that students and staff may have been exposed to levels higher that those measured as the sampling method could have missed significant peak exposure levels.

ii. The study population was aware of the potential hazards associated with exposure to harmful chemicals and this may have led to bias in their responses in the questionnaire survey.

iii. Due to various reasons such as scheduling of classes, examinations and vacations, student groups were often incomplete during the administration of questionnaires and the group sizes varied greatly; group 2 {n = 107 (1994) to n = 55 (1995)} and group 3 {n = 82 (1994) to n = 97 (1995)}, this may have influenced the result in that the absent students may have been more or less severely affected by their exposure to formaldehyde.

iv. Most students elected not to provide their names on the questionnaires and therefore specific exposure levels could not be related to specific individuals and individuals could not be followed up in the second sample. All data was therefore used in group data format only.

v. The sample group from which nasal scrapings was obtained was small (n=12) with a high turnover, hence no conclusions could be drawn from the findings.

5.2 SIGNIFICANCE OF RESULTS

No published literature on formaldehyde levels in Anatomy facilities or symptom prevalence among exposed medical students in South Africa was found, hence this report may be the first published on this topic in South Africa. The most significant findings were as follows:

5.2.1 Formaldehyde levels

Formaldehyde levels (prior to intervention), measured during the latter period of sampling were lower (mean 0.3 ppm) than during other stages of dissection, except for brain dissection (mean 1.48). In addition it was found that formaldehyde vapour levels were elevated when cavity structures of the cadavers were opened (mean 0.67), compared with the findings of Skisak (1983) where it is reported that 62% of daily mean formaldehyde exposures of medical students were between 1 and 2 ppm. Perkins and Kimbrough (1985) measured a mean student exposure level of 1.53 ppm. Uba et al. (1989) measured mean exposures of less than 1 ppm and a peak of 5 ppm formaldehyde in an Anatomy laboratory, formaldehyde levels also declined over time (7 month period). Akbar Khanzadeh et al. (1994) reported a range of 0.07 ppm to 2.95 ppm and a 94% contravention of the 0.3 ppm formaldehyde TLV in an Anatomy laboratory.

5.2.2 Symptomatology

In an analysis of the questionnaire data on symptom prevalence it was found that exposed students as well as staff members suffered from irritational symptoms normally associated with exposure to formaldehyde vapour. The most significant symptoms measured in all groups were eye irritation and lacrimation. Staff members also suffered from phlegm and dry throat and were more prone to illness as they took sick leave more regularly than a control group.

In addition to the common symptoms mentioned above, students also reported depression, dry skin, menstrual irregularity, headache, throat irritation and thirst upon awakening.

Uba et al.(1989) performed a study on 103 medical students and found, (as in this study), that itchy eyes, burning eyes, watery eyes, and burning nose were significant symptoms ($p<0.001$) of formaldehyde exposure. In addition it was reported that students suffered significantly from Rhinorrhea ($p<0.001$). Cough, wheezing and dyspnoea were identified as possible symptoms of formaldehyde exposure in one out of two groups of Anatomy students, however, the results of our study indicate that the frequency of these symptoms in students is very low, but staff members with long term exposure are likely to suffer from wheezing.

Depression was identified as a possible symptom of formaldehyde exposure (ACGIH 1992), and was found to be a significant symptom among students in our study, however verification of this finding was not possible as no literature relating the frequency of depression in anatomy students could be found.

Akbar Khanzadeh et al. (1994) in a study of Anatomy laboratories found that 88% of students suffered from eye irritation, 74% from nose irritation and 29% from throat irritation, as compared to the results of our study where eye irritation was reported by 52.6% (group 3) and 62.3% (group 2), blocked nose was reported by 60% (group 3) and 61% group 2) and throat irritation was reported by 50% (group 3) and 58.5% (group 2). The large difference in the frequency of symptoms reported by Akbar Khanzadeh et al. (1994) can be attributed to the fact that formaldehyde vapour levels in the laboratory studied appear to be significantly higher than those measured in our study (94% of samples over a period of six weeks exceeded 0.3 ppm formaldehyde.

Furthermore, headache among students in our study was found to be a significant problem, however, it is hypothesised that the aetiology of the headaches is not related to formaldehyde exposure but some other cause. The reasons for formulating this hypothesis being:

i. Studies of formaldehyde exposure in industry (ACGIH 1992 and WHO 1989), of medical students (Uba et al. 1989 and Akbar Khanzadeh 1992) as well as group 1 (staff members) in this study did not identify headache as a symptom of formaldehyde exposure.

ii. Symptoms of headache did not improve significantly upon removal from exposure.

