

Pulmonary function in histology technicians compared with women from Michigan: effects of chronic low dose formaldehyde on a national sample of women

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ABSTRACT Chronic workplace exposure to formaldehyde and solvents at low doses reduced pulmonary function in 280 non-smoker white women working as histology technicians. They were studied during national workshops at four United States cities for four years. Height and age adjusted comparisons of pulmonary function were made with women in a stratified random population sample of Michigan and with a selected subset of the population that was used to model predictive pulmonary equations for function. The major functional change in histology technicians was a steeper decrement in vital capacity and flows from age 20 to 60 by regression analysis than occurred in the modelled Michigan population. Furthermore non-smoking and currently smoking women studied at two sites had significantly lower flows than were found in the sample of Michigan women. There was no consistent effect of an aerosol bronchodilator on flows of women at the four sites. Diffusing capacity for carbon monoxide single breath and alveolar volume were below the comparison group of Michigan women only when tested at Washington DC.

Formaldehyde (HCHO) is a pungent and chemically reactive gas heavily used in many industries which is also a component of cigarette smoke and diesel exhaust. It is found frequently in indoor and outdoor air. It causes cancer in the nasal passages and lungs of rodents¹ and may be a human carcinogen for these respiratory tissues.^{2,3} Controversy surrounds its acute and chronic effects on the function of the respiratory system. On the one hand, occupational formalin asthma has been described in renal haemodialysis nurses⁴ and pathologists.⁵ Five of 28 members of a haemodialysis unit staff had attacks of wheezing lasting for 10 hours to 10 days.⁶ Some subjects have responded to bronchial provocation,⁶ others have not.⁷

Investigation of 230 suspected cases of asthma due to HCHO in Finland produced 12 (5%) with typical symptoms responsive to bronchial provocation of 2.5 mg/m³.⁸ Thus it is not surprising that 15 asthmatic volunteers, naive for formaldehyde, when challenged with it lowered their threshold to methacholine challenge but showed no measurable acute effect on pulmonary function.⁹ They included 12 subjects with occupational HCHO asthma,⁸ workers making acrylic

wool filters impregnated with phenol-formaldehyde resin¹⁰ and those making fibreglass batts similarly impregnated.¹¹ Three groups of subjects studied before exposure were not significantly below predicted levels for FVC, FEV₁, and FEF₂₅₋₇₅. Cigarette smokers in the last group had significant cross shift decrements in these functions and in diffusing capacity, although non-smokers did not decrease. Since the type and magnitude of chronic effects of formaldehyde on pulmonary function were unresolved by these studies, we studied female histology technicians for chronic effects by comparing them with a stratified random population sample of Michigan women.^{12,13}

Methods

Volunteers were recruited from attendees of four national conventions of the National Society of Histotechnology. In the first cross sectional study in Boston in 1982 spirometry was measured in 260 of 625 women who attended. In Anaheim in 1983, 208 of 644 women were studied by spirometry and in Washington in 1985, 131 of 585 were similarly studied. At Little Rock in 1986, 137 of 570 attending were studied. It was decided to consider only those studied initially at each site in analysis (table 1) to avoid a training bias. Because our recruitment was directed at neuro-

Table 1 Pulmonary function in non-retested white women who had never smoked when attending national conventions in Boston 1982, Anaheim 1983, Washington 1985, and Little Rock 1986 as percentage predicted (%p) of Michigan women¹²

Year	Boston		Anaheim		Washington		Little Rock	
	1982	%p	1983	%p	1985	%p	1986	%p
No	77		60		35		62	
Age (y)	39		38.6		37.7		39.9	
Height cm/sd	162.6 ± 7.47		163.1 ± 6.88		164.1 ± 7.80		163.9 ± 5.69	
FVC/sd	3.650 ± 0.620	(100.5)	3.630 ± 0.507	(99.6)	3.826 ± 0.427	(103.0)	3.600 ± 0.598	(98.2)
FEV ₁ /sd	3.045 ± 0.579	(101.1)	2.956 ± 0.446	(97.9)*	3.202 ± 0.425	(104.4)	3.015 ± 0.544	(99.8)
FEF ₂₅₋₇₅ /sd	3.186 ± 1.031	(105.1)	2.920 ± 0.896	(96.0)*	2.926 ± 0.770	(94.5)*	3.192 ± 1.096	(106.2)
FEF ₇₅₋₈₅ /sd	1.100 ± 0.704	(111.4)	0.861 ± 0.519	(86.2)*	0.967 ± 0.603	(98.5)	0.932 ± 0.499	(96.7)

*p < 0.05.

behavioral symptoms and testing a biased selection for pulmonary function testing seems unlikely. For table 2, all non-smoking white women studied in Boston, the initial site, were considered and for table 3, the attendees at Washington and Little Rock who had not been studied previously were analysed. Only slight variability for mean values for pulmonary function was noted between sites (table 1). For regression analysis of spirometry v age we used the largest sample of histology technicians who were thus uncomplicated and also the first group studied.

