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REVIEW

Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis

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Abstract

Purpose To conduct a systematic literature review and meta-analysis of studies of lympho-hematopoietic cancers (LHC) and breast cancer risk among persons occupationally exposed to ethylene oxide (EO).

Methods We performed a literature search for articles available in PubMed and Web of Science databases to identify literature and subsequently systematically searched the reference lists of identified studies, published review papers and meta-analyses, as well as relevant government or regulatory documents. We qualitatively reviewed 30 studies and conducted meta-analyses on 13 studies. Pooled risk estimates were calculated using random effects models, stratifying by occupational group, cancer type and decade of publication.

Results The overall meta-relative risks (meta-RRs) for LHC and breast cancer, respectively, were 1.48 (95% CI 1.07–2.05) and 0.97 (95% CI 0.80–1.18). The meta-RR's for LHC among EO production and EO sterilization workers were 1.46 (95% CI 0.85–2.50) and 1.07 (95% CI 0.87–1.30), respectively. We observed higher risks of LHC in the earlier published studies, compared to the later studies, and the meta-RR's for the 1980s, 1990s, 2000s, and the 2010s, respectively, were 3.87 (95% CI 1.87–8.01), 1.38 (95% CI 0.85–2.25), 1.05 (95% CI 0.84–1.31), and 1.19 (95% CI 0.80–1.77).

Conclusions The most informative epidemiology studies, which were published in the 2000s and 2010s, do not support the conclusion that exposure to EO is associated with an increased risk of LHC or breast cancer.

Keywords Epidemiology · Ethylene oxide · Occupational exposure · Meta-analysis · Lymphohematopoietic cancers · Breast cancer

Introduction

Ethylene oxide (EO, CAS no.: 75-21-8) is a highly reactive chemical produced in large volumes. EO is used primarily as an intermediate in the production of several industrial chemicals, and derivatives of EO are commonly used in several industries, including plastics, polyester fibers, detergents and ethylene glycol antifreeze. EO is also used as a fumigant or insecticide for use in certain agricultural products and as a sterilant for medical equipment and supplies. A very small proportion (0.05%) of the annual production of EO is used as a sterilizing agent or fumigant or insecticide (Dever et al. 2004).

Two primary sources of occupational exposure to EO are from production facilities (via the older chlorohydrin process or the direct oxidation process) and sterilization operations. Workers involved in the sterilization of medical equipment and in the direct oxidation process are predominately exposed to EO. Through the chlorohydrin method of EO production, exposure may be: (1) solely to EO (and the raw material ethylene chlorohydrin) if conducted in a separate unit from the one producing ethylene chlorohydrin, or (2) to EO and associated chemicals if production of ethylene chlorohydrin and EO occurs in the same unit (NTP 2015).

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The current permissible exposure limit for EO is an 8-h time-weighted average (8-h TWA) of 1 ppm (OSHA 2018).

The National Toxicology Program (NTP) classifies EO as *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological studies and studies on mechanisms of carcinogenesis (NTP 2015). Notably, NTP's definition of *sufficient evidence of carcinogenicity from studies in humans* groups together traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question (NTP 2016).

Epidemiological studies, reviews, and evaluations of the carcinogenicity of EO made by the US Environmental Protection Agency (EPA) and the International Agency for Research on Cancer (IARC) note the inconsistency between the toxicological and epidemiological evidence. IARC's (2008) classification of EO as carcinogenic in humans (Group 1) was based on a combination of mechanistic data and sufficient evidence for carcinogenicity in experimental animals, but the evidence for carcinogenicity in humans was assessed as limited (IARC 2008). At the 2010 EO Working Group meeting, IARC reaffirmed the Group 1 classification for EO via: (1) limited evidence in humans for a causal association of EO with lympho-hematopoietic cancers (LHCs) (specifically lymphoid tumors, i.e., non-Hodgkin lymphoma (NHL), multiple myeloma and chronic lymphocytic leukemia), and breast cancer; (2) sufficient evidence of carcinogenicity in experimental animals, and (3) strong evidence of a genotoxic mechanism (IARC 2012).

The EPA's Integrated Risk Information System (IRIS) final report, Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide, characterized EO as carcinogenic by the inhalation route of exposures based on the "total weight of the evidence," including: (1) "strong, but less than conclusive on its own, epidemiological evidence of lympho-hematopoietic cancers and breast cancer" in EO exposed workers; (2) "extensive evidence of carcinogenicity in laboratory animals, including LHCs in rats and mice and mammary carcinomas in mice following inhalation exposure"; (3) "clear evidence that EO is genotoxic and sufficient weight of evidence to support a mutagenic mode of action for EO carcinogenicity", and (4) "strong evidence that the key precursor events are anticipated to occur in humans and progress to tumors, including evidence of chromosome damage in humans exposed to EO" (USEPA 2016, p. 1–1, 1–2). The focus of the IRIS summary evaluation was on a specific subset of the epidemiological literature, and no attempt was made to evaluate the epidemiological evidence collectively. Furthermore, a peer-reviewed summary of the IRIS evaluation considered the observations of LHC in both males and females as well as female breast cancer to be the strongest evidence of EO's carcinogenicity in humans (Jinot et al. 2018).

The aim of the current systematic review and meta-analysis is to provide an evaluation of the available epidemiological evidence regarding the risk of LHCs and breast cancer as a result of occupational exposure to EO, and to determine whether the epidemiological evidence is supportive of a causal association.

Methods

Literature search

We conducted this study using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al. 2009) and the Meta-analysis of Observational Studies in Epidemiology (Stroup et al. 2000) guidelines. Two systematic literature searches were conducted using the National Center for Biotechnology Information's (NCBI) PubMed and the Institute for Scientific Information's Web of Science search engines to identify published articles available from 1946 to March 2018. The following operators were used for our literature search: (ethylene oxide) AND (cancer epidemiology). Additionally, in order to identify relevant articles that may not have been captured in the primary literature search, all references in the EO evaluation by IARC (2012) were obtained and the bibliographies of all articles identified in our literature review were systematically searched. All abstracts and articles were reviewed by at least two authors to determine if the inclusion criteria were met.

Studies were selected for the meta-analysis based on the following criteria:

1. Only studies published in English were considered for inclusion.
2. Human subject epidemiological studies (case–control and cohort studies) were considered for inclusion and descriptive epidemiological studies (case reports and case series) were excluded.
3. The health endpoint(s) of interest were defined as LHC or breast cancer.
4. Only occupational exposures to EO occurring during the production or manufacturing of EO or the use of EO during sterilization processes were considered for inclusion.
5. For any exposure group assessed multiple times, only the most recent evaluation with the longest follow-up time was included in the meta-analysis.
6. Studies that reported effect estimates or provided enough information to calculate an effect estimate were considered for inclusion.

The following data were extracted for all studies that met the aforementioned inclusion criteria: first author, publication year, study design, study location, cancer type [all LHC combined, LHC subcategories (including myeloma, leukemia, NHL and Hodgkin's disease) or breast cancer], occupational group (EO production vs. EO sterilization), sex of the exposed subjects, number of cases, and effect estimate [odds ratio (OR), risk ratio (RR), standardized incidence ratio (SIR), or standardized mortality ratio (SMR)] and corresponding confidence intervals (CIs).

Meta-analysis

We performed meta-analyses to calculate pooled effect estimates, stratifying for: (1) type of cancer, (2) occupational groups, (3) type of cancer within occupational groups, and (4) decade of publication. Four of the studies that met our inclusion criteria did not provide effect estimates for all of the endpoints of interest, therefore, we manually calculated crude (unadjusted) effect estimates and/or corresponding confidence intervals (CIs) using the data provided (Hogstedt 1988; Norman et al. 1995; Olsen et al. 1997; Steenland et al. 2004). The appendix provides technical details of the data extraction and calculations performed to generate effect estimates for the aforementioned studies. Additionally, in order to reflect the improved quality and informativeness of recently published studies, we conducted time period analyses that stratified overall effect estimates for all lympho-hematopoietic cancers (all LHC) by the four decades of publication (1980s, 1990s, 2000s, 2010s). Detailed decade of publication analyses were not performed for the individual LHC subcategories or for breast cancer due to the limited number of effect estimates. In our decade of publication analysis for all LHC, we included in the respective period of publication the earlier reports of studies that were subsequently updated and published in later decades. If there was a cohort with two studies in a given decade, the study with the longest follow-up and/or the larger case ascertainment was chosen for that decade. We also included in the respective decade of publication only the updated findings of studies that were published in previous decades. This was done by subtracting out the observed and expected numbers of deaths or cases that were reported in the earlier updates and computing a revised risk estimate (SMR or SIR).

Upon extraction or derivation of effect estimates and/or CIs, fixed effects models were performed on the aforementioned stratifications and the I^2 statistic was used to assess the potential for heterogeneity. Heterogeneity is defined as variation in study results greater than what is expected by chance and exists when the true effects being evaluated differ between studies (Higgins and Thompson 2002; Rothman et al. 2008). Significant heterogeneity was defined as an $I^2 > 75\%$ and a p value of < 0.05; borderline heterogeneity was defined as an I^2 between 25 and 75% and a p value of 0.05–0.20; and homogeneity was defined as an $I^2 < 25\%$ and a p value of > 0.20 (Higgins et al. 2003; Higgins and Thompson 2002). If the I^2 statistic was rejected ($p < 0.05$), DerSimonian and Laird random effects models were then fit to determine an overall effect estimate for EO exposure (DerSimonian and Laird 1986; Elwood 2007a, b). The meta-analyses results are reported as a meta-relative risk (meta-RR), with the corresponding 95% CIs.

