ECETOC Document

No 26

ECETOC Statement on Ethylene Oxide Toxicology and its Relevance to Man

October 1986

ECETOC

Brussels, 8 October 1986

DOC N° 26

ECETOC STATEMENT ON ETHYLENE OXIDE-TOXICOLOGY AND ITS RELEVANCE TO MAN

European Chemical Industry
Ecology & Toxicology Centre

Avenue Louise 250, B. 63
B - 1050 Brussels, Belgium

ECETOC

CENTRE D'ECOLOGIE ET DE TOXICOLOGIE
DE L'INDUSTRIE CHIMIQUE EUROPEENNE

EUROPEAN CHEMICAL INDUSTRY ECOLOGY
AND TOXICOLOGY CENTRE

Avenue Louise 250, Bte 63
B-1050 Brussels
Telex APME B 61 523
Téléphone: (02) 649 94 80
T.V.A. 418 344 469

ECETOC Document No.26

WJB/am/66

Brussels, 8 October 1986.

ECETOC Statement on Ethylene Oxide Toxicology and its Relevance to Man

On September 20, 1982 the European Chemical Industry Ecology and Toxicology Centre (ECETOC) issued Technical Report No.5 summarising findings concerning the effects of ethylene oxide (EO) on animals and humans, and their significance for man under current working conditions. The availability of further results from a number of biological and epidemiological studies indicated a need for an up-dating which resulted in the publication of Technical Report No.11 in March 1984. In the last report it was recommended that there is a need for further epidemiological investigations on the reproductive toxicity, neurotoxicity and carcinogenicity of EO.

Recently, Dr. C. Hogstedt and his co-workers at the National Board of Occupational Safety and Health in Solna, Sweden published the results of a study concerning the mortality and cancer incidence in three cohorts of workers (two of which have been the subject of previous reports) occupationally exposed to EO (Hogstedt et al.,1986).

A number of experts from member companies of ECETOC have analysed the study and their views are given in this Statement. At the same time the opportunity was taken to review any literature on the toxicity of EO since the publication of Technical Report No.11 (ECETOC, 1984).

1. Epidemiological Results

The Hogstedt et al.(1986) study is a follow-up during the period 1978-1982 of the two earlier reported cohort studies (Hogstedt et al., 1979 a and b). In addition, the results of a new cohort study of 355 persons occupationally exposed to EO and/or propylene oxide and other chemicals are reported.

According to the authors, this study indicated that workers who had extended and intermittent exposure to EO, even at low concentrations, are ten times more likely to develop leukaemia and stomach cancer.

Details on the cancer cases and exposures to EO are provided in the attached Table.

The finding of 5 fatal cases of stomach cancer and one fatal case of oesophagus cancer among the 89 members of cohort 2 is remarkable especially as no cases of stomach cancer were reported in the other two cohorts. This finding might therefore be related to the different production process in the second plant and/or to the mixed exposure of the workers to a range of other chemicals. In addition, the authors reported that "these workers in the 1940's tasted the chemical reaction products to assess the results of EO synthesis".

The finding of 8 leukaemia cases, throughout the full study period, in all three cohorts combined, is reason for concern. Although the cohorts were selected from 3 different plants with completely different production processes involving exposure to mixtures of chemicals in two of the 3 cohorts, they had exposure to EO in common. For that reason no clear relationship between exposure to EO and the response can be drawn from this study. Different types of leukaemia were reported and it is doubtful whether this is a direct result of only one and same aetiological factor, i.e. exposure to EO. Furthermore, the data presented by Hogstedt et al. are difficult to interpret due to limited and non-homogeneous information on age of death, exposure time and induction-latency time of the individual leukaemia cases of three different cohorts (see Table).

Exposure levels to EO reportedly varied in plant 1 and 2 from 5-25 ppm 8 hours TWA. However, these are based on estimates from a limited number of grab samples. In plant 1 and 2 much higher (peak) exposures occurred, upto the odour

threshold of EO (650 ppm). Thus, precise information on the actual exposure levels to EO, in particular of the individuals in cohort 1 and 2, is lacking.

One leukaemia case was reported from the third cohort in a maintenance worker. The estimated 8 hours TWA EO exposure of the maintenance workers in this plant was estimated 1-3 ppm before 1977. However, data on duration of exposure and age of death of this case have not been presented by the authors and therefore the finding in the third cohort is difficult to interpret.

In conclusion, this new publication by Hogstedt et al. is reason for concern and may provide further support for the possible causal relationship between exposure to EO and the occurrence of leukaemia. Due to the uncertainties about the actual exposure levels and the mixed exposures, the study is inconclusive.

Recently a mortality study was reported among EO workers in 8 chemical production plants in the Fed. Rep. of Germany (Kiesselbach and Lange, 1986). At present only summarised results are available which do not permit a full evaluation. The total study group comprised 2658 men exposed to EO for at least one year (exposure level is not indicated). The observed mortality was 268 vs 311.5 expected (SMR: 0.86). No increased mortality from leukaemia was seen in this study. No significant SMR values were found for other malignant neoplasms.

2. Further Human Data

Stolley et al.(1984) and Richmond et al.(1985) have reported cytogenetic changes in sterilisation workers in medical supply facilities. No such changes were observed in a study by Van Sittert et al.(1985) in workers exposed to very low levels (mean <0.05 ppm, occasional peaks of upto 8 ppm) of EO.

