A Study of Sister Chromatid Exchange and Somatic Cell Mutation in Hospital Workers Exposed to Ethylene Oxide

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To investigate the risks of exposure to ethylene oxide (EO) at current permissible levels and at past higher levels, an inception cohort of sterilizer operators and supervisors from the Central Processing Department (CPD), respiratory therapists, and engineers exposed to EO were identified at the McMaster University Medical Centre. A comparison group from Nutrition Services (NUTR) were matched with the CPD workers on the basis of sex, age, and smoking habit. The present report is based on genetic test results for the 94 CPD and matched NUTR workers only. Statistical analysis based on the mean SCE frequency in the top 5, top 10, and all cells (50 cells scored per individual) and high frequency cells (HFC) based on the 95th percentile for nonsmoking control subjects showed a direct association with current smoking but not with EO exposure. Similarly, statistical analysis of the somatic cell mutation (SCMT) variant frequencies did not demonstrate an association with EO exposure, nor with smoking. Regression analysis indicated that sex was the only other covariate that significantly affected SCE. Age was weakly associated with SCMT. A statistically significant interaction between occupational exposure and smoking habits was observed only for the mean SCE frequency of the top 5 and top 10 cells when the 11 current CPD/NUTR pairs were not included. Thus, this interaction should be interpreted with caution.

Introduction

Ethylene oxide (EO) is used extensively in health care institutions for sterilization of heat-sensitive materials and is considered irreplaceable for this purpose. Exposure of hospital workers to EO can occur even in the usual operation of properly maintained sterilizers. Malfunction of equipment or improper procedures have resulted in high levels of exposure.

EO is a suspected human carcinogen. EO is carcinogenic in animals; in rats it causes dose-related increases in mononuclear cell leukemias, peritoneal mesotheliomas, and cerebral gliomas (1). Epidemiologic evidence supports the possibility that EO causes cancer in man, increasing the risk of leukemia and stomach cancer (2). Recent evidence suggests that excess hematopoietic cancer, at least in males, may be associated with a long duration of EO exposure and long latent periods (3). This association may be the result of exposure to higher levels of EO in the past.

The genotoxic risks of exposure to EO in the range of 10–50 ppm are relatively well understood. However, it is uncertain whether exposure at the levels now prevalent in Ontario hospitals (generally well under an 8-hr TWA of 1 ppm) poses these risks. In addition, there is little information concerning whether workers previously exposed to higher levels and not currently exposed might have persisting evidence of toxicity.

A group of hospital workers brought their concerns regarding the possible health effects of past and current exposure to EO to the Occupational Health Program, McMaster University. A study of all employees ever significantly exposed to EO at the McMaster University Medical Centre, Chedoke-McMaster Hospitals, was initiated to investigate health effects of exposure to EO from commencement of operation in 1971 to the present. The present report is restricted to the results of the genotoxicologic aspects of the investigation.

Study Groups

An inception cohort of sterilizer operators and supervisors from the Central Processing Department (CPD), respiratory therapists, and engineers exposed to EO were identified at the McMaster University Medical Centre.
There was an overall recruitment of more than 80% into the study: 47 CPD workers, 6 respiratory therapists, and 1 engineer. For the period from 1971 until 1981, there is no record of exposure measurement. However, during the same period, in some instances hospital exposures in Ontario and the United States were estimated to have exceeded an 8-hr TWA of 10–50 ppm (4,5). In 1981, a tabletop sterilizer was discovered to have a leak; no record of exposure measurement has been found, but this sterilizer has been discarded. In 1982, levels exceeding 1000 ppm were detected in front of an Amseo sterilizer from a leaking door, and levels between 32 and 93 ppm were recorded around edges of the closed door on two other occasions. In the latter instances, faulty equipment was repaired, and three additional aerators, another sterilizer, and local exhaust ventilation were installed. By the end of 1984, no EO was detected by the threshold limit value (TLV) sniffing around operating machines. In 1985, levels of 100 ppm were measured immediately after sterilization before aeration, and a level of 2 ppm was noted above the load during transfer to aerator. However, after aeration, there was no detectable EO. Since January 1986, personal diffusion monitors with a detection limit of 0.1 ppm have indicated moderate EO elevation on two occasions: on one occasion a worker’s monitor was positive for EO exposure after an episode of manual transfer of sterilized objects to the aerator when a load tipped over. On the other, a positive monitor indicated a ventilation malfunction, which was rectified. An area alarm system for EO was subsequently installed, and no further episodes of elevated exposures have been recorded.