Begg's rank correlation method and Egger's weighted regression method were utilized to assess the potential for publication bias (Begg and Mazumdar 1994; Egger et al. 1997). Additionally, funnel plots were generated to visually evaluate the potential for bias by plotting all LHC categories by decade of publication effect estimates on a log scale against the standard error, which was used as a measure of study size. All statistical analyses were performed using StataMP 14 (StataCorp LP, College Station, TX, USA).

Results

Literature search

The PubMed and Web of Science literature searches, unpublished data, as well as the references from the IARC monographs resulted in 106 unique articles to consider for the evaluation of EO exposure and cancer (Fig. 1). Ninety-five studies were excluded from the meta-analysis because they were: review papers or commentaries ($n = 22$), the predominant exposures were not specific to EO ($n = 19$), focused on biomarker endpoints ($n = 17$), the health outcomes were not LHC or breast cancer ($n = 8$), not epidemiological in nature ($n = 14$), there was insufficient information to estimate risk ($n = 1$), or the study populations had been evaluated multiple times ($n = 14$). An additional analysis conducted by Divine (1990) was identified through Teta et al.'s (1999) previously published EO meta-analysis. Although this study was unpublished, we acquired it from Dr. Teta for inclusion in the updated review and meta-analysis presented here. Overall, 13 studies met the inclusion criteria, of which four studies reported effect estimates for both LHC and breast cancer (Norman et al. 1995; Coggon et al. 2004; Steenland et al. 2004; Mikoczy et al. 2011), eight studies reported effect estimates for only LHCs (Hogstedt 1988; Divine 1990; Kiesselbach et al. 1990; Bisanti et al. 1993; Swaen et al. 1996, 2009; Olsen et al. 1997; Kiran et al. 2010), and one study reported effect estimates only for breast cancer (Steenland et al. 2003). Of note, studies that reported zero cases for a respective health outcome were not included in the statistical portion of the meta-analysis.

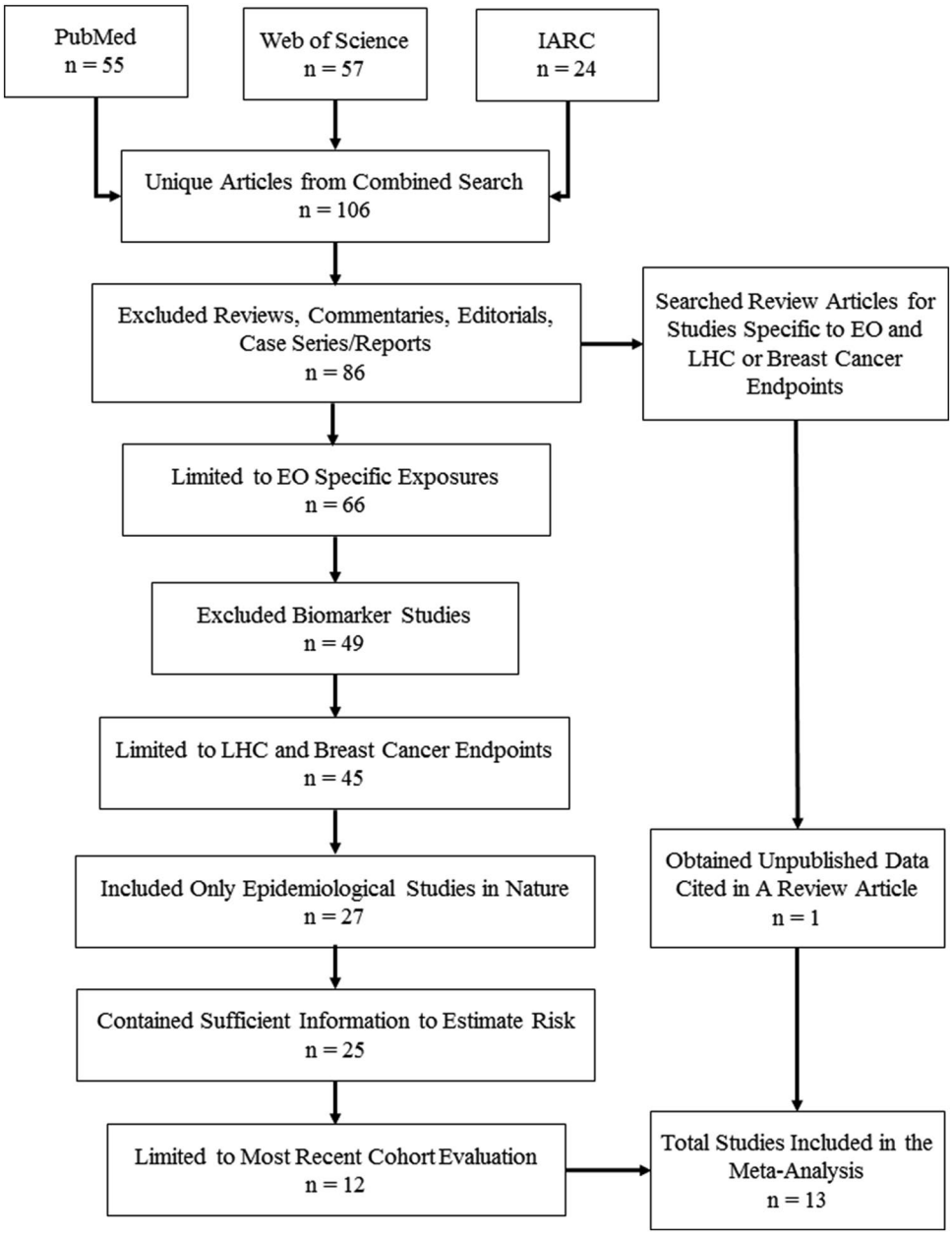

Fig. 1 Flow diagram of studies included in the meta-analysis

Qualitative evaluation of the epidemiological evidence

As specified by our inclusion criteria, the current analysis is focused on occupational exposures to EO and health outcomes of LHC and breast cancer. Many of the studies reviewed here provided data on EO exposure and cancers from other sites (e.g., stomach, brain, pancreas); however, the data were generally sparse and provided no consistent evidence of an association with EO exposure for any cancer site. IARC (2012) arrived at this same conclusion and did not include these other sites in the synthesis component of their latest evaluation of EO. While our meta-analysis includes only the most recent evaluation of a given eligible cohort, we qualitatively reviewed the key characteristics, results, and limitations of all relevant literature (Table 1).

Lympho-hematopoietic cancers

Prompted by the earlier reports of EO mutagenicity and genotoxicity (Ehrenberg and Gustafsson 1959; Ehrenberg and Hallstrom 1967; Rapoport 1948), Hogstedt et al. conducted the first epidemiology studies of EO in two small, independent cohorts of Swedish workers in a hospital equipment sterilization plant that were followed from 1972 to 1977 (Hogstedt et al. 1979a) and workers exposed to EO

Table 1 Summary of key characteristics, results, and methodological limitations of studies of the risk of lympho-hematopoietic cancer and breast cancer from occupational exposure to ethylene oxide in production and sterilization industries

Study	LHCs	Breast cancer	Methodological limitations[a]							
	Total number of subjects (sex)	Total number of subjects (sex)	Small cohort size < 5000 or no. cases < 100	< 10 total observed cases/ deaths for some outcome categories	Insufficient cohort follow-up (< 90%) or case–control participation (< 60%)	Low EO exposures[b]	Lack of individual EO exposure data	Lack of quantitative exposure–response analysis	Presence of co-exposures	Lack of latency or lagged exposure analysis
Hogstedt (1988)	709 (539 M; 170 F)	NA	●	●	?	○	●	●	●	●
Divine (1990)	767 (M)	NA	●	●	○	●	●	●	?	●
Kiesselbach et al. (1990)	2658 (M)	NA	●	●	○	?	●	●	●	●
Bisanti et al. (1993)	1971 (M)	NA	●	●	○	?	●	●	●	o
Norman et al. (1995)	1132 (204 M; 928 F)	1132 (204 M; 928 F)	●	●	●	○	●	●	○	●
Swaen et al. (1996)	10 cases (M) 200 controls (M)	NA	●	○	?	●	○	○	●	●
Olsen et al. (1997)	1361 (M)	NA	●	●	○	?	●	●	●	●
Steenland et al. (2003)	NA	7576 (F)	○	○	●	○	○	○	○	○
Coggon et al. (2004)	2876 (1864 M; 1012 F)	1012 (F)	●	●	○	○	●	●	●	●
Steenland et al. (2004)	18,235 (45% M; 55% F)	9908 (F)	○	○	○	○	○	○	○	○
Swaen et al. (2009)	2063 (M)	NA	●	●	○	○	○	○	●	●
Kiran et al. (2010)	2347 cases (1314 M; 1033 F) 2463 controls (1321 M; 1142 F)	NA	○	●	○	○	○	○	●	●
Mikoczy et al. (2011)	2171 (1309 M; 862 F)	2171 (1309 M; 862 F)	●	●	○	●	○	○	○	○

NA not applicable, *M* male, *F* female

[a]The cut points used for the quantitative characteristics are indicated in the column headings unless otherwise specified

[b]Low EO exposure designation for each group was determined by exposures below the current OSHA TWA limit of 1 ppm or cumulative exposures below 45 ppm-years for all exposure categories

