Persistently Elevated Sister Chromatid Exchanges in Ethylene Oxide-exposed Primates: The Role of a Subpopulation of High Frequency Cells

Karl T. Kelsey, John K. Wiencke, Ellen A. Eisen, Dennis W. Lynch, Trent R. Lewis, and John B. Little

ABSTRACT

Ethylene oxide (EtO) is a potent DNA-alkylating agent which has been shown to induce sister chromatid exchanges (SCE) in the peripheral blood lymphocytes of exposed workers. To study further the persistence of EtO-induced SCE, we have examined lymphocytes from a group of cynomolgus monkeys exposed to EtO in control, 50-ppm, and 100-ppm concentrations for 7 h/day, 5 days/week over the years 1979-1981. The data collected in 1987 were compared with those generated immediately prior to the cessation of exposure in 1981. EtO-induced SCE persisted at levels significantly above those of the nonexposed controls. Comparison of the distributions of SCE between 1979 and 1987 shows that, although mean SCE decreased from 1981 to 1987, the mean SCE in the top 10% of the distribution has not diminished over time. Consequently, the increased level of SCE is entirely attributable to a subpopulation of cells with high frequencies of SCE. These findings suggest that long-lived lymphocytes may inefficiently repair EtO-induced lesions which produce SCE. The results also have important implications for the proper use of SCE analytical techniques in the epidemiological study of cytogenetic damage after chronic exposure to DNA-alkylating agents.

INTRODUCTION

EtO is a monofunctional DNA-alkylating agent which is widely used as a sterilant. It is also an intermediate in the production of numerous compounds, including glycol ethers and polyester fibers. NIOSH has estimated that 100,000 people in the United States are exposed annually to EtO (1). This compound is a suspect human carcinogen (2, 3); initial epidemiological studies of EtO-exposed workers reported significantly elevated risks for leukemia, lymphoma, and solid tumors (4, 5). The risk of leukemia and lymphoma has been estimated to be 13-fold higher in EtO-exposed workers compared to control populations (6). It is also well known that in vivo exposure to EtO can induce SCE and chromosomal aberrations in peripheral blood lymphocytes of exposed workers (7-13). Chronic, high level EtO exposure in workers produced elevations of SCE in peripheral blood lymphocytes that persisted up to 41 months after the last exposure (12). In some of these highly EtO-exposed individuals, a bimodal distribution of SCE frequencies has been observed when they were studied 2 years or more after cessation of exposure (14).

Persistent elevations in the frequency of SCE (elevations above control lasting longer than one year after cessation of exposure) have not been observed with in vivo exposure to other alkylating agents, although these agents efficiently induce acute cytogenetic damage (Refs. 15-28; reviewed in Ref. 29). This difference in the temporal evolution of the cytogenetic response of lymphocytes to EtO and other DNA-alkylating agents is incompletely understood. The significance of these unique, persistent cytogenetic changes, in terms of individual cancer risk, is also unknown.

To test whether EtO-induced SCE persist even 6 years after cessation of exposure, we have studied a group of cynomolgus monkeys that was exposed by NIOSH to 50-ppm and 100-ppm concentrations of EtO and sham control exposures, all lasting 7 h/day, 5 days/week over the 2 years 1979-1981. The initial examination of EtO-induced SCE in the peripheral blood lymphocytes of these animals was carried out immediately prior to cessation of exposure and was reported in 1984 (30). At that time, SCE increased linearly with dose, to a maximum of approximately 3 times the background SCE frequency. In the present study, we have reexamined the SCE frequencies from these same animals 6 years after their last exposure to EtO. The results indicate that SCE frequencies in the lymphocytes of these monkeys continue to be elevated in a dose-related fashion. In addition, while the mean frequency of SCE in the exposed animals has declined compared to that observed in 1981, the fraction of cells with high frequencies of SCE (representing the tail of the SCE distribution) was increased or remained essentially unchanged when compared to the 1981 data.

