Exposure Reconstruction and Risk Opinion for Six Employees Diagnosed with Hematopoietic Cancers

Methods, Results and Conclusions

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Contents

1 Introduction

ENVIRON International Corporation ("ENVIRON") was retained by Samsung Electronics Co. Ltd. ("Samsung") to perform an evaluation of exposure potential in several current and historical operating lines, and to evaluate the potential for increased risk of hematopoietic or lymphatic cancers among six employees as a result of potential exposures in the work environment.

Samsung operates two semiconductor fabrication facilities in the Republic of Korea located in Giheung and Onyang. The Giheung facility is further divided into the Giheung complex, established in 1984, with 9 fabrication lines, and the Hwaseong complex, established in 2002, with 6 fabrication lines (KOSHA, 2009). In 2010, approximately 27,700 workers (13,000 production workers and 14,700 office workers) were employed at the Giheung facility. The Onyang facility began operations in 1991. In 2010, approximately 4,900 workers (3,600 manufacturing workers and 1,300 office workers) were employed at the Onyang facility.

Six workers at these two semiconductor facilities have been diagnosed with various hematopoietic or lymphatic cancers and have alleged that their cancers were caused by workplace exposures[4].

The Korean Occupational Safety and Health Agency ("KOSHA") conducted an evaluation of the workplace for these six former employees and concluded that workplace exposures did not cause their cancers.

To further evaluate this matter, Samsung requested that ENVIRON perform the following occupational exposure assessments:

- The Worker Exposure Characterization Study included a qualitative assessment and quantitative assessment for various chemical and physical agents potentially encountered during the current-day semiconductor wafer manufacturing process in two fabrication lines and one test facility and packaging line; and
- The Historical Exposure Reconstruction Study included a qualitative evaluation of process changes from 1990 based on manufacturing process era with consideration for tools, process chemical and physical agents, and process and exposure controls; and quantitative assessment for chemical and physical agents that would have been potentially encountered during historical manufacturing operations.

Based on the information from the historical exposure reconstruction study, Samsung requested that ENVIRON calculate hematopoietic and lymphatic cancer risks associated with the workplace exposures estimated for the six specific employees diagnosed with hematopoietic and lymphatic cancers alleged to have been caused by workplace exposures.

4 In addition to these six employees, additional lymphatic and hematopoietic cancer cases have been identified by KOSHA and/or other Korean government agencies among current and/or former employees of semiconductor and liquid crystal manufacturing facilities, including other Samsung facilities. ENVIRON does not have specific information about these cases and consideration of those cases was beyond the scope of this work.

This report describes the Historical Exposure Reconstruction Study, and its application to the evaluation of excess cancer risks among the six employees resulting from employment in Samsung semiconductor manufacturing facilities. The Worker Exposure Characterization Study is described in a separate report, titled "Samsung Worker Exposure Characterization Final Report Draft," September 2011.

Both studies were conducted using rigorous scientific methodologies and were designed to be consistent with methodologies developed and endorsed by the American Industrial Hygiene Association ("AIHA") (Armstrong et al., 2009; Ignacio and Bullock, 2006).

The Exposure Reconstruction Study was conducted as a consultative effort to Samsung by ENVIRON with critical peer review from an independent panel of distinguished occupational health and risk assessment scientists currently engaged at prestigious American universities ("the Scientific Advisory Panel" or "Panel"). The Study has been subject to critical review at milestone points by the Panel. The Panel has reviewed methodologies, results and conclusions and provided peer review and critical feedback to the ENVIRON study team to assure that the methods used and results provided are relevant, reliable and reproducible in accordance with key components of the scientific method.

To assist in understanding the project, the Panel visited the Samsung facilities in Korea and specifically reviewed the lines of interest.

1.1 Background

1.1.1 Samsung Semiconductor Process

The Study included Samsung-operated semiconductor manufacturing facilities located in the Republic of Korea in Giheung and Onyang. The six workers with cancers worked on three lines at these facilities. Two of the lines were 200 millimeter ("mm") wafer fabrication lines, termed Line 3 and Line 5 (Giheung), which manufactured semiconductor devices as individual die (i.e. chips) on 200-mm diameter silicon wafers. The third line was a testing and assembly line, termed Line 1 (Onyang). In Line 1, completed silicon wafers of semiconductor devices are separated into individual die, packaged as individual products (i.e. chips) in an end-use configuration, and tested for proper functionality.

ENVIRON included information pertaining to two 200-mm manufacturing lines in the Exposure Reconstruction Study: Line 3 (Giheung) and Line 5 (Giheung). Line 3 is now closed, while Line 5 is currently in operation. Line 5 is similar to Line 3. Line 3 and Line 5 were built in the same era, using the same architecture and controls; and produced the same products. Line 3 hygiene monitoring data are available from 2001 until 2008, when the line was shut down. Line 5 hygiene monitoring data are available from 2006 until 2010. Additional industrial hygiene monitoring was conducted by ENVIRON on Line 5 in 2011. After review of tools and processes, and comparisons of monitoring data collected on Line 3 and Line 5, no conditions were identified which suggested that the potential for and magnitude of exposures on Line 5 differed from those on Line 3. This analyses are described subsequently in this report. As a result, hygiene monitoring data from Lines 3 and 5 were combined for the reconstruction of exposures.

Semiconductor devices are manufactured on wafers utilizing eight (8) distinct process areas, each area performing a certain set of manufacturing operations utilizing a defined set of equipment, process chemicals/gases and input energies (e.g., non-ionizing radiation). The process areas utilized in semiconductor wafer fabrication for lines 3 and 5 consist of:

- Chemical-Mechanical Planarization ("CMP")
- Chemical Vapor Deposition ("CVD")
- Clean (also referred to as Wet Etch in semiconductor industry publications)
- Diffusion
- Etch
- Implantation
- Photo (also referred to as Photolithography in semiconductor industry publications)
- Thin-Films Metal

Line 1 is a testing and assembly semiconductor manufacturing facility. In order to complete the testing and assembly process, up to thirteen (13) process areas are utilized, each performing a certain set of process steps utilizing a defined set of equipment, process chemicals/gases and input energies (e.g., marking lasers). Depending on the product being produced not all process areas may be utilized. Line 1 monitoring data are available from 2004 to 2010. The testing and assembly process areas are:

- Assembly – Backlap
- Assembly – Sawing
- Assembly – Die Attach
- Assembly – Plasma
- Assembly – Wire Bonding
- Packaging – Molding
- Packaging – Marking
- Packaging – Trim Sort Form
- Packaging – Tin Plating
- Packaging – Solder Ball Attach
- Test – Monitor Burn-in Testing (MBT)
- Test – Testing
- Test – Marking Visual Packing (MVP)

In all of Samsung's operations, including Lines 1, 3, and 5, there are two essential, exclusive categories of work. The first category is "normal operations," and refers to operators performing the routine tasks supporting and required by the process area operations listed above. The

second category is “maintenance,” and refers to maintenance activities for the specific tools and process equipment. Many tools have routinely scheduled maintenance. Workers in the normal operations category do not perform maintenance work, and maintenance workers do not perform normal operations work. Typically in the semiconductor industry, maintenance workers have higher exposure potential than normal operations workers due to the worker being intimately engaged with the interior of the tools at the time of maintenance. Most maintenance activities at Samsung are conducted by third-party vendors, though the work is overseen by Samsung employees.

1.1.2 Review and Observation of Work Practices

ENVIRON conducted site visits of Samsung Lines 1 and 5 in July and August of 2010, January 2011 and April 2011. During these site visits ENVIRON performed a detailed review of all process areas of Lines 1 and 5, specifically identifying potential hazards in the workplace, work practices, tools, equipment, and chemical use and storage. In addition, ENVIRON conducted extensive quantitative reviews of the facilities in January 2011 and April 2011. The data collected at these visits have been considered in this Study.

1.1.3 Description of the Six Cases

Between 2004 and 2008, six former employees who worked on Giheung Lines 3 and/or 5 and Onyang Line 1 developed specific types of lymphatic and hematopoietic system cancers. Characteristics of these cases including their diagnoses are described in Sections 4.3 and 4.4.