○Absence of characteristic

●Presence of characteristic

?Unable to evaluate due to absence of reported information

and other chemicals in a chlorohydrin production facility followed from 1961 to 1977 (Hogstedt et al. 1979b). These were later combined with a third cohort of workers exposed to EO in a direct oxidation production facility and updated through 1983 for incidence and 1985 for mortality (Hogstedt et al. 1986; Hogstedt 1988). At the hospital equipment sterilization plant, sampling for EO was conducted in 1977 and the mean estimated exposure was approximately 20 ppm (peak: not given) in the sterilization room and 2–70 ppm in the storage hall (peak, 150 ppm) (Hogstedt et al. 1986). Specific to production facility that produced EO by the chlorohydrin process, Hogstedt et al. (1979b) provided "rough estimates of exposure levels" to EO from 1941 to 1947 and from the 1950s to 1963, respectively, which were "probably below" 14 ppm[1] (peak: 722 ppm) and approximately 6–28 ppm (peak, 722 ppm). Although EO production ceased at the facility in 1963, EO was still used in manufacturing various products, and random workplace samples taken in the 1970s measured concentrations ranging from 0.6 to 6 ppm with "occasional" higher values (Hogstedt et al. 1979b). In the plant that produced EO by direct oxidation, the average 8-h TWA concentration of EO was 1–8 ppm (peak: 333–1000 ppm) from 1963 to 1976 and 0.4–2 ppm (peak: 333–1000 ppm) from 1977 to 1982 (Hogstedt et al. 1986). Although exposure to EO was calculated from air samples, the most recent follow-up of these three cohorts qualitatively evaluated EO exposure by duration of employment categories (1–9 years, ≥ 10 years, and all years) (Hogstedt 1988). The combined analysis of 709 production and sterilization workers from the three facilities revealed statistically significant elevated mortality risks for all LHC and leukemia, although no trends were observed by length of employment.

The elevated risks suggested by the first epidemiological cohort studies prompted cohort studies of EO workers in the US (Morgan et al. 1981) and Europe (Thiess et al. 1981) to be published in the early 1980s. Morgan et al. (1981), which was later updated by Divine (1990), conducted a mortality study from 1955 to 1985 of production workers with potential exposure to EO at a Texas chemical plant. The chemical plant produced EO by the chlorohydrin process from 1948 to 1964 and by direct oxidation beginning as early as 1958 (Divine 1990). An industrial hygiene survey was conducted at this plant in 1977 and all samples that were taken in production areas were less than 10 ppm EO (Morgan et al. 1981). The study authors attributed the low levels of EO throughout the plant to engineering controls and precautionary measures intended to reduce potential exposures to workers.

In the US, there have been numerous evaluations of EO-exposed workers from three Union Carbide Corporation (UCC) facilities in West Virginia (Benson and Teta 1993; Greenberg et al. 1990; Swaen et al. 2009; Teta et al. 1993). Environmental monitoring data for EO was routinely collected at in EO using/producing department at one UCC facility beginning in 1976 and subsequent exposures were < 1 ppm as an 8-h TWA, although there were measurements as high as 66 ppm (Greenberg et al. 1990; Teta et al. 1993). It was estimated that the 8-h TWA concentration of EO in the 1960s ranged from 3 to 20 ppm in direct oxidation units and that the levels were higher in the units producing EO by the chlorohydrin process (Teta et al. 1993).

In a follow-up of Greenberg et al. (1990), Benson and Teta (1993) conducted a mortality follow-up from 1940 to 1988 among a subset of 278 workers from the chlorohydrin unit who intermittently used and handled EO in small volumes. A three-fold statistically significant excess of LHC was observed but the study authors attributed this finding to by-products in the production of ethylene chlorohydrin (Benson and Teta 1993). Additionally, Teta et al. (1999) conducted a follow-up during the same time period of 1896 men employed in departments using or producing EO, excluding the chlorohydrin workers that were included in Benson and Teta (1993). This was only the second US cohort study to include EO exposure estimates for individual workers, albeit relatively crudely, along with a quantitative evaluation of EO exposure–response using both external and internal comparisons. There were not statistically significant excess of deaths observed due to any lymphatic and hematopoietic tissue cancers and there were no statistically significant trends for leukemia by cumulative duration of assignments in EO departments. Subsequently, Swaen et al. (2009) conducted an update of the cohort and a total of 2063 men who were employed between 1940 and 1980 were observed for mortality through 2003. The authors used historical measurements in comparable facilities as well as exposure monitoring data in the relevant facility to estimate individual EO exposures. Despite relatively high past EO exposures and extensive follow-up, the study authors found no elevated mortality for LHC cancers, or any indication of an exposure–response relationship with cumulative exposure to EO (Swaen et al. 2009).

Subsequently, other smaller and less informative studies were conducted in the US. For example, Norman et al. (1995) conducted a cancer incidence study of mostly females (928 vs. 204 males) employed in a medical sterilizing plant from 1974 to 1980 and observed only one case of leukemia by 1987. During this time period, EO exposure monitoring was intermittent. Three, 2-h samples were taken in 1980 and the 8-h TWA exposure to EO for sterilizer operators ranged from 50 to 200 ppm, although corrective action was taken to lower exposures and subsequent samples ranged

[1] For the purposes of consistency, values that were reported in mg/m^3 were converted to ppm, assuming that 1 ppm = 1.8 mg/m^3.

from 5 to 20 ppm. Additionally, Olsen et al. (1997) conducted a cohort mortality study of 1361 males who worked in ethylene and propylene chlorohydrin production facilities located in Texas, Louisiana, and Michigan from 1940 to 1992. In contrast to Union Carbide, the production of these two products occurred within the EO production units at all four plants. No data were reported on exposure levels. The study authors found a small, non-statistically significant 1.29-fold excess for LHC.

Several other studies conducted in Europe were small and subject to many limitations. In the UK, Coggon et al. (2004) reported an update of an earlier cohort mortality study (Gardner et al. 1989) of 1864 male and 1012 female workers from a variety of EO exposure scenarios: three EO production facilities (two using both chlorohydrin and direct oxidation processes), one facility that used EO as an intermediate for other chemicals, and eight hospitals that used EO in sterilizing units. All of the chemical companies produced or used ethylene oxide beginning in the 1950s and the hospitals had sterilizing units since the 1960s. Industrial hygiene data were available beginning in 1977 and it was reported that subsequent 8-h TWA exposures to EO were less than 5 ppm for "almost all jobs" and less than 1 ppm "in many" jobs. Additionally, it was reported that occasional peaks of exposure occurred up to several hundred ppm as a result of operating difficulties in chemical plants and during the loading and unloading of sterilizers in hospitals. Gardner et al. (1989) believed that there were higher average EO exposures in earlier years and that peak exposures above the odor threshold of 700 ppm had been reported by manufacturers at the hospitals. Mortality was slightly increased, although not statistically significant for Hodgkin's disease and NHLs, multiple myeloma and leukemia. This study was limited by small numbers of observed deaths, lack of individual EO exposure data, presence of co-exposures and lack of latency analysis.

In Germany, Kiesselbach et al. (1990) conducted an updated cohort mortality study of 2658 males from eight chemical companies in Germany that were exposed to EO through production or maintenance activities for at least 12 months between 1928 and 1981. Some of the subjects were part of an earlier study by Thiess et al. (1981) and were exposed to numerous chemicals in addition to EO. Kiesselbach et al. (1990) found no excess risk from overall LHCs or from leukemia. However, this study was limited because exposure information was only available for 67.2% of the cohort and categorized into three qualitative levels: weak, medium and strong exposure.

A subsequent Italian cohort mortality study was conducted by Bisanti et al. (1993) of 1971 male chemical workers licensed to handle EO for at least 1 year between 1938 and 1948. There were two categories of workers: those who had a license for all toxic chemicals ($n = 1971$) and those who had a license for only EO ($n = 637$). Among the 637 workers that were only licensed to handle EO, statistically significant excess risks for the all LHCs and lymphosarcoma/reticulosarcoma were observed, while there was an increased, although non-significant, risk for leukemia (Bisanti et al. 1993). This study did not have quantitative exposure information, had insufficient follow-up time (only 4% of EO licensed workers were deceased), and it is likely that these workers had co-exposures to other carcinogenic chemicals (Bisanti et al. 1993).

Hagmar et al. (1991, 1995) assessed cancer incidence among 2170 Swedish workers (861 male, 1309 female) in two medical sterilizing plants from 1972 and 1976 to 1990. No statistically significant excesses were observed for overall LHCs or any subtypes, regardless of whether an induction latency period was applied or not. Sterilization operations began in the first plant in 1970, during which exposures were estimated to be as high as 40 ppm, and air monitoring demonstrated that exposures continuously decreased to < 0.2–0.75 ppm in 1985–1986 (Hagmar et al. 1991, 1995). In the second plant, sterilization operations began in 1964, during which estimated exposures ranged from < 0.2 to 75 ppm, although subsequent monitoring showed a continuous decrease in exposure to < 0.2–0.5 ppm in 1985 and 1986 (Hagmar et al. 1991, 1995). Although this study included EO exposure estimates for individual workers, it was limited by short follow-up time and low EO exposures among a large percentage of workers, lessening its usefulness for evaluating EO-related cancer risks.

In Belgium, Swaen et al. (1996), performed a nested case–control study of Hodgkin's disease among workers at a large chemical plant to evaluate a suspected cluster of ten cases exposed to EO between 1966 and 1992. For all subjects, occupational exposures were identified and categorized by work history and process, medical records, and industrial hygiene data. The study authors reported a statistically significant association for benzene, ammonia, sodium hydroxide, oleum and EO, but the interpretation of these findings are constrained by the exclusion of inactive workers and the presence of many other chemical exposures. Further dose–response analyses were conducted for EO but failed to provide support for a causal relationship. Into the 2000s, Kardos et al. (2003) evaluated causes of death during 1987–1999 among 299 female workers from a pediatric clinic in Hungary where EO was used as a sterilant. No individual monitoring data was available for review. One case of lymphoid leukemia was observed, although no quantitative information (i.e., leukemia-specific risk estimates or expected number of cases to calculate a risk estimate) was available regarding EO exposure risks.