Comparison subjects from Nutrition Services (NUTR) were matched with EO workers on the basis of sex, age (classified either as 40 and greater, or less than 40 years of age) and smoking habit (classified as currently smokers or non-smokers). Both current and past CPD workers were matched with current NUTR employees, as it was not feasible to match past workers on the basis of the intervening work experience. The present report is based on the genetic test results from the 94 CPD and matched NUTR workers; the other job categories had small numbers of individuals (six exposed respiratory therapists and one exposed engineer). Table 1 shows that the two groups were very similar for the characteristics for which they were matched.

### Table 1. Characteristics of Central Processing Department (CPD) and Nutrition Services (NS) groups.

| Characteristic          | All CPD | All NS |
|-------------------------|---------|--------|
| Smoking                 |         |        |
| Current (%)             | 18 (38) | 18 (38) |
| Quitter (%)             | 10 (21) | 7 (15) |
| Never (%)               | 19 (40) | 22 (47) |
| No. cigarettes/daya, mean (SD) | 17.2 (7.7) | 17.7 (6.8) |
| Lifetime pack-years, mean (SD) | 16.4 (13.9) | 16.8 (12.2) |
| Age, years, mean (SD)   | 42.1 (12.8) | 43.0 (13.9) |
| Male (%)                | 4 (9)   | 4 (9)  |
| Female (%)              | 43 (91) | 43 (91) |

aAmong current smokers.

bAmong current and past smokers.

### Genetic Tests

EO has been shown to cause genetic damage in vivo in several studies of workers exposed to high levels. A striking increase in chromosomal aberrations (CA) was observed in workers accidentally exposed 18 months previously to 1500 ppm EO for 2 hr (6). Several studies have shown that CA are increased after exposure to high EO levels (7,8) but sensitivity of CA to low levels is less certain (8–10).

Statistically significant increases in sister chromatid exchange (SCE) have also been reported after exposure to moderately high levels of EO (8,11–14). The situation with low-level exposure is less clear; with certain studies demonstrating increased SCE at TWA exposures of less than 0.5 ppm (8,15), but others not at TWA exposures of less than 5 ppm (16–18). Several investigators have found the elevation in SCE was persistent after high-level exposure to EO (8,11,13).

Recent analysis of SCE frequencies in monkeys chronically exposed to EO has shown that persistent, elevated SCE may be due to a subpopulation of long-lived lymphocytes with unusually high SCE counts (19). The analysis of these high-frequency cells (HFC) has become an important adjunct to the study of SCE (20,21), particularly in the case of EO exposure in man (15,22). As SCEs have proven to be sensitive to fairly low EO levels, persistent after higher exposures, relatively easy to score, and to have low interobserver variability, SCE analysis was chosen for investigation of genotoxicity in the entire cohort.

It was decided to include a test for gene mutation as well as SCE, as EO is known to be a DNA alkylating agent. The somatic cell mutation test (SCMT), developed by Albertini and collaborators (23), was chosen for investigation of genotoxicity in the current CPD group and the past CPD group with the longest regular EO exposure. Two methods for detecting hypoxanthine phosphoribosyl transferase (hprt) mutants have been developed: an autoradiographic assay that detects 6-thioguanine (TG)-resistant variants and a clonal assay that allows for the expansion of hprt mutant clones, which can then be used to characterize the molecular alteration in the gene. Thirty-nine CPD workers and their matched control subjects were included in an autoradiographic SCMT analysis. The 10 subjects with the highest variant frequency (VF) and their matches were further investigated with the clonal assay to characterize the hprt mutation at the molecular level. The work on cloned mutants is still in progress.

