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Exposure Reconstruction and Risk Analysis for Six Semiconductor Workers With Lymphohematopoietic Cancers

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Objective: To investigate whether workplace exposures to recognized lymphohematopoietic carcinogens were possibly related to cancers in six semiconductor-manufacturing workers. **Methods:** A job-exposure matrix was developed for chemical and physical process agents and anticipated by-products. Potential cumulative occupational exposures of the six cases were reconstructed. The role of workplace exposures in cancer was evaluated through quantitative risk assessment and by comparison with epidemiological literature. **Results:** Two workers were potentially exposed to agents capable of causing their diagnosed cancers. Reconstructed exposures were similar to levels in outdoor environments and lower than exposures associated with increased risks in epidemiological studies. Cancer risks were estimated to be less than 1 in 10,000 persons. **Conclusions:** The development of cancer among the six workers was unlikely to be explained by occupational exposures to recognized lymphohematopoietic carcinogens.

Semiconductor manufacturing uses numerous chemicals in highly controlled manufacturing environments engineered to minimize airborne contaminants that adversely affect product quality.[1] Chemical and physical agents used include acids, solvents, and radiation, as well as gases that may have toxic effects. Concerns about the possibility of excess cancer risks among employees engaged in semiconductor manufacturing have been expressed for many years.[2–5] Several large industry-based epidemiological studies have reported inconsistently increased mortality or cancer incidence, including brain and central nervous system tumors,[6,7] prostate cancers,[6] lung cancers,[8] pancreatic cancer,[9] melanoma,[9] thyroid cancers,[10] leukemia,[11] and non-Hodgkin lymphoma (NHL).[10] Although many of these studies included large cohorts, their interpretation is limited by length of follow-up, small numbers of rare cancers, inconsistency of results by sex or geography, and lack of quantitative exposure measures for individual study subjects or similar exposure groups (SEGs).

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Clinical reports of lymphohematopoietic cancers among six workers at three semiconductor-manufacturing facilities operated by Samsung Electronics Co, Ltd (the company) in the Republic of Korea provided the impetus for this study.[12,13] At least five of the workers and/or their families filed for workers' compensation with the Korean Workers Compensation and Welfare Service. From 2007 to 2010, the Occupational Safety and Health Research Institute of the Korea Occupational Safety and Health Administration (KOSHA) investigated claims that occupational exposures caused the cancers of six workers.[13] Among the six workers, four discrete types of lymphohematopoietic cancers were reported. Four female workers between the ages of 20 and 36 years were diagnosed with acute myelocytic leukemia (AML), including two diagnosed with the M2 variant according to the French American British system for classification and two diagnosed with the M3 variant according to the French American British classification; one 29-year-old male worker was diagnosed with acute lymphocytic leukemia (ALL) pre–B cell type; and one 38-year-old male worker was diagnosed with diffuse large B-cell lymphoma (NHL).[13]

Although the total number of employees at the facilities of these six workers is unknown, these cancers are not unknown among young adults. During the period 1999 to 2010, NHL and AML were the second and fifth most common cancers diagnosed among adolescent and young adults aged 15 to 29 years in South Korea.[14] The age-standardized rate for 15- to 29-year-old Koreans was 17.1 per million for NHL, 11.0 per million for AML, and 3.9 per million for ALL.[14]

Epidemiological studies are often conducted in response to clinical observations of a specific type of cancer among employees in a workplace. Well-conducted epidemiological studies provide the best information regarding whether one or more workplace cancer hazards possibly exist, and identifies which specific cancer(s) shows increased risk, or whether random variation possibly explains the observed cancers. Moreover, an epidemiological study that analyzes relative risk in relation to exposure gradients can elucidate exposure–response patterns and identify exposure concentrations at which excess cancer occurrence is observed. Epidemiological studies, however, are costly, typically require years to complete, and may not yield useful information until after enough time has passed to allow for disease latency associated with chronic diseases. In the absence of epidemiological data on the study population at risk, methods and information that can be applied by occupational physicians and others to evaluate evidence that one or more individuals' diseases may be related to a common workplace exposure are needed.

In this work, we illustrate more practical approaches to assist occupational physicians and others (eg, workers' compensation boards) facing the challenges of making informed judgments as to whether one or more individuals' diagnosis is related to workplace exposure. Specifically, we evaluate evidence available to inform judgment about whether this group of six cancers—a case series—is plausibly related to exposures to recognized lymphohematopoietic carcinogens in several semiconductor worksites operated by one company. We define "recognized lymphohematopoietic carcinogen" as a chemical, biological, or physical agent that has been classified as a human carcinogen that targets the lymphohematopoietic system

by an authoritative agency such as the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), or the US Environmental Protection Agency (EPA). To support this effort, we used an exposure assessment performed in the same workplace[15] to develop a job-exposure matrix (JEM) containing qualitative and quantitative data, when available, about exposures to process agents and anticipated process by-products. With this JEM, the magnitude of the six workers' potential cumulative occupational exposure was reconstructed. Two approaches were used to evaluate whether each worker's cancer is related to workplace exposure. The first approach was to apply toxicity values to calculate the excess lifetime cancer risk associated with potential exposure to specific carcinogens. The toxicity values used included the inhalation unit risk (IUR) value derived for the US EPA Integrated Risk Information System and the lifetime attributable cancer risk associated with ionizing radiation from the Biological Effects of Ionizing Radiation (BEIR) model.[16] The IUR is a conservative value, based on upper bound excess risk, to include sensitive subpopulations. The second approach was to evaluate existing published epidemiological literature with respect to (1) the risk of similar cancers reported in the semiconductor industry elsewhere and (2) the magnitude of the workers' potential exposure relative to exposure levels for which excess cancer occurrence was reported in published epidemiological studies cited by consensus panels or government agencies in their evaluations of the carcinogenicity of specific agents. Agents to which these workers were potentially exposed have been identified previously,[13] but potential exposures to agents specifically associated with the diagnosed cancers and the resulting cancer risks have not been quantified.

METHODS

The Facilities

The specific facilities characterized were two semiconductor wafer fabrication lines (Lines A and D) located in Giheung and one wafer test and packaging facility (Line C) in Onyang. Lines A and D were built in 1990 and 1987, respectively, and used the same production technology to manufacture 200-mm wafers. Line D was closed in 2008, but Line A is currently in operation. Line C has been in continuous operation since 1991. Line A involved a 121,000 ft^2 area, with downdraft laminar flow and flow-through ventilation from fab to subfab areas; the facility uses an open bay and chase design, such that SEGs may overlap within process bays or maintenance chases. Line A includes Class 1 clean rooms. Line D was similar to Line A in size and had the same ventilation design. Line C was greater than 200,000 ft^2 with general supply ventilation and exhaust ventilation from tools: The facility uses an open ballroom configuration, such that SEGs are mostly separated by process area with some overlap where process areas are adjacent. Because the product in a wafer test and packaging facility is largely encapsulated, Line C included Class 1000 clean rooms. Additional information about the process activities is provided elsewhere.[17]

Identification of Agents Classified as Carcinogens

Process agents and anticipated by-products were identified by review of process chemistry, engineering documentation, monitoring data, and experience of the authors with these facilities and the semiconductor industry in general. We compared this list of chemicals with lists of agents classified as carcinogens by consensus panels or government agencies. Specifically, we identified agents that were classified as (1) Group 1, Group 2A, and Group 2B carcinogens by the IARC[18]; (2) "carcinogenic to humans" or "likely to be carcinogenic to humans" by the US EPA[19]; and/or (3) "Known to be a Human Carcinogen" or "Reasonably Anticipated to be a Human Carcinogen" by the NTP.[20] We restricted this list to those carcinogens reported in association with lymphohematopoietic malignancies.