Returning to the US, as part of an earlier quantitative risk assessment for EO, Teta et al. (1999) conducted an update of the meta-analysis conducted by Shore et al. (1993) that

included leukemia and NHL findings from many of the studies reviewed above. The authors found no statistically significantly elevated meta-SMRs for these categories and no evidence of overall trends in relation to duration or intensity of EO exposure or latency.

Arguably, the most scientifically sound and informative epidemiological study of EO-related cancer risk was a NIOSH cohort mortality study that followed 18,235 employees (45% male, 55% female) at 14 facilities where EO was used to sterilize medical supplies and spices from 1987 to 1998 (Stayner et al. 1993; Steenland et al. 1991, 2004). Wong and Trent (1993) essentially published a duplication of the study conducted by Steenland et al. (1991), but with far more limitations that the initial study, and thus will not be reviewed for the purposes of this paper (Steenland and Stayner 1993). Steenland et al. (1991) reported that the average 8-h TWA exposures to EO from 1976 to 1985 were 4.3 ppm and 2.0 ppm, respectively, for sterilizer operators and for other exposed workers (i.e., production, maintenance, warehouse, and laboratory workers). Furthermore, Stayner et al. (1993) reported that the average exposure to EO for all exposed workers was 5.5 ppm and ranged from 0.05 to 77.2 ppm. In the most recent report with mortality follow-up through 1998 (Steenland et al. 2004), industrial hygiene measurements and historical data regarding process changes at the plants were used to assess the exposure of each individual worker and the categories of exposure were: > 0–1199 ppm-days; 1200–3679 ppm-days; 3680–13,499 ppm-days; and 13,500+ ppm-days. Steenland et al. (2004) found no statistically significant excesses in males or females combined for all LHCs, including Hodgkin's disease, NHL, multiple myeloma and leukemia, when analyses were conducted using no lag and a 10-year lag. The 10-year lag model resulted in a statistically significant 2.37-fold risk for NHL among males only in the highest EO exposure category (≥ 13,500 ppm-days), based on 8 deaths. Furthermore, internal analyses found statistically significant exposure–response relationships in males only between log cumulative EO exposure (using a 15-year lag) for all LHCs combined and the subcategory "lymphoid cell line tumors" (NHL, multiple myeloma and lymphocytic leukemia). No positive trends were found in males or females for the EO exposure metrics, duration of exposure, peak exposure, average exposure or cumulative exposure. The sex-specificity of the exposure–response findings, which were limited to the transformed metric log cumulative exposure, weaken the overall evidence for EO as a risk factor for LHC. This weakened evidence was also noted by the authors (Steenland et al. 2004). Notably, the NIOSH studies had none of the limitations we considered in Table 1. The relative strengths of the NIOSH studies were also noted by IARC, which gave the greatest weight to the findings of this study when assessing the balance of the epidemiological evidence on EO (IARC 2012).

As part of a quantitative risk assessment for EO, Valdez-Flores et al. (2010) combined primary data from the NIOSH (Steenland et al. 2004) and UCC cohorts (Swaen et al. 2009). In separate and combined gender-specific external mortality comparisons, the authors found no statistically significant excesses for all LHCs, including the subcategories Hodgkin's disease and NHL. Internal exposure–response analyses of LHC overall and several subtypes (lymphoid tumors, NHL, multiple myeloma, lymphocytic leukemia, myeloid leukemia and leukemia) found no positive trends relative to cumulative EO exposure with and without lags for any of six cohort/gender combinations examined. Valdez-Flores et al. (2010) also challenged Steenland et al.'s (2004) use of the log cumulative EO exposure metric describing several interpretational issues related to the apparent supra-linear exposure–response relationship resulting from the log-transformed EO exposure scale. In the present meta-analysis, Swaen et al. (2009) and Steenland et al. (2004) were used and Valdez-Flores et al. (2010) was excluded.

Two epidemiology studies of LHC in relation to EO exposure were published after the 2010 IARC evaluation (Kiran et al. 2010; Mikoczy et al. 2011), and each is associated with several methodological limitations. Kiran et al. (2010) described a population-based and hospital-based case–control study of 2347 lymphoma cases diagnosed between 1998 and 2004 and 2463 controls from six European countries [part of European EPILYMPH Study (Besson et al. 2006)]. These authors defined lymphoma (all types) according to the World Health Organization classification and found an overall, non-statistically significant 1.3-fold increased risk for persons ever exposed to EO (versus never exposed). We note that the risk estimate for lymphoma as reported by these authors for all lymphoma types was included in the presented meta-analysis for all LHCs. The highest risk, though not statistically significant, was reported for chronic lymphocytic leukemia (OR 2.0; 95% CI 0.8–4.7). Additionally, intensity and frequency of exposure to EO were categorized into unknown exposure, low exposure, medium exposure, and high exposure and then used to calculate an individual's cumulative exposure score. Subgroup analyses of lymphoma subtype by cumulative exposure found several statistically significantly elevated ORs, however interpretation is limited by the population-based and hospital-based case–control design, very low EO exposure frequency in cases/controls (1.3%/1.1%), differential case/control participation (88%/52%), small numbers of cases/controls in subgroup analyses and reliance of self-reported socio-demographic and work history data. We note that small numbers of cases and limited covariate data were limitations inherent in many of the case–control and cohort studies reviewed.

Mikoczy et al. (2011) reported a 16-year mortality and cancer incidence update of the Hagmar et al. (1991, 1995) cohort of Swedish sterilant workers employed before 1986 and reviewed in detail above. The authors found small, non-statistically significant elevations in mortality and cancer incidence for LHC and some subtypes that decreased with additional follow-up time. Exposure–response analyses using external and internal comparisons provided no evidence of increasing LHC risk with increasing cumulative EO exposure. Although having estimates of individual worker exposures to EO and exposure–response analyses, the Mikoczy et al. (2011) study was limited by small numbers of observed cases and deaths, insufficient follow-up and relatively low cumulative EO exposures.

Breast cancer

As seen in Table 1, several previously discussed studies also provided data on the association between EO exposure and breast cancer (Coggon et al. 2004; Mikoczy et al. 2011; Norman et al. 1995; Steenland et al. 2003, 2004). The UK cohort mortality study reported by Coggon et al. (2004) found no overall excess in breast cancer; while the Norman et al. (1995) US cohort incidence study (and assuming follow-up through 1985) found a statistically significant 2.55-fold overall excess in the most recent follow-up of the cohort. The Hungarian cohort study by Kardos et al. (2003) was uninformative regarding breast cancer risks related to EO because the authors only reported three breast cancer deaths, but did not provide the expected number of deaths by cancer endpoint.

As with LHC, the most informative epidemiological study of breast cancer risk in relation to EO was the large U.S. NIOSH cohort mortality study (Steenland et al. 2004) that included a nested breast cancer incidence study of 7576 females employed in commercial EO sterilization facilities from the 1940s to the 1980s (Steenland et al. 2003). The mortality study revealed no overall excess for breast cancer, but internal exposure–response analyses found a statistically significant positive trend for breast cancer using the log of cumulative EO exposure with a 20-year lag (Steenland et al. 2004). This pattern of findings was repeated in the incidence study, which found no overall excess in breast cancer among the total cohort. However, the authors caution that due to under-ascertainment of cases the reported SIRs underestimate risk. An analysis of an internal nested case–control study of subjects with complete cancer ascertainment data found evidence of an exposure–response relationship with log cumulative EO exposure using a 15-year lag. The authors caution against over-interpreting the positive exposure–response because the trend analysis may have been biased due to increased breast cancer rates among women who were more highly exposed because of longer durations of employment. Steady employment may have led to more cancer screenings because of insurance coverage (Steenland et al. 2003). The methodological issues raised by Valdez-Flores et al. (2010) and discussed above regarding the log-transformed EO exposure scale in the mortality study also apply to the breast cancer incidence analyses.

The Mikoczy et al. (2011) study, an update of the Swedish cohort incidence study, also provides information on breast cancer in relation to EO exposure. The authors found overall deficits in breast cancer cases and deaths compared to the regional Swedish population with and without consideration of a 15-year induction period. Internal analyses of cumulative EO exposure in relation to breast cancer incidence revealed statistically significant elevated incidence rate ratios (IRRs) in the two highest categories (IRR = 2.76 and 3.55, respectively) compared to the baseline category of low-exposed workers (defined as 50% of workers with cumulative exposures less than the median). This finding led to the authors' conclusion of a positive-exposure relationship with EO and breast cancer, which in turn has been interpreted by others as lending support for a causal association (e.g., USEPA 2014).