Technicians completed symptom indices and medical history and exposure questionnaires and had pulmonary and neurobehavioral testing. Only methods relevant to this paper will be described. Because environmental sampling of each laboratory from which a participating histology technician came would

be a mammoth nationwide task we elected to sample exposure to formaldehyde and solvents in 10 laboratories within the Los Angeles area. Area sampling was done for formaldehyde, xylene, toluene, and chloroform for one to four hours by the regional NIOSH laboratory using sorbent tubes for HCHO and impingers for solvents and analysed by gas chromatography. For all four agents the levels varied widely: therefore only ranges are given. Mean one to four hour HCHO concentrations in specimen preparation and sampling areas were from 0.2 to 1.9 ppm with peaks to 5 ppm. In the rooms containing tissue processors xylene ranged from 8.9 to 12.6 ppm and chloroform varied from 2 to 19.1 ppm. In staining and cover slipping operations xylene was from 3.2 to 102 ppm and toluene was from 8.9 to 12.6 ppm. These wide variations in concentrations were explained by the

Table 2 FEV₁ and FEF₂₅₋₇₅ in 97 non-smoking white women compared with Michigan women

	Age	Histotech	Miller	Diff
FVC	20	4203	4099	+104
	30	3907	3867	+40
	40	3611	3635	+24
	50	3316	3403	-87
	60	3020	3171	-151
Dec/year (ml) FEV ₁		29.6	23.2	
	20	3705	3494	+211
	30	3356	3244	+112
	40	3006	2992	+14
	50	2657	2741	-84
Dec/year (ml) FEF ₂₅₋₇₅		35	25	
	20	4279	3754	+505
	30	3707	3329	+378
	40	3135	2935	+182
	50	2563	2619	-56
Dec/year (ml)	60	1992	2323	-331
		57	36	

FVC = Histo = - 2.057 + 0.0417 Ht cm - 0.0273 age.
 = Miller = - 2.198 + 0.0414 Ht cm - 0.0232 age.
 FEV₁ = Histo = - 0.836 + 0.0318 Ht cm - 0.0329 age.
 = Miller = - 0.3801 + 0.0268 Ht cm - 0.0251 age.
 FEF₂₅₋₇₅ = Histo = 1.598 + 0.0227 Ht cm - 0.0545 age.
 = Miller = logFEF₂₅₋₇₅ = 1.5628 - 0.0120 age.

Table 3 Comparison of histology technicians studied at Little Rock and Washington with all Michigan white women by never smoked and currently smoking^{12,13}

	Never smoked		Currently smoking	
	L Rock (60)	Wash (70)	L Rock (22)	Wash (14)
FVC (l)	- 0.19*	- 0.03	- 0.20*	0.02
FEV ₁ (l)	- 0.11*	0.00	- 0.24*	- 0.10
FEF ₂₅₋₇₅ l/sec	- 0.02*	- 0.11*	- 0.20*	- 0.33*
FEF ₇₅₋₈₅ l/sec	- 0.17*	- 0.27*	- 0.50*	- 0.67*
DLCO (ml/min/mmHg)	- 0.49	- 3.15*	- 1.21	- 0.74
Alveolar volume (l)	- 0.01	- 0.05	- 0.13	0.00

*p < 0.05.

variety of mixtures of solvents used, diversity of activities, and large variations in ventilation within and between laboratories.

Spirometric measurements were obtained with rolling seal (waterless) spirometers with subjects standing and using a nose clip following ATS Snowbird recommendations.¹⁴ Subjects were carefully instructed and encouraged to achieve maximal inspiration and to expire fully. Three or more forced expiratory efforts from full inspiration were recorded and the best two required to agree within 5%. DLCO and alveolar volume single breath were measured with carbon monoxide during a 10 second breathhold by the method of Ogilvie *et al*¹⁵ as modified by Miller *et al*.¹³

Statistical analyses are based on white women. Statistical calculations, including regression analysis, were performed with a Hewlett-Packard 9816 microcomputer using the HP statistical library. Analysis of variance using the PC SAS statistical program in an IBM computer compared function values for white female histology technicians with the entire sample of Michigan women. This probability sample of a large 9 000 000 population industrial state was initially constructed via random choice of residential telephone numbers as controls to subjects on farms quarantined for polybrominated biphenyls. An adult and child from each selected household was invited for study, contacted, scheduled for examination at one of six Michigan sites, and studied in detail in 1978. Approximately 42% of those originally invited had pulmonary functions measured from which normal values were developed using the 235 considered normal on the basis of medical history and examination. For further details of the selection process see Miller *et al*.^{12,13} The entire Michigan sample of 486 white women which provided a representative sample of women in the United States was compared with white women in this paper. It appeared reasonable to compare them with a representative population for evidence of an occupational exposure rather than with a hand picked normal group selected for modelling.

What this meant was that we restored to the group used for "normal" predictive pulmonary function

modelling^{12,13} those excluded because of clinical abnormalities. Subjects returned to the Michigan population sample for these analyses included those with chronic cough with phlegm, asthma, wheezing, dyspnoea, angina pectoris, and hypertension or with a diagnosis of chronic bronchitis, emphysema, tuberculosis, pneumoconiosis, and coronary heart disease. Thus the comparison group included all adult women studied in Michigan. A p value of < 0.05 was used to demonstrate significance. They were compared smoking specific to 70 non-smoking women studied at Washington, DC, 60 at Little Rock, Arkansas, and 14 and 22 current smokers at the respective sites. Individual percentages of predicted were calculated for each measurement and averaged for each measurement by site.

