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An epidemiological study of cancer risk among workers exposed to ethylene oxide using hemoglobin adducts to validate environmental exposure assessments

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Summary. Cancer morbidity was investigated in a cohort of 2,170 ethylene oxide (EO)-exposed workers from 2 plants producing disposable medical equipment. The subjects had been employed for at least 1 year during the periods 1970–1985 and 1964–1985, respectively. The exposure to EO was assessed for each of six job categories in the plants with respect to each calendar year, on which basis values for individual cumulative exposure to EO (ppm-years) were calculated. The levels of hydroxyethyl adducts to N-terminal valine (HOEtVal) in hemoglobin fitted well with the values estimated for airborne exposure to EO. No increased cancer incidence was found [standardized morbidity ratio (SMR), 0.78; 95% CI, 0.49–1.21)]. No leukemia was observed, but one case of non-Hodgkin's lymphoma, one case of myeloma, and one case of polycythemia vera were diagnosed as compared with two expected hematopoietic and lymphatic tumors (SMR, 1.54; 95% CI, 0.32–4.5). No stomach cancer was detected as compared with the 0.5 case expected. There were no significant exposure-response associations between estimates of exposure to EO and cancer morbidity.

Key words: Cohort study – Ethylene oxide – Hemoglobin adducts – Dosimetry – Leukemia

Introduction

Ethylene oxide (EO) is an important intermediate industrial chemical that is also used for sterilizing medical products and hospital equipment. EO is a reactive epoxide whose genotoxic properties have been extensively reviewed [6, 8, 15, 16]. Animal experiments have clearly demonstrated that EO is carcinogenic. Increased incidence of leukemia, gliomas of the brain, peritoneal mesotheliomas, and squamous-cell carcinomas of the forestomach have been found in Fischer 344 rats [15]. Tumours at multiple sites have also been demonstrated in the mouse [22]. These animal experiments were carried out as 2-year inhalation studies using exposure levels in the range of 10–100 ppm.

Occupational exposure to EO has been shown to increase the levels of chromosome aberrations, sister chromatid exchange, and micronuclei [15]. In 1979, two cases of leukemia and one case of Waldenström's macroglobulinemia were reported among a small group of Swedish workers exposed to a mixture of EO and methyl formate [13]. This initially observed cluster initiated a retrospective cohort study [14]. The risk for leukemia as well as that for stomach cancer showed 10-fold increases. Five other cohort studies of EO-exposed workers have been published [1, 9, 10, 17, 20], but no unequivocal increase in the risk for leukemia or stomach cancer was observed.

The interpretation of these investigations is complicated by a lack of exposure data, the small numbers of cases involved, and the possibility of confounding exposure to other carcinogens in the plants. The aim of the present study was to add more data on cancer incidence in subjects exposed to relatively well-defined levels of EO in the absence of confounding exposure to other known carcinogens. Some of the workers had previously displayed increased levels of chromosome aberrations in their bone marrow [11], showing that at least the prior EO-exposure levels in the plants had caused clastogenic effects.

Subjects and methods

The plants. Plants A and B produce disposable medical equipment that is sterilized with EO. The sterilization if performed in autoclaves containing a mixture of EO and carbon dioxide. The autoclaves are placed in separate rooms and are handled by the sterilizers. Other staff categories exposed to EO include packers of sterilized materials, store workers, controllers, repairmen, laboratory technicians, development engineers, and foremen. Currently, the material is packed before autoclaving, degassed in the autoclave

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before being removed, and then directly transported to quarantine storage for further degassing before being handled. However, the previous hygienic conditions were quite different.

EO sterilization started in plant A in 1970. The goods were sterilized in cotton bags using a 1:1 (v/v) mixture of EO and methyl formate. The sterilized goods were then packed without being quarantined. A new autoclave and a new ventilation system were installed in 1975. Further major improvements included the discontinuation of packing of recently sterilized material in 1977 and the introduction of a quarantine storage facility in 1980. The concentration of EO in air was first monitored in 1973 using both personal and area sampling. Air sampling and analyses were performed using 30-ml glass syringes and gas chromatography (GC); area monitoring was also done with an infrared spectrophotometer and a gas cuvette. Area sampling over 2.5 h during which the autoclave was open indicated an EO level of about 75 ppm in the room. Two packers displayed an exposure level of 24 ppm. Monitoring has been repeated over 1–3 days once a year since 1981 but has been restricted to sterilizers and packers. The results have indicated a continuous decrease in EO exposure. Since 1985, only the sterilizers have exhibited levels of >0.2 ppm, which is the detection limit of the GC method used. The use of methyl formate ceased in 1981, after which EO was mixed with fluorochlorocarbons or carbon dioxide.