The validity of the Mikoczy et al. (2011) finding and conclusion can be challenged, however, on the basis of several methodological issues. First, the greater than two-fold *relative* excesses in breast cancer incidence risk in the two highest cumulative EO exposure categories were ensured by an inordinately large, statistically significant 48% *deficit* in breast cancer incidence in the baseline category. The inordinately low baseline SIR for breast cancer is puzzling given that regional rates were used in the external comparisons and that there was no apparent problem with under-ascertainment of breast cancer cases. The healthy worker effect is also not a reasonable explanation for the low baseline breast cancer rate (Gridley et al. 1999). It appears that for unknown reasons, the baseline group used by Mikoczy et al. (2011) differs from the highest two cumulative EO exposure groups on factors other than EO exposure that may be related to breast cancer. Second, cumulative EO exposure levels in the Mikoczy et al. (2011) study were very low relative to both the UCC cohort (Swaen et al. 2009) and NIOSH breast cancer cohort incidence study (Steenland et al. 2003). For example, in the Mikoczy et al. (2011) study the median cumulative EO exposure values of workers in both the second and third cumulative EO exposure categories (0.17 and 0.39 ppm-years, respectively) fall well within the *lowest* non-baseline cumulative EO exposure category (> 0 to < 2.34 ppm-years) used in the NIOSH study (with no exposure lag as in Mikoczy et al. (2011). In this category, Steenland et al. (2003), using internal comparisons, found a deficit in breast cancer cases compared with the strikingly disparate, statistically significant 2.76- and 3.55-fold excesses reported by Mikoczy et al. (2011) for workers

Table 2 Studies of occupational exposure to ethylene oxide in production and sterilization industries and the risk of lympho-hematopoietic cancer and breast cancer

Study	Study population	Previous evaluations	Exposure assessment	Deceased (%)	Cancer endpoint[a] (ICD revision: ICD code)	Cases (sex)	Exposure type	Effect estimate	95% CI
Hogstedt (1988)	Sterilizers and production workers in three industries, Sweden	Hogstedt et al. (1979a, b, 1986)	Duration of employment	12	Blood and lymphatic (ICD-8: 200-209)	9 (M + F)	Sterilization + production	SMR = 4.59	2.10–8.72[b c]
					Leukemia (ICD-8: 204-207)	7 (M + F)		SMR = 9.21	3.70–18.98[c]
Divine (1990)	Production workers at a Texas chemical plant, USA	Morgan et al. (1981)	Reviewed work histories and included jobs on production units, maintenance, QC lab, and engineers	11.2	All lymphopoietic (ICD-8: 200-209)	3 (M)	Production	SMR = 1.01	0.20–2.96[b]
					Hodgkin disease (ICD-8: 203)	3 (M)		SMR = 8.34	1.68–24.38
					Leukemia (ICD-8: 204-207)	0		SMR = 0	0–3.28[d]
					Other lymphatic tissue (ICD-8: 202, 203, 208)	0		SMR = 0	0–4.04[d]
Kiesselbach et al. (1990)	EO exposed workers at 8 chemical plants, Germany	Thiess et al. (1981)	Job task from company records	10.1	Lymphatic and hematopoietic tissue (ICD-9: 200-208)	5 (M)	Production	SMR = 1.00	0.32–2.34[b]
					Leukemia (ICD-9: 204-208)	2 (M)		SMR = 0.85	0.10–3.07
Bisanti et al. (1993)	Chemical workers licensed to handle EO and other toxic chemicals, Italy	–	Only included chemical workers licensed to handle EO	11.9	All hematopoietic (ICD-9: 200-208)	5 (M)	Production	SMR = 7.00	2.27–16.37[b]
					Leukemia–aleukemia (ICD-9: 204-208)	2 (M)		SMR = 6.50	0.79–23.49
Norman et al. (1995)	Sterilizers of medical equipment and supplies that were assembled at a New York plant, USA	–	EO was the only major process chemical used and historical records suggest widespread exposure	NA	Breast (ICD revision/codes: NR)	8 (F)	Sterilization	SMR = 2.55	1.31–4.98
					All LHC (ICD revision/codes: NR)	2 (M + F)		SMR = 3.19	0.48–21.22[b e]
					Multiple myeloma (ICD revision/codes: NR)	1 (F)		SMR = 5.56	0.14–30.95[c]
					Leukemia (ICD revision/codes: NR)	1 (M + F)		SMR = 1.85	0.05–10.32[c]

Table 2 (continued)

Study	Study population	Previous evaluations	Exposure assessment	Deceased (%)	Cancer endpoint[a] (ICD revision: ICD code)	Cases (sex)	Exposure type	Effect estimate	95% CI
Swaen et al. (1996)	EO exposed workers at a large chemical production plant, Belgium	–	Industrial hygiene data from the facility, work histories, and processing categories	NA	Hodgkin's disease (ICD revision NR: 201)	3 (M)	Production	OR = 8.5	1.4–39.9
Olsen et al. (1997)	Production workers (chlorohydrin process) from four production plants, USA	–	NR	22	Lymphopoietic and hematopoietic (ICD-8: 200-209)	10 (M)	Production	SMR = 1.29	0.62–2.38[b]
					Hodgkin's disease (ICD-8: 201)	2 (M)		SMR = 2.86	0.35–10.32[c]
					Leukemia and aleukemia (ICD-8: 204-207)	2 (M)		SMR = 0.67	0.08–2.42
Steenland et al.—incidence (2003)	Sterilization workers at 14 plants, USA	–	IH measurements and historical data regarding process changes	18	Breast (ICD-9: 174, 233)	230 (F)	Sterilization	RR = 0.89	0.78–1.01
Coggon et al. (2004)	Sterilization workers at eight hospitals and production workers at three manufacturing facilities, England and Wales	Gardner et al. (1989)	Environmental and personal monitoring with TWA exposure < 5 ppm for almost all jobs, peaks up to several hundred ppm	19.6	Breast (ICD-9: 174)	11 (F)	Sterilization	SMR = 0.84	0.42–1.51
					All LHC (ICD-9: 200-208)	12 (M + F)	Production	SMR = 1.53	0.79–2.95[b e]
						5 (M + F)	Sterilization	SMR = 1.51	0.51–4.53[b e]
						17 (M + F)	All	SMR = 1.33	0.78–2.27[b e]
					Non-Hodgkin's lymphoma (ICD-9: 200, 202)	4 (M + F)	Production	SMR = 1.38	0.38–3.53
						3 (M + F)	Sterilization	SMR = 1.59	0.33–4.66
						7 (M + F)	All	SMR = 1.46	0.59–3.02
					Hodgkin's disease (ICD-9: 201)	1 (M + F)	Production	SMR = 1.40	0.04–7.82
						1 (M + F)	Sterilization	SMR = 2.98	0.08–16.62
						2 (M + F)	All	SMR = 1.91	0.23–6.89
					Multiple myeloma (ICD-9: 203.0)	3 (M + F)	Production	SMR = 2.03	0.42–5.94
						0	Sterilization	SMR = 0	0–3.57[d]
						3 (M + F)	All	SMR = 1.20	0.25–3.49
					Leukemia (ICD-9: 204-208)	4 (M + F)	Production	SMR = 1.41	0.39–3.62
						1 (M + F)	Sterilization	SMR = 0.55	0.01–3.06
						5 (M + F)	All	SMR = 1.08	0.35–2.51

Table 2 (continued)

Study	Study population	Previous evaluations	Exposure assessment	Deceased (%)	Cancer endpoint[a] (ICD revision: ICD code)	Cases (sex)	Exposure type	Effect estimate	95% CI
Steenland et al.—mortality (2004)	Sterilization workers at 14 plants, USA	Steenland et al. (1991) and Stayner et al. (1993)	IH measurements and historical data regarding process changes	15.6	Breast (ICD-9: 174)	103 (F)	Sterilization	SMR = 0.99	0.84–1.17
					All hematopoietic (ICD-9: 200-208)	79 (M + F)		SMR = 1.00	0.79–1.24[b]
					Non-Hodgkin's lymphoma (ICD-9: 200, 202)	31 (M + F)		SMR = 1.00	0.72–1.35
					Hodgkin's disease (ICD-9: 201)	6 (M + F)		SMR = 1.24	0.53–2.43
					Myeloma (ICD-9: 203)	13 (M + F)		SMR = 0.92	0.51–1.53[c]
					Leukemia (ICD-9: 204-208)	29 (M + F)		SMR = 0.99	0.71–1.36
Swaen et al. (2009)	Workers at EO production plants, USA	Greenberg et al. (1990) and Teta et al. (1993)	Exposure estimates were based on environmental monitoring data	50.8	All lymphatic and hematopoietic (ICD revision/codes: NR)	27 (M)	Production	SMR = 0.89	0.59–1.29[b]
					Non-Hodgkin lymphoma (ICD revision/codes: NR)	12 (M)		SMR = 1.05	0.54–1.83
					Hodgkin disease (ICD revision/codes: NR)	0		SMR = 0	0–2.22[d]
					Leukemia (ICD revision/codes: NR)	11 (M)		SMR = 0.93	0.47–1.67
Kiran et al. (2010)	EO exposed workers in 6 European countries (Czech Republic, France, Germany, Italy, Ireland, Spain)	–	Exposures were assessed retrospectively by industrial hygienists based on information obtained survey responses	NA	Lymphoma (ICD revision/codes: NR)	31 (M + F)	NR	OR = 1.3	0.7–2.1[b]

Table 2 (continued)

Study	Study population	Previous evaluations	Exposure assessment	Deceased (%)	Cancer endpoint[a] (ICD revision: ICD code)	Cases (sex)	Exposure type	Effect estimate	95% CI
Mikoczy et al. (2011)	Workers at two disposable medical equipment production facilities, Sweden	Hagmar et al. (1991, 1995)	Industrial hygiene data and work histories were used to develop job specific exposure matrices	7.9	Breast (ICD-7: 170)	41 (F)	Sterilization	SIR = 0.81	0.58–1.09
					Lympho-hematopoietic (ICD-7: 200-209)	18 (M + F)		SIR = 1.25	0.74–1.98[b]
					Non-Hodgkin's lymphoma (ICD-7: 200, 202)	9 (M + F)		SIR = 1.44	0.66–2.73
					Hodgkin's lymphoma (ICD-7: 201)	1 (M + F)		SIR = 0.76	0.02–4.25
					Multiple myeloma (ICD-7: 203)	2 (M + F)		SIR = 0.96	0.12–3.47
					Leukemia (ICD-7: 204-205)	5 (M + F)		SIR = 1.40	0.45–3.26