It is unlikely that the high frequency of headache symptoms is associated with building air quality, due to the absence of headache symptoms among staff members, it is more likely to be related to other factors such as curriculum pressures and stress.

The symptoms of exposed students improved significantly after removal from formaldehyde exposure; and the symptoms of non exposed students increased significantly after initiation of their exposure, however there was no statistical difference in symptoms experienced by the exposed students after the improvement of the laboratory environment, compared to symptom levels before the intervention. On face value this is a disappointing finding considering the amount of money spent on improving the ventilation system (approximately R 250 000), however one must consider that symptoms of irritation may occur at levels well below the TLV (ACGIH 1992).

Furthermore the monitoring technique used did not allow for the measurement of peak formaldehyde levels which could greatly contribute to symptom frequency. It was possible that even at the post intervention stage there were peaks with some procedures such as brain dissection, which were missed, this could account for the lack of difference in symptoms in exposed students.

One pack of cigarette smoke contains approximately 0.82 mg of formaldehyde and therefore additional statistical analysis (logistic regression) was performed in order to ensure that the increase in smoking was not influencing results, $r = 0.22$ ($p = 0.15$). It is however possible that symptoms reported may have been influenced by the increasing smoking prevalence among students; from first year (6.1 %) to second year (12.4 %) and from second to third year (16.36 %), chi square = 4.2 ($p = 0.08$), 2df. This is an issue that may require further investigation as such a trend among doctors is a cause for concern.

Exposed staff were significantly more likely to have fewer columnar cells than unexposed staff ($p = 0.002$), this requires further investigation as literature to support the finding could not be found. The other main parameters measured (squamous cells and metaplastic cells) did not show any significant difference between the exposed and control groups, however contrary to expectations more controls than exposed persons had metaplastic changes of the nasal epithelium. This again requires further investigation.

Since formaldehyde is a proven human sensitizing agent as well as a proven animal and a suspected human carcinogen, it is of utmost importance that the lowest practicable exposure levels be maintained through the implementation of adequate engineering controls, as there is no "safe" level of exposure to such substances. The ultimate goal however should be to eliminate the chemical entirely by substitution of either the teaching method or the embalming technique.

CHAPTER 6

CONCLUSIONS

Due to the high levels of formaldehyde measured during 1993 and 1994, specific environmental control recommendations were made to the University. The University authorities responded promptly and implemented the recommended ventilation controls, which were re - evaluated in 1995 and are deemed to be effective in terms of measured formaldehyde vapour concentrations. It appears as if the frequency of formaldehyde associated symptoms although reduced still persist at very low vapour levels, nevertheless the results all show a change in the same direction (reduction in symptoms) and this is therefore indeed suggestive of a trend.

In view of the proven potential of formaldehyde to act as a sensitizing agent as well as a carcinogen and the fact that adherence to legal limits will not necessarily prevent exposed persons from displaying symptoms of formaldehyde exposure, the maintenance of the lowest possible personal exposures it advised.

6.1 RECOMMENDATIONS

i. The curriculum requirements of medical students need to be established in order to investigate the feasibility of introducing alternative methods of teaching anatomy, such as computer aided methods (virtual reality).

ii. Alternative methods of embalming or preserving cadavers should be investigated.

iii. The long term formaldehyde exposure effects upon an exposed human population must be established.

iv. A biological method of screening for formaldehyde exposure effects in exposed persons should be developed.

v. The synergistic effect of exposure to a mixture of both phenol and formaldehyde must be established.

vi. The prevalence and cause of headache symptoms experienced by medical students must be determined.

6.2 RECOMMENDATIONS WHILE FORMALDEHYDE IS USED AS A PRESERVATIVE

i. Regular environmental monitoring must continue in order to ensure that engineering controls are operating efficiently and to ensure compliance with legal limits.

ii. Regular maintenance and cleaning of the ventilation system is essential in order to ensure adequate performance of the system.

iii. The ventilation system is to remain operational 24 hours a day, including week - ends, in order to prevent a build up of formaldehyde vapour, resulting in high exposures upon the return to work in the morning.

iv. Laboratory practices such as the storage of brain specimens in open containers should be discontinued in order to prevent the high formaldehyde vapour levels experienced during brain dissection procedures.

v. The exposed students and staff need to be informed of the hazards present in the anatomy laboratory and their own duties and responsibilities regarding the reduction of formaldehyde vapours must be made clear.

REFERENCES

1. (ACGIH) American Conference of Government Industrial Hygienists. Threshold limit values for chemical substances and physical agents and biological exposure indices ACGIH 22 - 122 (1994-1995).