In plant B, the sterilization process started in 1964. In this plant as well, the material was packed soon after autoclaving. The exposure decreased for the packers in 1973, when the material was sterilized in baskets instead of in cotton bags and was stored for 4–16 h before packing. A 1:1 (v/v) EO/methyl formate mixture was used as of 1973 but was replaced by an EO/carbon dioxide mixture in 1978. Beginning in 1978, the material was packed before sterilization and then transported to quarantine storage. The first monitoring of EO was performed in 1975 by personal and area sampling. Air sampling and analyses were carried out using 30-ml glass syringes and GC. The exposure for the sterilizer was 30 ppm during the removal of goods from the autoclave following sterilization. Four packers were exposed to 4–5 ppm EO. Shortterm measurements (minutes to hours) have been obtained on 25 occasions since 1980, but they were done almost exclusively on sterilizers and workers in the stores. The 8-h time-weighted exposure levels since 1985 have been <0.2 ppm for all employees except sterilizers and store workers.

Due to the recirculation of EO from the air outlets of the autoclaves to the air inlets of the factory, all employees in both plants have been exposed to increased levels of EO.

Exposure estimates. Exposure to EO was assessed for each of six job categories in plants A and B. Exposure data were scarce and existed only from 1973 and 1975, respectively. For each job category, exposure estimates were constructed, incorporating the data and information about major changes in production methods and environmental control as well as subjective memories and fitted time trends. Thus, for each category of workers, the average daily exposure was assessed for each year from 1970 to 1986 and from 1964 to 1986 in plants A and B, respectively (Tables 1, 2).

Based on this information, the individual cumulative exposure to EO (ppm-years) was calculated by adding the exposure estimates for each calendar year of employment. This was expressed as ppm-years (exposure for 8 h/day, 5 days/week). However, for 35 subjects (3%) in the cohort from plant A and for 115 subjects (11.3%) in the cohort from plant B, no cumulative EO exposure could be calculated due to a lack of data. We have reason to believe that these subjects have never been exposed to high levels of EO. The limit of detection for air monitoring was 0.2 ppm. For the cumulative-dose calculations, a value of 0.1 ppm was used for workers in job categories involving direct exposure to EO, whereas the estimated exposure was <0.2 ppm. For job categories involving indirect exposure ("others"), we used 0.02 ppm.

In vivo dose of EO. The measurement of levels of hydroxyethyl adducts to N-terminal valine (HOEtVal) in hemoglobin (Hb) can be used in dosimetry for EO [5, 27]. As the adduct levels reflect the average exposure during the last few months, they could be used to verify our estimated values for airborne exposure. Blood samples from 20 subjects from plant A, 19 employes from plant B, and 4 individuals serving as control were collected in heparinized tubes with gamma-sterilized cannulae. The red cells were recovered by centrifugation and were then carefully washed with 0.9%

Table 1. Assessment of personal exposure to EO for six different job categories in plant A involving direct EO contact and for the other job categories in the plant that involved indirect exposure

Job category	Calendar year					
	1970–1972	1973–1975[a]	1976–1978	1979–1981	1982–1984	1985–1986
Sterilizers	40	20	15	10	3	0.75
Development engineers	20	12	7	5	1	<0.2
Packers	35	20	3	1	0.5	<0.2
Laboratory technicians	3.5	2	0.5	<0.2	<0.2	<0.2
Repair men	4	2	1	0.5	<0.2	<0.2
Store workers	15	10	5	2.5	<0.2	<0.2
Others	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2

Data are expressed in parts per million
[a] EO air monitoring was initiated during this period

Table 2. Assessment of personal exposure to EO for six different job categories in plant B involving direct EO contact and for the other job categories in the plant that involved indirect exposure

Job category	Calendar year							
	1964–1966	1967–1969	1970–1972	1973–1975[a]	1976–1978	1979–1981	1982–1984	1985–1986
Sterilizers	75	60	40	10	4	2	1	0.5
Packers	50	50	40	5	1	0.5	<0.2	<0.2
Store workers	10	10	5	5	3	2	1	0.5
Repair men	5	5	2.5	2.5	1	0.5	<0.2	<0.2
Controllers	5	5	3	2	1	0.5	0.2	<0.2
Foremen	10	5	1	<0.2	<0.2	<0.2	<0.2	<0.2
Others	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2	<0.2

