CYTOGENETIC EFFECTS OF ETHYLENE OXIDE, WITH AN EMPHASIS ON POPULATION MONITORING

R. Julian Preston
Chemical Industry Institute of Toxicology
6 Davis Drive
Research Triangle Park
NC 27709, USA

IARC, 1994

In making the overall evaluation, the Working Group took into consideration the following supporting evidence. Ethylene oxide is a directly acting alkylating agent that:

- induces a sensitive, persistent dose-related increase in the frequency of chromosomal aberrations and sister chromatid exchange in peripheral lymphocytes and micronuclei in bone-marrow cells of exposed workers;

- has been associated with malignancies of the lymphatic and haematopoietic system in both humans and experimental animals;

- induces a dose-related increase in the frequency of haemoglobin adducts in exposed humans and dose-related increases in the numbers of adducts in both DNA and haemoglobin in exposed rodents;

- induces gene mutations and heritable translocations in germ cells of exposed rodents; and is a powerful mutagen and clastogen at all phylogenetic levels.

Overall evaluation

Ethylene oxide is carcinogenic to humans (Group 1)

Human Population Monitoring

Cell Type

- Peripheral lymphocytes
- Bone Marrow

Endpoints

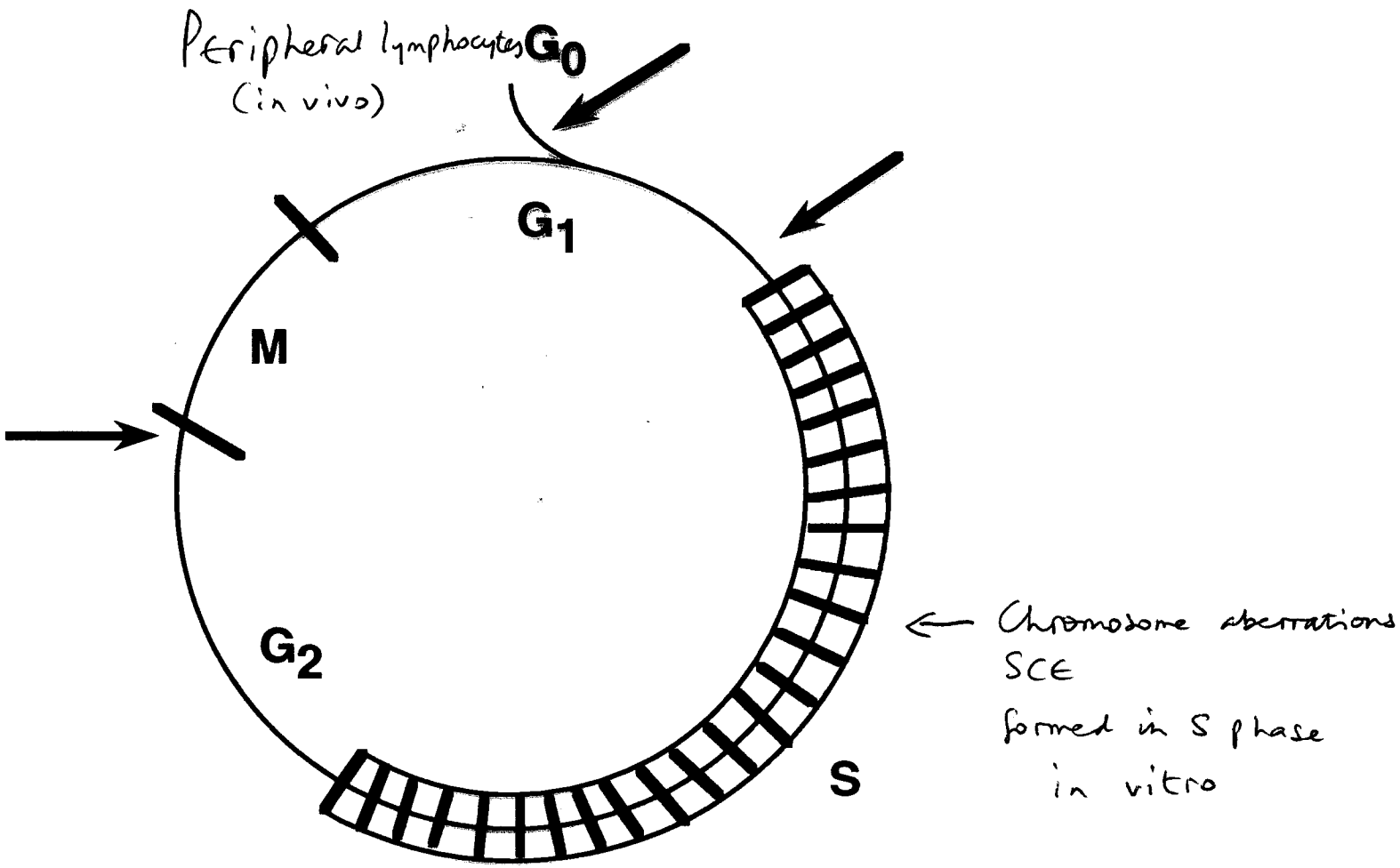
- Chromosome aberration
- Micronuclei
- Sister chromatid exchanges