2. (ACGIH) American Conference of Industrial Hygienists; Notice of intended change - formaldehyde. Applied Occupational Environmental Hygiene 1992; 7(12); 852 - 874.

3. Akbar-Khanzadeh F, Vaquerano MU, Akbar-Khanzadeh M and Bisesi MS. Formaldehyde exposure, acute pulmonary response, and exposure control options in a gross anatomy laboratory. Medical College of Ohio, School of Allied Health, Occupational Health Program, Toledo. American Journal of Industrial Medicine 1994; 26(1): 61 - 75.

4. Balarin C, Sarto F, Giacomelli L, Bartolucci GB, Clofero E. Micronucleated cells in nasal mucosa of formaldehyde exposed workers. Mutation Research 1992; 280; 1 - 7

5. Bardana EJ, Montanaro A. Formaldehyde: An analysis of it's respiratory, cutaneous and immunologic effects. Annals of Allergy 1991; 66: 441 - 452.

6. Beal JR, Formaldehyde and hepatotoxicity: A review. Journal of Toxicology in Environmental Health 1984; 13: 1-21.

7. Bernstein R. Inhalation exposure to formaldehyde: An overview of it's toxicology, epidemiology, monitoring and control. American Industrial Hygiene Association Journal 1984; 45(11); 778 - 785.

8. Blair A, Saracci R, Stewart PA, Hayes RB and Shy C. Epidemiologic evidence on the relationship between formaldehyde exposure and cancer. Scandinavian Journal of Work, Environment and Health 1990; 16(6): 381 - 393.

9. Blair A and Stewaet MS. Do quantitative exposure assessments improve risk estimates in occupational studies of cancer? American Journal of Industrial Medicine 1992; 21 : 53-63.

10. Boeniger MF, Formate in urine as a biological indicator of formaldehyde exposure:a review. American Industrial Hygiene Association Journal 1987; 48(11) 900 - 908.

11. Boysen M. Nasal mucosa in workers exposed to formaldehyde: a pilot study. British Journal of Industrial Medicine 1990; 47 116 - 121.

12. Burge PS, Harries MG, Lam WK et al.: Occupational asthma due to formaldehyde, Thorax 1985; 40: 225 - 260.

13. Burge PS, Hedge A, Eilson S, Harris J and Robertson A. Sick Building Syndrome: a study of 4373 office workers, Annals of Occupational Hygiene 1987; vol 31 493 - 504.

14. Clayton GD and Clayton FE. Patty's Industrial Hygiene and Toxicology John Wiley and Sons, New York. Third revised edition 1981; 2645.

15. Daggett DL and Stock TH. An investigation into the storage stability of environmental formaldehyde samples. American Industrial Hygiene Association Journal 1985; 46(9): 497 - 504.

16. "Dragerwerk Aktiengesellschaft Lubeck" ; Instructions for use of Drager tube 81 01 641, Drager methods 1992. (Phenol)

17. Edling C, Odkvist L, Hellquist H; Formaldehyde and the nasal mucosa. British Journal of Industrial Medicine 1985; 42 570 -571.

18. Ellwood PA. Evaluation of a diffuse sampler for formaldehyde. Annals of Occupational Hygiene 1990; 34(3) 305 - 313.

19. Fisher F. Environmental and Occupational Risk of Health Care; British Medical Association 1994. p 30.

20. Frigas E, Filley WV and Reed CE. Bronchial challenge with formaldehyde gas: lack of bronchoconstriction in 13 patients suspected of having formaldehyde - induced asthma. Mayo Proceedings 1984; 59 295 - 299.

21. Gray H; Anatomy of the Human Body 27th edition (Goss CM) Lea and Febiger Philadelphia 1959 pp. 1167 - 1176.

22. Hellquist HB; Pathology of the nose and paranasal sinuses Butterworths London 1990, pp. 6 - 8 and 49 - 54.

23. Holstrum M. Lund V. Malignant melanomas of the nasal cavity after occupational exposure to formaldehyde. British Journal of Industrial Medicine 1992; 48 9 - 11.

24. Kerfoot EJ and Mooney TF. Formladehyde and para-formaldehyde study in funeral homes. American Industrial Hygiene Association Journal 1975 36: 533-537.

25. Klein - Szanto AJ, Ura H and Resau J. Formaldehyde induced lesions of xenotransplanted human nasal respiratory epithelium. Toxicologic Pathology 1989 17(1 Pt 1): 33 - 37.

26. Malaka T and Kodama AM. Respiratory health of plywood workers occupationally exposed to formaldehyde. Archives of Environmental Health 1990 45: 288 - 294.