For each of the six employees known to Samsung and working on Giheung Lines 3 and/or 5 on Onyang Line 1, “personal epidemiological investigations” were performed by KOSHA and the Occupational Safety and Health Research Institute (“OSHRI”) within KOSHA, at the request of the Korea Workers’ Compensation & Welfare Service. The purpose of these investigations was to assess whether the employees’ diseases were work-related, and employees due worker’s compensation benefits. Reports by these agencies summarized information on: type of cancer and diagnosis date; work history, including jobs and tasks; chemicals used in process areas where the individual employee worked; and potential for exposure to ionizing radiation. The reports also summarized existing industrial hygiene measurements provided by Samsung as well as industrial hygiene measurements newly collected by OSHRI. For each employee, the Korean investigation concluded that worker’s compensation was not required because the cancer was not work-related.

1.2 Objectives

The specific objectives of the Exposure Reconstruction Study were to:

- Develop similar exposure groups (“SEGs”) based on manufacturing process areas on Lines 1, 3 and 5.
- Develop a job exposure matrix (“JEM”) to describe the exposure profiles in each SEG. The JEM includes quantitative estimates of exposure for all process chemicals, physical agents and anticipated by-products for lines 1, 3 and 5 that were detected by industrial hygiene monitoring in the work environment.

- Assign SEGs to each employee based on the work histories, and use the JEM to reconstruct exposures to those chemical and physical agents that are capable of causing their specific cancer and that have been measured and detected in the Samsung work environment.
- Evaluate reconstructed exposures to disease-specific carcinogens for each of the six employees to provide an expert opinion as to whether the potential exposure(s) caused their individual diagnosed cancers. This was accomplished by:
  - Comparing the magnitude and duration of the individual's estimated exposure to identified disease-specific carcinogens to exposure levels reported in well-conducted epidemiological studies to be associated with increased risks of cancer. These epidemiological studies were identified by authoritative bodies (e.g., IARC, US EPA, etc.) as the human evidence that contributed to the overall weight-of-evidence for classifying the carcinogenicity of the agent. (Note: A comparison to exposure levels in the semiconductor industry was not possible because there are no documented quantitative exposure estimates in relation to cancer risks for the semiconductor industry).
  - Calculating excess or attributable lifetime cancer risk resulting from each individual's exposure to carcinogens. The risk estimates were then compared to the upper bounds on the range of excess lifetime cancer risks (between 1×10^{-6} and 1×10^{-4}) considered by the US EPA in the setting of regulatory policy.

2 Literature Review

2.1 Descriptive Epidemiology of Cancers of Interest

The six cases were diagnosed with one of the following cancers of the hematopoietic system: acute myeloid leukemia (n=4), acute lymphocytic leukemia (n=1), and non-Hodgkin's lymphoma (n=1). Based on the diagnoses of the six cases, the descriptive epidemiology for the cancers of interest is described below.

2.1.1 Acute Myeloid Leukemia

Acute myeloid leukemia ("AML"), also known as acute myelocytic leukemia, acute myelogenous leukemia, acute granulocytic leukemia, and acute non-lymphocytic leukemia, develops primarily from myeloid stem cells that proliferate but never fully mature into white blood cells. In the United States, AML accounts for 28.4% of total leukemias (Schottenfeld 2006). Incidence is higher in men than in women, and varies by age. AML incidence has a slight peak in infancy, is uncommon between the ages of 10 and 40, and increases rapidly thereafter until about age 70 (American Cancer Society 2010b). Acute promyelocytic leukemia ("APL") is a subtype of AML, accounting for approximately 10% of adult AML cases. APL has the best prognosis compared to other subtypes of AML (American Cancer Society 2010b). In the U.S., approximately 50 children are diagnosed with APL each year, which makes up about 1% of all childhood leukemia. APL is most commonly found in children between 2 and 3 years of age and in adults over 40 (St. Jude Children's Research Hospital 2011).

According to the "Annual Report of Cancer Statistics in Korea in 2008", published in 2010 by the Korean National Cancer Center, the age-standardized AML rate per 100,000 person-years country-wide was 10.8 among males, 8.9 among women, and 9.9 among both. In children, incidence rates were 11.3 among those 0-4 years of age, 8.3 among those 5-9 years of age, and 9.8 among children 10-14 years of age (Korean National Cancer Center 2010).

Age-adjusted incidence rates for AML vary threefold internationally, and have increased slightly since the late 1980s (Schottenfeld 2006). The highest rates of AML are seen in both sexes of white populations in North America, northern and western Europe, Oceania, and Hispanics in Los Angeles. Populations with rates in the middle tier include both sexes of African Americans; Israeli Jews; populations in France, Spain, and Sweden; males in Japan; females in Italy and Switzerland; and female Hispanic whites in Los Angeles. The lowest rates occur in Asians, primarily Indians in Bombay and Chinese in Shanghai (Schottenfeld 2006). The highest incidence rates of adult APL occur in populations of Latin American and Southern European descent (Deschler 2006).

The exact causes of AML are unknown, but several factors have been shown to increase risk. Exposure to high doses of ionizing radiation, chemotherapy alone or in combination with radiation therapy for treatment of other malignancies, and chronic exposure to high levels of benzene are known risk factors for AML (Adami 2008; American Cancer Society 2010b; National Cancer Institute 2008; Schottenfeld 2006). It is not clear whether exposure to lower levels of radiation therapy, x-rays, or CT scans (without chemotherapy drug exposure) increase risk of AML. Males are at greater risk for AML than females, and cigarette smoking has been identified as a risk factor. Certain blood disorders, such as chronic myeloproliferative disorders,

chronic myeloid leukemia ("CML"), and myelodysplastic syndrome increase risk of subsequent AML. There does not appear to be an inheritance factor in the risk for AML, but some congenital syndromes, including Down syndrome, Fanconi anemia, Bloom syndrome, Ataxia-telangiesctasia, and Blackfan-Diamond syndrome, may increase risk.

In 2009, the IARC re-evaluated the carcinogenicity of formaldehyde and found there was sufficient evidence for formaldehyde to cause leukemia, specifically AML (Baan 2010). This determination was based on new data from three studies: a cohort of formaldehyde workers (Beane Freeman 2009), a nested case-control study of embalmers (Hauptmann 2009), and a meta-analysis of formaldehyde and leukemia (Zhang 2009). Beane Freeman (2009) followed a cohort of formaldehyde workers for mortality from 1934 through 2004. The researchers found a non-statistically significant increased risk for myeloid leukemia (Relative Risk ("RR") = 1.78; 95% CI = 0.87-3.64), with a statistically significant excess of myeloid leukemia found in the highest peak exposure group with follow up until 1994 (RR = 2.79; 95% CI = 1.08-7.21). Hauptmann (2009) looked at 168 deaths between 1960 and 1986 from lymphohematopoietic malignancies among embalmers and found a statistically significant increase in deaths from myeloid leukemia with increasing duration (OR = 13.6; 95% CI = 1.6-119.7 for greater than 34 years) and number of embalmings (OR = 12.7; 95% CI = 1.4-112.8). Zhang (2009) performed a meta-analysis of 15 leukemia studies (6 with results for myeloid leukemia) and reported a statistically significant increased risk of myeloid leukemia (RR = 1.90; 95% CI = 1.31-2.76). The IARC's decision is controversial because there is much debate about the mechanism by which formaldehyde induces leukemogenesis. Zhang (2009) postulates that formaldehyde causes genetic damage to circulating bone marrow stem cells that leads to leukemia. Zhang's theory conflicts with the fact that formaldehyde naturally occurs in the humans due to oxidative metabolism (National Toxicology Program 2004) and does not accumulate in the body because it is metabolized quickly and efficiently. Recently, the National Research Council of the National Academies (NRC, 2011) criticized the US EPA's draft risk assessment for formaldehyde (EPA, 2010), in part because it did not adequately support its conclusion that there was sufficient evidence for formaldehyde to cause leukemia. The committee had several substantive criticisms of the draft risk assessment, including: the EPA grouped all types of leukemias and lymphomas despite evidence that these represent diverse cancers that are not closely related and the EPA speculated extensively with respect to how formaldehyde reacts in the body but did not provide adequate evidence in its assessment that formaldehyde causes leukemia (NRC, 2011).

