Supplemental Materials for "**Carcinogenicity of Ethylene Oxide: Key Findings and Scientific Issues**"

Jennifer Jinot, Jason M. Fritz, Suryanarayana V. Vulimiri, Nagalakshmi Keshava

National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, D.C., USA

Corresponding Author:
Jason M. Fritz
National Center for Environmental Assessment – 8601P
U.S. Environmental Protection Agency
One Potomac Yard
2777 S. Crystal Drive
Arlington VA 22202
Phone: (703) 347-0332
E-mail: fritz.jason@epa.gov

Table of Contents:

Table S1 Epidemiological studies of ethylene oxide and human cancer—lymphohematopoietic cancer results[a]

Study/population/ industry	Number of subjects	Lymphohematopoietic cancer results				Comments
Hogstedt (1988) and Hogstedt et al. (1986). Sterilizers, production workers, Sweden.	709 (539 men, 170 women)	*Cancer deaths*	*Observed*	*Expected*	*SMR (95% CI)*	Insufficient follow-up; 12.0% of cohort had died (85 deaths). Exposure to other chemicals.
		leukemia (ICD-8 204−207)	7	0.8	9.2 (3.7, 19)[b]	
		lymphohematopoietic (ICD-8 200−208)	9	2.0	4.6 (2.1, 8.7)[b]	
Coggon et al. (2004). Update of Gardner et al. (1989). Sterilizing workers in eight hospitals and users in four companies, Great Britain.	2,876 (1,864 men, 1,012 women)	*Cancer deaths*	*Observed*	*Expected*	*SMR (95% CI)*	Short follow-up; 19.6% of cohort had died (565 deaths). Exposure to other chemicals.
		leukemia (ICD-9 204−208)	5	4.6	1.1 (0.35, 2.5)	
		leukemia (definite or continual exposure)	5	2.6	1.9 (0.62, 4.5)[b]	
		NHL (ICD-9 200 + 202)	7	4.8	1.5 (0.58, 3.0)[b]	
		lymphohematopoietic (ICD-9 200−208)	17	12.9	1.3 (0.77, 2.1)[b]	
Kiesselbach et al. (1990). Production workers (methods unspecified) from eight chemical plants in West Germany.	2,658 men	*Cancer deaths*	*Observed*	*Expected*	*SMR (95% CI)*	Insufficient follow-up; 10.1% of cohort had died (268 deaths). Exposure to other chemicals.
		leukemia (ICD-9 204−208)	2	2.35	0.85 (0.10, 3.1)	
		lymphohematopoietic (ICD-9 200−208)	5	5	1.0 (0.32, 2.3)	
Benson and Teta (1993). Follow-up of only the chlorohydrin-exposed employees from Greenberg et al. (1990) cohort. Production workers at a chemical plant in West Virginia.	278 men	*Cancer deaths*	*Observed*	*Expected*	*SMR (95% CI)*	EtO exposures reported to be low in the chlorohydrin process. Exposure to other chemicals. Very small cohort; thus, small numbers of specific cancers despite long follow-up (52.9% had died; 147 deaths).
		leukemia and aleukemia	4	1.14	3.5 (0.96, 8.9)	
		lymphosarcoma and reticulosarcoma	1	0.50	2.0 (0.05, 11)	
		lymphohematopoietic (ICD NS)	8	2.72	2.9 (1.3, 5.8)	

Study/population/ industry	Number of subjects	Lymphohematopoietic cancer results				Comments
Swaen et al. (2009). Update of Teta et al. (1993) [Greenberg et al. (1990) cohort minus all chlorohydrin-exposed employees] plus cohort enumeration extended an additional 10 years, adding 167 workers. Production workers and users at two chemical plants in West Virginia.	2,063 men	*Cancer deaths*	*Observed*	*Expected*	*SMR (95% CI)*	Small cohort; long follow-up time (50.8% had died; 1,048 deaths). Crude exposure assessment, especially for the early time periods. Exposure to other chemicals.
		leukemia	11	11.8	0.93 (0.47, 1.7)	
		leukemia (in workers hired before 1956)	9	NR	1.5 (0.69, 2.9)	
		NHL	12	11.5	1.05 (0.54, 1.8)	
		lymphohematopoietic (ICD NS)	27	30.4	0.89 (0.59, 1.3)	
		Internal Cox regression analyses: No statistically significant trends were observed for lymphoid (17 deaths) or leukemia (11 deaths) cancer categories for continuous cumulative exposure.				
Steenland et al. (2004). Update of Steenland et al. (1991), Stayner et al. (1993). Sterilizers of medical equipment and spices; and manufacturers and testers of medical sterilization equipment, in 14 plants in the United States.	18,254 (45% male, 55% female)	*Cancer deaths*	*Observed*	*Expected*	*SMR (95% CI)*	Large cohort; thus, substantial number of deaths (2,852) despite short follow-up (15.6% had died). High-quality exposure assessment. No evidence of exposure to other occupational carcinogens. No increase in lymphohematopoietic cancer risk with increase in exposure in women. Results from internal Cox regression analyses for both sexes combined are from Sections D.3 and D.4 of Appendix D of U.S. EPA (2016b).
		leukemia (ICD-9 204−208)	29	NR	0.99 (0.71, 1.36)	
		NHL (ICD-9 200 + 202)	31	NR	1.00 (0.72, 1.35)	
		lymphohematopoietic (ICD-9 200−208)	79	NR	1.00 (0.79, 1.24)	
		Internal Cox regression analyses: "lymphoid" cancers (ICD-9 200, 202, 203, 204): OR = 3.0 (p = 0.046) in highest cumulative exposure group, with 15-yr lag; significant regression coefficient for continuous log cumulative exposure (p = 0.02). lymphohematopoietic cancer (ICD-9 200−208): OR = 2.96 (p = 0.03) in highest cumulative exposure group, with 15-yr lag; significant regression coefficient for continuous log cumulative exposure (p = 0.009).				

