

**Table 2.1. Cohort studies of ethylene oxide and lymphohaematopoietic cancer**

| Reference, location   | Cohort description  | Exposure assessment                               | Organ site (ICD code)                  | Exposure categories            | No. of cases/deaths | Relative risk (95% CI)               | Adjustments and comments   |
|---|---|---|--|--------------------------------|---------------------|--------------------------------------|--|
| Hogstedt <i>et al.</i> (1979a, 1986), Sweden                              | 89 operators with regular exposure to ethylene oxide and 78 maintenance staff with intermittent exposure, employed for > 1 year at a chemical plant, followed 1962–85 |   | Leukaemia                              | Operators<br>Maintenance staff | 2<br>1              | [10]<br>[5]                          | Estimated average exposure before 1963, 5–25 ppm [9–45 mg/m <sup>3</sup> ]; one CML, one acute leukaemia, one CLL  |
| Morgan <i>et al.</i> (1981), (reported in Shore <i>et al.</i> , 1993) USA | 767 men employed in 1955–77 at a chemical plant for > 5 years with potential exposure to ethylene oxide, followed 1955–85   | Industrial hygiene survey in 1977                 | All LH<br>Leukaemia                    | All cohort members             | 3<br>0              | 1.0 (0.21–2.9)<br>0.0 (0.0–3.4)      | Exposures in 1977 < 10 ppm [18 mg/m <sup>3</sup> ]; included 2 cases of Hodgkin disease  |
| Thiess <i>et al.</i> (1981), Germany                                      | 602 male employees in a company in western Germany who worked for at least 6 months in ethylene oxide production, followed to June 1980                               |   | Myeloid leukaemia<br>Lymphatic sarcoma |                                | 1<br>1              | 6.67<br>NR                           |  |
| Hogstedt <i>et al.</i> (1986), Sweden                                     | 203 workers employed > 1 year in production of sterilized supplies, followed 1978–82  |   | All LH (200–209)                       | All cohort members             | 2                   | [15]                                 | Estimated average past exposure in storeroom, 20 ppm [36 mg/m <sup>3</sup> ]; one AML was part of a cluster which had originally prompted the study; one acute blastic leukaemia |
| Hogstedt <i>et al.</i> (1986), Sweden                                     | 355 chemical workers and maintenance and technical personnel employed at a chemical plant, followed 1964–81   | Air sampling and interview with experienced staff | CML                                    | All cohort members             | 1                   | 11.6 deaths expected from all causes | TWA exposures, 1–8 ppm [1.8–14.4 mg/m <sup>3</sup> ] in 1963–76; 0.4–2.0 ppm [0.7–3.6 mg/m <sup>3</sup> ] in 1977–82   |

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|---|--|---------------------|--|---------------------|---------------------|------------------------------------|---|
| Hogstedt (1988), Sweden                   | Follow-up of Hogstedt <i>et al.</i> (1979a,b, 1986)  |                     | Leukaemia  | All cohort          | 7                   | SMR<br>9.21 (NR)                   |   |
|   |  |                     |  | Men                 | 6                   | 3.54 (1.3–7.7)                     |   |
|   |  |                     |  |                     |                     |                                    |   |
|   |  |                     | Blood and lymphatic malignancies                         | All cohort          | 9                   | 4.59 (NR)                          |   |
|   |  |                     |  | Men                 | 4                   | 6.11 (1.7–15.7)                    |   |
| Kiesselbach <i>et al.</i> (1990), Germany | 2658 employees from 6 chemical companies exposed to ethylene oxide for > 12 months during 1928–82, followed to 31 December 1982            |                     | All LH<br>Leukaemia                                      | All cohort members  | 5<br>2              | 1.00 (0.32–2.3)<br>0.85 (0.10–3.1) | No data on exposure levels; risk estimates may have been seriously biased since most deaths in cohort were not ascertained from death certificates. |
| Benson & Teta (1993), USA                 | 278 men intermittently exposed to ethylene oxide in a chlorohydrin unit since 1949, followed to 1988                                       |                     | All LH   | All cohort members  | 8                   | 2.94 (1.27–5.80)                   | Primarily exposed to ethylene chlorohydrin, ethylene dichloride and bischloroethyl ether  |
| Teta <i>et al.</i> (1993), USA            | 1896 men potentially exposed to ethylene oxide since 1940 at 2 chemical plants but who never worked in chlorohydrin unit, followed to 1988 |                     | All LH<br>Lymphosarcoma and reticulosarcoma<br>Leukaemia | All cohort members  | 7                   | 0.6 (0.2–1.2)                      |   |
|   |  |                     |  |                     | 2                   | 1.0 (0.1–3.56)                     |   |
|   |  |                     |  |                     | 5                   | 1.1 (0.4–2.5)                      |   |
| Norman <i>et al.</i> (1995), USA          | 1132 workers employed in 1974–80 at a sterilizing plant that used ethylene oxide, followed for cancer incidence to 1957                    |                     | Leukaemia  | All cohort members  | 1                   | 1.85 ( $p = 0.42$ )                |   |