Chemicals frequently associated with the specific lymphohematopoietic malignancies diagnosed in the cases and associated with the semiconductor industry include 1,3-butadiene, 1,2-dichloroethane, and benzene. Other chemicals classified by the IARC as Group 1 carcinogens and associated with lymphohematopoietic cancers, but not with the semiconductor industry specifically, included ethylene oxide and formaldehyde (Table 2). None of these agents were identified as process chemicals.

Exposure Monitoring Data

The company provided monitoring data for normal operations on Line A (2006 to 2010), Line C (2004 to 2010), and Line D (2001 to 2008), as well as for maintenance tasks on Line A (2007 to 2009). These data were supplemented by monitoring data newly collected by the authors in 2011 for normal operations and maintenance tasks on Lines A and C. The monitoring data are described in more detail by Torres et al.[15] Of the company monitoring data, 62.2%, 59.7%, and 48.0% of measurements were below limits of detection on Lines A, C, and D, respectively. Of the authors' monitoring data, 84.6% and 95.6% of measurements were below limits of detection on Lines A and C, respectively. For normal operations, we used shift duration or multishift (adjusted to an 8-hour time-weighted average [TWA]) exposure measurements in the exposure reconstruction. For maintenance operations, we separately considered task duration and shift-duration exposure measurements.

The sampling strategy for chemical agents employed by the company was not documented but was known to reflect normal operations. We considered it likely that the sampling strategy was designed for legal compliance with occupational exposure limits and/or routine ongoing monitoring. The authors identified combinations of agents and SEGs (Table 1) for monitoring on the basis of a number of factors, including limited monitoring by the company, and agents classified as causing lymphohematopoietic cancers, even when the agent was not used as a process chemical and was not anticipated to be a by-product.[15] Workers in SEGs of interest were randomly identified for personal breathing zone monitoring, and locations thought

TABLE 1. Similar Exposure Groups for Normal Operations Operators and Maintenance Workers, Separately

Line C	Lines D and A
Assembly—Backlap	Chemical–Mechanical Planarization
Assembly—Die Attach	Chemical Vapor Deposition
Assembly—Plasma	Clean*
Assembly—Sawing	Diffusion
Assembly—Wire Bonding	Etch
Chemical Support	Implantation
Laboratory	Photo†
Packaging—Marking	Thin-Films Metal
Packaging—Molding	
Packaging—Solder Ball Attach/Stack	
Packaging—Tin Plating	
Packaging—Trim Sort Form	
Test—Marking Visual Packing	
Test—Monitor Burn-in Testing	
Test—Testing	

*Also termed Wet Etch.
†Also termed Photolithography.

TABLE 2. Agents Linked With Lymphohematopoietic Cancers and Their Presence in the Workplace

Agent	Classification*			Cancer	Inhalation Unit Risk per $\mu g/m^3$	Agent Use in Workplace		
	IARC[18]	EPA[19]	NTP[20]			Process Agent	Process Byproduct	Quantified in Work Environment†
Ionizing radiation (x- and γ-radiation)	1		Known	Leukemia		Yes	Yes	Yes
Benzene	1	Carcinogenic	Known	Leukemia and others		No	No	No
1,3-Butadiene	1	Carcinogenic	Known	Leukemia and others		No	No	No
1,2-dichloroethane	2B	Likely carcinogenic	Reasonably anticipated	Lymphoma		No	Yes	No
Ethylene oxide	1			Lymphoma		No	No	No
Formaldehyde	1		Known	Leukemia	4.6×10^{-6} (33)	No	No	Yes§
Trichloroethylene	1	Carcinogenic	Reasonably anticipated	Lymphoma	2×10^{-6} (31)‡	Yes‖	No	No¶

*EPA classifications include carcinogenic to humans (carcinogenic) and likely to be carcinogenic to humans (likely carcinogenic). NTP classifications include known to be a human carcinogen (known) and reasonably anticipated to be a human carcinogen (reasonably anticipated).

†Agent was measured above the limits of detection by the company and/or authors.

‡This inhalation unit risk is only for lymphoma, not kidney cancers, liver cancers, and lymphoma combined.

§The 75th percentile of formaldehyde concentrations in the Line C Tin Plating SEG was estimated to be 0.0053 ppm, compared with the OSHA PEL of 0.75 ppm and ACGIH TLV of 0.3 ppm.

‖Use of trichloroethylene was discontinued in 1995.

¶All monitoring by the authors found the concentration of TCE to be below the limit of detection.

EPA, Environmental Protection Agency; IARC, International Agency for Research on Cancer; NTP, National Toxicology Program; TCE, trichloroethylene.

to represent exposure levels in a work area were selected for fixed area location monitoring.

For agents classified as causing lymphohematopoietic cancers (Table 2), only ionizing radiation and trichloroethylene were known to be used in current or historical processes at these facilities. In addition, plasma-etching processes may have produced 1,2-dichloroethane as a by-product at these facilities; 1,2-dichloroethane had been previously monitored for at the facilities but was not quantified (limit of detection: 0.002 ppm as 8-hour TWA).

Benzene was not identified as a process chemical at these facilities. Benzene has been detected in 5 of 40 samples at low concentrations (less than 0.3 ppb or 0.96 $\mu g/m^3$) in four photolithography processes at three semiconductor-manufacturing facilities elsewhere in Korea, and the airborne concentrations measured inside those fabrication facilities were not different from those measured in the outdoor environment.[21] Benzene has not been detected in other investigations, including in wafer-fabrication facilities.[13,22] Monitoring for benzene at the facilities by the authors did not identify detectable concentrations (limits of detection: 0.006 to 0.008 ppm for 8-hour TWA, and 0.01 to 0.09 ppm for task-based samples).

Previous experience and data from these facilities did not identify 1,3-butadiene as a known or anticipated airborne by-product in semiconductor manufacturing, and monitoring at the facilities by the authors did not identify detectable concentrations (limits of detection: 0.04 to 0.05 ppm as 8-hour TWA).

Monitoring for ethylene oxide and formaldehyde was performed by the authors because of the chemicals' possible link to lymphoma and leukemia, respectively, and not because they were used as a process agent or anticipated to be a by-product.[15] Ethylene oxide was not identified in detectable concentrations (limits of detection: 0.001 to 0.12 ppm as 8-hour TWA). Formaldehyde was detected in low concentrations. The process sources of formaldehyde exposure were not identified, although formaldehyde is ubiquitous in the environment.

For physical agents, the authors measured ionizing and nonionizing radiation levels throughout Lines A and C, using a Victoreen 190 survey and count rate meter with a Victoreen 489-110D Geiger-Mueller probe; a Holaday HI-4416 Broadband RF meter with an HI-4433-HCH magnetic field probe measuring frequencies ranging from 5 to 300 mHz and an HI-4433-MSE electric field probe measuring frequencies from 500 kHz to 500 GHz; and a Dexsil Field Start FS100 meter measuring extremely low frequency magnetic fields from 55 to 65 Hz.