The method for SCE involved setting up two 10-mL cultures per subject with 6 × 10⁶ mononuclear cells (MNC) from density gradient centrifugation (Histopaque; Sigma, St. Louis, MO) in RPMI 1640 medium with 10% fetal bovine serum (FBS; Gibco, Burlington, ON), 2% phytohemagglutinin (PHA; Burroughs-Wellcome, Guelph, ON) and one drop from a Pasteur pipette of the packed red blood cells. Cultures were incubated in a 37°C incubator with 5% CO₂ for 68 hr with 20 μg/mL 5-bromodeoxyuridine (BrdUrd) added for the final 44 hr before harvesting. Slides were stained by Hoescht 33258/fluorescence plus Giemsa (24). Twenty-five cells were scored from both cultures, giving a total of 50 cells per individual.
The method for the autoradiographic SCMT involved cryopreservation of MNCs for 3 days before initiation of 2 mL cultures with $2 \times 10^6$ viable MNCs in RPMI 1640 medium with 10% FBS and 2% PHA, either with (test) or without (control) $2 \times 10^{-4}$ M TG. Cells were incubated at 37°C and 5% CO$_2$ for 30 hr before addition of tritiated thymidine. Cultures were harvested 18 hr later and slides prepared and stained for autoradiography (25,26). Labeled nuclei were enumerated in control and test cultures and VF was calculated by dividing the total number of labeled nuclei in the test cultures by the number in the control cultures (27).

**Study Design**

Samples were collected from both members of a matched pair on the same day, after obtaining informed consent and completing a questionnaire. Information on EO exposure and on potential confounding factors, including illnesses, treatments, and other relevant hazardous exposures, was collected by interviews using questionnaires.

For SCE and SCMT analyses, 60 mL of venous blood was collected into vacuum blood containers (Venoject; sodium heparin). Care was taken to ensure that all needles, containers, and tissue culture plasticware were not contaminated with EO. Mononuclear cells were separated by gradient centrifugation to be used immediately for SCE cultures or to be cryopreserved for the SCMT.

**Estimation of Exposure and Statistical Analyses**

For this analysis, the exposure variable was based on the number of months of “regular work” (MOREG) that individuals worked in the CPD area. For example, a supervisor who does not work fulltime in the sterilizing facility would accumulate months of regular exposure at a proportionately lower rate than a sterilizer operator. Thus, this exposure variable combines both a component of dose and one of duration.

The SCE data were analyzed in several ways. In addition to considering the mean frequency of SCE for all 50 cells of a subject (all 50), it was also possible to study a subset of cells with a high frequency of SCE (HFC). The mean SCE frequency for each subject's top 10 and top 5 cells (top 10 and top 5, respectively) were calculated. Whereas the data for all 50 cells closely approximated a normal distribution, the data for top 10 and top 5 were log transformed before analysis to make the distributions conform to normality assumption requirements. These continuous variables were then analyzed by linear regression analysis (MDP Statistical Software, Inc., University of California Press, Berkeley, CA, 1990) using MOREG as the exposure variable; number of cigarettes currently smoked (CIGNOW), age and sex as covariates; and all exposure-related interactions in the model.

Another approach was to consider the SCE frequency distribution of the nonsmoking NUTR controls and to take the 95th percentile of that distribution to be the cut-off, above which a cell would be defined as an HFC. Binomial distribution theory was used to determine the expected (or normal) number of HFC for an individual (28). If an individual had >5 HFC cells, that individual was considered “abnormal.” The HFC count data were therefore categorical and were analyzed by a logistic regression analysis. In addition to the logistic regression analysis of this data, the chi-square test was used to compare groups (22).

**Results**

Linear regression analysis of the mean SCE for all 50 cells and the log-transformed mean SCE for the top 5 cells for the 94 CPD and NUTR workers indicated that there was a significant association with CIGNOW but not with EO exposure history (MOREG). Logistic regression demonstrated the same relationships for the proportion of individuals who were classified as having an abnormally high number of HFC. Table 2 shows the results for all CPD workers and their NUTR matches; Table 3 shows the results for smokers, individuals who had stopped smoking, and those who had never smoked. A significant association with sex was found for all 50, top 10, and top 5, with females having higher SCE frequencies ($p = 0.04$, 0.03, 0.03, respectively). There were no males classified as having an abnormal number of HFC, so the logistic regression analysis of the HFC count data gave a meaningless F-ratio and p-value for sex. The result of the chi-square test on HFC count showed borderline significance ($\chi^2 = 3.71$, $p = 0.05$).