MATERIALS AND METHODS

Animals. The study was initiated with 36 adult male cynomolgus monkeys (Macaca fascicularis; Primate Imports Corp., Port Washington, NY), assigned randomly to exposure groups of 12 animals. At the initiation of the study, the monkeys weighed 5.31 ± 0.82 (SD) kg. The animals have been continually housed in stainless steel cages with automatic watering and a 12-h on-12-h off (7 a.m.-7 p.m.) lighting system. They have been fed a standard pellet diet (Purina monkey chow) supplemented with fresh fruit two to three times per week. These animals have not been subjected to any subsequent experimental manipulations and have not been exposed to any known mutagens or carcinogens since the cessation of EtO exposure in 1981.

Test Materials and Inhalation Exposures. These have been described previously (30). Briefly, EtO (99.7% pure) was instilled under dynamic flow conditions in 4.5-m³ stainless steel and glass inhalation chambers providing 12 to 15 air changes/h, with controlled temperature (24 ± 3°C) and humidity (50 ± 10%). EtO was vaporized and metered into a filtered, conditioned, air intake, with IR analysis of the EtO concentration. The monkeys that was exposed by NIOSH to 50-ppm and 100-ppm concentrations of EtO and sham control exposures, all lasting 7 h/day, 5 days/week over the 2 years 1979-1981. The initial examination of EtO-induced SCE in the peripheral blood lymphocytes of these animals was carried out immediately prior to cessation of exposure and was reported in 1984 (30). At that time, SCE increased linearly with dose, to a maximum of approximately 3 times the background SCE frequency. In the present study, we have reexamined the SCE frequencies from these same animals 6 years after their last exposure to EtO. The results indicate that SCE frequencies in the lymphocytes of these monkeys continue to be elevated in a dose-related fashion. In addition, while the mean frequency of SCE in the exposed animals has declined compared to that observed in 1981, the fraction of cells with high frequencies of SCE (representing the tail of the SCE distribution) was increased or remained essentially unchanged when compared to the 1981 data.
were prepared by the air dry technique. The chromosomes were stained (3:1, v/v). The cell suspension was washed twice in fixative, and slides via express package service in insulated boxes for peripheral blood decrease in SCE frequency is significant except for animals above control values, although at a level significantly less than ual mean SCE frequencies in 1987 with data from 1981 shows did not grow in response to mitogen stimulation in either 1981 and two controls (60 and 65 months postexposure). In each case, the deaths which occurred after the cessation of exposure and for the pooled exposure groups. 

RESULTS

Animals. Two monkeys (one each from the 50-ppm and 100-ppm exposure groups) died during the initial exposure. These deaths appeared unrelated to EtO exposure. Two monkeys per group were sacrificed at the termination of exposure. Since the cessation of exposure five more animals have died; two in the 100-ppm exposure groups (51 and 57 months postexposure), one in the 50-ppm exposure group (46 months postexposure), and two controls (60 and 65 months postexposure). In each case, the deaths which occurred after the cessation of exposure also appeared to be unrelated to EtO exposure. One monkey in the 50-ppm group is diabetic and lymphocytes from this animal did not grow in response to mitogen stimulation in either 1981 or 1987.

Sister Chromatid Exchange Analysis. Comparison of individual mean SCE frequencies in 1987 with data from 1981 shows that SCE frequencies in EtO-exposed animals remain elevated above control values, although at a level significantly less than those observed in 1981 (Table 1). For individual animals this case, the deaths which occurred after the cessation of exposure also appeared to be unrelated to EtO exposure. One monkey in the 50-ppm group is diabetic and lymphocytes from this animal did not grow in response to mitogen stimulation in either 1981 or 1987.