NA not applicable, *NR* not reported in text, *M* male, *F* female, *ICD* International Classification of Diseases, *CI* confidence interval, *SMR* standardized mortality ratio, *SIR* standardized incidence ratio, *OR* odds ratio, *RR* relative risk

[a]Cancer endpoint as described in each respective study

[b]Effect estimate used in the "all LHC" analysis

[c]Crude effect estimates and/or 95% CIs were calculated from the raw data provided in the study. Technical details provided in online supplementary appendix

[d]Cancer endpoints that had a reported number of 0 cases were included in the table for reference but were not included in the meta-analysis

[e]Effect estimates were combined together using DerSimonian and Laird random effects models

Table 3 Random effects analysis by cancer type and occupational group

Cancer type	All effect estimates			EO production/use[a]			EO sterilization[a]		
	N[b]	Meta-RR	95% CI	*N*[b]	Meta-RR	95% CI	*N*[b]	Meta-RR	95% CI
Breast	5	0.97	0.80–1.18	–	–	–	5	0.97	0.80–1.18
All LHC	11[c,d]	1.48	1.07–2.05	6[d]	1.46	0.85–2.50	4[d]	1.07	0.87–1.30
Leukemia	9[d]	1.62	0.87–3.01	5[d]	1.21	0.66–2.21	4[d]	1.03	0.76–1.39
NHL	4[d]	1.09	0.85–1.40	2[d]	1.12	0.65–1.90	3[d]	1.08	0.82–1.43
Myeloma	4[d]	1.01	0.63–1.63	1[d,e]	2.03	0.42–5.94	3	0.99	0.59–1.65
Hodgkin's disease	6[d]	2.76	1.21–6.27	4[d]	5.36	2.31–12.44	3[d]	1.27	0.63–2.58

N number of studies, *Meta-RR* meta-relative risk, *CI* confidence interval, *LHC* lympho-hematopoietic cancer

[a]With the exception of the effect estimates reported in Kiran et al. (2010) and Hogstedt (1988), the effect estimates could be classified by occupational group

[b]Total number of effect estimates per category

[c]Nine studies provided effect estimates for all LHC combined. In two instances (Coggon et al. 2004; Norman et al. 1995), effect estimates for individual blood and lymphatic malignancies were combined using DerSimonian and Laird random effects models to determine a combined LHC effect estimate

[d]Coggon et al. (2004) provided an overall effect estimate for workers from both chemical manufacturing and sterilization facilities, which was used in the overall analysis, as well as effect estimates by occupational group, which was used in the occupational group sub-analysis

[e]As reported, Coggon et al. (2004) was the sole study for this category

with similar levels of cumulative EO exposure. This marked contrast provides further support that the non-baseline IRRs reported by Mikoczy et al. (2011) were inflated by the inordinately low baseline breast cancer rates.

Meta-analysis

Thirteen studies were identified for use in the meta-analysis of LHC and breast cancer, which constituted 11 effect estimates categorized as all LHC, nine effect estimates for leukemia, four effect estimates for NHL, four effect estimates for myeloma, six effect estimates for Hodgkin's disease, and five effect estimates for breast cancer (Table 2). Analysis by cancer type demonstrated significant heterogeneity for leukemia ($I^2 = 74.6\%$; p value < 0.05), breast cancer ($I^2 = 62.2\%$; p value < 0.05), and all LHC ($I^2 = 68.9\%$; p value < 0.05), borderline heterogeneity for Hodgkin's disease ($I^2 = 45.6\%$; p value $= 0.101$), and homogeneity for myeloma ($I^2 = 0\%$; p value $= 0.634$) and NHL ($I^2 = 0\%$; p value $= 0.708$) (data not shown). Therefore, to account for the almost universal heterogeneity demonstrated across the studies, we present results from our random effects models exclusively.

Overall analysis by cancer type

Table 3 presents results of the random effects meta-analyses models and corresponding 95% CIs, for all effect estimates by LHC cancer type and LHC cancer type within occupational groups. The meta-RRs for the all LHC and Hodgkin's disease categories, respectively, were statistically significantly elevated at 1.48 (95% CI 1.07–2.05) and 2.76 (95% CI 1.21–6.27). Slight to moderate excess risks, although not statistically significant, were observed for leukemia, NHL, and myeloma. Based on five effect estimates, the meta-RR for breast cancer revealed no evidence of an elevated risk (0.97; 95% CI 0.80–1.18).

Analysis by occupational group and cancer type

Within the EO production/using group, there were slightly elevated meta-RRs, although not statistically significant for all LHC (1.46; 95% CI 0.85–2.50), leukemia (1.21; 95% CI 0.66–2.21), NHL (1.12; 95% CI 0.65–1.90), and myeloma (2.03; 95% CI 0.42–5.94). However, EO producers and users had a statistically significantly increased risk for Hodgkin's disease (meta-RR = 5.36; 95% CI 2.31–12.44). No cases of breast cancer were reported in the EO production group. Additionally, the meta-RRs for the EO sterilization group were close to the null value and not statistically significant for breast cancer, all LHC, and LHC subcategories.

Analysis by decade of publication

Overall, the decade analysis (Fig. 2) demonstrated statistically significant borderline heterogeneity with an I^2 of 59.6% (p value = 0.002), although heterogeneity improved from an I^2 of 61.3% (p value = 0.012) in the 1990s to an I^2 of 0% (p values ≥ 0.563) in both the 2000s and 2010s. When effect estimates were stratified by decade, there was nearly a four-fold and statistically significantly increased risk for all LHC in papers published in the 1980s (meta-RR = 3.87; 95% CI 1.87–8.01) and an elevated, although