Exposure Modeling

One of the six employees diagnosed with lymphohematopoietic cancer routinely walked through the area in which trichloroethylene-wetted swabs were used by another worker. Tichloroethylene (TCE) use was discontinued in 1995. No monitoring data were available for tasks in which trichloroethylene-wetted swabs were used for cleaning. Instead, we used a two-zone model[23] to estimate by-stander exposures. The work area volume was 1281 m^3, and we considered only the fresh air component of the ventilation, which provided approximately 13.5 air changes of fresh air per hour. The task was described as involving a closed 200-mL container of TCE, and performing 100 to 200 cleaning tasks using a TCE-wetted swab per day. It was not clear that the total container volume was used daily. One milliliter TCE was considered used per 30-second cleaning task, with complete evaporation, giving an emission rate of 2940 mg TCE per minute. The task was considered to occur for 50, 75, or 100 minutes per 8-hour day corresponding to 100, 150, and 200 cleaning tasks per day, respectively. These conditions were used to estimate the 8-hour TWA TCE concentration in the far-field. By-stander exposure was considered to occur for 15, 30, or 45 minutes per 8-hour day, where exposure during 15 to 45 minutes was equal to the 8-hour TWA in the far field and considered zero otherwise. Given TCE use for 50 minutes, by-stander exposure for 15 minutes was estimated to result in TCE exposure of 0.033 mg/m^3 as an 8-hour TWA. Given TCE use for 100 minutes,

by-stander exposure for 30 and 45 minutes was estimated to result in TCE exposures of 0.13 mg/m^3 and 0.20 mg/m^3 as an 8-hour TWA. Statistical uncertainty analyses were not performed, but model assumptions considered a range of plausible values and risk analyses considered longer TCE use durations and by-stander exposure to reduce the risk of underestimating exposure. The two-zone model has been shown to effectively represent airborne concentrations proximal and remote to a point source.[24,25]

Job-Exposure Matrix

Through review of engineering documents, process operations documents, and material safety data sheets, we identified agents used as process chemicals or anticipated as process by-products in each SEG. The SEGs were organized around processes common to the semiconductor industry (Table 1) and were defined separately for the exclusive populations of operators and maintenance workers. By using processes to define SEGs, multiple SEGs included the same physical space because tools for different processes were interspersed. All combinations of agents and SEGs were used to define a JEM.

The primary work activity of operators during normal operations was to move wafers, contained in closed lot-boxes, between tools. At the facilities studied, tools were fully enclosed with integrated ventilation systems. The time activity pattern of the operators varied from day to day and was not captured for specific workers. Nevertheless, little systematic variation in exposure potential between workers in a process area was expected because frequency of use of a particular tool and performance of a particular task were more dependent on production requirements than individual employee methods.

Exposure monitoring and modeling data were tabulated and incorporated into the JEM. To increase the number of samples in chemical agent exposure monitoring data, we pooled some types of data. Data collected in the personal breathing zones of workers and data collected at fixed area locations were pooled because review of the monitoring data did not suggest substantive differences, which is expected from the use of fully enclosed ventilated tools. Data from Lines A and D were pooled because review of the monitoring data did not suggest substantive differences, which is expected because these lines use the same manufacturing processes to manufacture the same product. After pooling, the data were characterized by lognormal distributions. The geometric mean and geometric standard deviation were calculated using the maximum likelihood method in IH Data Analyst software version 1.25 (Exposure Assessment Solutions, Inc, Morgantown, WV). When possible, the maximum likelihood method was used to address monitoring results below limits of detection. Otherwise, one-half the detection limit was substituted. Subsequently, we tabulated the 75th percentile of the lognormal distribution. The magnitude of potential exposure to physical agents at each Line was reported as the range of measurements, in millisieverts per hour.

To evaluate changes in potential exposures over time (from the 1990s to the 2000s), we assessed changes to tools, processes, and work activities that may have impacted exposure potential at the facilities under study over time.[26] We reviewed engineering, maintenance, and operations documents and interviewed company employees to identify process operations and work tasks that influence exposure potential, and changes to those operations and work tasks but we found little support for concluding that exposures have changed during these periods.[15] The primary difference between Lines A and D was that manual dipping of wafers into chemical baths was performed in the Clean SEG on Line D, but not on Line A. In addition, we explored the company's monitoring data and the authors' monitoring data for temporal patterns; evidence of temporal trends was not observed.[15] Overall, on the basis of these analyses, we consider it reasonable to use data collected during the 2000s to estimate potential exposures that occurred during the 1990s at these lines.

Exposure Reconstruction

Work histories of the six workers were described in case investigations conducted by KOSHA.[13] KOSHA developed these reports from work histories provided by the company and interviews with the workers, their families, and/or coworkers. We linked the work activities and process areas described in the work histories with SEGs in the JEM. The cumulative potential exposures of each worker to each chemical agent associated with their diagnosed cancer in the linked SEGs were calculated in units of mg/m^3-years on the basis of the product of the 75th percentile of the probability distribution (log-normal) of TWA chemical concentrations and the total hours of work in the particular SEG. The 75th percentile was chosen as a more conservative value than the median; we also calculated potential exposures based on the 95th percentile of the exposure distribution. Overtime work hours described in the KOSHA reports were included. For ionizing radiation, the potential dose (mSv) was calculated separately for each calendar year.

Calculation of Excess Lifetime Cancer Risk

When available, we used the US EPA IUR values for agents associated with the specific lymphohematopoietic cancer to calculate the additional cancer risk associated with the potential exposure over a lifetime. Specifically, we converted potential cumulative occupational exposure to estimate an equivalent environmental exposure over a lifetime (70 years), assuming the inhalation of 10 m^3 and 20 m^3 of air in an 8-hour work day and 24-hour day, respectively.[27] In the case of ionizing radiation, we used generally accepted methods from BEIR VII 2006 to calculate lifetime attributable risk of leukemia.[16]

Quantitative Exposure Data in Epidemiological Studies

Quantitative exposure data for specific chemicals have not been reported previously in large epidemiological studies of cancers in the semiconductor industry. Exposure assessment has been limited to job classifications[6,8,28] or dichotomous (ever or never) chemical exposure classifications.[7] In the absence of quantified estimates of exposure–risk relationships from the semiconductor industry, we reviewed the most recent IARC and/or US EPA monograph for each chemical agent to identify the epidemiological studies that the working groups relied upon to inform the classification of the agent as a possible, probable, or human carcinogen. Information about the characteristics of the study population, quantitative exposure metrics, and lymphohematopoietic cancer risks was extracted from the individual epidemiological studies (Supplemental Digital Content Tables S.I and S.II, available at: http://links.lww.com/JOM/A194). We used this information to make qualitative comparisons between exposure concentrations at which excess cancer risks were observed in the epidemiological studies and the reconstructed potential exposures for the six employees.

RESULTS

We reviewed 259 agents used as process chemicals, anticipated to be by-products, or detected by exposure monitoring and identified seven agents classified by consensus panels or government agencies as carcinogens on the basis of increased risk of lymphohematopoietic cancers in humans or causing lymphohematopoietic cancer in animals (Table 2).

Subsequently, ionizing radiation, TCE, and formaldehyde were considered relevant for risk assessment because they were known to be used as a process agent or process byproduct (ionizing radiation and TCE) or because they were measured in exposure monitoring despite lack of use as a process agent or process

by-product (formaldehyde) in the process areas where the six employees worked.

Ionizing radiation has been causally associated with all types of leukemia except chronic lymphocytic leukemia and NHL.[20,29] Sources of ionizing radiation in the facilities included the ion implantation process during wafer fabrication and chip testing equipment during testing and packaging. The source of ionizing radiation in ion implantation is bremsstrahlung x-rays (ie, braking radiation) generated as a by-product of equipment operation. This radiation decreases rapidly with distance from the source and is readily controlled by interlocked equipment shielding.