Cytogenetic Endpoints and Cancer

- SCE - no relationship between SCE and cancer
- Micronuclei - cell lethal event
- Chromosome aberrations - types analyzed are cell lethal
- Peripheral lymphocyte not relevant for predicting tumors in other tissues and organs

Potential Confounders

- Size of study population
- Adequate matched controls
- Accurate information on exposure
- Ability to account for confounders
  - known (e.g., age, gender, smoking, radiation)
  - unknown
- Other exposures



Critical points in cell cycle regulation

Cytotoxicity would be expected to act initially at $G_0 \rightarrow G_1$

Coincident or subsequent alterations in other genes could affect regulation of cell cycle and genomic stability

Schulte et al. (1992)

- Control values for SCE much lower than for other larger studies
- Limited nature of exposure information
- Statistical analysis - accounting for possible confounders SCE values used were adjusted values

Ribeiro et al. (1994)

- 75 factory workers in Brazil using ethylene oxide

  22 unexposed controls

- Authors concluded that positive effects seen in their study, at relatively low ethylene oxide concentrations

  "Could be due to the possibility that the workers in Brazil were exposed not only to EtO but also to other chemicals used in the workplace".

Tates et al. (1995)
Mutation Res. 329. 63-77

Group I	acute high doses (29 ppm to 436 ppm)
Group II	chronic exposure, low doses <5 years
Group III	chronic exposure, low doses >5 years 0.01 - 0.03 ppm
Group IV	unexposed controls

No increase in SCE, micronuclei or hprt mutations in Groups I, II, III

Group I sampled 89-180 days after exposure:

No persistence of preclastogenic lesions

CONCLUSION

The requirement for assessing transmissible chromosomal alterations has not been met by any of these studies, and so the observed events are actually produced *in vitro* for lymphocytes or by the last one or perhaps two cell cycles prior to sampling for bone marrow. Thus, consideration has to be taken of DNA repair characteristics during exposure, and in particular the amount of DNA damage remaining that can be converted into aberrations or SCE at the first *in vitro* S phase. This has not been done.

CONCLUSION

For human studies, considerable importance has to be attached to the selection of study populations, with emphasis on accounting for known or possible confounders of response. In general, this has not been done, leading to the conclusion that population monitoring studies have only limited value, as typically conducted, for assessing effects of long-term ethylene oxide exposures.

CONCLUSION

It does appear that acute, high concentration (accidental) exposure to ethylene oxide, with sampling shortly after exposure, can be detected by assessment of chromosome aberrations or SCE in peripheral lymphocytes. However, it is to be noted that even in such cases, the cytogenetic endpoint serves as an indicator of exposure not a harbinger of a subsequent adverse health outcome.