Data are expressed in parts per million
[a] EO air monitoring was initiated during this period

Table 3. Vital status as of December 31, 1986, in the cohort of EO-exposed workers

Vital status	Plant A		Plant B		Total	
	n	%	*n*	%	*n*	%
Living	1,122	97.4	993	97.4	2,115	97.4
Dead	8	0.7	7	0.7	15	0.7
Emigrated	21	1.8	19	1.9	40	1.8
Totals	1,151	100	1,019	100	2,170	100

Table 4. Person-years under observation in the cohort of 2,170 EO-exposed workers

Calendar period	Age (years)			
	< 30	30–59	60–79	Totals
1972–1980	2,026	3,143	64	5,233
1981–1986	3,763	7,143	318	11,224
Totals	5,789	10,286	382	16,457

NaCl solution before being stored at −70°C. Globin was precipitated according to the method described by Mowrer et al. [21]. The samples were analyzed by GC-mass spectrometry (GC-MS) for levels of HOEtVal in Hb using an updated version [29] of the *N*-alkyl Edman method [27]. The results obtained for 11 of the 19 subjects from plant B and the 4 control subjects have previously been published elsewhere [15]. One cigarette/day has been calculated to add 0.01 nmol/HOEtVal/g Hb [28]; the present data on HOEtVal were corrected for smoking habits.

Cohort. For plant A, the name, date of birth, address, and date of the start and the end of employment were obtained from the company records on 1,151 workers (557 women and 594 men) who had been employed for ≥ 12 months during the period 1970–1985. However, the record contained no data on workers who had left employment or died before June 1, 1975. One subject whose personal identification code could not be retrieved was not included in the cohort. For plant B, the same information was obtained from the company records on 1,019 workers (752 women and 267 men) who had been employed for ≥ 12 months during the period 1964–1985. However, the record contained no data on workers who had left employment or died before January 1, 1972. Therefore, the total cohort consisted of 2,170 workers (1,309 women and 861 men). Vital status was determined as of December 31, 1986 (Table 3). Nobody was lost to follow-up. Table 4 shows the distribution of person-years in the cohort according to age group and calendar year.

Information on causes of death and tumors. Information on the cause of death (1972–1986) was obtained from Statistics Sweden. The death certificates were coded according to the International Classification of Diseases (ICD) by Statistics Sweden, which is responsible for the coding of all Swedish death certificates. All codes were transformed into those used in the 8th revision of the ICD. Information on a maximum of two tumors (coded according to the ICD, 7th revision) diagnosed between 1972 and 1985 was obtained from the National Swedish and the Southern Swedish Regional (1972–1986) Tumor Registries.

Mortality and morbidity ratios. Expected mortality for the periods 1976–1986 (cohort A) and 1972–1986 (cohort B) was calculated using calendar-year-, cause-, gender-, and 5-year age-group-specific mortality rates for inhabitants of the county (Malmöhus, excluding Malmö town; about 500,000 inhabitants). These rates were calculated from death and population counts obtained from Statistics Sweden. The date of death or emigration or a person's 80th birthday was used as an individual endpoint, whichever occurred first.

Expected cancer morbidity for the periods 1976–1986 (cohort A) and 1972–1986 (cohort B), was calculated using calendar-year-, site-, gender-, and 5-year age-group-specific rates for inhabitants of Malmöhus county. These rates were obtained from the Southern Swedish Regional Tumor Registry. The date of death or emigration, the date of diagnosis of a second tumor, or a person's 80th birthday was used as an individual endpoint, whichever occurred first. Cause-specific standardized morbidity ratios (SMRs) and 95% confidence intervals were calculated using the Poisson distribution.

Exposure-response relationships were assessed by analyses of SMRs over strata based on the individual cumulative-exposure estimates for EO [2]. Each individual successively contributes person-years to each exposure stratum with increasing duration of employment [25]. Significance was indicated when $P < 0.05$ or when the 95% confidence intervals (CI) for SMR did not include a value of 1. All tests used were two-tailed.

Results

Mortality

At the end of the follow-up period, 15 subjects had died (0.7% of the total cohort) as compared with the 25.7 expected (SMR, 0.58; 95% CI, 0.33–0.96; Table 5). The low overall mortality was mainly due to very low risks of violent death (SMR, 0.46; 95% CI, 0.09–1.33) and cardiovascular death (SMR, 0.34; 95% CI, 0.04–1.22). The SMR for death in malignant tumors was also low (SMR, 0.89; 95% CI, 0.38–1.75).