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Table 2 Persistence of SCE in EtO-exposed monkeys by exposure group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>No. of Animals</th>
<th>Mean SCE ± SD</th>
<th>% of HFC*</th>
<th>Treatment Group</th>
<th>No. of Animals</th>
<th>Mean SCE ± SD</th>
<th>% of HFC*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Control</td>
<td>12</td>
<td>5.4 ± 1.0</td>
<td>0</td>
<td>D. Control</td>
<td>8</td>
<td>6.8 ± 1.5</td>
<td>0</td>
</tr>
<tr>
<td>B. 50 ppm</td>
<td>10</td>
<td>10.2 ± 1.7</td>
<td>0.4</td>
<td>E. 50 ppm</td>
<td>7</td>
<td>7.7 ± 0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>C. 100 ppm</td>
<td>9</td>
<td>15.1 ± 2.8</td>
<td>4.0</td>
<td>F. 100 ppm</td>
<td>7</td>
<td>9.4 ± 2.0</td>
<td>4.9</td>
</tr>
</tbody>
</table>

* Fifty cells/monkey in 1981; 100 cells/monkey in 1987.

mean SCE/cell in Group C significantly different than that in A or B, *P* < 0.05; mean SCE/cell in Group B significantly different than that in A, *P* < 0.05; F: mean SCE/cell in Group F significantly different than that in E or D, *P* < 0.05; mean SCE/cell in Group E not significantly different than that in D, *P* > 0.05.

**Fig. 1.** Distribution of SCE/cell, pooled over exposure groups, by the year in which the SCE frequency determinations were completed. Only data on surviving animals are included (animals deceased since the 1981 data were generated are not included).

Phytoce populations than is analysis of the mean SCE frequency. This analysis avoids the arbitrary definition of a numerical threshold for a HFC and is, therefore, a preferable analytical approach. We computed the mean SCE frequency of all of the cells with SCE in the upper 10th percentile (the tail) of the distribution of the SCE in each animal in all of the exposure groups. We also computed the mean SCE in the remaining 90%, or the body, of the same SCE distributions. This analysis includes only those animals that survived and were available for study in 1987 (inclusion of data from the animals studied in 1981 that did not survive for study in 1987 does not significantly alter the analysis). The mean SCE frequencies in the tail and body of the distributions for each animal are compared in Table 3. The mean SCE frequency in the upper 10th percentile of the SCE frequency distributions in the EtO-exposed animals is similar in 1981 (highest 5 cells) and 1987 (highest 10 cells). The mean SCE frequency in the upper 10th percentile in the controls in 1987 is higher in 6 of the 8 animals when compared to similar data compiled in 1981 (Table 3). Comparison of the mean SCE frequencies in the body of the distributions (lower 90th percentile) by animal over the years of study reveals that the significant dose response noted in this portion of the SCE distribution in 1981 is no longer present in 1987. Instead, there is no exposure-related elevation in SCE frequency in the lower 90% of the distribution in 1987 in either exposed group (Table 3). The mean SCE frequency in the lower 90th percentile of the SCE distribution in the controls has increased over the 6 years since last exposure.

Since the analysis of the HFC in individual animals is limited by the number of cells scored, we have pooled the data from all of the animals in each exposure group and examined the SCE frequency means in a more restricted tail and body of this pooled SCE distribution. The upper 5% of the SCE frequency distribution was designated as the tail, and the lower 95% was accordingly designated as the body. This analysis reveals that the mean SCE frequency of the upper 5% of this distribution (pooled by exposure group) has increased in the highest (100-ppm) exposure group, remained unchanged in the 50-ppm exposure group, and increased in the controls. The mean SCE frequency in the tail of the overall distribution (excluding the
The effect of individual animal) had increased from 47.4 ± 1.9 SCE/cell (N = 14 cells of 250 cells scored from 5 animals) in 1981 to 60.0 ± 2.0 SCE/cell (N = 34 cells of 700 cells scored from 7 animals) in 1987 in the 100-ppm exposure group. Hence, not only are the HFC more numerous in the 100-ppm exposure group in 1987 (Tables 1 and 2), but the mean SCE/cell is higher in these cells in 1987. This elevation in mean SCE/cell may, however, be partially attributable to the presence of data from animals A39 and A242 only in 1987. As previous analysis has shown, the body (lower 95%) of the pooled SCE frequency distribution revealed an exposure-related dose response in 1981 and no difference from control level in 1987. In addition, the control SCE frequency in the lower 95% of the pooled distribution is slightly higher in 1987 than was observed in 1981, consistent with the previous analysis which included the effect of individual animals.