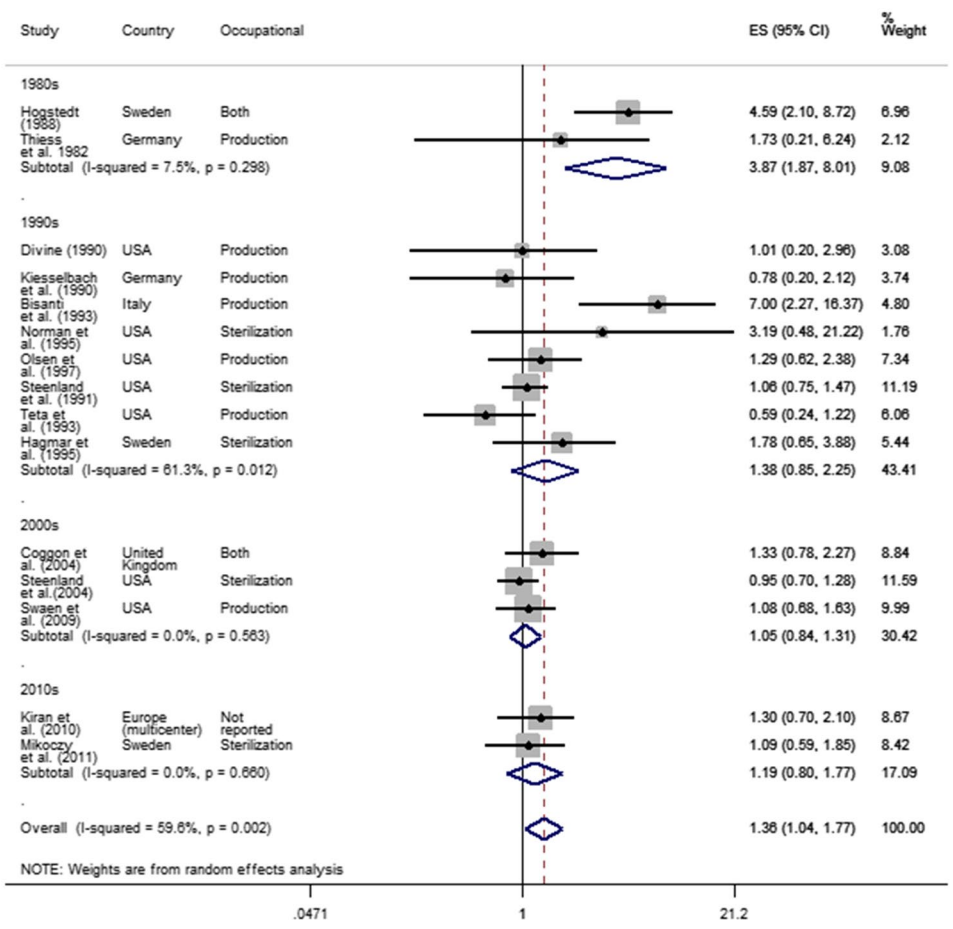

Fig. 2 Forest plot of random effects model of all LHC by decade of publication

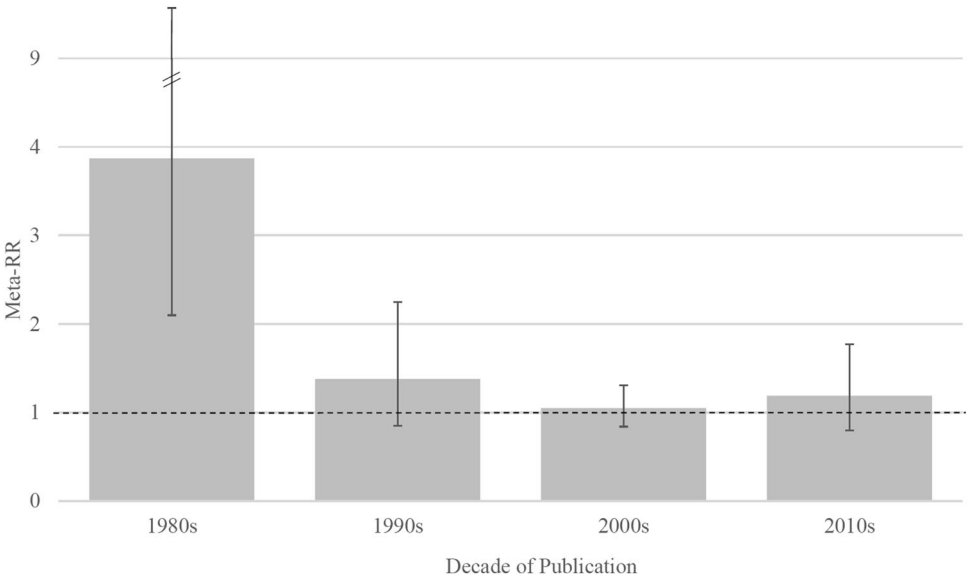

Fig. 3 Time-trend analysis by decade of publication for all LHC

non-significant, meta-RR of 1.38 (95% CI 0.85–2.25) in the 1990s. In contrast to the results for the 1980s and 1990s, we found a near-baseline-level risk for all LHC in the papers published in the 2000s (meta-RR = 1.05; 95% CI 0.84–1.31) and a small, non-statistically significantly elevated risk in the 2010s (meta-RR = 1.19; 95% CI 0.80–1.77).

Moreover, the precision of the meta-RRs calculated across decade increased markedly in studies conducted in

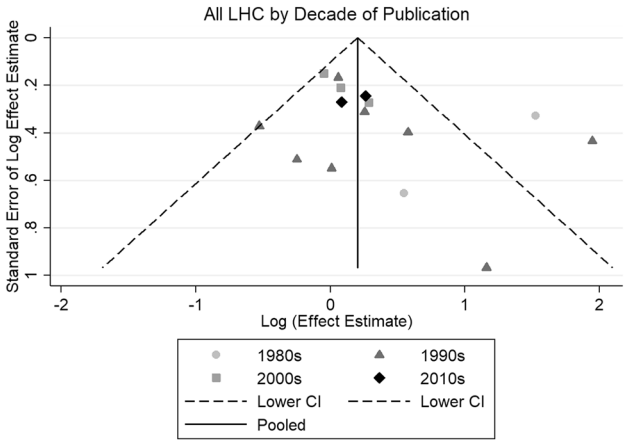

Fig. 4 Funnel plot of all LHC effect estimates by decade of publication

the 2000s and 2010s compared to those conducted in the 1980s and 1990s. Figure 3 illustrates the reduction in effect estimates and increase in precision of studies between the two 20-year periods of publication. We considered industry and cancer type-specific subcategories for all LHC studies by decade; however, the small number of specific studies by decade precluded a detailed evaluation.

Evaluation of publication bias for LHC studies

To evaluate the publication bias for LHC studies, a funnel plot was generated for all LHC effect estimates by decade of publication (Fig. 4). The Egger test did not measure statistically significant asymmetry in the funnel plot ($p=0.13$), but the Begg's test was borderline statistically significant ($p=0.048$), results consistent with the visual representation shown in the funnel plot. The plot suggests that effect estimates that demonstrated an absence of LHC risk may have been underrepresented in studies conducted in the 1980s and 1990s, and that the studies published in the earlier decades were associated with less precision due to small size or otherwise poor study quality (Table 1). For example, in the 1980s and 1990s, both the reported effect estimates and standard errors were considerably larger than those from papers published in the later decades. As the decades advance, the effect estimates and standard errors decrease in size among the studies illustrated in the forest plot.

Sensitivity analysis for leukemia studies

A time period analysis (pre- and post-2000s) for leukemia was conducted to evaluate potential sources of heterogeneity (Fig. 5). For the papers published prior to 2000, there was more than a two-fold increased risk of leukemia, although the meta-RR was not statistically significant (2.61; 95% CI 0.77–8.90), while there was a baseline level risk for papers published after the 2000s (meta-RR = 1.01; 95% CI 0.77–1.32). Heterogeneity was observed in the pre-2000s ($I^2=66.6\%$; $p<0.05$) but not in the post-2000s ($I^2=0\%$; $p=0.916$). We also performed a time period analysis excluding Hogstedt (1988), which resulted in a reduction in the overall leukemia meta-RR from 1.62 (95% CI 0.87–3.01) to 1.05 (95% CI 0.81–1.35). In addition to the lower observed risk estimate, the overall heterogeneity improved from an I^2 of 73.6% ($p<0.001$) to an I^2 of 0% ($p=0.596$) (results not shown).

Discussion

Since a systematic review and risk assessment was published by Teta et al. (1999), additional studies or cohort updates have been published regarding occupational exposures to EO and the development of LHCs and/or breast cancer. Therefore, we performed an updated meta-analysis to include literature from the past two decades, examined additional subcategories of LHC and breast cancer, as well as performed analyses by occupational group (production vs. sterilization) and by decade of publication. Specifically, the previous meta-analysis included 10 studies of unique cohorts (Bisanti et al. 1993; Divine 1990; Gardner et al. 1989; Hagmar et al. 1995; Hogstedt 1988; Kiesselbach et al. 1990; Olsen et al. 1997; Steenland et al. 1991; Teta et al. 1993). Since the 1999 meta-analysis, one additional study (Kiran et al. 2010) and four updates of previously evaluated cohorts (Coggon et al. 2004; Mikoczy et al. 2011; Steenland et al. 2004; Swaen et al. 2009) have been published. Additionally, two papers were included in our analysis but were not included in the original analysis (Norman et al. 1995; Swaen et al. 1996). Teta et al. (1999) reported no statistically significant positive trends among leukemia and NHLs at the time of their analyses, which is consistent with the results of this study.

Overall findings for LHC

Accounting for the latest updates of the cohort studies reviewed, only the early Swedish (Hogstedt 1988) and Italian Bisanti et al. (1993) studies reported statistically significant LHC effect estimates greater than 2.0 (relative risks greater than 2.0 are less likely to be the results of uncontrolled confounding factors, especially in presence of sparse data) or statistically significant EO exposure–response relationships. Clearly, the most informative study for evaluating LHC and breast cancer risk in relation to EO exposure is the large NIOSH study (Steenland et al. 2003, 2004; Valdez-Flores et al. 2010). The NIOSH study results, observed elevated risks only in the exposure–response analyses, and the results were

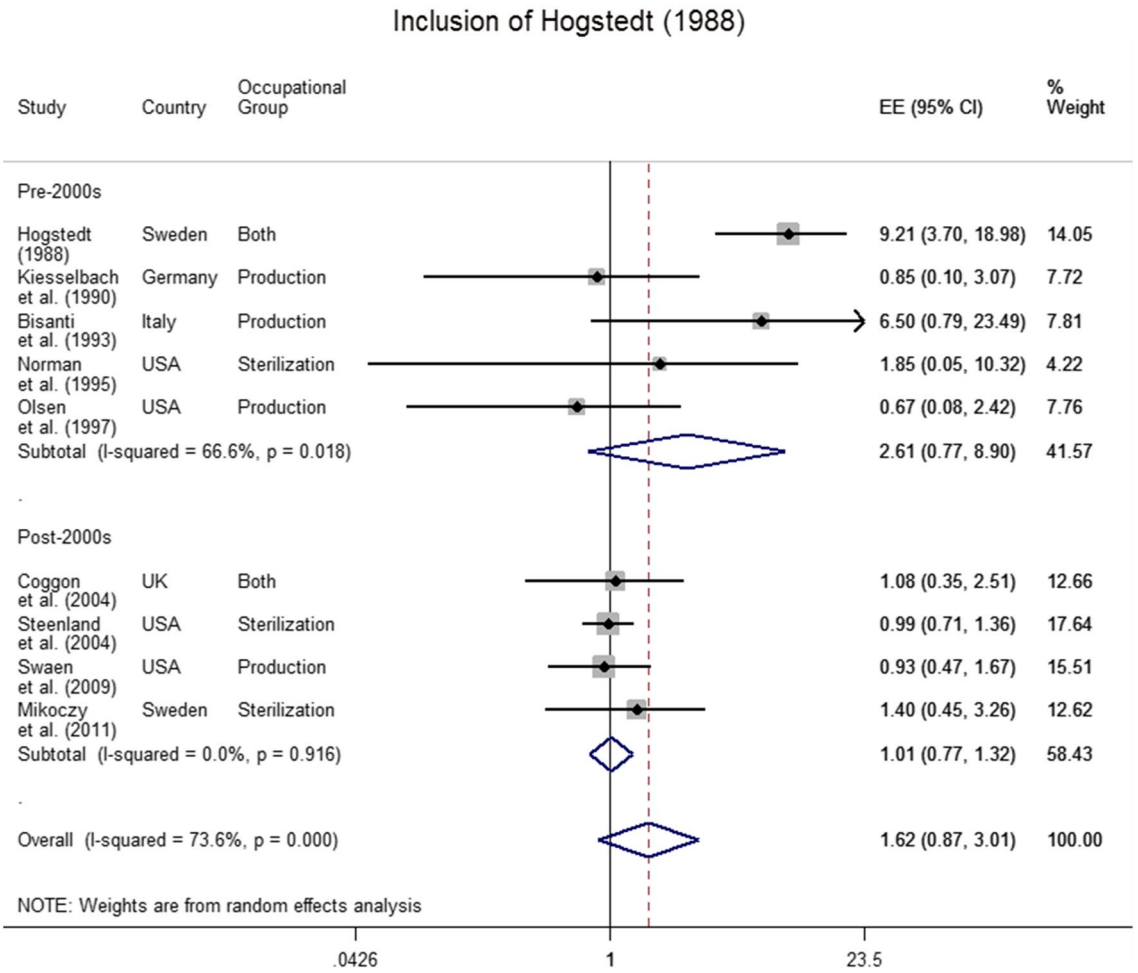

Fig. 5 Forest plot of random effects model of leukemia by pre- and post-2000s time periods