Study/population/ industry	Number of subjects	Lymphohematopoietic cancer results				Comments
Bisanti et al. (1993). Chemical workers licensed to handle EtO and other toxic chemicals, Italy.	1,971 men	*Cancer deaths*	*Observed*	*Expected*	*SMR (95% CI)*	Insufficient follow-up; 3.9% of cohort had died (76 deaths). Exposure to other chemicals.
		leukemia (ICD-9 204−208)	2	1.0	1.9 (0.23, 7.0)	
		lymphosarcoma and reticulosarcoma (ICD-9 200)	4	0.6	6.8 (1.9, 17)	
		lymphohematopoietic (ICD-9 200−208)	6	2.4	2.5 (0.91, 5.5)	
		*In group only licensed to handle EtO (*n = *637):*				
		leukemia	2	0.3	6.5 (0.79, 23)	
		lymphosarcoma and reticulosarcoma	3	0.2	17 (3.5, 50)	
		lymphohematopoietic	5	0.7	7.0 (2.3, 16)	
Mikoczy et al. (2011). Update of Hagmar et al. (1995) and Hagmar et al. (1991). Two plants that produced disposable medical equipment, Sweden.	2,171 (862 men, 1,309 women)	*Cancer cases*	*Observed*	*Expected*	*SIR (95% CI)*	Small, young cohort (171 deaths; 203 cancer cases). Estimated cumulative exposures were generally low. There was no unexposed referent group in the internal analyses.
		leukemia (ICD-7 204−205)	5	3.58	1.40 (0.45, 3.26)	
		NHL (ICD-7 200 + 202)	9	6.25	1.44 (0.66, 2.73)	
		lymphohematopoietic (ICD-7 200−209)	18	14.4	1.25 (0.74, 1.98)	
		In internal analyses of lymphohematopoietic cancer:			*IRR (95% CI)*	
		0−0.13 ppm-yr (*n* = 1,039; 7 cases)			1.00	
		0.14−0.21 ppm-yr (*n* = 486; 5 cases)			1.17 (0.36, 3.78)	
		≥0.22 ppm-years (*n* = 495; 5 cases)			0.92 (0.28, 3.05)	
Norman et al. (1995). Sterilizers of medical equipment and supplies that were assembled at this plant, New York.	1,132 (204 men, 928 women)	*Cancer cases*	*Observed*	*Expected*	*SIR (95% CI)*	Short follow-up period and small cohort (only 28 cancer cases).
		leukemia (ICD NS)	1	0.54	1.85 (0.05, 10)[b]	
Swaen et al. (1996). Nested case-control study; cases and controls from a large chemical production plant, Belgium.	10 cases of Hodgkin lymphoma (3 exposed; 7 confirmed) and 200 controls; all male	*Cancer*			*OR (95% CI)*	Hypothesis-generating study to investigate a cluster of Hodgkin lymphomas observed at a chemical plant. Exposure to other chemicals.
		Hodgkin lymphoma (ICD 201)			8.5 (1.4, 40)	

Study/population/ industry	Number of subjects	Lymphohematopoietic cancer results				Comments
Olsen et al. (1997). Four EtO production plants (chlorohydrin process) in three states.	1,361 men	*Cancer deaths*	*Observed*	*Expected*	*SMR (95% CI)*	Short follow-up and small cohort; 22.0% had died; 300 deaths. Exposure to other chemicals.
		leukemia (ICD-8 204−207)	2	3.0	0.67 (0.08, 2.4)	
		lymphosarcoma and reticulosarcoma (ICD-8 200)	1	1.1	0.91 (0.02, 5.1)	
		lymphohematopoietic (ICD-8 200−209)	10	7.7	1.3 (0.62, 2.4)	
Kardos et al. (2003). Female workers from pediatric clinic of hospital in Eger, Hungary.	299 women	1 lymphoid leukemia death; expected number not reported.				Short follow-up period and small cohort (11 cancer deaths). Possible exposure to natural radium, which permeates the region.

