ETHYLENE OXIDE (Group 2A)

A. Evidence for carcinogenicity to humans (*limited*)

Five studies[1,2] have investigated the cancer mortality of workers exposed to ethylene oxide.

Case reports of two myeloid leukaemias and one morbus Waldenström (later reclassified as a non-Hodgkin's lymphoma) were initially found among persons on the work force of a small Swedish factory who had been exposed primarily to ethylene oxide during a sterilizing process. In a subsequent five-year follow-up, a further death from leukaemia (acute 'blastic') was reported. Hence, altogether, four deaths from malignancies of the lymphatic and haematopoietic system (three leukaemias) occurred among the workers, compared with 0.3 expected[1,2].

Another Swedish study comprising 89 ethylene oxide operators with all-day exposure and 86 intermittently exposed maintenance workers involved in the production of ethylene oxide by the chlorohydrin process showed a statistically significant excess of leukaemia, based on two deaths and two incident cases (two lymphocytic, two myelogenous). The

expected number was 0.52. There was also a statistically significant excess of deaths from stomach cancer (5 observed, 0.6 expected; in addition, a sixth incident case was reported). These excesses were confined to the workers exposed all day[1,2]. It should be noted that these workers had been exposed to a mixture of chemical compounds, including dichloromethane (see p. 194), ethylene chlorohydrin and small amounts of bis(2-chloroethyl)ether[1].

A third Swedish cohort consisted of 355 workers exposed at a plant producing ethylene oxide through oxygenation of ethylene. Of these, 128 workers had had almost pure exposure to ethylene oxide. Eight deaths occurred compared with 11.6 expected. There was one case of myelogenous leukaemia (0.16 expected) and one of lung cancer among men with mixed exposure[2].

The total number of leukaemias observed in the three Swedish studies was thus eight, with 0.83 expected. Stomach cancer occurred in excess in one plant only (six cases in a group of 89 workers)[2].

In a cohort study of 767 ethylene oxide production workers in the USA, no case of leukaemia was found. However, there was only low potential exposure to ethylene oxide among the workforce and an unusually large deficit in total deaths compared to the number expected, indicating diluting errors in the design of the study[1].

A cohort study of 602 factory workers in the Federal Republic of Germany exposed to ethylene oxide, propylene oxide (see p. 328), benzene (see p. 120) and ethylene chlorohydrin showed a deficit of all deaths compared with four different expected figures. There were 14 deaths due to cancer (16.6 expected from national statistics), one of which was a myeloid leukaemia (0.15 expected) and four of which were stomach cancers (2.7 expected). The expected numbers used were not calendar period-specific over the whole observation period, however, and it is not clear whether they were computed on the basis of the 92% of identified workers or the full cohort[1].

In the light of these data, a causal relationship between exposure to ethylene oxide and leukaemia is possible, but the five small epidemiological studies so far available suffer from various disadvantages, especially confounding exposures, which make their interpretation difficult.

B. Evidence for carcinogenicity to animals (*sufficient*)

Ethylene oxide was tested by intragastric intubation in rats and produced local tumours, mainly squamous-cell carcinomas, of the forestomach. When rats were fed diets fumigated with ethylene oxide, no increased incidence of tumours was observed[1]. In two experiments in which rats of one strain were exposed by inhalation, ethylene oxide increased the incidences of mononuclear-cell leukaemia, brain tumours and proliferative lesions of the adrenal cortex in animals of each sex and of peritoneal mesotheliomas in males[1,3,4]. In mice, inhalation of ethylene oxide resulted in increased incidences of alveolar/bronchiolar lung tumours and tumours of the Harderian gland in animals of each sex and of uterine adenocarcinomas, mammary carcinomas and malignant lymphomas in females[5]. Ethylene oxide was also tested by subcutaneous injection in mice, producing local tumours, which were mainly fibrosarcomas[1].

C. Other relevant data

Significant increases in haemoglobin alkylation, in the incidences of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes and, in a single study, micronuclei in erythrocytes have been observed in workers exposed occupationally to ethylene oxide[6].

Ethylene oxide induced chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes of monkeys exposed *in vivo*. It alkylated haemoglobin and DNA and induced chromosomal aberrations, micronuclei, dominant lethal mutations, heritable translocations and sister chromatid exchanges in rodents treated *in vivo*. In human cells *in vitro*, it induced sister chromatid exchanges, chromosomal aberrations and unscheduled DNA synthesis. It enhanced cell transformation in virus-infected Syrian hamster embryo cells and induced mutation in rodent cells *in vitro*. Ethylene oxide induced somatic and sex-linked recessive lethal mutations and heritable translocations in *Drosophila*. It induced mutation and chromosomal aberrations in plants. Ethylene oxide was mutagenic to fungi and bacteria and induced DNA damage in bacteria[6].

References

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[3]Garman, R.H., Snellings, W.M. & Maronpot, R.R. (1985) Brain tumors in F344 rats associated with chronic inhalation exposure to ethylene oxide. *Neurotoxicology, 6*, 117-138

[4]Garman, R.H., Snellings, W.M. & Maronpot, R.R. (1986) Frequency, size and location of brain tumours in F-344 rats chronically exposed to ethylene oxide. *Food chem. Toxicol., 24*, 145-153

[5]National Toxicology Program (1986) *Toxicology and Carcinogenesis Studies of Ethylene Oxide (CAS No. 75-21-8) in B6C3F$_1$ Mice (Inhalation Studies) (NTP TR 326; NIH Publ. No. 86-2582)*, Research Triangle Park, NC

[6]*IARC Monographs, Suppl. 6*, 300-303, 1987