gender-specific and limited to the transformed metric log cumulative EO exposure, which weakened the overall evidence for EO as a risk factor for LHC. The overall findings from the NIOSH study was equivalent to the null (SMR = 1.00; 95% CI 0.79–1.24). To a lesser extent, the UCC cohort study (Swaen et al. 2009; Valdez-Flores et al. 2010) also provides methodologically sound, useful information regarding LHC risks. Moreover, Valdez-Flores et al. (2010), who challenged NIOSH's use of the log-transformed EO exposure metric on interpretation grounds, found in their reanalysis of the NIOSH and UCC cohorts, no positive trends relative to cumulative EO exposure with and without lags for any of six cohort/gender combinations examined.

When evaluated without regard to publication date, our meta-analysis of all LHC and its subgroups by occupational revealed uniformly higher risks among EO production workers compared with workers exposed during EO sterilization processes. While cancer risks among EO production workers ranged from 1.38 for NHL to 4.98 for Hodgkin disease and many were statistically significant, most of the effect estimates for EO sterilization workers were close to the null value and none was statistically significant. As noted in our following discussion of the time-trend analysis, the elevated risks for all LHC and its subgroups among EO production workers were observed in relatively imprecise and uninformative studies published in the 1980s.

Time-trend and sensitivity analysis for LHC

The epidemiological evidence of the risk for human cancer from EO used in the IARC evaluation came from 12 cohort studies of exposed workers in the US and Europe, employed in chemical plants where EO was produced or used, or in facilities where EO was used as a sterilizing agent (IARC 2012). Aside from the relatively uninformative population-based and hospital-based case–control study reported by Kiran et al. (2010) and the methodologically problematic update of the Swedish cohort study (Mikoczy et al. 2011),

all epidemiological evidence for the potential human carcinogenicity of EO was available to IARC at their Working Group meeting in 2010 and most of this evidence relates to LHC (IARC 2012).

As we show in Tables 1 and 2, the earlier epidemiological studies of EO were limited by factors such as small population size and/or observed number of cases or deaths (ten studies). These limitations can lead to low statistical power to detect important excess LHC risks, or in the case of studies reporting statistically significant results, imprecise risk estimates. Other limitations include insufficient follow-up or case–control participation rates (two studies), low EO exposure potential (three studies), lack of individual exposure data or exposure–response analysis (seven studies), inconsistencies in histopathological classification of diagnoses over time (variation between ICD 7–9 and ICD 10 (mortality) codes as well as ICDO (incidence) codes across time), with four studies not reporting classification), as well as the lack of latency analysis (not a major issue with LHC in general). Perhaps the key methodological issue of the earlier studies was the inability to account for residual confounding by factors including co-exposure to other chemicals (nine and eight studies, respectively). However, determining which occupational and/or non-occupational factors are potential confounding factors is difficult given the absence of knowledge on known risk factors for LHC.

Our qualitative findings regarding methodological limitations over time were corroborated in our meta-analyses of all LHC conducted by decade of publication. When stratified by decade of publication, the effect estimates from studies published in the 2000s and 2010s were homogeneous, whereas effect estimates from studies published in the 1990s revealed borderline heterogeneity. As for the 1990s, borderline heterogeneity may exist due to the nature of the decade categorization (this decade had the most studies when stratified), as well as in part due to the variation in disease inclusion over time.

While relatively few studies were conducted within each decade, our decade-specific meta-analyses revealed a clear pattern of increasing study quality (as measured by precision) and decreasing LHC risk with increasing decade from the 1980s to the 2010s. This pattern was observed across all studies combined and within studies of EO production or EO sterilization workers. For example, meta-RRs for LHC from all studies published in the 2000 and 2010s are about four times lower than the effect estimate reported by Hogstedt (1988). This observed trend over time could be due to improved disease diagnostic accuracy and/or improved study quality including larger study sizes and better adjustment for potential confounding factors and other study biases.

The results of our sensitivity analysis of LHC cancers confirmed our observation that the older studies, particularly those of Hogstedt (1988) and Swaen et al. (1996), are indeed inherently different from the more recent and updated evaluations of EO-exposed cohorts. In addition, our funnel plot evaluation of potential publication bias revealed that studies showing an absence of LHC risk among EO exposed populations may have been underrepresented in studies conducted in the 1980s and 1990s.

Thus, based on our meta-analyses by decade of publication, our sensitivity analysis of LHC cancers and our funnel plot evaluation of publication bias, the most accurate and meaningful information regarding breast cancer and LHC risks comes from studies published in the 2000s and 2010s. These more recent and more informative studies do not support the conclusion that exposure to EO during production or use in sterilization processes is associated with an increased risk of breast cancer or LHC.

Overall findings for breast cancer

With the exception of the large and informative NIOSH (Steenland et al. 2003, 2004) study and the methodologically problematic Swedish study (Mikoczy et al. 2011), none of the available studies found two-fold or greater elevated relative risks for breast cancer, although some studies reported risks greater than 1.0 but less than 2.0. However, similar to the LHC results, the NIOSH findings, which revealed no overall excess for breast cancer, were limited to the exposure–response analyses using the log-transformed EO exposure metric and were questioned by the authors due to their inconsistency across the other EO metrics considered and potential case over-ascertainment in the higher exposure categories. As discussed above, due to the questionable validity of the positive EO exposure–response of Mikoczy et al. (2011), these findings add little weight to the overall evidence for EO exposure and breast cancer.

Although based on a limited number of effect estimates ($n = 5$), our meta-analysis found no evidence of an elevated risk for breast cancer among workers exposed to EO during sterilization processes (meta-RR = 0.97; 95% CI 0.80–1.18) (no effect estimates were available for EO production workers). As noted with studies evaluating LHC risks, the largest effect estimate for breast cancer were observed in a relatively imprecise and uninformative study published in the 1990s (Norman et al. 1995).

Overall findings for other cancer endpoints

In addition to the findings presented for all LHC and breast cancer, we note that no statistically significant increased risks of cancer were observed for in either exposure group for NHL, leukaemia, or multiple myeloma. Furthermore, the presented meta-RRs for these cancer endpoints are overestimated. As shown in Table 2, several studies reported zero cases for these disease endpoints. To err on the side of

conservatism, we excluded such risk estimates from the presented meta-analysis. Had these risk estimates been included in the meta-analyses, the overall level of risk would have been further reduced for these endpoints.

Future directions

Future opportunities of exploring the association between occupational exposure to EO and risk of specific lymphoma subtypes might be afforded by pooled analyses of international lymphoma studies such as the International Lymphoma Epidemiology Consortium. Further evaluation of the association between EO exposure and breast cancer should consider the possible interactions between potential risk factors, including possible exposures early in life and during breast gland development, as well as the large diversity of breast cancer itself.

Conclusions

Based on our analysis, the most accurate and meaningful information regarding breast cancer and LHC risks in relation to EO exposure comes from epidemiology studies published in the 2000s and 2010s. These more recent and more informative studies do not support the conclusion that exposure to EO during production or use in sterilization processes is associated with an increased risk of LHC. Evaluations of workers exposed during sterilization processes do not support the conclusion that EO exposure is associated with an increased risk of breast cancer.

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Author contributions GMM developed the idea for the manuscript, assisted with the biostatistical approach to the analysis, and was responsible for the overall quality of work. KAK reviewed the literature and confirmed the inclusion and exclusion of various studies, drafted text, created figures, and assisted with conducting the analyses. ASR reviewed the literature and confirmed the inclusion and exclusion of various studies, drafted text, and assisted with conducting the analyses. EAB reviewed the literature and confirmed the inclusion and exclusion of various studies, drafted text, assisted with conducting the analyses, and created figures. SMB reviewed the literature and confirmed the inclusion and exclusion of various studies, drafted text, and created figures.

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Compliance with ethical standards

Conflict of interest The financial sponsor ACC was given the opportunity to review and comment on the draft manuscript, but the study design, the synthesis of findings, the conclusions drawn and the preparation of the manuscript are the exclusive professional work product of the authors, and may not necessarily be those of Cardno ChemRisk or ACC. GM performed part of this work as a private consultant and part as Consulting Senior Science Advisor for Epidemiology at Cardno ChemRisk. In addition to his role as a consultant, GM is Professor of Biostatistics and Director and Founder of the Center for Occupational Biostatistics and Epidemiology at the University of Pittsburgh, Graduate School of Public Health. For more than 42 years, GM has directed or co-directed epidemiological research on the potential carcinogenicity of numerous chemical agents. SB, KK, EB and AR are epidemiologists at Cardno ChemRisk with experience in environmental and occupational health research.

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