Many additional environmental, occupational, and lifestyle exposures have been investigated as potential risk factors for AML. These include: electromagnetic field exposure; occupational exposure to diesel and gasoline exhausts; pesticide or herbicide exposure; occupational exposure to other chemicals including styrene, butadiene, and ethylene oxide; work in embalming, pathology, metal and foundry industry, barbering and hairdressing, dry cleaning, painting, coal mining, garage and transport, clinical laboratories, and underground mining (Adami 2008; American Cancer Society 2010b; National Cancer Institute 2008; Schottenfeld 2006).

2.1.2 Acute Lymphocytic Leukemia

Acute lymphocytic leukemia ("ALL"), also called acute lymphoblastic leukemia, develops from lymphoid stem cells that continually divide and never fully mature into white blood cells (lymphocytes) (American Cancer Society 2010a). ALL cases comprise about 11.3% of all leukemia in the United States (Schottenfeld 2006). ALL occurs consistently more often in men than in women, and in whites than in blacks and is the primary form of childhood leukemia; 77.8% of leukemias in children under age 14 are lymphocytic in nature, and the majority of these are ALL cases. The incidence rate of ALL is highest in children between age 2 and 4, declines slowly until the mid-20s where the rate plateaus, and then rises again slowly after age 50 (Schottenfeld 2006).

The age-standardized incidence rate of lymphoid leukemia (including acute and chronic types) per 100,000 person-years in Korea was 1.6 among men and 1.1 among women in 2002 (International Agency for Research on Cancer 2007).

Age-adjusted incidence rates for ALL vary about threefold internationally. The highest age-adjusted incidence rates are found in both sexes of Hispanics in Los Angeles, and in Spain, northern Italy, and in whites in New Zealand. The lowest rates are typically observed in African Americans and Asians (Adami 2008; Schottenfeld 2006). Childhood ALL incidence is highest in Costa Rica and Hispanics in Los Angeles, while the lowest rates are among African Americans, populations in the Middle East, and in India (Schottenfeld 2006).

The causes of ALL remain unknown, and only a few risk factors have been identified: prenatal diagnostic x-ray exposure for children diagnosed with ALL, high-dose radiation exposure, certain chemotherapy drugs, and chronic high-level exposure to benzene. A rare type of ALL can be caused by infection with the human T-cell lymphomas/leukemia virus (HTLV-1). In Africa, Burkitt lymphoma has been linked to infection with the Epstein-Barr ("EB") virus and to a type of acute lymphocytic leukemia. There does not appear to be an inheritance factor in the risk for ALL, but some congenital syndromes seem to raise the risk. These include: Down syndrome, Klinefelter syndrome, Fanconi anemia, Bloom syndrome, Ataxia-telangiesctasia, and Neurofibromatosis. There are no known lifestyle-related risk factors for ALL. Research is ongoing to determine the role, if any, of potential risk factors, such as electromagnetic field exposure; occupational exposure to diesel, gasoline, pesticides and other chemicals; smoking; maternal reproductive factors; socioeconomic and household characteristics; and exposure to hair dyes (Adami 2008; American Cancer Society 2010a; National Cancer Institute 2008; Schottenfeld 2006).

2.1.3 Non-Hodgkin's Lymphoma

Non-Hodgkin's Lymphoma ("NHL") is a form of cancer that originates in the lymphoid tissues, including the lymph nodes, spleen, thymus, tonsils and adenoids, and bone marrow. NHL is comprised of more than 20 lymphoproliferative malignant cancers or subtypes that originate in the B and T lymphocytes and are heterogeneous in clinical course and in etiology (Schottenfeld 2006). Few epidemiological studies have examined risk factors by NHL subtypes. Diffuse large B-cell lymphomas are the most common type in western countries, accounting for 30-40% of NHL. In the United States, NHL is the 6th most common cancer diagnosis in men and the 5th

most common in women (Alexander 2007). NHL is more common in men than in women and is primarily a cancer of adults, although the median age differs by subtype (Lenhard 2001). The age-standardized incidence rate of NHL per 100,000 person-years in Korea was 5.6 among men and 3.3 among women in 2002 (International Agency for Research on Cancer 2007).

Worldwide, the incidence of NHL has been increasing dramatically in both genders since the early 1970s, most rapidly in men in the United States and Italy with increases exceeding 85% (Schottenfeld 2006). Asian and African countries have the lowest incidence, while North America and Australia have the highest (Grulich 2005). Over the years, diagnostic procedures and changes in cancer classification have complicated the interpretation of the epidemiology of NHL. Cancer classification is complex: the World Health Organization ("WHO") classification of NHL incorporates information on diagnostic features including morphology, immunophenotype, genetic features, clinical features, race, geographic distribution and microbiological features. Despite the changes in classification over time, diagnostic error and established risk factors cannot account for the continuing upward trend in incidence, especially in the younger population (Adami 2008; Grulich 2005).

While some risk factors for NHL have been identified, the causes of the majority of lymphoma cases are unknown (Schottenfeld 2006). Identified risk factors include: long-term use of immunosuppressive agents, inherited immune defects, rheumatoid arthritis, HIV/AIDS, and various infectious agents including Heliobacter pylori bacteria and hepatitis C (Lenhard 2001). Other risk factors have been investigated, such as exposures to some occupational and environmental toxins, including pesticides, herbicides, and agricultural-related chemicals; blood transfusions; vaccine and medicines usage; lifestyle behaviors such as smoking and alcohol consumption, physical activity and nutrition; and reproductive or genetic susceptibility (Alexander 2007). A recent review suggests that obesity increases risk of NHL, while moderate physical activity decreases risk (Skibola 2007). Certain risk factors, such as HIV infection, are common to multiple forms of NHL while other risk factors are associated with a specific histological subtype, suggesting some etiological differences among subtypes. Different incidence patterns by age, sex, race, and geography for different subtypes also suggest etiologic heterogeneity (Alexander 2007).

The US EPA (2009) conducted a critical assessment of available epidemiological evidence on the carcinogenicity of TCE, and concluded that TCE was carcinogenic to humans. Evidence was considered strongest for kidney cancer, described as "compelling" for lymphoma (including NHL), and more limited for liver and biliary tract cancer (US EPA, 2009). Several cohort and case control studies have shown increased risks of NHL associated with TCE exposure. In a cohort of 803 TCE-exposed Danish workers, Hansen et al. (2001) found a statistically significant increased overall incidence of NHL in men (SIR = 3.5; 95% CI = 1.5-6.9) based on 8 cases. Analyses by exposure characteristics showed a statistically significant increased incidence for those working at least 75 months, but no exposure-response pattern was observed by individual mean exposure or cumulative exposure to TCE. An expanded cohort of 40,049 workers in Danish companies that use TCE found a non-statistically significant increased incidence of NHL in the overall cohort (SIR = 1.2; 95% CI = 1.0-1.5), but reported a significant association in a subcohort of workers expected to have higher exposure levels (SIR = 1.5; 95% CI = 1.2-2.0) (Raaschou-Nielsen 2003). A population-based case-control study in Germany of 710 malignant

lymphoma cases reported associations with the highest TCE cumulative exposure category (>35 ppm-years) and B-NHL (OR = 2.3; 95% CI = 1.0-5.3) and T-NHL(OR = 4.7; 95% CI = 0.8-26.1) (Seidler 2007). In a case control study of 199 NHL cases and 479 controls, Persson and Fredrikson (1999) reported an odds ratio of 1.2 (95% CI = 0.5-2.4) for TCE, based on 16 exposed cases. A statistically significant association between NHL and TCE based on 4 exposed cases (OR = 7.2; 95% CI = 1.3-42) was reported in a Swedish case-control study on 105 cases and 335 controls (Hardell 1994). Wang et al. (2009) conducted a population-based case-control study of 601 cases of NHL in Connecticut women and 717 controls, and reported an odds ratio of 1.2 (95% CI = 0.9-1.8) for TCE exposure. Analyses by intensity of TCE exposure initially suggested an exposure-response relationship, but the author noted the relationship did not hold for analyses restricted to only those cases with medium to high probability of exposure. A recent meta-analysis and review identified 14 studies that reported results for NHL and TCE exposure (Mandel 2006). The overall summary risk estimate was positive (SRR = 1.29; 95% CI = 1.00-1.66), and summary risk estimate for those studies identifying a specific TCE-exposed subcohort was significantly increased (SRR = 1.59; 95% CI = 1.21-2.08). Summary risk estimates by cumulative exposure did not indicate an exposure-response relationship, and there was large variability in results across studies. For these reasons, as well as a lack of supporting evidence from toxicological and mechanistic studies, the authors conclude that there is insufficient evidence to interpret a causal association (Mandel 2006). As part of a recent assessment of the carcinogenicity of TCE, the EPA conducted a meta-analysis on TCE and lymphoma. Two cohort studies and one case-control study were considered by EPA (2009) to be of high methodological quality reported statistically significant increased risk of NHL in TCE-exposed populations: Hansen et al. (2001), Raaschou-Nielson et al. (2003), and Seidler et al. (2007). The EPA meta-analysis found statistically significant pooled estimates for the overall estimates (RR_{pooled} = 1.23; 95% = 1.04-1.41) and for estimates from the highest exposure groups (RR_{pooled} = 1.57; 95% CI = 1.27-1.94).