Linear regression analysis of the log-transformed variant frequency found no significant association with either CIGNOW or MOREG. A weak association of VF with age was observed ($p = 0.06$). The linear regression for VF included the labeling index of the control cultures as an independent variable, but it did not significantly affect VF.

Table 4 summarizes the SCE and SCMT data for hospital workers who worked in the CPD area or Nutrition Services either currently or in the past. Regression analyses for the 72 past employees only gave similar results to the analysis based on all 94 workers, except that signifi-

| Variable | All CPD (SCE, $n = 47$) | All NS (SCE, $n = 47$) |
|----------|-------------------------|------------------------|
| SCE      |                         |                        |
| All 50, mean (SD) | 14.5 (2.1) | 14.6 (1.6) |
| Top 10, geometric mean | 20.6 | 20.6 |
| Top 5, geometric mean | 22.4 | 22.4 |
| % HFC, median | 6.0 (8.0) | 6.0 (8.0) |
| HFC count, (%) | 14 (30) | 14 (30) |
| SCMT VF × 10$^{-6}$, geometric mean | 7.4 | 7.8 |

Abbreviations: SCE, sister chromatid exchange; SCMT, somatic cell mutation test; CPD, Central Processing Department; NS, Nutrition Services; HFC, cells with high frequency of SCE; VF, variant frequency.

*See text for details.

*Interquartile range in parentheses.
Table 3. Descriptive statistics for SCE and SCMT variables by smoking group.

| Variable  | Current smoker (SCE, n = 36; SCMT, n = 34) | Quit smoking (SCE, n = 17; SCMT, n = 11) | Never smoked (SCE, n = 41; SCMT, n = 33) |
|-----------|-------------------------------------------|------------------------------------------|------------------------------------------|
| SCE       |                                            |                                          |                                          |
| All 50, mean (SD) | 15.6 (1.8)                               | 14.1 (1.2)                               | 13.8 (1.7)                               |
| Top 10, geometric mean | 22.1                                      | 20.0                                     | 19.6                                     |
| Top 5, geometric mean | 24.0                                      | 21.8                                     | 21.2                                     |
| % HFC, median⁵ | 12.0 (11.5)                               | 4.0 (5.0)                                | 4.0 (6.0)                                |
| HFC count, (%) | 19 (53)                                   | 2 (12)                                   | 7 (17)                                   |
| SCMT      |                                            |                                          |                                          |
| VF × 10⁻⁶, geometric mean | 8.2                                       | 6.8                                      | 7.3                                      |

Abbreviations: SCE, sister chromatid exchange; SCMT, somatic cell mutation test; HFC, cells with high frequency of SCE; VF, variant frequency.

*aSee text for details.

Table 4. Descriptive statistics for SCE and SCMT variables by past or current exposure groups.

| Variable  | Current CPD (SCE, n = 11; SCMT, n = 11) | Past CPD (SCE, n = 36; SCMT, n = 28) | Current NS (SCE, n = 11; SCMT, n = 11) | Past NS (SCE, n = 36; SCMT, n = 28) |
|-----------|------------------------------------------|---------------------------------------|------------------------------------------|----------------------------------|
| SCE       |                                          |                                       |                                          |                                  |
| All 50, mean (SD) | 15.3 (1.7)                                | 14.3 (2.1)                             | 14.7 (1.4)                               | 14.5 (1.7)                       |
| Top 10, geometric mean | 21.6                                      | 20.3                                   | 21.0                                     | 20.5                             |
| Top 5, geometric mean | 23.3                                      | 22.1                                   | 22.9                                     | 22.2                             |
| % HFC, median⁵ | 8.0 (12.0)                                | 5.0 (9.5)                              | 8.0 (8.0)                                | 5.0 (10.0)                       |
| HFC count, (%) | 5 (45)                                    | 9 (25)                                 | 4 (36)                                   | 10 (25)                          |
| SCMT      |                                          |                                       |                                          |                                  |
| VF × 10⁻⁶, geometric mean | 10.4                                     | 6.5                                    | 20.4                                     | 5.4                              |

Abbreviations: SCE, sister chromatid exchange; SCMT, somatic cell mutation test; CPD, Central Processing Department; NS, Nutrition Services; HFC, cells with high frequency of SCE; VF, variant frequency.