Formaldehyde has been classified by the IARC and NTP as leukemogenic (myeloid types, especially AML).[20,30] Although formaldehyde has not been used as a process chemical and is not an expected process by-product in these lines, it was quantified by the authors in 1 of 10 samples collected in the Tin Plating SEG (Line C) at concentrations similar to levels in ambient air. Substituting one-half the limit of detection for left-censored results, the 8-hour time-weighted average concentration of formaldehyde was described by a log-normal distribution with geometric mean 0.0058 mg/m^3 and geometric standard deviation of 1.19. The 75th percentile of the distribution is 0.0065 mg/m^3 (0.0053 ppm). The 95th percentile of the distribution is 0.0077 mg/m^3 (0.0094 ppm).

TCE has been classified by the IARC and the US EPA as a known carcinogen based in part on epidemiological evidence for increased risk of NHL.[31,32] The TCE was used until April 1995.

The JEM for process agents and anticipated process by-products in the SEGs relevant to the six workers, and specifically associated with the diagnosed cancers, is presented in Table 3. Monitoring data were not available for all agents in the SEGs of interest.

The job histories of the six workers are summarized in Table 4. Details on the clinical course and job histories for the six workers are described elsewhere.[13] Cases 4 and 6 were determined to be potentially exposed to agents classified as carcinogens specifically linked with their diagnosed cancers (Table 4). For Case 4, who was diagnosed with AML, we estimated cumulative potential exposure to formaldehyde to be 0.0047 mg/m^3-years (0.0038 ppm-years) and a cumulative potential dose of ionizing radiation of 0.14 mSv. Based on the 95th percentile of distribution of formaldehyde concentrations, the cumulative exposure of Case 4 was estimated to be 0.0056 mg/m^3-years (0.0069 ppm-years). For Case 6, who was diagnosed with NHL, using the two-zone model, we estimated cumulative potential exposure to TCE to be 0.405 mg/m^3-years (0.076 ppm-years) on the basis of an 8-hour TWA exposure of 0.13 mg/m^3. Considering an 8-hour TWA exposure to TCE of 0.20 mg/m^3, we estimated the cumulative potential exposure of Case 6 to TCE to 0.622 mg/m^3-years (0.116 ppm-years). Cases 1, 2, 3, and 5 were determined not to have been potentially exposed to carcinogens linked with their diagnosed cancer; none worked in or adjacent to ion implantation, nor did their work activities involve processes in which chemical agents linked with their diagnosed cancers were used, anticipated as by-products, or quantified in exposure monitoring.

Excess lifetime cancer risk posed by potential occupational exposures to chemical agents was calculated for Cases 4 and 6. The cumulative potential occupational exposures (Table 4) are equivalent to environmental lifetime exposures of 0.02 μg/m^3 (1.6×10^{-5} ppm) formaldehyde for Case 4 and 19.6 μg/m^3 (0.0036 ppm) TCE for Case 6. Given an IUR value for leukemia associated with formaldehyde exposure equal to 4.6×10^{-6} per μg/m^3,[33] the excess risk of the AML due to potential occupational formaldehyde exposure for Case 4 is less than 1×10^{-6}. This is still the case when the potential formaldehyde was equated with the 95th percentile of the exposure distribution. Given an IUR value for lymphoma (not kidney cancers, liver cancers, and lymphoma combined) associated with TCE exposure equal to 2×10^{-6} per μg/m^3,[31] the excess risk of NHL due to potential occupational TCE exposure for Case 6 is approximately 8×10^{-5}. Considering the potential 8-hour TWA exposure of Case 6 to TCE be 0.20 mg/m^3 instead of 0.13 mg/m^3, the excess risk of NHL is approximately 1×10^{-4}. As a comparison, these values are in the range of excess cancer risks (10^{-6} to 10^{-4}) considered acceptable by the US EPA for the general population living near contaminated sites.

TABLE 3. Job-Exposure Matrix, With Monitoring Data When Available, for Process Agents or Anticipated Byproducts Identified as Carcinogens Specifically Associated With the Diagnosed Diseases of Workers and Anticipated to Be Present in the Workers' Similar Exposure Groups

Line	Similar Exposure Group	Agent*	Operation	Authors' Data		
				GM, mg/m^3	GSD	Range, mSv/h
C	SBA	Trichloroethylene	Normal			
C	Marking	Trichloroethylene	Normal			
C	Molding	Trichloroethylene	Normal			
C	Tin plating	Trichloroethylene†	Normal	0.0214	1.58	
C	TSF	Trichloroethylene	Normal			
C	Tin plating	Trichloroethylene	Maintenance Task‡	0.537	1.0	
C	All process areas	Ionizing radiation	Normal			1.6×10^{-5} to 2.8×10^{-4}
C	QE inspection room§	Ionizing radiation	Normal			7.0×10^{-5} to 1.0×10^{-4}
A	All process areas	Ionizing radiation	Normal			2.0×10^{-7} to 2.58×10^{-4}

*Trichloroethylene use was discontinued in April 1995. No agents were identified for Line D. No monitoring data were provided by the company for these agents.

†All measurements are below the LOD, such that the GM and GSD are calculated using one-half the LOD for all results. For exposure reconstruction, modeled values were used rather than the concentrations measured by the authors.

‡Maintenance task of adding coating solution. Exposures estimates are based on task-duration monitoring.

§This room is reported separately as a case worked in this room performing a task that involved x-rays.

GM, geometric mean; GSD, geometric standard deviation; LOD, limit of detection; QE, quality engineering; SBA, Solder Ball Attach; TSF, Trim Sort Form.

TABLE 4. Reconstruction of Workers' Potential Exposures to Agents Specifically Associated With the Diagnosed Cancers Based on Work History*

		Duration			Potential Exposure Level§	
SEG	**Line**	**Calendar Years**	**Work Years†**	**Agent‡**	**8h TWA**	**Cumulative**
Case 1 (operator), diagnosed with AML						
Diffusion	D	1.19	1.43	None	–	–
Administrative‖	D	0.22	0.26	None	–	–
Clean	D	0.22	0.27	None	–	–
Case 2 (operator), diagnosed with AML						
Thin-films metal	D	6.45	7.75	None	–	–
CVD	D	3.00	3.60	None	–	–
Administrative‖	D	0.75	0.89	None	–	–
Clean	D	0.52	0.64	None	–	–
Diffusion	D	0.58	0.69	None	–	–
Case 3 (maintenance), diagnosed with ALL						
CMP	A	5.19	6.23	None	–	–
Backlap	C	2.67	3.20	None	–	–
Case 4 (operator), diagnosed with ALL						
Multiple¶	C	2.87	4.34¶	None	–	–
Marking	C	–	0.73	None	–	–
SBA	C	–	0.73	None	–	–
TSF	C	–	0.73	None	–	–
MVP	C	–	0.73	None	–	–
Tin plating	C	–	0.73	Formaldehyde	0.0065 mg/m^3	0.0047 mg/m^3-y
QE inspection	C		0.70	Ionizing Radiation	0.0001 mSv/h	0.14 mSv
X-ray task					0.0056 mSv/y	
Case 5 (operator), diagnosed with AML						
Marking	C	5.04	10.16	None	–	–
Case 6 (maintenance), diagnosed with NHL						
Tin plating	C	5.67	9.14#	None	–	–
By-stander	C	1.93**	3.11**	Trichloroethylene	0.13 mg/m^3	0.405 mg/m^3-y

*Job title has been given parenthetically.
†Equivalent to 2000 hrs/yr.
‡Agent identified as specifically associated the worker's specific cancer type.
§The 75th percentile calculated from the distribution in the job exposure matrix.
‖Administrative tasks occurred in offices, and employees were assumed not to enter the production or testing work area unless specified otherwise in the work histories obtained by KOSHA.
¶Individual worked in multiple process areas. Duration of time performing QE Inspection X-ray task specified in KOSHA work histories as 5.8 eight-hour days per month for 30 months. The remainder of work time divided among other SEGs.
#Reflects time spent in office.
**Trichloroethylene use discontinued in April 1995, during the employment of Case 6, and reflects time spent passing through process areas where trichloroethylene was used.
ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia; CMP, chemical–mechanical planarization; CVD, chemical vapor deposition; MVP, marking visual packing; NHL, non-Hodgkin lymphoma; SBA, solder ball attach; SEG, similar exposure group; TSF, Trim Sort Form; TWA, time-weighted average.