3. Experimental Results

The ECETOC experts were also informed about the draft report of the NTP-EO study where B6C3F1 mice of each sex were exposed to 0, 50 and 100 ppm EO, 6 h/d, 5 d/wk for 102 weeks. In male mice, alveolar/bronchiolar carcinomas, alveolar/bronchiolar adenomas, and papillary cystadenomas of the harderian gland occurred with positive trends. In female mice, alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, papillary cystadenomas of the

harderian gland, malignant lymphomas, and uterine adenocarcinomas occurred with positive trends. The peer review of this report is imminent.

4. General Conclusions

The latest experimental results reinforce the previous conclusion (ECETOC, 1984) that EO is a "putative human chemical carcinogen". Although the latest epidemiological study by Hogstedt et al.(1986) is inconclusive, the observed excess incidence of leukaemias is consistent with the experimental data and should be treated with concern. Judgements about the human hazard are clouded by imprecise estimates of exposures and by mixed exposures to other chemicals. The occurrence of stomach and oesophagus cancer found in only one cohort is very difficult to attribute to EO exposure.

The present available information however point to a need for further studies on EO exposed populations.

Dr. Walter J. Bontinck
for Dr. P. Wright
Task Force Director

---

* Putative human chemical carcinogen :
"A putative human carcinogen is a clearly-defined chemical substance which causes malignant neoplasms in adequate animal experimentation, under exposure conditions which correspond to those in man, or where the relevance of the exposure conditions can be deduced" (ECETOC, 1980).

5. Bibliography

- ECETOC (1980). Contribution to Strategy for Identification and Control of Occupational Carcinogens. Monograph No.2.
- ECETOC (1982). Toxicity of Ethylene Oxide and its Relevance to Man. Technical Report No.5.
- ECETOC (1984). Ethylene Oxide Toxicology and its Relevance to Man : An Up-dating of ECETOC Technical Report No.5. Technical Report No.11.
- Hogstedt, C., Berndtsson, B.S., Rohlen, O. and Ehrenberg, L.(1979-a). A cohort study on mortality and cancer incidence in ethylene oxide production workers. Br. J. Ind. Med., 36, 276.
- Hogstedt, C., Malmquist, N. and Wadman, B.(1979-b). Leukaemia in workers exposed to ethylene oxide. JAMA, 241, 1132.
- Hogstedt, C., Aringer, L. and Gustavsson, A.(1986). Epidemiologic support for ethylene oxide as a cancer-causing agent. JAMA, 255, 1575.
- Kiesselbach, N. and Lange, H.J.(1985). Multicentral epidemiological study on ethylene oxide. A preliminary report. Presentation at Medichem Conference, 14th International Congress on Occupational Health in the Chemical Industry on 16-19 Sept. at Ludwigshafen, F.R.G..
- NTP (National Toxicology Programme)(1986). Etlylene Oxide, NTP TR 326, Draft 8.
- Richmond, G.W., Abrahams, R.H. and Nemenso, J.H.(1985). An evalution of possible effects on health following exposure to ethylene oxide. Arch. Environm. Health, 40, 20.
- Stolley, P.D., Soper, K.A. and Galloway, S.M.(1984). Sister-chromatid exchanges in association with occupational exposure to ethylene oxide. Mutat. Res., 129, 80.
- Van Sittert, N.J., de Jong, G., Clare, M.G., Davies, R., Dean, B.J., Wren, L.J. and Wright, A.S.(1985). Cytogenetic, immunological and haematological effects in workers in an ethylene oxide manufacturing plant. Br. J. Ind. Med., 42, 19.

Overview of Cancer Cases and Exposure in 3 Different Cohorts (Hogstedt et al.,1986)

Cohort	Type of leukaemia or cancer	Year of diagnosis	Age of death	Years of exposure to EO	Estimated intensity of exposure to EO (8 hours - TWA) ppm	Latency time * (years)
1 (N=203)** Total deaths unknown	1 chronic myelogenous	1972	56	6 (1966 - 1972)	20	6
	1 acute myelogenous	1977	39	9 (1968 - 1977)	20	9
	1 acute blast cell leukaemia	1979	?	3 (1969 - 1972)	? (<20)	10
2 (N=175) In 89 full-time exposed to EO : 23 deaths;*** expected 13.5; in 86 maintenance workers no "increased mortality"	1 chronic lymphocytic	1961	?	>10 years	5 - 25 (<1970)	>20
	1 acute myelogenous	1971	?	>1<10 years	5 - 25 (<1970)	>10
	1 chronic lymphocytic	1972	?	>1<10 years	5 - 25 (<1970)	>10
	1 chronic myelogenous	1979	alive at closure of study	?	?	?
	3 stomach cancers	<1978	?	>1<4 years	0.5 - 5 (>1970)	>10
	1 stomach cancer	1978 - 1982	?	>5<9 years	0.5 - 5 (>1970)	>10
	1 stomach cancer	1978 - 1982	?	>10 years	?	>10
3 (new cohort) (N=355)	1 chronic myelogenous	1976	?	?	1 - 3	?

Total observed deaths = 8;
Total expected deaths = 11.6.

* defined as a period between start of exposure to death.

** N : number of exposed workers.

*** During the follow-up of this cohort (1978-1982) 7 additional deaths occurred among the full time exposed EO operators against 6.6 expected.