27. Maurice F, Rivory JP, Larsson PH et al. : Anaphylactic shock caused by formaldehyde in a patient undergoing long term hemodialysis. Journal of Allergy and Clinical Immunology 1986; 77: 594 - 597.

28. Merk and company, Merk Index; 10 th edition 1983. 604, 4115

29. Molhave L, Dueholm S and Jensen LK; Assessment of Exposures and Health Risks Related to Formaldehyde Emissions from Furniture: a Case Study; Indoor Air 1995; 5(2) 113 - 114.

30. Morgan KT, Jiang XZ, Starr TB et al.: More precise localization of nasal tumors associated with chronic exposure of F344 rats to formaldehyde gas. Toxicology of Applied Pharmacology 1986; 82: 264 - 271.

31. 3M Company Occupational Health and Safety Products Laboratory. Organic Vapour Analytical Method 4D, 1985.

32. 3M Formaldehyde Vapour Monitor # 3720/3721; Instructions for use 1985.

33. NIOSH (National Institute of Occupational Safety and Health). Pocket guide to chemical hazards NIOSH 1985; 128 - 129.

34. Nordman H, Keskinen H, Tuppurainen M; Formaldehyde Asthma - Rare or overlooked? Journal of allergy and clinical immunology 1985; 75: 91 - 99.

35. Occupational Health and Safety Act, (Act 85 of 1993) and the Regulations for Hazardous Chemical Substances.

36. Perkins JL, Kimbrough JD. Formaldehyde exposure in a gross anatomy laboratory. Journal of Occuptional Medicine 1985; 27 813 - 815.

37. Plog BA. Fundamentals of Industrial Hygiene National Safety Council USA. Third edition 1988; 455 - 521.

38. Rush GM, Clary JJ, Rinehart et al.: A 26 week inhalation toxicity study with formaldehyde in the monkey, rat and hamster. Toxicology in Applied Pharmacology 1983; 68: 329 - 343.

39. Salkie ML, Allergens in the workplace. Clinical Biochemistry 1994; 27(2): 81 - 5.

40. Schachter EN, Witek TJ, Tosun T. et al.: A study of respiratory effects from exposure to 2 ppm formaldehyde in healthy subjects. Archives of Environmental Health 1986; 41(4): 229 - 239.

41. Schoeman JJ and Schroder HHE. Occupational Hygiene Juta and co, ltd. Second edition 1994; 17 - 53, 489 - 500.

42. Skisak CM. Formaldehyde vapour exposures in anatomy laboratories. American Industrial Hygiene Association Journal 1983; 44(12) 948 - 950.

43. Suruda A, Schulte P, Boeniger M, Hayes RB et al. Cytogenetic effects of formaldehyde exposure in students of mortuary science. Cancer and Epidemiological Biomarkers 1993; 2(5): 453 - 60.

44. Thiel W. The preservation of the whole corpse with natural color. Anatomischer Anzeiger 1992; 174(3) 185 - 195.

45. Uba G, Pachorek D, Bernstein J, Garabrant DH, Balmes JR, Write WE and Amar RB. Prospective study of respiratory effects of formaldehyde among healthy and asthmatic medical students American Journal of Industrial Medicine 1989; 15(1) 91 - 101.

46. United States of America (USA); Department of Health and Human Services, Public Health Service, Centre for Disease Control, National Institute for Occupational Safety and Health. The Industrial Environment it's Evaluation and Control 1973; 511 - 519.

47. Wilhelmsson B, Holstrum M, Possible mechanisms of formaldehyde - induced discomfort in the upper airways. Scandinavian Journal; Work and Environmental Health 1992 18 403 - 407.

48. Winesaki LE and English AW, Phenoxyethanol as a nontoxic preservative in the dissection laboratory. Acta Anatomica 1989; 136(2) 155 - 158.

49. Witek TJ, Schachter EN, Tosun T. et al. An evaluation of respiratory effetcs following exposure to 2.0 ppm formaldehyde in Asthmatics: Lung function symptoms and airway reactivity. Archives of Environmental Health 1987; 42: 230 - 237.

50. World Health Organisation; Environmental Health Criteria 89 Formaldehyde; 1989 Vammala Finland. 77 - 85, 108 - 15 150 - 153 and 170 - 177.

Table AIII. Summary of epidemiological proportional mortality rate(PMR) studies with formaldehyde.