Ionizing radiation was measured in the areas in which Case 4 worked to be 0.0001 mSv/h (Table 2), for a potential dose of 0.056 mSv/yr (Table 4). According to the BEIR VII preferred model,[16] the lifetime attributable risk of incident leukemia (any kind except chronic lymphocytic leukemia, which is not associated with ionizing radiation) is 20 cases per 10 mSV for women aged 18 to 65 years, the demographic group of Case 4. Based on a maximum biological dose of 0.056 mSv/yr, and exposure occurring for 3 years between the ages of 18 and 20 years, the excess risk of leukemia experienced by Case 4 is 1.2×10^{-6}.

Few of the epidemiological studies reviewed by the IARC in the classification of formaldehyde as capable of causing leukemia employed quantitative exposure assessments (Supplemental Digital Content Table S.I, available at: http://links.lww.com/JOM/A194).[30] The reconstructed cumulative potential exposure of Case 4, 0.0047 mg/m^3-years (0.0038 ppm-years), would place Case 4 in the referent category (greater than 0 to less than 1.5 ppm-years) of the largest study of workers exposed to formaldehyde in industrial facilities, conducted by Beane Freeman et al.[34] In this study,[34] cumulative exposure was not found to be associated with excess risk of death from myeloid leukemia, where workers in the highest exposure category, 5.5 ppm-years or more, had RR = 1.02 (95% CI: 0.48 to 2.16). Among professionals in the funeral industry, Hauptmann et al[35] found the odds of mortality from myeloid leukemia to be statistically significantly increased among workers with an average-intensity (8-hour TWA) exposure more than 0.10 ppm, cumulative exposure more than 9253 ppm-hours (more than 4.6 ppm-years given 2000 hrs/yr), or with increased peak (15 minutes) exposures, relative to workers never exposed to formaldehyde. Exposure monitoring in Line C by the authors indicate the median (and mean) formaldehyde concentration to be 0.0058 ppm (0.0059 ppm), which falls near the lower cutpoint of the more than 0 to 0.10 ppm (8-hour TWA) category

for which a nonstatistically significant increased risk was observed (odds ratio [OR] = 8.1, 95% CI: 0.8 to 79.3); however, no trend was found with 8-hour TWA in this study by Hauptmann et al.[35] Although Coggon et al[36] did not explore the exposure–response relationship between formaldehyde and leukemia, the TWA concentrations measured at Line C would place Case 4 in the background exposure category, for which estimated TWA concentrations were less than 0.1 ppm. Other cohort studies cited by the IARC with quantitative exposure data did not observe elevated rates of leukemia mortality. These included garment workers exposed to log-normally distributed formaldehyde concentrations with geometric mean 0.15 ppm (geometric standard deviation 1.90 ppm)[37,38]; men who worked in an automotive iron foundry, 1.5 ppm, 0.55 ppm, and 0.05 ppm for high-, medium-, and low-exposure categories, respectively[39]; and workers in leather tanneries exposed to 8-hour TWA formaldehyde concentrations of 0.5 to 7 ppm, with mean 2.45 ppm.[40] Elevated leukemia mortality in another study was based on few deaths (2 or fewer): men manufacturing abrasive materials with moderate formaldehyde exposures of 0.1 to 1 mg/m^3 (0.08 to 0.83 ppm) or intermittent, heavy exposure up to 20 to 30 mg/m^3 (17 to 25 ppm).[41]

Trichloroethylene has been recently classified by the IARC as a Group 1 carcinogen: Although the causal association between TCE exposure and kidney cancers is strong, epidemiological evidence for association between TCE exposure and NHL or liver cancer is more limited, with weak exposure–response relationships observed for NHL.[32] As with formaldehyde, few epidemiological studies of TCE exposure and NHL reviewed by the US EPA and/or the IARC employed quantitative exposure assessment (Supplemental Digital Content Table S.II, available at: http://links.lww.com/JOM/A194, summarizes the studies reviewed).[31,32] Several studies evaluated by the US EPA included semiquantitative exposure ratings that yielded exposure measurements in ppm-hours in the analysis by the authors and/or the US EPA.[31,42–44] Purdue et al[44] found statistically significantly elevated odds NHL among workers with average weekly occupational exposures to TCE more than 150 ppm-hours per week, relative to workers with no exposure (OR = 2.5, 95% CI: 1.1 to 6.1), and among workers with cumulative exposure more than 234,000 ppm-hours (more than 117 ppm-years for 2000 hrs/yr) relative to workers with no exposure (OR = 3.3, 95% CI: 1.1 to 10.1). The cumulative potential exposure of Case 6 to TCE was 0.405 mg/m^3-years (0.076 ppm-years), which would place Case 6 in the nonreferent group with the lowest exposures, which was not associated with statistically significantly increased odds of NHL.[44] The other studies did not show statistically significantly elevated rates of NHL, among workers with EPA-calculated TCE exposures 17 or more ppm-years[31,42] and more than 25 ppm-years.[31,43] In a population-based case–control study, Seidler et al[45] found the odds of B-cell NHL approached statistically significant elevation among patients with TCE exposure more than 35 ppm-years (adjusted odds ratio [OR_{ADJ}] = 2.3, 95% CI: 1.0 to 5.3) relative to unexposed participants. Again Case 6 would fall into the lowest exposure category of this study (more than 0 to 4.4 or less ppm-years), which was not associated with increased odds of B-cell NHL (OR_{ADJ} = 0.7, 95% CI: 0.5 to 1.2) relative to unexposed participants.[45] Although the cohort studied by Anttila et al[46] experienced significantly elevated incidence of NHL overall (standardized incidence ratio [SIR] = 2.13, 95% CI: 1.06 to 3.80), small, nonsignificant increases in NHL incidence were observed among all workers exposed to TCE (SIR = 1.81, 95% CI: 0.78 to 3.56), and among workers with mean urinary-TCE levels 100 μmol/L or more (SIR = 1.40, 95% CI: 0.17 to 5.04). The US EPA[31] estimates that 100 μmol/L TCE in urine equals a mean air TCE concentration of 6 ppm. Similarly, Axelson et al[47] observed a nonstatistically significant elevated incidence of NHL among Swedish workers (SIR = 1.56, 95% CI: 0.51 to 3.64): In this population, 81% of workers had urinary TCE levels less than 50 mg/L (equal to 20 ppm in air). In contrast, a sixfold increased incidence was observed among workers with more than 2-year exposure to TCE and urinary TCE levels more than 100 mg/L (SIR = 6.25, 95% CI: 0.16 to 34.83).