Cancer morbidity

Up to the end of the present follow-up period, 21 malignant tumors had been detected as compared with the 26.8 expected (SMR, 0.78; 95% CI, 0.49–1.21; Table 6). No leukemia was observed, but one case of non-Hodgkin's lymphoma, one case of myeloma, and one case of polycythemia vera were diagnosed as compared with the 2 expected hematopoietic or lymphatic tumors (SMR, 1.54; 95% CI, 0.32–4.5). No stomach cancer was detected as compared with the 0.5 case expected. There was no indication that subjects showing a cumulative EO exposure of > 1 ppm-year were at increased risk of developing any malignant tumour, particularly a hematopoietic or lymphatic lesion (Table 7).

In vivo doses and exposure estimates

The level of adducts in individuals from each exposure category agreed with the exposure assessments (see Table 8). From the level of adducts corrected for contributions due to smoking and for normal background values; the integrated exposure during the last few months could be calculated. The relationship established by Duus et al. [5] between adduct and exposure levels (2.4 nmol HOEtVal/g per ppm EO during working hours) was based on adduct levels determined for 11 of the workers from plant B and for the 4 controls included in the present study. According to prior data, one cigarette per day

Table 5. Observed and expected mortality for the period 1972–1986[a] and specific causes of death in the cohort of EO-exposed workers

Cause of death	ICD-8	O	E	SMR	95% CI
Malignant tumors	140–209	8	9	0.89	0.38–1.75
Gastro intestinal tract	150–159	2	2.1	0.97	0.12–3.49
Respiratory tract	160–163	2	1.1	1.75	0.21–6.34
Lymphoma, leukemia	200–209	1	1	1.02	0.03–5.69
Cardiovascular diseases	390–458	2	5.9	0.34	0.04–1.22
Ischemic heart disease	410–414	0	3.8	0	0 –0.97
Cerebrovascular disease	430–438	2	1	2.11	0.25–7.6
Violent deaths	800–999	3	6.6	0.46	0.09–1.33
All causes	000–999	15	25.7	0.58	0.33–0.96

[a] The follow-up period was 1976–1986 for the 1,151 subjects (8,152 person-years) from plant A
Calculations were based on 2,170 subjects and 16,457 person-years. 0, Observed mortality; E, expected mortality

Table 6. Observed and expected cancer morbidity for the period 1972–1986[a] in the cohort of EO-exposed workers

Tumor site	ICD-7	O	E	SMR	95% CI
Gastrointestinal tract	150–158	2	3.5	0.57	0.07– 2.08
Stomach	151	0	0.5	0	0 – 7.38
Lung	162–164	2	1.3	1.52	0.18– 5.47
Breast	170	4	6.2	0.64	0.18– 1.65
Female genital organs	171–176	3	4.8	0.62	0.13– 1.82
Male genital organs	177–179	2	1	2	0.24– 7.22
Prostate	177	1	0.4	2.33	0.06–12.3
Urinary bladder	181.0	1	0.7	1.49	0.04– 8.32
Melanoma	190	2	2	1	0.12– 3.59
Skin	191	1	0.4	2.33	0.06–12.3
Brain	193.0	1	1.6	0.76	0.02– 4.25
Hematopoietic or lymphatic	200–209	3	2	1.54	0.32– 4.5
Lymphoma, myeloma	200–203	2	1.3	1.54	0.19– 5.56
Leukemia, polycythemia vera, myelofibrosis	204–209	1	0.7	1.54	0.04– 8.57
All	140–209	21	26.8	0.78	0.49– 1.21

[a] The follow-up period was 1976–1986 for the 1,151 subjects (8,152 person-years) form plant A
Calculations where based on 2,170 subjects and 16,457 person-years. O, Observed morbidity; E, expected morbidity

Table 7. Relationship between cumulative EO exposure and cancer morbidity

Cumulative exposure to EO (ppm-years)	Malignant tumours					
	Hematopoietic or lymphatic tumors (ICD-7, 200–209)			All (ICD-7, 140–209)		
	O	E	SMR	O	E	SMR
≤ 1[a]	2	1.5	1.32	17	21	0.81
> 1[b]	0	0.2	0	2	3.3	0.6

[a] 13,198 person-years under observation
[b] 198 subjects contributed for a total of 1,771 person-years; the mean cumulative EO-exposure value in this group was 25 ppm-years
O, observed number of cases; E, expected number of cases

adds 0.01 nmol HoEtVal/g Hb. The level of HoEtVal in the nonsmoking controls was 20 pmol/g, corroborating previous data on background levels [26]. An environmental exposure assessment was carried out in each individual studied over the 4 months preceding blood sampling, independently of the present environmental exposure assessment. This relationship is corroborated by data from Brugnone et al. [3] on environmental and instantaneous blood concentrations of EO in exposed workers (cf. [23]). The exposure levels calculated agreed well with the estimated values. Furthermore, previous data on adduct levels in samples collected in 1981 from a few subjects from plant A were consistent with our exposure assessements (see Table 8).