ICD NS = ICD codes not specified; NR = not reported; CI = confidence interval; OR = odds ratio; SMR = standardized mortality ratio; SIR = standardized incidence ratio; IRR = (internal) incidence rate ratio.

[a] Table S1, extracted from Table A-5 of Appendix A, of U.S. EPA (2016b), with addition of some summary results (e.g., SMRs); see Table A-5 and Appendix A for more study details.

[b] Calculated by the EPA assuming Poisson distribution.

Table S2 Summary of epidemiological results on ethylene oxide and female breast cancer (all sterilizer workers)[a]

Study	Number of women	Breast cancer results	Comments
Hogstedt et al. (1986) and Hogstedt (1988) Swedish incidence and mortality study	170	NR	Eight deaths (seven from cancer) had occurred among the women; breakdown by cancer type not reported.
Coggon et al. (2004) Great Britain mortality study	1,011 women hospital workers	*Exposure category* — *Observed* — *Expected* — *SMR (95% CI)* Continual — 5 — 7.2 Intermittent — 0 — 0.7 Unknown — 6 — 5.2 ALL — 11 — 13.1 — 0.84 (0.42, 1.51)	11 breast cancer deaths. 14% of the cohort of 1,405 (including males) hospital workers had died.
Steenland et al. (2004) U.S. mortality study	9,908	SMR in highest quartile of cumulative exposure (with 20-yr lag) = 2.07 ($p < 0.05$). Significant Cox regression coefficient for log cumulative exposure (20-yr lag) ($p = 0.01$).	103 breast cancer deaths.
Steenland et al. (2003) U.S. breast cancer incidence study; nested within Steenland et al. (2004) cohort	7,576 employed for ≥1 yr; 5,139 with interviews	*Full cohort results*: Cox regression analysis OR = 1.74 (95% CI: 1.16, 2.65) for highest cumulative exposure quintile (15-yr lag). $p = 0.05$ for regression coefficient with log cumulative exposure (15-yr lag). *Subcohort results*: Cox regression analysis OR = 1.87 (95% CI: 1.12, 3.10) for highest cumulative exposure quintile (15-yr lag). $p = 0.02$ for regression coefficient with cumulative exposure (15-yr lag); $p = 0.03$ with log cumulative exposure (15-yr lag).	319 breast cancer cases in full cohort. 233 breast cancer cases in subcohort with interviews.
Mikoczy et al. (2011). Update of Hagmar et al. (1995) and Hagmar et al. (1991). Swedish cancer incidence study	1,309	41 cases vs. 50.9 expected SIR = 0.81 (95% CI: 0.58, 1.09). *In internal analyses:* — *IRR (95% CI)* 0−0.13 ppm-years ($n = 615$; 10 cases) — 1.00 0.14−0.21 ppm-years ($n = 287$; 14 cases) — 2.76 (1.20, 6.33) ≥0.22 ppm-years ($n = 295$; 17 cases) — 3.55 (1.58, 7.93)	41 breast cancer cases.

Study	Number of Women	Breast Cancer Results	Comments
Norman et al. (1995) U.S. cancer incidence study	928	SIRs ranged from 1.72 (95% CI: 0.99, 3.00) to 2.40 (95% CI: 1.32, 4.37) depending on calendar year of follow-up, assumptions about completeness of follow-up, and reference rates used.	12 cases.
Kardos et al. (2003) Hungarian mortality study	299	11 cancer deaths observed compared with 4.38, 4.03, or 4.28 expected ($p < 0.01$), based on comparison populations of Hungary, Heves County, and city of Eger, respectively; 3 were breast cancer deaths (i.e., 3 breast cancer deaths vs. ~4.3 total deaths expected). Although the expected number of breast cancer deaths was not reported, the number of breast cancer deaths observed for the total deaths expected is indicative of an increased risk of breast cancer.[b]	Three breast cancer deaths.

NR = not reported; CI = confidence interval; OR = odds ratio; SMR = standardized mortality ratio; SIR = standardized incidence ratio; IRR = (internal) incidence rate ratio.

[a] Table S2, extracted from Table A-5 of Appendix A, of U.S. EPA (2016b); see Table A-5 and Appendix A for more study details, and also Table S-1 above.