DISCUSSION

Although numerous chemical and physical agents are used in the manufacturing and packaging of semiconductor wafers, relatively few of the agents used by the company in the production lines studied have been classified as carcinogens, and even fewer have been associated with lymphohematopoietic cancers in humans or animals. In a comprehensive exposure analysis at these production lines that employed structured qualitative risk analysis, exposure monitoring, and Bayesian Decision Analysis, Torres et al[15] found worker exposures to chemical agents to be consistent with an environment in which exposures are well-controlled (ie, in relation to OELs). Estimated potential exposures to carcinogens associated with the diagnosed cancers are low (Tables 3 and 4). The 75th and 95th percentile of the TWA concentrations of formaldehyde at the facility, 0.0065 mg/m^3, is within the range reported in outdoor air in the United States, 0.0007 to 0.045 mg/m^3.[29] The modeled TCE exposure estimate was 0.13 mg/m^3 (130 μg/m^3) as an 8-hour TWA for Case 6, who was a bystander to TCE use. Nationwide outdoor air quality monitoring of TCE by the US EPA from 1999 to 2006 observed a maximum concentration of 18.4 μg/m^3 TCE,[31] indicating that the potential occupational exposure of Case 6 was an order of magnitude greater than maximum outdoor TCE concentrations reported in the United States. The potential annual dose of ionizing radiation to Case 4, 0.14 mSv, is less than average annual exposures, worldwide, to natural radiation sources, which are between 1 and 10 mSv.[16]

The exposure reconstruction is based on monitoring data collected between 2001 and 2011. Exposure data before 2001 do not exist and represent a limitation in our analysis for workers employed prior to 2001 if processes and exposures changed over time. We reviewed production and engineering records and did not identify changes in production processes that were likely to substantially impact potential exposures and health risk.[15] This is consistent with the generational nature of manufacturing processes in the semiconductor industry,[26] in which production processes are maintained for the life of a particular generation of a product.

Cumulative potential exposure of the workers was calculated using shift-duration TWA inhalation exposure (Table 4). The shift-duration TWA exposure integrates short-term fluctuations in exposure to estimate the cumulative exposure. Cumulative exposure is the product of exposure intensity and duration and is generally held to be proportional to target organ dose and, therefore, proportional to risk.[48] Cumulative exposure is the standard approach for assessing risk of chronic disease, including cancers, and guidelines for carcinogenicity risk assessment suggest alternative summary measures (eg, short-term peak exposures) when existing data indicate that the alternative is more appropriate.[49] For the agents of interest in this study, epidemiological studies referenced by IARC and the US EPA in their classification of chemicals as human lymphohematopoietic carcinogens commonly identified workplace cumulative exposure as the summary measure of interest. Other summary measures (peak exposure or average exposure) were less commonly used in the epidemiology studies.

The choice of exposure metric in epidemiological studies can influence the outcome, and interpretation is complicated by exposure uncertainty. Consider the US EPA's draft IUR value for formaldehyde, which was based on cumulative exposure reported in an epidemiological study of lymphohematopoietic cancers among formaldehyde users and producers.[34] In this study, lymphohematopoietic cancers were most significantly associated with peak exposure, but this exposure measure was highly uncertain because of the absence of actual monitoring data of short-term peak exposures.

In contrast, risk of leukemias did not show trends with increasing average exposure or increasing cumulative exposure, summary measures for which uncertainty was lowest. In the face of conflicting results and uncertainty, causal mechanisms can provide insight. In the case of formaldehyde, the National Research Council recommended application of a causal framework to support the determination of causality for specific lymphohematopoietic cancers and further evaluation of dose–response models for specific cancers.[50]

Dermal exposure was assessed as part of a structured qualitative risk assessment and was not anticipated on the basis of full equipment enclosure in semiconductor tools and processes and use of gloves by workers.[15] In addition, an evaluation of manufacturing eras and associated characteristics reported few manual tasks involving direct material handling.[17] Gloves were worn as part of personal protective equipment throughout the 1990s and 2000s. Organic solvents, however, can break down some glove materials and penetrate the skin. For the specific workers whose risk was evaluated in this study, Case 6 was exposed to TCE as a by-stander and did not handle the chemical directly; no other workers were identified as having potential exposure to carcinogens recognized as capable of causing their diagnosed cancers. Thus, a dermal route was not further considered.

In general, a JEM based on SEGs seeks to represent the distribution of exposures to specific agents in the workplace. The representative nature of the distribution, however, depends upon the exposure monitoring strategy. The basis of the sampling strategy used by the company may have been designed to evaluate compliance with regulations, which tends to oversample workers potentially exposed to the highest concentrations of contaminants. The sampling strategy employed, however, was not recorded, although sampling involved normal operating conditions. Monitoring conducted by the authors randomly identified workers in SEGs of interest and placed samplers at fixed area locations expected to be representative of a work within- and between-variability in worker exposures. Nevertheless, given that work activities during normal operations are governed by production requirements, and the primary task of operators is to move closed boxes of wafers between tools, substantial exposure variability between operators would not be anticipated. Greater variability can be expected for maintenance workers owing to the greater variability in their work activities.

We applied a regulatory risk evaluation to determine whether occupational chemical exposures experienced by the six workers could plausibly be related to their specific lymphohematopoietic cancers; the two workers identified to have potential exposure to chemical agents capable of causing their cancer were determined to have their risk of cancer increased 8×10^{-5} (risk of NHL from TCE exposures for Case 6) and 1×10^{-6} (risk of AML from formaldehyde exposure for Case 4) above their background risk. Similarly, applying the BEIR VII preferred model, the ionizing radiation exposure to Case 4 was estimated to contribute 1.2×10^{-6} excess risk for leukemia diagnosis.

Such regulatory risk evaluations are necessarily limited to agents known to cause cancer in humans or animals under certain conditions of exposure. In this semiconductor workplace, these agent–disease relationships were ionizing radiation and lymphohematopoietic cancers; formaldehyde and myeloid leukemias; and TCE and NHL. In this type of risk assessment, the cumulative occupational exposure to an agent is equated with the concentration of the agent in ambient air that, over a lifetime of exposure, would yield the same cumulative exposure received in the workplace, and an IUR applied to estimate excess cancer risk attributed to this exposure.

Many limitations are associated with this risk assessment approach. Agencies that regulate chemical exposures often do so with the purpose of setting protective public health standards, with the implications that standards are developed even when scientific evidence for a chemical causing cancer in humans is weak, and that standards are designed to incorporate wide safety margins to protect the most susceptible members of a population.[51] As a result, IUR values, such as that developed for leukemia associated with formaldehyde exposure, can be controversial.[52,53] Furthermore, this risk assessment approach produces an incremental cancer risk over background (ie, 1-in-10^4 to 1-in-10^6) that is largely hypothetical; this type of incremental cancer risk is not detected using epidemiological data and statistics that compare relative risks of specific cancers between groups that differ according to exposure status and/or magnitude of exposure. In addition, these risk computations are intended to characterize risks from environmental exposures among populations living near contaminated sites or pollution sources, where populations experience daily continuous exposure over a lifetime, rather than to characterize risks from occupational exposures, where populations experience intermittent exposure over a period of years.