AUTHOR(S) YEAR	STUDY POPULATION	STUDY PERIOD	SITE	RISK ESTIMATE (PMR)	TOTAL DECE-DENTS
Marsh (1982)	Chemical Workers (USA)	1950 - 1976	respiratory system digestive system genital system lymphatic system	80 127 121 86	136
Walrath and Fraumeni (1983)	male embalmers (New York)	1925 - 1980	buccal and pharyngeal nasopharynx respiratory nasal prostate bladder brain leukaemia colon skin Hodgkins kidney lymphatic and haemato - poietic	126 - 102 - 89 92 157 132 140 253 - 170 115	**1010**

Walrath and Fraumeni (1984)	embalmers (california)	1925 - 1980	buccal respiratory nasal prostate brain & CNS leukaemia colon skin Hodgkins bladder kidney rectum gallbladder and liver pancreas stomach	131 94 - 175 194 175 187 59 - 138 100 102 85 135 79	1007
Stayner et al. (1985)	garment workers	1959 - 1982	buccal nasal digestive gallbladder and liver lung skin bladder and kidney lymphatic leukaemia	229 - 126 313 95 179 92 163 168	156

No controlling for tobacco exposure was done.

(WHO table 37 pp. 153 - 154)

Table AIV. Summary of epidemiological case - control studies with formaldehyde.

AUTHOR YEAR	STUDY POPULA-TION	STUDY PERIOD	TYPE OF EXPOSURE	CASES	CON-TROLS	SITE	RISK	COMMENTS
Jensen et al. (1982)	Physi-cians	1943-76	speci-ality	84	252	lung	1.0	
Fayer-weather et al. (1983)[a,b]	chemical workers	1957-79	levels and duration	481	481	multiple; buccal cavity oesophagus stomach liver, gall bladder lung	1.0 0.5 1.0 0.9 0.8	risk estimate used = odds ratio
Coggon et al. (1984)[c]	workers (UK)	1975-79 1975-79	occupa-tional occupa-tional	296 132	472 268	bronchus bladder	1.5 1.0	r.r 0.9 in higher exposure r.r. 1.5 in higher exposure
Olsen et al. (1984)	workers Denmark	1970-82	exposure assessed	754	2465	nasal nasopharynx	2.8 0.7	o.r. 1.8 for exposure to wood dust, men

Partanen et al. (1985)[a]	wood workers	1957-80	levels and duration	57	171	respir atory	1.3	no exposure-response relationship
Bond et al. (1986)[a]	chemical workers	1940-80	occupa-tional	308	588	lung	0.6	dose-respon-se relationship
Hayes et al. (1986)[a]	wood workers (Nether-lands)	1978-81	levels	91	195	nose and nasal sinuse s	2.5 1.9	low wood dust exposure high wood dust exposure
Vaughan et al. (1986_a)[a]	Tumour registry	1979-83	occupa-tional	285	552	nasoph arynx nasoph arynx buccal cavity buccal cavity	1.4 2.1 0.6 1.3	for high exposure 20+ years for high exposure 20+ years
Vaughan et al. (1986_b)[a]	Tumour registry	1979-83	residen-tial	285	552	nasoph arynx nasal cavity buccal cavity	**5.5** **0.6** **0.8**	10+ years in mobile home **odds ratio used**
Brinton et al. (1984)[a]	industria l workers	1970-80	occupa-tional	160	290	nasal cavity	0.4	

Olsen and Asnaes (1986)	Tumour registry Denmark	1970-82	occupa-tional	759	2465	nasal cavity nasoph arynx	2.3 2.2	squamous cell car-cinoma only; wood dust adencarci-noma looked for but not found
Rouch et al. (1985)	Tumour registry Sweden	1940-81	occupa-tional	371	605	nasoph arynx nasal cavity	1.1 0.8	
Hardell et al. (1982)[a]	Tumour registry Sweden	1970-79	occupa-tional	44	541	nasal	6.1	r.r calcula-tion based on 2 exposed out of 44 nasal cancers versus 4 out of 541 controls

[a] Study controlled for tobacco use.
[b] Selection criteria < 20 years after first exposure.
[c] Selection criteria male < 40 years.

(WHO 1989 table 38 pp 155 - 156)

Table AV. Summary of epidemiological cohort studies with formaldehyde. (SMR)

AUTHOR(S) YEAR	STUDY POPULATION	STUDY PERIOD	SITE	RISK ESTIMATE (SMR)	STUDY POPULATION	TYPE OF EXPOSURE	COMMENTS
Harrington $ Oakes 1984	male pathologists	1974-80	digestive lung bladder brain/cns lymphatics leukaemia	20 41 107 331 54 90	2307		all brain cancers were gliomas
Levine et al. 1984	embalmers (canada)	1950-77	bucco-pharyngeal lung prostate urinary organs brain/cns colorectal leukaemia lymphatic digestive	48 94 88 54 115 85 160 124 75	1477		all brain cancers were gliomas
Stroup et al. 1986	anatomists	1925-79	bucco-pharyngeal naso-pharynx lung nasal prostate bladder brain/cns leukaemia colon lymphatic	15 - 28 - 100 68 270 147 108 123	2317	duration, special	brain cancers were gliomas and increased with duration of employment