2.2 Epidemiological studies of the semiconductor industry

Few epidemiological studies have followed semiconductor industry workers for cancer incidence or mortality. Information on semiconductor industry studies that present results for leukemia or non-Hodgkin's lymphoma outcomes in workers is summarized separately and described below.

Mortality of 126,836 IBM workers from 1965 to 1999 was studied in three facilities: East Fishkill, San Jose, and Burlington (Beall 2005). Both East Fishkill and Burlington manufactured and packaged semiconductors, while San Jose manufactured storage devices, such as disk drives and network servers. No analyses by subtype of leukemia were reported, but mortality rates for total leukemia did not exceed expected or were not significantly elevated in the total cohort or in subsets of workers stratified by duration of employment and years since first employment in "potentially exposed" jobs (i.e., any type of work other than office). Similar results were observed for NHL and for both outcomes when analyses were restricted to workers from the two facilities that manufactured semiconductors.

When compared to mortality rates of unexposed workers within the same facilities, ever exposed workers showed no increased risk of leukemia (RR=1.0, 95% CI: 0.6, 1.6) or NHL (RR=0.7, 95% CI: 0.5, 1.0). Workers with at least five years employment and fifteen years since

first exposure were not at increased risk for mortality from NHL (RR=0.8, 95% CI: 0.5, 1.3) and did not show a significantly elevated risk for leukemia (RR=1.4, 95% CI: 0.8, 2.5) (Beall 2005).

A total of 89,054 workers from the East Fishkill facility, where semiconductors were manufactured, and the San Jose facility, where storage devices were manufactured, facilities were followed through 1999 for cancer incidence (Bender 2007). In East Fishkill workers, incidence rates were below expected for both leukemia and NHL for all workers and in those with at least five years employment and fifteen years since first exposure. Mortality risk was not significantly increased in exposed compared to unexposed workers within the same facility for either outcome. In the San Jose facility, where storage devices were produced, incidence rates were not significantly elevated for leukemia or NHL compared to expected rates. Compared to unexposed workers, exposed workers in San Jose did not have higher risks of NHL and risk of leukemia was not significantly elevated. No results by leukemia subtype are presented (Bender 2007).

A cohort of 100,081 workers from 10 facilities in two United States semiconductor companies was followed from 1983 to 2002 for mortality (Boice, Jr. 2010). Leukemia and NHL mortality rates did not exceed expected or were not significantly increased in the total cohort or when workers were grouped by work area, duration of employment, or employment prior to 1980. Analyses by leukemia subtype were performed only for chronic lymphocytic leukemia: all other leukemia subtypes were grouped together for analysis (Boice, Jr. 2010).

Two studies assessed leukemia morbidity and mortality in cohorts of semiconductor workers in the United Kingdom. A cohort of 4,388 workers in a semiconductor plant in Scotland was followed from 1970 to 2007 for mortality, and 1970 to 2006 for cancer incidence. One incident case (1.2 expected) and one death (0.8 expected) from all leukemia except chronic lymphocytic leukemia were observed in the cohort over this time period (Darnton 2010). In England, 1,807 workers at a semiconductor plant were followed from 1970 to 2002 for mortality and 1971 to 2001 for cancer incidence. Leukemia mortality and incidence rates in the overall cohort did not significantly exceed expected; three deaths (SMR=0.96, 95% CI: 0.20-2.82) and five cases (SIR=1.21, 95% CI: 0.39-2.83) were observed (Nichols 2005). Neither study presented results for NHL.

Overall, no significant excess risk of leukemia or NHL has been reported within the current body of epidemiological literature on semiconductor workers. Available studies share several limitations that can affect interpretation and generalizability of results. Only two studies present results by any leukemia subtype, and then only for chronic lymphocytic leukemia (CLL) or all leukemia except CLL. Worker exposures are not well characterized: none of the identified studies used quantitative exposure estimates. Instead, studies estimated exposures using surrogate measures, such as duration of employment, or classification by work groups, job groups, and other employment factors (Beall 2005; Herrick 2005). Small cohort size (Darnton 2010; Nichols 2005) and inadequate length of follow-up (Boice, Jr. 2010) may have prohibited the detection of excess cancer in some studies.

3 Methods

3.1 Approach for Exposure Reconstruction

The approach for the exposure reconstruction is detailed in the document entitled, "Exposure Reconstruction for Samsung: Analysis Plan for Exposure Reconstruction". The Analysis Plan for Exposure Reconstruction was reviewed by the Advisory Panel prior to the reconstruction.

A job-exposure matrix ("JEM") was developed for Lines 1, 3, and 5. A JEM summarizes the estimates for exposure to agents present in each "job" (Hoar, 1983/1984). However, similar exposure groups ("SEGs") were used rather than "jobs," because the concept of SEGs bridges the process areas identified on each Line with job titles in employment records. The term SEG indicates that normal operations (or maintenance) workers employed in a particular process area and doing the same tasks, and would be expected to have similar exposure levels. Practically speaking, the JEM is a large table, with one row for each chemical or physical agent in each SEG, and columns defining the exposure level. The JEM developed in this study includes descriptive statistics for chemical and physical agents detected in each SEG in the work environment, separated by normal operations and maintenance tasks.

The JEM does not include the chemicals benzene, ethylene oxide, and 1,3-butadiene. All of these chemicals have been reported to be associated with lymphatic and hematopoietic cancers in general, and were monitored for in the work environment based on these concerns. Benzene, 1,3-butadiene and ethylene oxide were monitored for by ENVIRON during the Worker Exposure Characterization Study but not detected in the work environment at Samsung; similarly ethylene oxide was monitored for but not detected historically by Samsung. Formaldehyde is included in the JEM. Formaldehyde was also measured by ENVIRON and historically by Samsung, and detectable concentrations were documented on Line 1 in the Packaging-Tin Plating (mean 0.0058 mg/m^3or 0.047 ppm) and Packaging-Molding SEGs (mean 0.0092 mg/m^3or 0.0075 ppm). The detected concentrations were low, such that the resulting exposure profile for formaldehyde was consistent with trivial exposures (i.e. less than 1% of related OEL at least 95% of the time, See Table II in Section 3.4.1.).

The reconstruction of exposures for the six workers identified by Samsung to have developed lymphatic or hematopoietic cancers uses the JEM exposure values combined with the individual work histories. By matching the job title and work location to an SEG, and with consideration for the duration of employment in the SEG, the cumulative exposure resulting from this work can be computed. In the Study, cumulative exposure estimates were computed for each of the six workers only for agents identified by authoritative bodies as suspected or known to be related to their disease. Cumulative exposure has units of mg/m^3-years or ppm-years for airborne chemicals and particulates, mSv for ionizing radiation, and V/m or mW/cm^2 for non-ionizing radiation exposures.

To assure the scientific rigor and objectivity required for the Study, ENVIRON approached the worker exposure reconstruction in accordance with the approach published by the American Industrial Hygiene Association ("AIHA"), specifically by Armstrong et al., (2009).