### DISCUSSION

We have demonstrated that chronic inhalation exposure to EtO in nonhuman primates results in elevated SCE frequencies in peripheral blood lymphocytes which persist at least 6 years after cessation of EtO exposure. While the mean SCE/cell in 1987 for each of the exposure groups (controlling for the effect of individual animals) was greater than the mean SCE/cell in control animals, it is also evident that the SCE frequency of each of the exposed groups has decreased markedly since 1981. For the 50-ppm group, an 80% reduction in EtO-induced mean SCE frequency was observed (compared with the EtO-induced SCE in 1981) whereas a 70% reduction was seen in a similar comparison of animals exposed to 100 ppm. In addition, the mean SCE frequency in the control animals has increased over time, consistent with age-related increases which have been reported in humans (12). It should be noted, however, that the elevation in SCE frequency in the control animals which we observed over time (1981–1987) may be influenced by differences between studies, including reader differences, and differences such as serum source, and in vitro culture conditions (33).

It is of interest to consider that, if the decrease in mean SCE frequencies were to have occurred uniformly among all cells, the distribution of SCE in 1987 for exposed animals should resemble that observed in 1981, but the entire distribution should be shifted towards lower SCE values. Since previous workers have shown bimodal SCE distributions in individuals with a history of chronic EtO exposure (14), it was important to determine whether the decrease in SCE frequency which we observed was indeed uniform. Therefore, we compared the distributions of SCE recorded in 1981 with those from 1987.

This comparison showed that cells with very high SCE frequencies did not decrease as would have been predicted if SCE decreased uniformly among all cells. Instead, the SCE frequency was observed (compared with the EtO-induced SCE in 1981) whereas a 70% reduction was seen in a similar comparison of animals exposed to 100 ppm. In addition, the mean SCE frequency in the control animals has increased over time, consistent with age-related increases which have been reported in humans (12). It should be noted, however, that the elevation in SCE frequency in the control animals which we observed over time (1981–1987) may be influenced by differences between studies, including reader differences, and differences such as serum source, and in vitro culture conditions (33).

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term in vivo exposures to agents such as EtO is best approached by methods originally suggested by Stetka et al. (34) and formalized by Moore and Carrano (32). In these situations, it is apparent that the study of the outliers in the SCE distributions may be the only informative approach.

Our observation of persistent elevation of SCE after chronic inhalation exposure to EtO is similar to those of others studying animals and occupational cohorts. Nichols et al. (14) previously observed bimodal distributions of SCEs in workers chronically exposed to EtO whose last exposure occurred more than 24 months prior to study. Yager and Benz (35) observed elevated SCEs in rabbits up to 15 weeks after the last EtO exposure. Yager (36) has recently reported persistently elevated SCE in rabbits, detectable 13 weeks after last EtO exposure. Garry et al. (7) reported persistent SCE elevation 8 weeks after termination of exposure of hospital sterilizer operators. Stolley et al. (12) also reported persistently elevated SCE in EtO-exposed sterilizer operators up to 41 months after cessation of exposure. In some of these individuals, the mean SCE levels varied quite significantly over time.

The present study of EtO-induced SCE represents the longest follow-up time after chronic in vivo inhalation exposure yet reported. The results indicate that persistence of elevated SCE frequencies occurs preferentially in a small population of cells that comprise the upper tail of the SCE distribution. Other studies of EtO-induced SCEs after in vivo exposure have reported bimodality in the response to EtO over time (14), but none have concluded, as we have, that the persistence of SCE is attributable to an outlier population of cells. This may in fact be due to the chronic nature of the original exposure and the longer follow-up time of the current study. If this is true, our results would predict that continued follow-up of human cohorts chronically exposed to EtO could reveal a similar persistence of SCE occurring in a small subpopulation of long-lived cells.