Blair et al. 1986	workers	1934-1980	buccal cavity naso-pharynx lung/pleurnasal cavity prostate bladder kidney brain leukaemia colon skin hodgkins	96 300 111 91 115 96 123 81 80 87 80 142	26 561	levels duration peaks	exposure response for prostate and Hodgkins disease
Blair et al. 1987	workers	1930-80	naso-pharynx oropharynx	384 167	26 561		dose - reponse relationship for those also exposed to particulates.
Bertazzi et al. 1986	resin workers	1959-80	bucco-pharyngeal digestive oesophagus stomach lung lymphatic	- 156 - 148 236 201	1332		

Edling et al. 1987	abrasive manufacturers	1958-83	bucco-pharyngeal naso-pharynx stomach colon pancreas lung prostate lymphatic	- - 80 100 180 57 85 200	521		no correlation with exposure
Stayner et al. 1988	textile workers	1953-77	buccal cavity digestive lung bladder kidney brain lymphatic leukaemia	343 58 114 112 55 71 91 114	11 030		
Acheson et al. 1984	chemical workers	1941-81	bucco-pharyngeal nasopharynx lung nasal digestive larynx	109 - 95 - 101 88	7680	levels duration	a) lung cancer increased with level of exposure in one factory b) lung cancer not increased with cumulative exposure

(WHO 1989 table 39 pp 157 - 159)

Table AVI. Mortality from subsites of cancer of the buccal cavity and pharynx through cumulative exposure to formaldehyde.

MORTALITY AFTER FORMALDEHYDE EXPOSURE AT:

SITE	0 mg/m3			< 0.6 mg/m3			0.6 - 6.6 mg/m3			> 6.6 mg/m3		
	ob	ex	smr	ob	ex	smr	ob	ex	smr	ob	ex	smr
lip	0	0.1	b	1	0.2	477	0	0.2	b	1	0.1	764
tongue	0	0.5	b	0	1.8	b	2	2.1	96	0	1.3	b
salivary glands	0	0.2	b	0	0.5	b	0	0.6	b	0	0.3	b
gum, floor, other oral	0	0.4	b	1	1.5	66	0	1.8	b	1	1.1	88
nasopharynx	1	0.2	530	2	0.7	271	2	0.8	256	2	0.5	433
oropharynx	0	0.3	b	4	0.9	**443**	1	1.0	95	0	0.7	b
hypopharynx	1	0.2	594	1	0.6	172	0	0.7	b	0	0.4	b
other parts of pharynx	0	0.4	b	1	1.4	73	0	1.6	b	0	1.0	b

(ob) observed, (ex) expected, (smr) standard mortality ratio
(b) no deaths, **443** $p < 0.05$

(WHO 1989 table 39 pp 160)

APPENDIX B

LABORATORY ANALYSIS OF FORMALDEHYDE SAMPLES

Formaldehyde vapours were adsorbed on bisulphite impregnated paper in the monitors. Both ports of the closure cap were opened and 3.0 ml of formaldehyde free distilled water was added to each monitor through the centre port using a syringe. The ports were immediately resealed and each system was allowed to elutriate for 30 minutes with occasional gentle agitation. A 2.0 ml aliquot of the eluate was transferred into a 30 ml screw cap glass vial and reserved for colour development.

The amount of eluate taken varied to be sure that each sample solution was within the calibration curve and was diluted to 2.0 ml w/1% $NaHSO_3$ solution each time. 1.0 ml of chromotropic acid solution was added to each sample and mixed well. 5 ml of concentrated sulphuric acid was added slowly with mixing. The solution was allowed to cool to room temperature the absorbance was measured at 580 nm using 1 cm cells. Distilled water was used in the reference cells.

The control monitor (field blank) was carried through all the steps of the sample analysis. The absorbance of the blank was subtracted from that of the sample and reference was made to the calibration curve to determine the micrograms of formaldehyde present.

The calibration curves were prepared as follows :

> To a series of 1.0, 3.0, 5.0, 10.0, 15.0 and 20.0 microliters of standard formaldehyde solution equivalent, 1.0, 3.0, 5.0, 10.0, 15.0 and 20.0 micrograms of formaldehyde was carefully added. The volumes were adjusted to 3 ml with 1 % $NaHSO_3$ solution. The colour was developed on a 2 ml aliquot as described above.