3.2 Exposure Reconstruction Background and Assumptions

ENVIRON reviewed and extracted data from the following sources: existing industrial hygiene data provided by Samsung; industrial hygiene data generated by ENVIRON during it Worker Exposure Characterization Study; three original laboratory reports provided by Samsung; and Personal Epidemiological Investigation reports.[5]

While the total number of industrial hygiene data points was sizable, in general the number of samples for a specific chemical in an SEG was small. The AIHA recommends the use of six or more samples for the quantitative estimation of exposure variability occurring between days and between workers (Ignacio and Bullock, 2006). This sample size was available for only a fraction of the chemical-SEG combinations, which means that the true variability in exposures may not be captured for all chemicals in all SEGs.

ENVIRON based its work on the work histories of the six employees of interest described in the KOSHA Personal Epidemiological Investigation reports (provided in translation by Samsung). KOSHA reported developing these work histories from data provided by Samsung, and from interviews with the cases, their families and/or co-workers. Exposures were reconstructed for each employee by matching each employment period with an SEG based on the process area in which the employees worked, and the tasks performed.

In interviews with KOSHA, two employees described potential exposure to trichloroethylene ("TCE"). TCE exposures were not monitored prior to the discontinuation of TCE use in Samsung facilities in April 1995. As a result, a mathematical model was used to estimate TCE exposures. Input information for the model, however, was limited: the volume of TCE used per task, and the frequency and duration of the task were not described in detail. Model input information was therefore determined based on the limited available descriptions and observations of similar work in other semiconductor facilities by ENVIRON industrial hygienists.

3.3 Industrial Hygiene Monitoring Data

Three sets of hygiene monitoring data were available:

- **Historical Samsung Data**: Historical monitoring of normal operations was conducted by Samsung on Line 1 from 2004 to 2010 and Line 3 from 2001 to 2008. The results are referenced to process areas on Line 1 or Line 3. Monitoring of normal operations was conducted by Samsung on Line 5 from 2006-2010. Line 5 processes are similar to Line 3, which discontinued semiconductor operations in 2008. Line 5 data was used to supplement the historical monitoring for Line 3. Full-shift (6-8 h) TWA measured in the personal breathing zone of operators or at fixed locations in work areas were included in the analysis. This data set comprises 872 measurements one Line 1, 396 measurements on Line 3 and 563 measurements on Line 5.

5 Only a small subset of the data was verified against original laboratory reports as only three original laboratory reports were available (from 2010, translated). For these data, a match between numeric values in the lab reports and the compiled monitoring data was noted.

- **Historical Vendor Data:** Historical monitoring of maintenance tasks was conducted by contractors to Samsung on Line 5 from 2007 to 2009. This dataset comprises 66 measurements (10 chemicals) of full-shift (6-8 h) TWA measured in the personal breathing zone of the maintenance worker on Line 5.
- **ENVIRON Data**: Current monitoring of normal operations and maintenance tasks was conducted by ENVIRON on Lines 1 and 5 in 2011 as part of the Worker Exposure Characterization Study. This dataset comprises 600 measurements of task-duration, full-shift (7-8 h) and multi-shift (adjusted to 8 h) TWA measured in the personal breathing zone of operators or in work areas. Ionizing and non-ionizing radiation levels were measured. The results are referenced to Line process areas and tasks.

3.4 Data Management and Summary Analysis

Prior to the development of quantitative exposure estimates for agents by SEG, a series of data management and analysis steps were undertaken. These steps included:

- Step 1: The development of Excel spreadsheets containing the historical Samsung and historical Vendor data, which could be sorted, searched and imported into the analysis software. The ENVIRON data had previously been organized in this manner as part of the Worker Exposure Characterization Study.
- Step 2: The evaluation of the potential to merge data for statistical description. Specifically, the similarity between personal breathing zone and fixed area location data on each line, the similarity between line 3 and line 5 data, and the similarity between the historical and ENVIRON data sets were evaluated.
- Step 3: Descriptive statistics were computed for each agent in each SEG for which monitoring data was available.

3.4.1 Data Provided by Samsung

Samsung provided the historical Samsung data and historical Vendor data. The raw data provided hygiene monitoring results from lines 1, 3, and 5 for the years 2001 to 2010 .

3.4.2 ENVIRON Data

Industrial hygiene monitoring data collected by ENVIRON as part of the Worker Exposure Characterization Study (Stage 2) in 2011 were organized similarly to the historical data. Only data collected for lines 1 and 5 were utilized.

3.4.3 Combined Data Spreadsheet

All data were compiled in a single Excel® spreadsheet with the following variables:

- Year
- Department or process area
- Floor
- Work unit location / Bay number

- Hazardous element / analyte assessed
- Number of workers in area
- Number of workers monitored
- Sampling start time
- Sampling stop time
- Duration of sampling
- Worker initials or area sample location descriptor
- Measurement result (result or detection limit)
- Occupational exposure limit
- Analytical method

Once all data was combined into the single excel spreadsheet, filters were created to allow sorting of the data first by line, then by process area, and then by chemical, as to identify all sample results representative of a particular analyte within a SEG.

To insure data integrity during this data manipulation step, a quality assurance/quality control ("QA/QC") check was performed by randomly selecting 10% of the data set and cross-referencing the values in the combined Excel spreadsheet back to the original line/year specific raw data files provided by Samsung. This QA/QC approach ensured that blocks of data were copied and sorted properly and screened for data transcription errors.

3.4.4 SEG Definition

The monitoring data were matched to similar exposure groups, based on the process area specified for each monitoring result in the combined data spreadsheet. The linkage between process areas and SEG is defined separately.

For normal operations workers, similar exposure groups were defined which reflected process areas in which workers have similar exposures. Semiconductor manufacturing process areas include numerous tools, and over normal operations, the primary task of the operation is to move wafers between tools, which are fully enclosed with integrated ventilation systems. The time activity pattern of the operators may vary from day to day, and is unknown for specific workers; however, since the use of a particular tool or performance of a particular task depends on production requirements, we expect little systematic variation in exposure potential between workers in the process area due to the frequency with which specific tasks are performed or tools utilized.

For the wafer fabrication facilities, lines 3 and 5, chemicals for a given SEG associated with normal operations included those chemicals used in the process or anticipated or known to be by-products formed during processing, but also process chemicals and by-products associated with tools and tasks in different SEGs but co-located in the same production bay. Therefore a worker conducting normal operations for a given SEG would be in close proximity to the tools and tasks comprising a different SEG. As a result some industrial hygiene monitoring may

reflect these indirect exposures. Those analytes directly associated with the SEG that the normal operations worker was assigned to are referred to as 'Direct', whereas those analytes associated with SEGs in the same production bay where normal operations tasks occurred are referred to as 'Indirect".

For maintenance workers, data were matched to specific maintenance tasks whenever possible.

3.4.5 Supportive Analysis for Data Merge

Prior to assigning exposure estimates to each SEGs, a series of analysis steps were undertaken to evaluate if there was evidence to support the merging of different sections of the data. Specifically, the historical Samsung normal operations data were evaluated for evidence of:

- strong temporal trends in contaminant concentrations,
- similarity of contaminant concentrations in the personal breathing zone and area of normal operations, and
- similarity in contaminant concentrations at Line 3 and Line 5.

In conclusion, there was no evidence of strong time trends; there was evidence to support the similarity in contaminant concentrations in the personal breathing zone and at fixed area locations on lines 1, 3 and 5; and there was evidence to support the similarity in contaminant concentrations on Line 3 and line 5.

Subsequently, the historical Samsung data were compared to the ENVIRON data. Due to the low frequency of detected contaminant concentrations in the ENVIRON dataset, these comparisons are more limited than those made within the historical Samsung dataset. However, there is no evidence that the contaminant concentrations differ substantially between 2011 and 2001-2010.

As a result of these analyses, time-windows were not defined within the SEGs, the personal breathing zone and fixed area monitoring data were combined for analysis, and line 3 and line 5 data were combined for analysis.

3.4.6 Generation of Summary Statistics

The bulk of the summary statistics were generated using an automation program (RoboTask ver. 4.4, robotask.com) to extract data from the combined data spreadsheet, input the data into the IH Data Analyst ("IHDA") software (Version 1.0.1, Exposure Assessment Solutions, Inc.) for statistical analysis, and extract the descriptive (summary) statistics from the IH Data Analyst reports.