Results

A total of 280 white women who had never smoked cigarettes were studied at the four sites from 1982 to 1986. Forty were restudied and 240 were studied only once. The mean ages of yearly groups were 37.6 to 39.9 years and mean height of 162.6 to 165.3 cm (table 1). When the 77 non-smoking women in the 1982 group studied in Boston were compared with normal women in Michigan, these women had almost identical mean FVC, FEV₁, and flows which slightly exceeded 100% of predicted (table 1). The same comparisons, however, for the 1983 group of 60 women who have never smoked in Anaheim, which is in the Los Angeles basin, showed that mean FEV₁ and flows were decreased compared with Michigan values and the values were substantially decreased compared with the members of the group studied in Boston. These differences (table 2) were 0.4% for vital capacity, 3.2% for FEV₁, 9.1% for midflow, and 15.2% for terminal flow. The 1985 study in Washington once again showed mean FVC and FEV₁ above the Michigan women population values and considerably above the Anaheim levels. Flow FEF₂₅₋₇₅ that was 94.5% of the Michigan value differed from Anaheim. Study of the group in 1986 in Little Rock showed that mean FVC

and FEV₁ resembled earlier studies and were near the Michigan values, but flows returned to Boston levels compared with Michigan levels at 106.2% of midflow and 96.7% for terminal flow.

None of the mean values differed significantly from those for the modelled population from Michigan. The entire group tested at each site was used to develop regression equations. The first step was to base regression equations for this group on the 106 Boston female non-smokers (table 2). This permitted estimates to be made of the effect of age and height on FVC, FEV₁, and flows for subjects in each decade to compare with Michigan predicted values. The histotech predictive equations for FVC, FEV₁, and FEF₂₅₋₇₅ produced higher values in the younger ages and low values after age 40. In effect, the values for histotechs were higher at age 20 and cross the Michigan population values because their calculated age decrement coefficients were greater (figure).

The second analytical step was to compare the pulmonary function values measured at Washington and Little Rock for women who had never smoked and for current smokers with the corresponding values from the Michigan population study. This population cross comparison (table 3) showed that the non-smoking histology technicians at Washington and Little Rock as groups, corrected for age and height, had lower flows than the corresponding stratified random sample of Michigan women. The Little Rock test group also had significantly lower FVC, FEV₁, and flows whereas DLCO_b was significantly lower only in the women who had never smoked who were studied in Washington.

The current cigarette smokers group when adjusted for effects of smoking, based on the Michigan

studies,^{12,13} showed identical changes to the never-smokers in Little Rock and differed from those who had never smoked in Washington only in that the difference for DLCO_b was not significant.

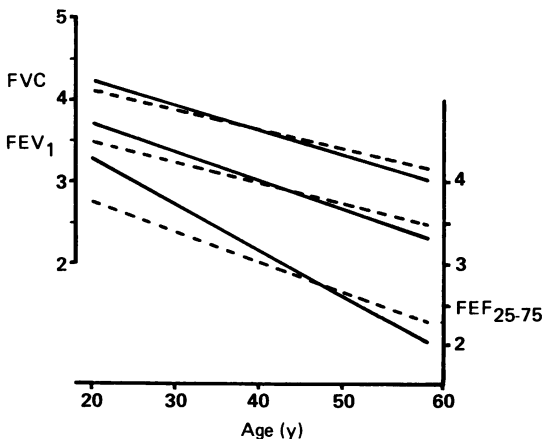
Discussion

The pulmonary function measurements for histology technicians sampled from their national population four times across five years did not vary in a systematic or statistically significant way from year to year. Although different individuals were studied each year, as repeated samples of a national population, they behaved similarly and thus predictably each time. This observation provides assurance in ascribing significance to differences across time and site. Two major conclusions are suggested by these observations. The first is that this population appears to have better function than the comparison population from Michigan at age 20 but has greater decrements with time, resulting in lower function values at age 60. Sampling the population at the mean age of 40 each year minimised the apparent differences because the histology technicians regression lines cross the Michigan womens regression lines near age 40. A second comparison by analysis of variance showed that histology technicians have significantly lower flows, although again the differences are small.

These complementary analyses of large groups suggest that there is a low magnitude chronic reduction of pulmonary function by formaldehyde which may be contributed to by solvent exposure. This reduction is not predicted from cross shift decreases which are not found (unpublished observations) except in asthmatics⁸ or in some cigarette smokers.¹¹ In effect, we have shown a long term low magnitude decrement that occurs without a positive workplace challenge. The apparent reduction in function charted in Anaheim was not repeated. It may be related to exposure of Los Angeles basin air pollution and is being studied.

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Age related decrements in FVC and FEV₁ (1) and for FEF₂₅₋₇₅ (l/s) (mid-flow) plotted for — female histology technicians compared with --- reference population.¹²

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- 2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosino-phil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;294:687-90.
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