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|---|---|---------------------|--|--|---------------------|--------------------------------------|--|
| Hagmar <i>et al.</i> (1991, 1995), Sweden | 2170 workers employed for > 12 months during 1964–85 at 2 plants where medical equipment was sterilized with ethylene oxide, followed for cancer incidence to 1990      |                     | All LH<br>Leukaemia                                      | All cohort members   | 6                   | 1.8 (0.65–3.88)                      |  |
|   |   |                     |  | All cohort members   | 2                   | 2.4 (0.30–8.81)                      |  |
|   |   |                     |  | > 0.14 ppm-years with induction period of 10 years   | 2                   | 7.1 (0.87–25.8)                      |  |
| Swaen <i>et al.</i> (1996), Belgium       | 210 employees of a chemical manufacturer between 1966 and 1992  |                     | Hodgkin lymphoma   | All cohort members   | 3                   | OR<br>8.5 (1.4–39.9)                 | Nested case-control analysis   |
| Olsen <i>et al.</i> (1997), USA           | 1361 men employed for > 1 year and potentially engaged for > 1 month in ethylene or propylene chlorohydrin production since 1941 at 4 chemical plants, followed to 1992 |                     | All LH   | Ever in ethylene chlorohydrin production   | 10                  | SMR<br>1.29 (0.62–2.38)              |  |
|   |   |                     |  | Ever in ethylene chlorohydrin production with allowance for 25-year induction period from first exposure | 6                   | 1.4 (0.52–3.12)                      |  |
| Bisanti <i>et al.</i> (1993), Italy       | 1971 male chemical workers licensed to handle ethylene oxide for > 1 year during 1938–84, followed 1940–84  |                     | All LH<br>Lymphosarcoma and reticulosarcoma<br>Leukaemia | All cohort members   | 6                   | 2.5 (0.91–5.5)                       | The 2 leukaemia deaths occurred in men with < 5 years of exposure and < 10 years after first exposure. |
|   |   |                     |  |  | 4                   | 6.8 (1.9–17)                         |  |
|   |   |                     |  |  | 2                   | 1.9 (0.23–7.0)                       |  |
| Kardos <i>et al.</i> (2003), Hungary      | 299 women employed on a hospital ward using ethylene oxide sterilizer in 1976–93, followed 1987–99  |                     | Leukaemia  | All cohort members   | 1                   | 4.38 deaths expected from all causes | Deaths in the cohort ascertained from a different source from the reference rates                      |