*aSee text for details.

*bInterquartile range in parentheses.

cant interactions between smoking and occupation were observed for the top 5 and top 10 cells (p = 0.01 and 0.02, respectively). No other interactions in any other analyses were found to be statistically or clinically significant. Thus, the main effects reported above are taken from regression analyses that excluded interaction terms (Table 5).

Discussion

Studies in the past have demonstrated that EO exposures of TWA greater than 5 ppm result in increased chromosome aberrations, sister chromatid exchange, and other genotoxic effects such as damaged unscheduled DNA synthesis. However, the results of studies where the exposures were less than 1 ppm have been inconsistent. Recently, a study of 34 hospital workers exposed to less than 1 ppm (TWA) and 23 controls working in a university library found a significant effect of exposure on SCE and EO–hemoglobin adducts, but not with micronuclei, chromosomal aberrations, single-strand DNA breaks, or an index of DNA repair (15). However, the effect of EO exposure on SCE was statistically significant only in an analysis of variance where smokers and quitters were combined, even though quitters were not found to be statistically different from lifetime nonsmokers. When quitters and nonsmokers were combined, no statistically significant effect of EO exposure was shown.

Table 5. Statistical significance on regression analyses.

| Dependent variable  | Group (df) | MOREG | Age | CIGNOW | Sex |
|---------------------|------------|-------|-----|--------|-----|
| All 50              | All (89)   | NS    | NS  | 21.6, <0.0001 | 4.460,0.088 |
| Top 5 (Ln)          | All (89)   | NS    | NS  | 28.5, <0.0001 | 4.600,0.035 |
| HFC count           | All (89)   | NS    | NS  | 19.7, <0.0001 | 3.650,0.060 |
| VF (ln)             | All (73)   | NS    | 3.58,0.064 | NS    |
|                     | Past (51)  | NS    | 3.78,0.057 | NS    |

Abbreviations: df, degrees of freedom; MOREG, months of regular work; CIGNOW, cigarettes currently smoked; HFC, cells with high frequency of SCE; VF, variant frequency.

*aSee text for details.

*bAs there were no males with abnormal numbers of HFC, the F-ratio and p-value for sex as an independent variable were meaningless.
The results of the present study, and a previous one in a steel foundry (29), indicate that lifetime nonsmokers and quitters have similar SCE frequencies, significantly lower than smokers. Therefore, an analysis of variance combining quitters with smokers would not be justifiable. The present regression analyses with CIGNOW as a covariate combined nonsmokers and quitters in the sense that both groups currently smoked zero cigarettes per day. Stepwise regression of smoking variables in our data had shown the major contribution to SCE variance to arise from current smoking, with no additional effect of previous smoking history.

No significant association of elevated SCE or SCMT with EO exposure history was demonstrated in this group of hospital workers. Interaction between smoking and EO exposure was observed only when the 11 currently exposed workers and their matches were excluded from the analysis. Given that there was no evidence of an interaction when all workers were included in the analyses, even though the current workers also had past exposures, it is hard to conclude that this is a biologically important interaction. No interactions were observed for the genetic variables in the study of Mayer and co-workers (15).

The SCMT test has recently been evaluated in two occupational groups exposed to EO: hospital workers with an 8-hr TWA of about 1 ppm and factory workers with an 8-hr TWA of about 15 ppm (22). A significant association of mutant frequency with exposure was found in the factory workers, but not in the hospital workers. This indicates that the SCMT is less sensitive than SCE, as a small but statistically significant increase in SCE was observed in the hospital workers in the same study.

In the present study, there was no detectable change in SCMT in hospital workers currently exposed to less than 1 ppm (TWA) or exposed to higher levels in the past. Preliminary work from the study reported above indicates that that there may be a hot spot for a base substitution in exon 9 of the hprt gene (Van Zeeland, personal communication). Therefore it may be possible to detect a change in mutational spectrum in cryopreserved mutant T-cell clones from the EO-exposed hospital workers.

No association between EO exposure history and genetic indicators were found in the present study. These findings are consistent with some, but not all, results of recent studies of low-level EO exposure (15–18). However, the number of currently exposed workers in the project \( n = 11 \) is too small to exclude with confidence the possibility of a link between current exposure levels and genotoxicologic effects.

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