Specifically, RoboTask was used to generate IHDA input files for all analyte-SEG combinations by working through a string of filters applied to the combined data spreadsheet until all possible combinations were exhausted. This process totally extracted the combined data set into a format readable by the IDHA software, creating a total of 264 IHDA input files reflecting data from:

- Line 3 and Line 5 historical Samsung data (combined)
- Line 1 historical Samsung data
- Line 5 ENVIRON data
- Line 1 ENVIRON data
- Line 3 and Line 5 historical Samsung data and Line 5 ENVIRON data (combined), and
- Line 1 historical Samsung data and ENVIRON data (combined).

IH Data Analyst is primarily designed for Bayesian decision analysis, and was utilized for this purpose in the Worker Exposure Characterization Study. However, the software also computes descriptive statistics. In this automated process, the 264 input files were read into the IH Data Analyst software in series, and the software output report (a Microsoft Word document, *.rtf) were created. This yielded 264 output reports.

It should be noted that while treatment of left-censored data (i.e. non-detectable exposure data)[6] does not impact the results from the BDA approach, it does have the potential to impact the calculation of traditional statistics measures. For instances when the Maximum Likelihood Estimate ("MLE") approach was allowable by the data set of interest, as described in the Annals of Occupational Hygiene article titled *A Comparison of Several Methods for Analyzing Censored Data*[7] it was used as the preferred substitution method for the non-detect data point. When MLE was not allowable, the analytical method's limit of detection divided by two (LOD/2) was used as the substitution method for that data point. Of the 264 data sets evaluated within IHDA, MLE was used for 96, and direct substitution was used for 154. Fourteen data sets required no treatment of censored data.

6 Left-censored data consists of exposure monitoring data that are below detectable concentrations according to the sampling and analytical methods employed (i.e. non-detectable). There are several methods that have been employed to include left-censored data during statistical analysis. The approaches employed for this Study are described herein.

7 Ann. Occup. Hyg., Vol. 51, No. 7, pp. 611–632, 2007. A Comparison of Several Methods for Analyzing. Censored Data. Paul Hewett and Gary H. Ganser. Exposure Assessment Solutions, Inc., Morgantown, West Virginia; Department of Mathematics, West Virginia University, Morgantown, West Virginia. Received 5 March 2007; in final form 17 August 2007

The descriptive statistics contained within each IH Data Analyst output report included the following (if feasible for a given data set):

- Number of samples
- % Censored data
- Geometric mean
- Geometric standard deviation
- Arithmetic mean
- Standard deviation
- Minimum value
- Maximum value
- Range of values

A QA/QC check of the reports output by IH Data Analyst was performed to ensure that all data points were properly included in the input files. This process involved random selection of one chemical analyte per SEG, for which all data input values were manually checked against the IHDA output report. An internal audit form was developed which standardized the data review process and serves as documentation of the process.

The descriptive statistics contained in the IH Data analyst reports were extracted into an Excel spreadsheet, with each row representing an analyte-SEG combination.

A QA/QC check of the summarized descriptive statistics was performed to ensure that all data was properly extracted from the IHDA reports. This process involved random selection of one chemical analyte per SEG, for which the statistical values in the IHDA output report were compared to the statistical values in the combined spreadsheet. An internal audit form was developed which standardized the data review process and serves as documentation of the process.

A limitation of the IH Data Analyst software is the requirement that an occupational exposure limit be included in the input. For a subset of analytes in the historical Samsung dataset, no occupational exposure limit was available. In these instances, descriptive statistics were computed using R (R Project for Statistical Computing).

3.5 The Job Exposure Matrix

The descriptive statistics calculated for the historical Samsung data, historical Vendor data, ENVIRON data, and/or combined historical-ENVIRON data were used to describe quantitative exposure levels in the JEM. Specifically, for each analyte in each SEG the monitoring data was summarized by the geometric mean (“GM”) and geometric standard deviation (“GSD”), which was computed using IH Data Analyst or R. The GM and GSD were used because hygiene monitoring data are typically lognormally distributed, though the small sample sizes and highly censored nature of the data for specific analyte-SEG combinations limit the ability to evaluate the assumption of lognormality statistically (Esmen et al., 1999).

For the exposure reconstruction of normal operations, preference was given to exposure estimates based on the following hierarchy: historical Samsung data, merged Samsung-ENVIRON data, and then the ENVIRON data, if no historical data were available. For the exposure reconstruction of maintenance tasks, the historical Vendor data were prioritized over the ENVIRON data. Though in the Proposed Approach document we considered the inclusion of published literature data (available in the public domain), these data were ultimately judged to be too sparse and poorly described to be included.

Given the GM and GSD, the arithmetic mean or any percentile of the distribution can be computed for use in the exposure reconstruction. Specifically, the mean concentration was calculated using:

$$AM = GM \times \exp[0.5 \ln^2 GSD].$$

The median was equated with the GM. And, the 75th percentile of the lognormal distribution was calculated using:

$$C_{75th\%} = GM \times GSD^{0.674},$$

where 0.674 is the Z-value of the standard normal distribution corresponding to the 75th percentile of the standard normal distribution.

For ionizing radiation, the exposure was equated with the maximum value (mSv/h) measured in the survey conducted by ENVIRON in the Exposure Characterization Study.

3.5.1 Treatment of Process Chemicals and By-Products which were not detected or not monitored

Process chemicals and by-products which were measured but not detected or not measured were not included in the job exposure matrix. Evaluation of all process chemicals was conducted as part of the ENVIRON Worker Exposure Characterization Study. Process chemicals and by-products which were not identified for monitoring by ENVIRON during the qualitative risk were those for which the anticipated exposures were in Exposure Categories 0 or 1.The AIHA Exposure Characterization Scheme (Table II) used for the qualitative risk assessment is described below.

Table II. AIHA Exposure Categorization Scheme (Ignacio and Bullock, 2006)

Exposure Category	Rule-of-Thumb Description	Exposure Profile Description	Recommended Statistical Interpretation
0	Exposures are trivial to nonexistent	The true 95th percentile (X0.95) is calculated to be <1% of the OEL at a 95% confidence level for anticipated exposures in the SEG.	X0.95 ≤ 0.01 × OEL
1	Exposures are highly controlled	The true 95th percentile (X0.95) is calculated to be between 1% and ≤ 10% of the OEL at a 95% confidence level for anticipated exposures in the SEG.	0.01×OEL < X0.95 ≤ 0.1×OEL
2	Exposures are well controlled	The true 95th percentile (X0.95) is calculated to be between >10% and ≤ 50% of the OEL at a 95% confidence level for anticipated exposures in the SEG.	0.1 × OEL < X0.95 ≤ 0.5 × OEL
3	Exposures are controlled	The true 95th percentile (X0.95) is calculated to be between >50% and ≤ the OEL at a 95% confidence level for anticipated exposures in the SEG.	0.5 × OEL < X0.95 ≤ OEL
4	Exposures are poorly controlled	The true 95th percentile (X0.95) is calculated to exceed or be > than the OEL at a 95% confidence level for anticipated exposures in the SEG.	X0.95 > OEL

3.5.2 Treatment of Chemicals which were Monitored, but are not Process Chemicals or By-Products

Given that the six cases had lymphatic or hematopoietic cancers, Samsung requested that ENVIRON conducted industrial hygiene monitoring for several agents known to cause these cancers as part of the Worker Exposure Characterization Study, even though the chemicals have not been process chemicals or anticipated by-products. The three “non-expected” chemicals include: benzene, 1,3-butadiene, and ethylene oxide. In addition, the historical Samsung data included industrial hygiene monitoring for ethylene oxide. The chemicals were not detected in any samples.

3.5.3 Work Histories

The work histories for the six cases of interest were extracted from the KOSHA Personal Epidemiological Investigation reports. The work histories of the KOSHA Personal Epidemiological Investigation reports were developed from work histories provided by Samsung, and from interviews with the cases, their families and/or co-workers. For each case, each employment period was matched with an SEG based on the process area in which the cases were employed, and the tasks performed.