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|---|---|--|------------------------|--|---------------------|--|---|---|------------|--|-------------------|
| Coggon <i>et al.</i> (2004)<br>United Kingdom   | 1471 workers employed in production or use of ethylene oxide at 4 chemical companies in 1956–85, followed to 31 December 2000   | Environmental and personal monitoring since 1977   | Leukaemia (204–208)    | All cohort members   | 4                   | 1.41 (0.39–3.62)                             | Update of Gardner <i>et al.</i> (1989).<br>Measured TWA concentrations < 5 ppm [9 mg/m <sup>3</sup> ] in almost all jobs but with occasional peaks up to several hundred ppm; exposures probably higher in past   |   |            |  |                   |
|   |   |  | Hodgkin lymphoma (201) |  | 1                   | 1.40 (0.04–7.82)                             |   |   |            |  |                   |
|   |   |  | NHL (200)              |  | 4                   | 1.38 (0.38–3.53)                             |   |   |            |  |                   |
|   |   |  | Multiple myeloma (203) |  | 3                   | 2.03 (0.42–5.94)                             |   |   |            |  |                   |
| 1405 workers potentially exposed to ethylene oxide in sterilization units at 8 hospitals during 1964–86, followed to 31 December 2000 |   |  | Leukaemia              | All cohort members   | 1                   | 0.55 (0.01–3.06)                             |   |   |            |  |                   |
|   |   |  | Hodgkin lymphoma       |  | 1                   | 2.98 (0.08–16.6)                             |   |   |            |  |                   |
|   |   |  | NHL                    |  | 3                   | 1.59 (0.33–4.66)                             |   |   |            |  |                   |
| Steenland <i>et al.</i> (2004)<br>USA   | 18 235 workers employed at 14 industrial plants that used ethylene oxide for sterilization since 1943 with 3 months exposure to ethylene oxide, followed to 1998. Update of Steenland <i>et al.</i> (1991) and Stayner <i>et al.</i> (1993) | Exposure data over time based on a large number of measurements coupled with data of historical process changes, to quantitatively estimate cumulative exposure to ethylene oxide. | All LH (200-208)       | All cohort members<br><i>Cumulative exposure in ppm-days</i> | 79                  | SMR  | Adjusted for age, race (white/non-white), date of birth (within 5 years); in an internal case-control analysis (excluding 1 small plant), log cumulative exposure to ethylene oxide lagged by 15 years significantly related to mortality from All LH cancers in men ( $p = 0.02$ ), but not in women; duration of exposure, peak exposure and average exposure less predictive of mortality from LH cancer; similar pattern observed for lymphoid-cell tumours |   |            |  |                   |
|   |   |  |                        |  |                     | 1.00 (0.79–1.24)                             |   |   |            |  |                   |
|   |   |  |                        |  |                     | 0–1199                                       |   | 18  | 0.77 (NR)  |  |                   |
|   |   |  |                        |  |                     | 1200–3679                                    |   | 20  | 1.31 (NR)  |  |                   |
|   |   |  |                        |  |                     | 3680–13499                                   |   | 18  | 1.10 (NR)  |  |                   |
|   |   |  |                        |  |                     | > 13500                                      |   | 18  | 0.94 (NR)  |  |                   |
|   |   |  |                        |  |                     | Lymphoid-cell line tumours (200,202,203,204) |   | Men with 15- year lag (results from Cox regression)<br><i>Cum. exp. in ppm-days</i> | 0          |  | 1.00              |
|   |   |  |                        |  |                     |  |   |   | >0–1199    |  | 0.90 (0.16–5.24)  |
|   |   |  |                        |  |                     |  |   |   | 1200–3679  |  | 2.89 (0.65–12.86) |
|   |   |  |                        |  |                     |  |   |   | 3680–13499 |  | 2.74 (0.65–11.55) |
| > 13500   |   | 3.76 (1.03–13.64)  |                        |  |                     |  |   |   |            |  |                   |
|   |   |  |                        | $p$ -trend = 0.13  |                     |  |   |   |            |  |                   |

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|--|--|---------------------|------------------------|--|---------------------|------------------------|--------------------------|--|
| Steenland <i>et al.</i> (2004)<br>Contd. |  |                     | Hodgkin lymphoma (201) | All cohort members                     | 6                   | 1.24 (0.53–2.43)       |                          |  |
|  |  |                     |                        | <i>Cumulative exposure in ppm-days</i> |                     |                        |                          |  |
|  |  |                     |                        | 0–1199                                 | 0                   | 0 (NR)                 |                          |  |
|  |  |                     |                        | 1200–3679                              | 1                   | 0.99 (NR)              |                          |  |
|  |  |                     |                        | 3680–13499                             | 3                   | 2.97 (NR)              |                          |  |
|  |  |                     | > 13500                | 2                                      | 2.20 (NR)           |                        |                          |  |
|  |  |                     | NHL (200,202)          | All cohort members                     | 31                  | 1.00 (0.72–1.35)       |                          |  |
|  |  |                     |                        | <i>Cumulative exposure in ppm-days</i> |                     |                        |                          |  |
|  |  |                     |                        | 0–1199                                 | 7                   | 0.76 (NR)              |                          |  |
|  |  |                     |                        | 1200–3679                              | 8                   | 1.34 (NR)              |                          |  |
|  |  |                     |                        | 3680–13499                             | 6                   | 0.85 (NR)              |                          |  |
|  |  |                     | > 13500                | 9                                      | 1.21 (NR)           |                        |                          |  |
|  |  |                     | Multiple myeloma (203) | All cohort members                     | 13                  | 0.92 (0.54–0.87)       |                          |  |
| <i>Cumulative exposure in ppm-days</i>   |  |                     |                        |  |                     |                        |                          |  |
| 0–1199                                   | 1                                      | 0.26 (NR)           |                        |  |                     |                        |                          |  |
| 1200–3679                                | 5                                      | 1.89 (NR)           |                        |  |                     |                        |                          |  |
| 3680–13499                               | 3                                      | 0.92 (NR)           |                        |  |                     |                        |                          |  |
| > 13500                                  | 4                                      | 1.03 (NR)           |                        |  |                     |                        |                          |  |
| Leukaemia (204-208)                      | All cohort members                     | 29                  | 0.99 (0.71–1.36)       |  |                     |                        |                          |  |
|  | <i>Cumulative exposure in ppm-days</i> |                     |                        |  |                     |                        |                          |  |
|  | 0–1199                                 | 10                  | 1.15 (NR)              |  |                     |                        |                          |  |
|  | 1200–3679                              | 6                   | 1.06 (NR)              |  |                     |                        |                          |  |
|  | 3680–13 499                            | 6                   | 0.93 (NR)              |  |                     |                        |                          |  |
| > 13 500                                 | 3                                      | 0.43 (NR)           |                        |  |                     |                        |                          |  |