Table 8. Comparison of estimated exposure levels of EO in air with HOEtVal levels determined in Hb and with the airborne exposure levels independently calculated from the HOEtVal levels

Subjects (*n*)	Exposure estimated from air monitoring (ppm)	Median HOEtVal (nmol/g)	P^a	Exposure calculated from HOEtVal level[b] (ppm)
8	> 0.2	1.38	< 0.001	0.7
16	< 0.2 (estimated to 0.1 ppm)	0.23	0.004	0.1
15	Indirect (estimated to 0.02 ppm)	0.05	0.005	0.02
4	Controls	0.02[c]		0
Previous data (1981)[d] form plant A				
4	10 (Sterilizers)	10		4

[a] Comparison between groups; Mann-Whitney *U*-test
[b] Calculated from the increase in HOEtVal levels above the background value, from Duus et al. [5]
[c] Agrees with prior data on background levels [26]
[d] Cf. Högstedt et al. [12]

Discussion

Only 1 case of hematopoietic malignancy (polycythemia vera) was observed in the present cohort as compared with the 0.65 expected. The present follow-up, however, enabled (with a statistical power of 80%) only the detection of at least a "true" 7-fold increase in the risk for hematopoietic tumors. The corresponding SMR for all malignancies was 1.6.

In most previous epidemiological investigations clear-cut associations between EO exposure and excessive incidence of leukemia have not been observed. Among 767 workers in an American chemical plant who had "potentially" been exposed to EO, no death due to leukemia could be found as compared with the 0.7 expected [20]. In an another American cohort study consisting of 2,174 workers from a chemical plant in which EO was produced or used, 7 deaths due to leukemia were observed as compared with the 3 expected [10]. However, among the subcohort of men who worked in areas in which both average and peak exposure levels for EO were probably highest, no death caused by leukemia (0.7 expected) was observed. The excessive incidence of leukemia was instead primarily associated with the production of ethylene chlorohydrin or propylene chlorohydrin (4 observed vs. 0.7 expected cases), for which the exposure levels for EO had been low. In a West German study, among 2,658 workers exposed to EO for at least 1 year, 2 deaths due to leukemia were observed as compared with the 2.4 expected [17]. In a British cohort study among a total of 2,876 EO-exposed subjects from companies in which EO was produced or used and from hospitals with EO sterilizing units, 3 deaths caused by leukemia were observed as compared with the 2.1 expected [9]; however, all 3 deaths occurred among "definitely" exposed workers as compared with the 1.2 expected. An Italian study of licensed EO handlers revealed 2 deaths due to leukemia as compared with the 0.9 expected [1].

Considering these studies and the present results, 11 cases of hematopoietic malignancies were observed among workers mainly or "definitely" exposed to EO as compared with the 8.2 expected (SMR, 1.34; 95% CI, 0.67–2.46) [1, 9, 10, 17, 20]. When the 4 deaths due to leukemia that were associated with work in the chlorohydrin department [10] and the mortality of workers whose exposure to EO was "possible" or "unknown" in the English cohort study [9] are included, 15 cases of hematopoietic malignancies were found as compared with the 10.3 expected, corresponding to an SMR of 1.53 (95% CI, 0.86–2.52).

The main epidemiological support for a causal relationship between occupational EO exposure and leukemia comes from a previous Swedish cohort study, in which 8 cases of leukemia were observed as compared with the 0.8 expected [14]. That study comprised 203 subjects exposed to a time-weighted average (TWA) mixture of about 20 ppm EO and unknown levels of methyl formate from newly sterilized boxes stored at the workplace (plant 1), 175 workers at a plant in which EO was produced by the chlorohydrin method and TWA EO exposure was judged to have been about 5–25 ppm (plant 2), and, finally, (plant 3) 355 subjects at a plant in which EO was produced by direct oxidation of ethylene and the TWA EO exposure was judged to have been about 0.5–8 ppm.