An important consideration—in addition to dose—when assessing the relationship between a chemical or physical agent and disease occurrence is latency, or the time elapsed between a dose sufficient to cause the disease and the manifestation of the disease. The risk assessment approach does not specifically address latency. The duration of employment prior to diagnosis among these six cases ranged from 1.25 to 15.4 years.[13] The cases were aged 19 to 38 years at the time of diagnosis.[13] Monitoring data were available from the 2000s and were not available at the time the cases with the longest latencies were first employed. Among patients who developed AML secondary to chemotherapy, the latency interval is typically reported to be 2 to 10 years since exposure.[54] This latency period seems to be similar for benzene-induced leukemia[54] with the caveat that few benzene-exposed cohorts identify many AML cases. Cases in these cohorts were diagnosed among workers employed to high concentrations of benzene in the early years of industry before industrial hygiene controls were implemented (eg, rubber worker studies by Rinsky et al[55,56]) and before morphological criteria were agreed by consensus and modern diagnostic methods were developed for classifying specific leukemia types.

Epidemiological studies are preferred over a regulatory risk assessment approach to assess the risk of lymphohematopoietic cancers associated with workplace exposures, although rarely do epidemiological studies characterize cancer risks according to varying, but extremely low, workplace exposures such as those reported in this workplace.[15] Such epidemiological studies are costly and time intensive to enumerate an occupational cohort, especially when designed to calculate quantitative individual exposure estimates. Lymphohematopoietic cancers represent a heterogeneous group of diseases with different etiologies. In general, these cancers are rare, so evaluation of specific lymphohematopoietic cancer associations with chemical-specific exposure gradients requires relatively large numbers of observed and expected cancers. Considering all lymphohematopoietic cancers, an epidemiological study of cancer incidence using a SIR analysis of an occupational cohort would produce a statistically significant SIR of 2.72 (95% CI: 1.01 to 6.0) if six cancers are observed when 2.2 are expected. Twelve observed lymphohematopoietic cancers when 6 are expected would result in twofold statistically significant excess based on external referent rates (SIR = 2.0, 95% CI: 1.03 to 3.49).

Epidemiological studies, however, describe a population-level rate of disease and do not identify which, if any, individuals will develop disease as a result of exposure. Therefore, identifying the causes of disease in an individual is difficult, if not impossible, and valid guidance for clinicians to infer causation from occupational exposures for most diseases in specific patients is absent.[57] Lymphohematopoietic cancers are generally accepted to have a multifactorial etiology involving a combination of environmental (including lifestyle) factors and genetics. Evidence of the multifactorial nature of AML is shown with respect to its risk factors: smoking, exposure

to high doses of radiation (eg, atomic bomb or nuclear accident), and exposure to benzene. In contrast, the effects of low-dose radiation are not well understood and are largely based on cancer survivors who had been treated with radiation and/or targeted radionuclide therapy.

Relative to quantitative exposure estimates reported in epidemiological studies used to inform the classification of formaldehyde and TCE as human carcinogens, we found that the potential exposures of Cases 4 and 6 were lower than exposure estimates associated with observable increased risks of AML and NHL, respectively.

CONCLUSIONS

We developed and applied a JEM and reconstructed the potential exposures for six workers diagnosed with lymphohematopoietic cancers. We determined that two workers were potentially exposed to agents that have been classified as known, probable, or possible human carcinogens and associated with their specific cancers. Nevertheless, these workers' potential exposures to these agents are similar to outdoor environmental levels, and low relative to occupational exposures associated with increased risks of cancers in epidemiological studies. Based on the methods used in this study, no association between workplace exposures to the recognized lymphohematopoietic carcinogens identified at this company and the development of the worker's cancers could be demonstrated.

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REFERENCES

1. American Institute of Chemical Engineers. *Chemical Engineers in Semiconductor Manufacturing*. New York, NY: AIChE; 2009.
2. Sorahan T, Waterhouse JA, McKiernan MJ, Aston RH. Cancer incidence and cancer morality in a cohort of semiconductor workers. *Br J Ind Med*. 1985;42:546–550.
3. Garabrandt DH, Olin R. Carcinogens and cancer risks in the microelectronics industry. *Occup Med*. 1986;1:119–134.
4. Edelman P. Environmental and workplace contamination in the semiconductor industry: implications for future health of the workforce and community. *Environ Health Perspect*. 1990;86:291–295.
5. Bailar JC, Greenberg M, Harrison R, LaDou J, Richter E, Watterson A. Cancer risks in the semiconductor industry: a call for action. *Int J Occup Environ Health*. 2002;8:163–168.
6. Beall C, Bender TJ, Cheng H, et al. Mortality among semiconductor and storage device manufacturing workers. *J Occup Environ Med*. 2005;47:996–1014.
7. Darnton A, Miller BG, Maccalman L, et al. An updated investigation of cancer incidence and mortality at a Scottish semiconductor manufacturing facility with case–control and case-only studies of selected cancers. *Occup Environ Med*. 2012;69:767–769.
8. McElvenny DM, Darnton AJ, Hodgson JT, Clarke SD, Elliott RC, Osman J. Investigation of cancer incidence and mortality at a Scottish semiconductor manufacturing facility. *Occup Med (Lond)*. 2003;53:419–430.
9. Nichols L, Sorahan T. Cancer incidence and cancer mortality in a cohort of UK semiconductor workers, 1970–2002. *Occup Med (Lond)*. 2005;55:625–630.
10. Lee HE, Kim EA, Park J, Kang SK. Cancer mortality and incidence in Korean semiconductor workers. *Saf Health Work*. 2011;2:135–147.
11. Hsieh GY, Wang JD, Cheng TJ, Chen PC. Exploring cancer risks among workers in the semiconductor industry in Taiwan. *Occup Environ Med*. 2005;62:e15. In: 18th International Symposium on Epidemiology in Occupational Health; September 11–14, 2005; Bergen, Norway.
12. Kim I, Kim HJ, Lim SY, Kongyoo J. Leukemia and non-Hodgkin lymphoma in semiconductor workers in Korea. *Int J Occup Environ Health*. 2012;18:147–153.
13. Kim EA, Lee HE, Ryu HW, Park SH, Kang SK. Case series of malignant lymphohematopoietic disorder in Korean semiconductor industry. *Saf Health Work*. 2011;2:122–131.
14. Moon EK, Park HJ, Oh CM, et al. Cancer incidence and survival among adolescents and young adults in Korea. *PLoS One*. 2014;9:e96088.
15. Torres C, Jones RM, Dell L, Poole J, Boelter FW, Harper P. A model to systematically employ professional judgment in the Bayesian decision analysis for a semiconductor industry exposure assessment. *J Occup Environ Hyg*. 2014;22:343–353.
16. National Research Council of the National Academies. *Health Risks From Exposure to Low Levels of Ionizing Radiation: Biological Effects of Ionizing Radiation (BEIR) VII, Phase 2*. Washington, DC: National Research Council; 2006.
17. ENVIRON International Corporation. Exposure reconstruction and risk opinion for six employees diagnosed with hematopoietic cancers: methods, results and conclusions. Available at: http://www.samsung.com/global/business/semiconductor/minisite/EHS/pdf/Environ_Exposure_Reconstruction_&_Risk_Opinion.pdf. Published 2011. Accessed November 21, 2014.
18. International Agency for Research on Cancer. Agents classified by the IARC monographs, volumes 1–105. Available at: http://monographs.iarc.fr/ENG/Classification/ClassificationsAlphaOrder.pdf. Accessed September 13, 2012.
19. US Environmental Protection Agency. Integrated risk information system. Available at: http://www.epa.gov/iris/search_human.htm. Accessed October 29, 2012.
20. National Toxicology Program. *Report on Carcinogens, 12th Edition*. US Department of Health and Human Services National Toxicology Program; 2011. Available at: http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf. Accessed July 30, 2013.
21. Park SH, Shin JA, Park HH, et al. Exposure to volatile organic compounds and possibility of exposure to by-product volatile organic compounds in photolithography processes in semiconductor manufacturing factories. *Saf Health Work*. 2011;2:210–217.
22. Park H, Jang JK, Shin JA. Quantitative exposure assessment of various chemical substances in a wafer fabrication industry facility. *Saf Health Work*. 2011;2:39–50.
23. Nicas M. The near field/far field (two-box) model with a cant contaminant emission rate. In: Keil CB, Simmons CE, Anthony TR, eds. *Mathematical Models for Estimating Occupational Exposures to Chemicals*. 2nd ed. Fairfax, VA: AIHA Press; 2009:47–52.
24. Jayjock M, Logan P, Mader B, et al. Modeled comparisons of health risks posed by fluorinated solvents in a workplace spill scenario. *Ann Occup Hyg*. 2011;55:202–213.
25. Nicas M, Neuhaus J. Predicting benzene vapor concentrations with a near field/far field mode. *J Occup Environ Hyg*. 2008;5:599–608.
26. Herrick RF, Stewart JH, Blicharz D, et al. Exposure assessment for retrospective follow-up studies of semiconductor- and storage device-manufacturing workers. *J Occup Envion Med*. 2005;47:983–995.
27. US Environmental Protection Agency. *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*. Washington, DC: US EPA, Office of Research and Development, Office of Health and Environmental Assessment; 1994.
28. Boice JD Jr, Marauno DE, Munro HM, et al. Cancer mortality among US workers employed in semiconductor wafer fabrication. *J Occup Environ Med*. 2010;52:1082–1097.
29. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Ionizing Radiation, Part 1: X- and Gamma (γ)-Radiation, and Neutrons (Volume 75)*. Lyon, France: International Agency for Research on Cancer; 2000.
30. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Chemical Agents and Related Occupations (Volume 100F)*. Lyon, France: International Agency for Research on Cancer; 2012.
31. US Environmental Protection Agency. *Toxicological Review of Trichloroethylene: In Support of Summary Information on the Integrated Risk Information System (IRIS)*. EPA/635/R-09/011F. Washington, DC: US Environmental Protection Agency; 2011.
32. Guha N, Loomis D, Grosse Y, et al. Carcinogencitiy of trichloroethylene, tetrachloroethylene, some other chlorinated solvents, and their metabolites. *Lancet Oncol*. 2012;13:1192–1193.
33. US Environmental Protection Agency. *Toxicological Review of Formaldehyde—Inhalation Assessment in Support of Summary Information on the Integrated Risk Information System (IRIS) (External Review Draft)*. Washington, DC: US Environmental Protection Agency; 2010.