The dates of employment in each SEG were defined from the work histories for each case. The standard work shift was assumed to be 8 h per day, 6 days per week for 50 weeks per year. Several workers reported working overtime, up to 12 h per day for 28 days per month. The employment duration (including the standard work shift and overtime, if reported) was normalized to a work year of 8 h per day, 5 days per week, 50 weeks per year, which equals

2000 hours per year or 250 days per year. As a result, for all workers, the number of equivalent work years was greater than the employment duration based on calendar dates in the work history.

For example, assume an employee worked 8 hours per day, 3 days per week and 12 hours per day, 2 days per week, for one year. The equivalent number of equivalent work years (2000 h per year) is calculated:

(8 hours x 3 hours) + (12 hours x 2 hours) 50 weeks/year = 2400 hours worked/year

2400 hours worked/year ÷ 2000 hours in a work year = 1.2 equivalent work years

3.6 Cumulative Exposure Estimates

Cumulative exposure estimates for measured chemical agents were calculated as the product of the contaminant concentration as an 8 h time-weighted average and the equivalent work years, and had units of mg/m^3-years. The arithmetic mean, geometric mean (median) and 75^{th} percentile of the cumulative exposure calculated using the mean, median and 75^{th} percentiles of the contaminant concentration, respectively.

For ionizing radiation, the dose was calculated separately for each calendar year of exposure. The annual dose of ionizing radiation was mSv.

For the TCE model, conservative assumptions for the amount of chemical used and the work shift duration were made and applied for the mathematical model inputs. The mathematical model chosen was a two-zone model with constant emission rate described by Nicas (2009). In this model, the work environment is divided into two zones. One zone, termed the near-field zone, contains the source – in this case, the TCE-wetted swabs – and the personal breathing zone of the worker. The second zone, termed the far-field zone, is the remainder of the room where by-standers may be present. The TCE emitted from the swabs is assumed to be uniformly, instantaneously mixed in the near-field zone; the TCE is transported between the near-field and far-field zones due to random fluctuations in air movement in the space. TCE is removed from the far-field zone due to room ventilation rate. The model was implemented using the IH MOD software, which has been developed by members of the AIHA Exposure Assessment Strategies Committee.

3.7 Approach for Risk Analysis in Relation to Estimated Exposures and Development of Specific Cancers for the Six Employees

A protocol for the risk analysis and evaluation of reconstructed exposures to workplace agents that have been classified as capable of causing the cancers diagnosed in the six employees was reviewed by the Advisory Panel prior to the exposure reconstruction and the calculation of individual risks.

The approach is described briefly below:

- Categorization of chemical/physical agents used in manufacturing processes or anticipated to be present as process by-products as known, probable, or possible carcinogens capable of causing leukemias or lymphomas based on the classifications made by authoritative bodies (e.g., IARC, US EPA, etc.).
- Evaluation of estimated cumulative exposure for each chemical/physical agent classified as known or suspected to potentially cause the diagnosed cancer for the case. ENVIRON assumed exposure occurred for any case who worked in a process area in which a chemical/physical agent known or suspected carcinogen was present at detectable levels in the work environment, or otherwise had been measured and detected.
- Review and evaluation of quantified exposures reported in epidemiological studies that authoritative bodies included in their weight-of-evidence evaluations to classify carcinogens.
- Calculation of excess lifetime risk of the specific diagnosed cancer.

3.8 Risk Calculation Background and Assumptions

The etiology of most cancers is multifactorial with genetic, environmental and lifestyle factors contributing to their development. The scope of this investigation focused solely on occupational exposures because information on other factors was not available for assessment.

Cancers are complex diseases and their development involves a multistage process involving complex mechanisms of action to induce neoplastic changes in cells. Some interval of time passes after exposure before cancer can be diagnosed. Latency is defined as the time interval between exposure to an agent that causes cancer and the diagnosis of cancer. Latency varies according to cancer type and according to exposure. For example, latency periods for hematopoietic and lymphatic cancers can be as short as two years for patient cohorts that have been exposed to radiation for treatment of other cancers (National Research Council, 2006). Epidemiological studies of nuclear workers and other occupationally-exposed cohorts have used two years as a minimal latency periods in analyses of leukemias (Cardis 2005), although the latency interval for low-dose ionizing radiation exposures may be longer. The latency interval associated with occupational exposures to chemicals known to cause leukemia is generally not well understood but is believed to be consistent with the minimum latency interval for ionizing radiation (i.e., at least 2 years for high levels of exposure and 5 years or more for lower levels of exposure).

Risks of cancer (or any disease) associated with specific exposures in the Samsung-operated semiconductor facilities cannot be assessed in the absence of a well-conducted epidemiological studies that provide a basis for validly detecting and quantifying the association, if any, between levels of exposure and specific types of cancer. An epidemiological study that is capable of identifying exposures to chemical/physical agents associated with increased risks of cancer in the population at risk must: (i) comprehensively enumerate a cohort of employees engaged in semiconductor manufacturing, (ii) estimate exposure for study subjects, and (iii) follow the study subjects over time to compare cancer incidence in groups with higher exposures to cancer

incidence in groups with lower exposures (or to rates in the general population, which is presumed to be unexposed).

Such an epidemiological study – that assesses cancer risks using quantified exposure estimates for individual cohort members – has not been conducted specifically for Samsung employees in semiconductor manufacturing processes. Recently, the OSHRI of KOSHA conducted an epidemiological study of mortality among 113,443 employees and cancer incidence among 108,443 employees at eight semiconductor factories who worked between 1998 and 2008 (Lee 2011). The OSHRI study reported a standardized incidence ratio ("SIR") of 0.69 (95% CI 0.30–1.37) for leukemia in men based on 8 cases and 1.28 (95% CI 0.61 – 2.36) for leukemia in women based on 8 cases. Lee et al. (2011) reported an excess of non-Hodgkin's lymphoma in females based on 13 cases (SIR=2.31, 95% CI 1.23 – 3.95). Other epidemiological studies of the semiconductor industry have not detected consistently elevated rates of cancers among employees. To date, epidemiological studies of this industry have utilized broad job classifications to gauge exposure and risk, rather than quantitative estimates of exposure to chemical/physical agents. One reason for this has been the general lack of evidence suggesting increased rates of any cancers among semiconductor workers. As a result, no studies in the semiconductor industry meet the three criteria that define an epidemiological study capable of quantifying associations between exposures in the work environment and cancer.

In the absence of an appropriate epidemiologic study, risks may be estimated conservatively using risk assessment modeling. This approach identifies the excess lifetime cancer risk as a range of upper bound probabilities given exposure via a specific exposure pathway (e.g., inhalation, ingestion), where the exposure-risk relationship is based on population-based risk assessment. These exposure-risk relationships are determined by authoritative bodies that conduct population-based risk assessments, such as the US EPA, such that they can only be calculated for chemical/physical agents that have been subject to a regulatory risk assessment.

This risk-based approach can only give a broad sense of risk potential for individuals and small populations. Population-based risk assessments conducted for regulatory and policy purposes rely on extensive assumptions. It is unclear and unlikely that an individual has exposure and personal characteristics that comply with the assumptions. For example, risk assessments typically define exposure as the cumulative exposure over a lifetime (e.g. ppm-years), even though the magnitude, timing and duration of the exposure, may influence the risk of disease. Additionally, an individual may have unique lifestyle or genetic factors that influence the likelihood that he or she will develop disease. As a result, a risk-based and epidemiologic approach may identify different levels of risk for the same population.

The probability of excess lifetime cancer risk was used in this study. These comparisons were (and can be) made only for chemical/physical agents that have been classified by authoritative bodies as known or suspected to cause the specific cancers of interest and for which actual exposure is credible. For example, the use of a known or suspected carcinogen may occur in the fabrication facilities only under strictly controlled conditions (e.g., closed processes and/or while wearing personal protective equipment) such that the presence of the agent does not necessarily indicate that any biologically relevant exposures occurred.