The mechanism responsible for the nonuniform decrease in mean SCE frequency which we have observed is unclear. Following alkylating damage to DNA, cellular repair mechanisms can be activated that then remove the lesions in DNA that give rise to SCE. In addition, during normal lymphocyte repopulation damaged cells may simply be eliminated and replaced by newly formed, undamaged cells. With chronic exposures lasting several years as in the present study, both DNA repair and lymphocyte repopulation could be important factors influencing SCE frequencies. Despite the normal frequencies of SCE observed in the majority of lymphocytes from EtO-exposed animals, SCE frequencies in the tail of the distribution did not decrease. Because these cells have persistently high SCE frequencies, it is likely that they are long-lived lymphocytes that were present at the time of EtO treatments and are still viable 6 years after exposure, even though they appear to be highly damaged. This is consistent with observations of other investigators studying lymphocytes exposed to DNA-damaging agents in vitro (37). The monkey lymphocytes which display this very high level of cytogenetic damage also have probably not replicated their DNA or divided during this time. This, then, suggests that some long-lived lymphocytes do not efficiently repair the EtO-induced lesions that give rise to SCE. If this is true, it raises the question of whether some long-lived lymphocytes are constitutively deficient in repairing lesions that produce SCE or, alternatively, whether EtO treatments themselves produce long-term inhibition of repair processes. The latter hypothesis is consistent with the work of Pero et al. (38) who found that EtO inhibits unscheduled DNA repair synthesis in human lymphocytes.

Inefficient repair of EtO-induced damage by quiescent, long-lived cells could also explain why these cells preferentially exhibit a high degree of damage. Long-lived, nondoning cells would have accumulated damage over the entire 2-year exposure period, resulting in a higher cumulative EtO "dose" than the short-lived cells (cells that accumulated less damage due to repopulation and turnover). Over time, only the long-lived cells would remain, resulting in a SCE distribution similar to that which we have observed.

Our results also have important implications for the use of SCE analysis in the detection of cytogenetic damage after chronic human exposure to DNA alkylating agents. When SCE analysis has been used to monitor human populations, it has most commonly been interpreted as an indicator of mutagen exposure. SCE induction is also a marker of biological effect, although the health risk (if any) associated with this marker is unknown. The present study raises questions concerning the interpretation of SCE, as a marker of both exposure and effect. It is evident from our results that the most sensitive statistical approach to SCE data analysis in studies of exposure will vary, depending upon the nature of the exposure. Conventional analysis of mean SCE/cell may be appropriate following acute exposure. For example, Laurent (39) has studied three workers acutely exposed to EtO and reported that HFC in the SCE distribution do not persist. Yager (36) has also shown that rabbits subchronically exposed to EtO have persistent HFC but that their number diminishes over time. However, a discriminant type analysis focusing upon the tail of the SCE distribution may be the only informative approach in long-term follow-up of chronically exposed populations, such as those studied by Stolley et al. (12), Nichols et al. (14), and Richmond et al. (10). In addition, the presence of a subpopulation of high SCE frequency cells, arising as a result of past chronic mutagen exposure, would confound simple cross-sectional analysis of SCE in an acutely mutagen-exposed cohort. With respect to biological effect, we have shown that an elevation in mean SCE frequency can result from a small subpopulation of cells containing very high SCE frequency cells as well as from a uniform increase in the SCE distribution. The measurement of the mean SCE/cell cannot distinguish between these two very different situations. The latter (uniform increase in SCE) has been associated with both acute and chronic mutagen exposure and the former with chronic exposure studied many years after cessation of exposure. The biological consequences and possible health risks of these two situations may be very different. Therefore, it would seem prudent for future epidemiological studies which are designed to assess the possible risks associated with SCE induction to analyze their data using both conventional analysis and a more discriminant analysis, sensitive to the effects of outliers in the SCE distribution.

Current work is focused on further characterization of this subpopulation of cells with persistently high SCE frequency and the repair pathways that act on these lesions, as well as on identifying the DNA modifications produced by EtO that give rise to SCE. Further understanding of this phenomenon is important for the continued application of cytogenetic methodology in epidemiological studies and, possibly, for insight into the development of cancer, for the persistence of such cellular damage might play a critical role in tumor induction (40).
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