The absorbance at 580 nm was measured. A blank was carried through all these steps and it's absorbance was subtracted from that of the standard samples. A calibration curve was prepared by plotting absorbance versus micrograms formaldehyde. The slope of the best line fit was then determined by linear regression analysis.

The following calculations were performed :

a) $W = (As - Ab) / S$

where :

W - micrograms formaldehyde found.

As and Ab - absorbance units for sample and blank, respectively.

S - slope of calibration curve.

b) $C = (W \times 10\ 000 / K \times R.C. \times t) \times M.V. / M.W.$

where :

C - concentration of formaldehyde in air.

W - micrograms formaldehyde found

M.V. - molar volume of formaldehyde at given temperature and pressure (24.45 l/mole, 5 deg. C, 760 mm Hg)

M.W. - molecular weight of formaldehyde, 30 a.m.u.

K - sampling rate for formaldehyde, 61.4 cc/min.

R.C. - recovery coefficient for formaldehyde, 1.00

t - sampling time, minutes

STRICTLY CONFIDENTIAL

UNIVERSITY OF NATAL
DEPARTMENT OF COMMUNITY HEALTH : QUESTIONNAIRE

AN EVALUATION OF FORMALDEHYDE VAPOUR IN HUMAN ANATOMY LABORATORIES

BACKGROUND INFORMATION

A survey is being conducted in order to evaluate the formaldehyde vapour levels in the anatomy laboratory at the Medical School.

As part of the study it is necessary to establish a symptom profile of the exposed population and to compare this with a control group matched for age race and gender. It would be appreciated if you would complete this questionnaire.

IDENTIFYING INFORMATION

Section 1. **GENERAL INFORMATION** **card column**

1. How old are you _____ 1-2

please circle a number

2. What is your sex ?

Female	1	3
Male	2	

3. Race
(we need this information to match our sample and control groups)

Black	1	4
Indian	2	
Coloured	3	
White	4	

4. NAME _____

Section 2: EXPOSURE TO FACTORS WHICH MAY INFLUENCE HEALTH

card column

1. Are you
   a current smoker ? 1
   a former smoker ? 2
   a non smoker ? 3 (Please go to question 3) 5

2. How many do you smoke each day ?

   _____ (for pipe / cigar fill in 99) 6 - 7

3. Have you ever been exposed to formaldehyde in the course of your work ?

   yes 1
   no 2 (please go to section 3) 8

4. For how many years have you been exposed ?

   1 to 5 1
   5 to 10 2
   more than 10 3 9

Section 3: HEALTH OR ILLNESS INFORMATION card column

1. Have you ever been diagnosed as asthmatic ?

   yes 1
   no 2 10

---

2. Have you ever suffered from other chest illness ?

   yes 1
   no 2 11

---

3. In the past 6 months have you had more than two episodes of headaches ?

yes	1	
no	2	12

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	13
less often	4	

was this better on days away from work ?

yes	1	14
no	2	

---

4. In the past 6 months have you had more than two episodes of eye irritation ? card column

yes	1	
no	2	15

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	16
less often	4	

was this better on days away from work ?

yes	1	
no	2	17

---

5. In the past 6 months have you had more than two episodes of watering of the eyes ?

yes	1	
no	2	18

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	19
less often	4	

was this better on days away from work ?

yes	1	
no	2	20

---

6. In the past 6 months have you had more than two episodes of blocked or stuffy nose ?

yes	1	
no	2	21

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	22
less often	4	

was this better on days away from work ?

yes	1	
no	2	23

---

7. In the past 6 months have you had more than two episodes of runny nose ?

yes	1	
no	2	24

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	25
less often	4	

was this better on days away from work ?

yes	1	
no	2	26

---

8. In the past 6 months have you had more than two episodes of irritation of the nose / throat ?

yes	1	
no	2	27

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	28
less often	4	

was this better on days away from work ?

yes	1	
no	2	29

---

9. In the past 6 months have you had more than two episodes of a dry throat ?

yes	1	
no	2	30

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	31
less often	4	

was this better on days away from work ?

yes	1	
no	2	32

---

10. In the past 6 months have you had more than two episodes of coughing

yes	1	
no	2	33

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	34
less often	4	

was this better on days away from work?

yes	1	35
no	2	

---

11. In the past six months have you had more than two episodes of productive cough (phlegm) that lasted a week or more ?

yes	1	
no	2	36

If yes, do you have this

most days	1	
most weeks	2	
most months	3	37
less often	4	

was this better on days away from work ?