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|-------------------------------------|---|---|-----------------------------------|---------------------|---------------------|-------------------------|---|
| (Swaen, et al. 2009)<br>USA         | 2063 men employed in ethylene oxide production 1925-1988 and >1 January 1940, vital status through 2003   | Exposure assessment matrix (4 eras and 3 levels) + work histories to calculate cumulative doses | All lymphohematopoietic (200-208) | 0-15 ppm-year       | 12                  | SMR<br>1.20 (0.62-2.1)  | US national comparison rates<br>Age, year of death<br>Hazard Ratio per 1 ppm-yr (lymphoid only)<br>0.99 (0.985-1.0)<br>0.62 (0.20-1.95)<br>0.54 (0.13-2.26) |
|                                     |   |   |                                   | 15-65 ppm-year      | 9                   | 0.89 (0.41-1.7)         |   |
|                                     |   |   |                                   | 65 + ppm-year       | 6                   | 0.59 (0.22-1.3)         |   |
|                                     |   |   | Leukemia (204-208)                | 0-15 ppm-year       | 3                   | 0.78 (0.16-2.3)         |   |
|                                     |   |   |                                   | 15-65 ppm-year      | 6                   | 1.52 (0.56-3.3)         |   |
|                                     |   |   |                                   | 65 + ppm-year       | 2                   | 0.50 (0.06-1.8)         |   |
| (Valdez-Flores, et al. 2010)<br>USA | 2063 men employed in ethylene oxide production 1925-1988 and >1 January 1940, vital status through 2003 and 17,493 (9859 female, 7634 male) of the 18, 235 workers employed at 14 industrial plants that used ethylene oxide for sterilization since 1943 | Exposure assessment matrix (4 eras and 3 levels) + work histories to calculate cumulative doses | Haematopoietic (200-208)          | 0-15 ppm-year       | 106                 | SMR<br>0.97 (0.79-1.17) | US national comparison rates<br>Age, year of death  |
|                                     |   |   |                                   | 15-65 ppm-year      | 40                  | 0.97 (0.70-1.33)        |   |
|                                     |   |   | Leukemia (204-208)                | 0-15 ppm-year       | 43                  | 1.01 (0.73-1.36)        |   |
|                                     |   |   |                                   | 15-65 ppm-year      | 6                   | 0.92 (0.34-2.00)        |   |
|                                     |   |   | Non-Hodgkin lymphoma              | 0-15 ppm-year       |                     |                         |   |
|                                     |   |   |                                   | 15-65 ppm-year      |                     |                         |   |
| Hodgkin disease                     | 0-15 ppm-year   |   |                                   |                     |                     |                         |   |
|                                     | 15-65 ppm-year  |   |                                   |                     |                     |                         |   |

AML, acute myelogenous leukaemia; CI, confidence interval; CLL, chronic lymphocytic leukaemia; CML, chronic myelogenous leukaemia; ICD, International Classification of Diseases; LH, lymphohaematopoietic; NHL, non-Hodgkin lymphoma; NR, not reported; SIR, standardized incidence ratio; SMR, standardized mortality ratio; TWA, time-weighted average