One possible explanation for the discrepancy in risk estimates between the study by Hogstedt et al. [14] and the other investigations would be differences in levels of exposure to EO. Admittedly, the exposure estimates in the present study were only partially based on measurements and were mainly based on skilled, albeit subjective, assessments of exposure levels. Thus, the individual cumulative exposure estimates used were, as in most retrospective cohort studies, rather crude. However, it is reassuring that the in vivo doses of EO agreed well with the estimates for the present exposure. The exposure levels in the present study had indeed been high for certain job categories during the first years of production. However, only relatively few subjects in the cohort had been exposed for high levels of EO, and the majority of workers showed a cumulative exposure level of < 1 ppm-year. In the study by Greenberg et al. [10], the TWA levels of exposure to EO in the EO production departments were judged to have been at least as high as 10–20 ppm and those in the departments that used EO were < 1–3 ppm. In some of the other studies, no quantitative exposure data were presented [1, 17], whereas in others [9, 20], the EO exposure was obviously lower than that found for most of the workers in the cohort of Hogstedt et al. [14]. It is not likely that the discrepancy in SMRs between the studies can be explained by different exposure levels alone.

Another possibility could be that part of the excessive incidence of leukemia in the previous Swedish cohort study [14] may have been due to confounding exposure

to other chemical. Thus, it is noteworthy that 4 of 8 observed cases of leukemia (0.5 expected) occurred at a plant in which the chlorohydrin process was used to produce EO. This process also caused exposure to carcinogens such as ethylene dichloride, ethylene chlorohydrin, bis(2-chloroethyl) ether, and chloroform [13]. Furthermore, in one of the Amerian cohort studies, an increased risk for death due to leukemia was associated with chlorohydrin production rather than with the production or use of EO [10].

In the subcohort of workers from the Swedish chlorohydrin-processing plant [14], 5 cases of stomach cancer were observed as compared with the 0.65 expected; however, no increased risk was observed in the other two subcohorts. Moreover, in a large British cohort study of EO-exposed workers, 5 deaths due to stomach cancer were observed as compared with the 6.7 expected [9]. Other studies have shown only small increases in risk, if any. No case of stomach cancer was found in the present study. Thus, there is only limited support for an EO-associated increase in the risk for stomach cancer.

The jobs in the present plants have been relatively well paid and the work conditions have generally been considered to be good; therefore, there has been no difficulty in recruiting employees. The reduced overall mortality in the present cohort, which is attributable to decreased risks of deaths due to cardiovascular diseases or malignant tumours as well as of violent deaths, may thus be explained by a significant "healthy worker selection" [19]. Such a reduction in overall mortality was also observed in the other cohort studies of EO-exposed workers, with the exception of that conducted by Hogstedt et al. [14]. As stomach cancer has consistently been associated with low socioeconomic status [24], such a selection may have somewhat overestimated the expected number of cases. On the other hand, we have no reason to believe that the work force was selected with regard to the risk for leukemia.

In comparisons of EO and sparsely ionizing radiation using various systems designed to test genotoxic activity, an effectiveness ratio of about 80 rad/millimolar-hour (mMh) has been found [7, 18]. This value has been used in a tentative risk estimation for EO based on human doses monitored by Hb adducts and cancer risk coefficients established for gamma-radiation [4, 30]. According to the study by Duus et al. [5], occupational exposure to EO at an average level of 1 ppm for 40 h/week leads to an adduct level of 2.4 nmol HOEtVal/g Hb, corresponding to an annual in vivo dose of 0.29 mMh, or 23 rad-equivalents (for calculations, cf. Törnqvist et al. [27]). Using the risk coefficient 2×10^{-5} for radiation-induced leukemia, this implies that 2 excess cases would be induced in our group of 198 subjects (see Table 7), for a cumulative average exposure of 25 ppm-years [25 ppm-years $\times$ 23 rad-Eq (ppm-year)$^{-1} \times$ 198 men $\times 2 \times 10^{-5}$ cases (man-rad)$^{-1} = 2$ cases].

No case of leukemia was observed among our 198 subjects showing high exposure to EO. However, the estimated number (2 cases) lies within the 95% CI (0–3.69) for 0 observations. This means that due to its limited statistical power, the present study neither supports nor contradicts the "rad-equivalence approach" to risk estimation. Our cohort is young, and relatively little time has elapsed since the start of EO exposure. A further 10-year follow-up period will enable the evaluation of a $\geq 30\%$ increase in the risk for malignant tumours, yet only a ≥ 4-fold increase in the risk for leukemia.

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