[b] Hungarian age-standardized female cancer mortality rates reported by the International Agency for Research on Cancer (http://eu-cancer.iarc.fr/EUCAN/Country.aspx?ISOCountryCd=348) suggest that the ratio of breast cancer deaths to total cancer deaths in Hungarian females is about 0.14 (23.5/100,000 breast cancer mortality rate versus 163.6/100,000 total cancer mortality rate). A comparison of this general population ratio with the ratio of 0.68 for breast cancer to total cancer mortality in the Kardos et al. (2003) study is necessarily crude because the general population ratio is not based on the age-standardized rates that would correspond to the age distribution of the person-time of the women in the study, which are unknown. However, the large difference between the ratios (0.68 for the study versus 0.14 for the general population) indicates an increased risk of breast cancer in the study.

Supplemental References

Benson LO, Teta MJ. 1993. Mortality due to pancreatic and lymphopoietic cancers in chlorohydrin production workers. *Br J Ind Med*, 50, 710-716.

Bisanti L, Maggini M, Raschetti R, Alegiani SS, Ippolito FM, Caffari B, et al. 1993. Cancer mortality in ethylene oxide workers. *Br J Ind Med*, 50, 317-324.

Coggon D, Harris EC, Poole J, Palmer KT. 2004. Mortality of workers exposed to ethylene oxide: Extended follow up of a British cohort. *Occup Environ Med*m 61, 358-362.

Gardner MJ, Coggon D, Pannett B, Harris EC. 1989. Workers exposed to ethylene oxide: A follow up study. *Occup Environ Med*, 46, 860-865.

Greenberg HL, Ott MG, Shore RE. 1990. Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: A mortality study. *Br J Ind Med*, 47, 221-230.

Hagmar L, Welinder H, Lindén K, Attewell R, Osterman-Golkar S, Törnqvist M. 1991. An epidemiological study of cancer risk among workers exposed to ethylene oxide using hemoglobin adducts to validate environmental exposure assessments. *Int Arch Occup Environ Health*, 63, 271-277.

Hagmar L, Mikoczy Z, Welinder H. 1995. Cancer incidence in Swedish sterilant workers exposed to ethylene oxide. *Occup Environ Med*, 52, 154-156.

Hogstedt C, Aringer L, Gustavsson A. 1986. Epidemiologic support for ethylene oxide as a cancer-causing agent. *JAMA*, 255, 1575-1578.

Hogstedt LC. 1988. Epidemiological studies on ethylene oxide and cancer: An updating. Lyon, France.

Kardos L, Széles G, Gombkötö G, Szeremi M, Tompa A, Ádány R. 2003. Cancer deaths among hospital staff potentially exposed to ethylene oxide: An epidemiological analysis. *Environ Mol Mutagen*, 42, 59-60.

Kiesselbach N, Ulm K, Lange H, -J, Korallus U. 1990. A multicentre mortality study of workers exposed to ethylene oxide. *Br J Ind Med*, 47, 182-188.

Mikoczy Z, Tinnerberg H, Björk J, Albin M. 2011. Cancer incidence and mortality in Swedish sterilant workers exposed to ethylene oxide: Updated cohort study findings 1972-2006. *Int J Environ Res Public Health*, 8, 2009-2019.

Norman SA, Berlin JA, Soper KA, Middendorf BF, Stolley PD. 1995. Cancer incidence in a group of workers potentially exposed to ethylene oxide. *Int J Epidemiol*, 24, 276-284.

Olsen GW, Lacy SE, Bodner KM, Chau M, Arceneaux TG, Cartmill JB, et al. 1997. Mortality from pancreatic and lymphopoietic cancer among workers in ethylene and propylene chlorohydrin production. *Occup Environ Med*, 54, 592-598.

Stayner L, Steenland K, Greife A, Hornung R, Hayes RB, Nowlin S, et al. 1993. Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene oxide. *Am J Epidemiol*, 138, 787-798.

Steenland K, Stayner L, Greife A, Halperin W, Hayes R, Hornung R, et al. 1991. Mortality among workers exposed to ethylene oxide. *N Engl J Med*, 324, 1402-1407.

Steenland K, Whelan E, Deddens J, Stayner L, Ward E. 2003. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes Control*, 14, 531-539.

Steenland K, Stayner L, Deddens J. 2004. Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: Follow up extended from 1987 to 1998. *Occup Environ Med*, 61, 2-7.

Swaen GMH, Slangen JMM, Ott MG, Kusters E, Van Den Langenbergh G, Arends JW, et al. 1996. Investigation of a cluster of ten cases of Hodgkin's disease in an occupational setting. *Int Arch Occup Environ Health*, 68, 224-228.

Swaen GMH, Burns C, Teta JM, Bodner K, Keenan D, Bodnar CM. 2009. Mortality study update of ethylene oxide workers in chemical manufacturing: A 15 year update. *J Occup Environ Med*, 51, 714-723.

Teta MJ, Benson LO, Vitale JN. 1993. Mortality study of ethylene oxide workers in chemical manufacturing: A 10 year update. *Br J Ind Med*, 50, 704-709.