34. Beane Freeman LE, Blair A, Lubin JH, et al. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute cohort. *J Natl Cancer Inst*. 2009;101:751–761.
35. Hauptmann M, Stewart PA, Lubin JH, et al. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. *J Natl Cancer Inst*. 2009;101:1696–1708.
36. Coggon D, Ntani G, Harris EC, Palmer KT. Upper airway cancer, myeloid leukemia, and other cancers in a cohort of British chemical workers exposed to formaldehyde. *Am J Epidemiol*. 2014;179:1301–1311.
37. Pinkerton LE, Hein MJ, Stayner LT. Mortality among a cohort of garment workers exposed to formaldehyde: an update. *Occup Environ Med*. 2004;61:193–200.
38. Meyers AR, Pinkerton LE, Hein MJ. Cohort morality study of garment industry workers exposed to formaldehyde: update and internal comparisons. *Am J Ind Med*. 2013;56:1027–1039.
39. Andjelkovich DA, Janszen DB, Brown MH, Richardson B, Miller FJ. Mortality of iron foundry workers: IV. Analysis of a subcohort exposed to formaldehyde. *J Occup Environ Med*. 1995;37:826–837.
40. Stern FB, Beaumont JJ, Halperin WE, Murthy LI, Hills BW, Fajen JM. Mortality of chrome leather tannery workers and chemical exposures in tanneries. *Scand J Work Environ Health*. 1987;13:108–117.
41. Edling C, Jarvholm B, Andersson L, Axelson O. Mortality and cancer incidence among workers in an abrasive manufacturing industry. *Br J Ind Med*. 1987;44:57–59.
42. Hansen J, Rasschou-Nielsen O, Molin Christensen J, et al. Cancer incidence among Danish workers exposed to trichloroethylene. *J Occup Environ Med*. 2001;43:133–139.
43. Blair A, Harge P, Stewart PA, McAdams M, Lubin JH. Morality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow-up. *Occup Environ Med*. 1998;55:161–171.
44. Purdue MP, Bakke B, Stewart P, et al. A case–control study of occupational exposure to trichloroethylene and non-Hodgkin lymphoma. *Environ Health Perspect*. 2012;119:232–238.
45. Seidler A, Möhner M, Berger J, et al. Solvent exposure and malignant lymphoma: a population-based case–control study in Germany. *J Occup Med Toxicol*. 2007;2:2
46. Anttila A, Pukkala E, Sallmen M, Hernberg S, Hemminki K. Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. *J Occup Environ Med*. 1995;37:797–806.
47. Axelson O, Selden A, Andersson K, Hogstedt C. Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. *J Occup Environ Med*. 1994;36:556–562.
48. Kriebel D, Checkoway H, Pearce N. Exposure and dose-modelling in occupational epidemiology. *Occup Environ Med*. 2007;64:492–498.
49. US Environmental Protection Agency. 2005. *Guidelines for Carcinogen Risk Assessment*. Washington, DC: US Environmental Protection Agency. Available at: http://www.epa.gov/cancerguidelines. Accessed December 1, 2014.
50. National Research Council of the National Academies. *Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde*. Washington, DC: The National Academies Press. Available at: http://www.nap.edu/catalog/13142/review-of-the-environmental-protection-agencys-draft-iris-assessment-of-formaldehyde. Accessed December 5, 2014.
51. Lagiou P, Trichopoulos D, Adami H-O. Concepts in cancer epidemiology and etiology. In:Adami H-O, Hunter D, Trichopoulos D, eds. *Textbook of Cancer Epidemiology*. 2nd ed. New York: Oxford University Press; 2008:127–152.
52. Checkoway H, Boffetta P, Mundt DJ, Mundt KA. Critical review and synthesis of the epidemiologic evidence on formaldehyde exposure and risk of leukemia and other lymphohematopoietic malignancies. *Cancer Causes Control*. 2012;23:1747–1766.
53. Marsh GM, Youk AO. Reevaluation of mortality risks from leukemia in the formaldehyde cohort study of the National Cancer Institute. *Regul Toxicol Pharmacol*. 2004;40:113–124.
54. Natelson EA. Benzene-induced acute myeloid leukemia: a clinician's perspective. *Am J Hematol*. 2007;82:826–830.
55. Rinsky RA, Hornung RW, Silver SR, Tseng CY. Benzene exposure and hematopoietic mortality: a long-term epidemiologic risk assessment. *Am J Ind Med*. 2002;42:474–480.
56. Rinsky RA, Smith AB, Hornung R, et al. Benzene and leukemia: an epidemiologic risk assessment. *N Engl J Med*. 1987;316:1044–1050.
57. Vosbeek J. When work is related to disease, what establishes evidence for a causal relation? *Saf Health Work*. 2012;3:110–116.

