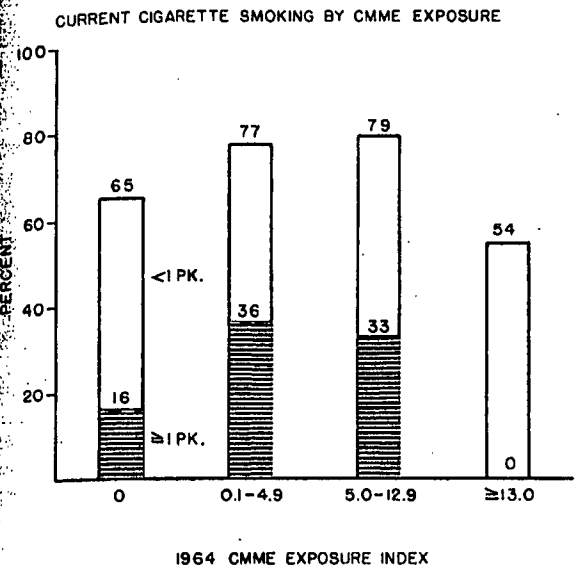


Fig 3. — Percent of men who were current cigarette smokers by daily amount smoked and degree of exposure to chloromethyl methyl ether.

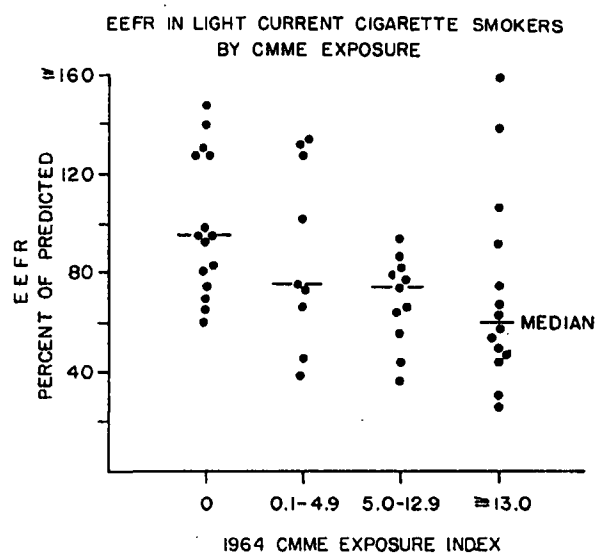


Fig 4. — Scattergram of end-expiratory flow ratos as percent of predicted in current cigarette smokers of less than one pack per day by degree of exposure to chloromethyl methyl ether.

of current cigarette smokers and of current cigarette smokers of one pack or more per day were examined in the various exposure groups (Fig 3). These proportions were highest in the light and moderate exposure groups and lowest in the heavy exposure group. Since the largest smoking habit group was composed of 49 men who were currently smoking less than one pack per day, the EEFR was studied by chemical exposure in these men in a partial attempt to control for smoking. Figure 4 and Table 3 suggest a gradient in the EEFR among these men although the results did not distinguish the lightly exposed men from those who were moderately exposed. After combining these two groups, the relationship between chemical exposure and the frequency of EEFR below 60% was statistically highly significant (chi square = 9.79, d.f. = 2, $P < 0.01$).

Discussion

Chloromethyl ethers are useful as transmethylating agents in the production of ion-exchange resins, pesticides, and other organic chemicals. Although chloromethyl methyl ether was the chemical used in the plant where the workers were studied in this investigation, it was contaminated with small amounts of bis(chloromethyl) ether so the adverse effects might have been due to either or both substances. Both are volatile and break down in the presence of moisture to hydrochloric acid, formaldehyde, and in the case of CMME, methanol.

Table 3. — The End-Expiratory Flow Rate by Degree of Exposure to Chloromethyl Methyl Ether in Light Current Cigarette Smokers

Exposure Index	No. of Men	End-Expiratory Flow Rate*				
		Median	Under 75%		Under 60%	
			No.	%	No.	%
0	15	95	4	27	0	0
0.1-4.9	9	74	5	56	2	22
5.0-12.9	11	74	6	55	3	27
13.0+	14	60	9	64	7	50
Total	49	74	24	49	12	24

*as percent of predicted

Extensive inhalation toxicologic studies of CMME and BCME in rats and hamsters[5,6,7] have shown that, in addition to acute toxic respiratory reactions and carcinogenic effects, these chemicals in small doses given repeatedly produce hyperplasia and metaplasia in the bronchial mucosa as well as metaplasia and atypicalities in peripheral bronchoalveolar tissues. Squamous metaplasia was documented at autopsy in a chemical worker who died of lung cancer.[2] The bronchial effects were reflected in humans by a dose-response relationship between CMME exposure and the frequency of chronic cough and expectoration.[2,3] The absence of demonstrable chemical effect on the FVC and FEV_1 in this group of workers[2,4] suggests that there was no marked abnormality of the large airways detectable by routine screening tests. However, the finding of an increased prevalence of low EEFR's in men exposed to CMME compared to unexposed men suggests that inhalation of chloromethyl ethers causes detectable small airway disease.

Since smoking also produces abnormalities of small airways,[1] and since smoking habits varied among the CMME exposure groups in this study, it was to be expected that smoking would confound the dose-response relationship between CMME and abnormality of the EEFR. The present data confirmed a relationship between smoking and abnormality of the EEFR but, because of the small number of men in the study, it was difficult to disentangle the effect of CMME from that of smoking. The data in light current cigarette smokers suggest that CMME may bear a dose-response relationship to abnormality of the EEFR but more information is needed to clarify the situation. It is unlikely that such information will ever be obtained, however, since exposure to chloromethyl ethers has been eliminated in the workplace since 1971.

The significance of the pulmonary functional abnormality reflected by the EEFR is not clear. It is suspected that chronic obstructive lung disease begins in the small airways and might be reversible in this stage.[8] However, long-term longitudinal studies are needed to elucidate the clinical meaning of a low EEFR. At this time only limited information of this nature is available.

During the five-year period 1963-68 in which the chemical workers were screened periodically there was a diminishing ex-