yes	1	
no	2	38

---

12. In the past six months have you had more than two episodes of feeling chest tightness, difficulty in breathing or wheezing ?

yes	1	
no	2	39

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	40
less often	4	

was this better on days away from work ?

yes	1	
no	2	41

---

13. In the past six months have you had more than two episodes of loss of smell ?

yes	1	
no	2	42

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	43
less often	4	

was this better on days away from work ?

yes	1	
no	2	44

---

14. In the past six months have you had more than two episodes of dry skin ?

yes	1	
no	2	45

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	46
less often	4	

was this better on days away from work ?

yes	1	
no	2	47

---

15. In the past six months have you had more than two episodes of disturbed sleep ?

yes	1	
no	2	48

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	
less often	4	

was this better on days away from work ?

yes	1	
no	2	49

---

16. In the past six months have you had more than two episodes of depression ?

yes	1	
no	2	50

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	51
less often	4	

was this better on days away from work ?

yes	1	
no	2	52

---

17. In the past six months have you had more than two episodes of thirst upon awakening ?(not related to drinking of alcohol)

yes	1	
no	2	53

If yes, do you have this,

most days	1	
most weeks	2	
most months	3	54
less often	4	

was this better on days away from work ?

yes	1	
no	2	55

---

18. Females, In the past six months have you noticed any menstrual disorders ?

yes	1	
no	2	56

---

19. Have you ever had to take time off work for any of the above mentioned conditions ?

yes	1	
no	2	57

more than once a week	1	
more than once a month	2	
more than once every six months	3	58
less often	4	

Section 4 : EXPOSURE TO EXTERNAL FACTORS

1. Do you live in an industrial area ?

yes	1	
no	2	59

If yes, for how long have you been living there ? (years) _____ 60 - 61

2. Do you share you home with people that smoke ?

yes	1	
no	2	**62**

If yes how many cigarettes are smoked inside your home every day ? _____ 63 - 64

3. Do you or your family burn any of the following at home ?

incense
wood
paraffin
coal
gas

yes	**1**	
no	**2**	**65**

Thank you for your assistance. If you have further questions or can provide more information about this problem, please call:

Dr A Raynall or Mr. J Oosthuizen
Department of Community Health

APPENDIX D

UNIVERSITY OF NATAL

FACULTY OF MEDICINE

DEPARTMENT OF COMMUNITY HEALTH

Informed consent for inclusion in a clinical trial

1. I, (name)_____

   hereby consent to the following procedure being conducted upon myself.

   Obtaining of a sample of my nasal epithelium cells by a medical doctor, with the aid of a cervical brush.

2. I acknowledge that I have been informed by Mr. Jacques De Villiers Oosthuizen concerning the possible adverse effects which may result from the above mentioned procedure.

3. I (name) _____

   hereby acknowledge that I understand and accept the "information to patients" leaflet handed to me in connection with this trial.

4. I agree that the above procedure will be carried out or supervised by Dr. MB Kistnasamy and Mr. Jacques Oosthuizen.

5. I acknowledge that I understand the contents of this form, including the "information to patients" leaflet and as the subject freely consent to the above procedure being conducted upon myself.

6. I am aware that I may withdraw my consent at any time without prejudice.

signed: _____ date: _____
subject

signed: _____ date: _____
witness

signed: _____ date: _____
informant

signed: _____ date: _____
Researcher

APPENDIX E

INFORMATION GIVEN TO SUBJECTS

My name is Jacques Oosthuizen. We have conducted a survey of the anatomy hall in order to measure the levels of formaldehyde in the air. In order for us to consider the effects of formaldehyde exposure to yourself, I would appreciate your co - operation in providing us with a sample of the superficial cells inside your nose.

A medical doctor will use a "brush" and will get a "scraping" of tissue from the front part of your nose (middle turbinate) **(I will illustrate)**, which will then be put onto a slide. I will then send this sample to the histology laboratory for microscopic examination. You will be informed of the results, unless you choose not to know.

The parameters evaluated will be ;

1. Number of eosinophils. (increase will indicate reactivity)
2. Number of plasma cells. (increase will indicate reactivity)
3. Number of squamous cells. (increase will indicate reactivity)
4. Number of columnar cells. (decrease will indicate reactivity)
5. Metaplasia

A simple scoring system (+, ++, +++) will be used to classify the samples according to estimated numbers of cells. Control samples will be evaluated in order to determine a "normal" level according to which the exposed population will be scored.

The results will not be made known to anyone but yourself, other than in group data format for publication purposes. There will be slight discomfort and you are free to discontinue involvement in the study at any time.

Jacques Oosthuizen
Community Health