For purposes of this investigation, ENVIRON assumed the following:

- Exposure to a chemical/physical agent that has been classified by authoritative bodies as known or suspected of causing cancer was assumed for an employee when that agent had been measured and detected in the employee's work environment. ENVIRON evaluated those agents in the workplace that have been classified by authoritative bodies as carcinogens known or suspected to cause the specific types of lymphohematopoietic cancers diagnosed in the six workers. These agents included chemicals used in the manufacturing process and anticipated by-products from those processes, and also additional agents that have been evaluated solely because they have been classified by authoritative bodies as carcinogens known to cause lymphohematopoietic cancers (e.g., benzene, ethylene oxide, formaldehyde). Nevertheless, we recognize that some chemical/physical agents are only used under tightly controlled conditions such that exposure to the chemical/physical agents is unlikely and therefore unlikely to influence cancer risk.
- When exposure was assumed, a minimum latency interval of two years from first exposure in the work environment to diagnosis must occur for cancer to develop as a result of workplace exposure.

3.9 Mathematical Models for Risk Calculations

For ionizing radiation, in addition to comparisons with published epidemiologic literature, ENVIRON estimated lifetime attributable risk ("LAR") based on the LAR model developed by the Biological Effects of Ionizing Radiation VII ("BEIR VII") Committee for incidence and mortality of leukemia from low level doses of ionizing radiation (NRC (NAS), 2006). This model was used to calculate the LAR to ionizing radiation for Case 4. For women exposed to 10 milligrays (mGy) per year from ages 18 to 65, the lifetime attributable risk of being diagnosed with leukemia was 270 per 100,000 and the lifetime attributable risk of dying from leukemia was 220 per 100,000.[8]

For chemical carcinogens, ENVIRON estimated lifetime extra cancer risk using US EPA draft mathematical models, which estimate the probability that a person develops specific types of cancer over his or her lifetime from inhalation exposure to a specified chemical concentration. Specifically, this approach was used for exposures to formaldehyde (US EPA 2010) and trichloroethylene (US EPA 2009).

Individual lifetime extra cancer risk is characterized by the following equation:

$$\text{Lifetime Extra Cancer Risk} = EC_{\text{LT inhalation exposure}} \times \text{IUR}$$

8 The unit gray (Gy) measures absorbed dose, while the unit sievert (Sv) measures the equivalent dose or biological dose. The equivalent dose may be calculated by multiplying the absorbed dose by a weighting factor, which varies according to radiation type and energy range. The weighting factor for gamma, x-ray, and beta radiation equals one. Therefore, 1 Gy=1 Sv.

where:

- Lifetime Extra Cancer Risk=added cancer (above background) risk to an individual expressed as an upper-bound risk of contracting cancer over a lifetime due to the chemical exposure;
- $EC_{LT\ inhalation\ exposure}$=estimate of long-term inhalation exposure concentration for a specific chemical; and
- IUR=corresponding inhalation unit risk for that chemical (calculated by the US EPA).

The inhalation unit risk is a value calculated by the US EPA that represents the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 µg/m^3 in air. The interpretation of inhalation unit risk would be as follows: If unit risk = 2×10^{-6} per µg/m^3, 2 excess cancer cases (upper bound estimate) are expected to develop per 1,000,000 people if exposed daily for a lifetime to 1 µg of the chemical per m^3 of air.

The EPA model assumes continuous exposure (24 hours per day for 365 days) and an inhalation rate of 20 m^3 per 24-hour day (0.83 m^3/h) over a 70 year lifetime. In contrast, occupational time-weighted average ("TWA") exposures are based on exposure occurring over 8 hours for 250 days per year. The default inhalation rate for light to moderate occupational work was assumed to be 10 m^3/ 8-hr day (1.25 m^3/h).

Therefore, to convert occupational exposure for each individual case to continuous environmental exposure and account for the difference in the number of days exposed per year (250 days vs. 365 days) and in the amount of air inhaled (10 m^3 vs. 20 m^3) (US EPA, 1994), ENVIRON used the following equation:

$$EC_{LT\ inhalation\ exposure} = [\mu g/m^3\text{-yrs} \times (10\ m^3/20\ m^3) \times (250/365)]/70\ years$$

where:

- $EC_{LT\ inhalation\ exposure}$=estimate of long-term inhalation exposure concentration for a specific chemical;
- µg/m3-yrs=cumulative exposure estimate for the cancer causing chemical calculated by multiplying the duration of exposure in the SEG to the summary value for the SEG in the JEM;
- 10 m^3/20 m^3 is the conversion between amount inhaled occupational and environmental inhalation (default assumption for EPA model is 20 m^3);
- 250/365 is the conversion between number of days exposed in workplace and number of days exposed per year (default assumption for EPA model is 365 days); and
- 70 years of exposure is the default assumption used in the EPA model

Exposure estimates were calculated using arithmetic mean, median and 75th percentile values to summarize more broadly the distribution of exposures in each SEG. The risk calculations used the arithmetic mean (or the maximum value) to provide conservative estimates because the arithmetic mean was typically higher than the median and frequently similar to the 75th percentile.

4 Results

4.1 Temporal Process Changes

4.1.1 Evaluation of Temporal Patterns 2000 - 2011

No evidence was found to suggest strong temporal trends in contaminant concentrations over the period for which monitoring data was available (2000-2011). As a result, no time-windows of exposure were defined for this period in the SEGs.

4.1.2 Evaluation of Process Changes 1990 - Present

Two types of semiconductor manufacturing facilities were assessed as part of the Study: Two wafer fabrication lines 3 and 5 (line 5 also serves as a surrogate for line 3 in some instances when data may be inadequate) and one testing and assembly line (line 1). Wafer fabrication facilities manufacture semiconductor devices as individual die (i.e. chips) on silicon wafers of varying sizes. Generally the manufacturing era for a given wafer fabrication facility is determined by the diameter of wafer utilized for the following reasons:

- The progression from a given wafer size to another is a significant change as entirely new manufacturing equipment is typically needed to handle larger diameter wafers even if the inherent operations, energies or chemicals employed may be the same.
- As wafer diameter increases the manufacturing equipment and support systems also increase in size. Therefore, updated facility designs are often required to accommodate the larger equipment footprints.
- While new facilities are designed and built advances in manufacturing technology which increase efficiency and productivity (e.g., automated delivery of wafer and chemicals to tools) are also integrated.
- Therefore, there are typically many obvious differences between semiconductor manufacturing facilities utilizing differing wafer diameters from the footprint of the manufacturing and support equipment employed to the overall size of the facility itself. For these reasons the wafer size is usually used as a de-facto shorthand to defining a given facility's manufacturing era.

By way of reference, currently operating high-volume wafer fabrication facilities most commonly use wafers of either 8 inches/200 mm or 12 inches/300 mm in diameter. Facilities that utilize 200 mm wafers were typically constructed and begun operations in the early to mid 1990s through the late 1990s. For the purposes of this Study these facilities will be considered to be associated with the most recent past manufacturing era. On the other hand, facilities that utilize 300 mm wafers were typically constructed and commenced operations beginning in the late 1990s to early 2000s up to present and would be considered to be part of the most current manufacturing era.

Previously, Herrick, et al. (2005) utilized manufacturing eras and associated characteristics to define identifying factors that may be used to qualitatively describe exposure potential differences over time. The identifying factors were listed for a given manufacturing facility by manufacturing era allowing for visual inspection to identify changes in exposure potential over

time. For the purposes of this Study a similar approach was taken by developing Tables III and IV below to allow for a qualitative determination of differences in exposure potential for a given Line over time. Many of the same identifying factors utilized by Herrick, et al were also used for this Study as well, with some changes made to account for specific facility differences that exist. The qualitative assessment of differences in exposure potential by line over time accomplished by the manufacturing era tables complements the statistical evaluation of exposure data by year to test if a quantitative difference in exposures is observable over time.

Tables III and IV below provide a listing of the identifying factors for the semiconductor wafer fabrication facilities of interest (Line 1 and Lines 3 and 5). The manufacturing era assessment was conducted for Line 5 and is also representative of qualitative differences in exposure potential for Line 3 as Line 5 is considered a surrogate for Line 3, both of which are/were 200mm wafer fabrication facilities.

Table III. Evaluation of process changes impacting exposure potential on Line 1 from the 1990s to 2000s.

Manufacturing Eras and Associated Characteristics	Samsung - Line 1	
Identifying Factors	**1990 - 1999**	**2000 – Present**
Manual application of chemicals	None	None
Manual refilling of chemicals in tools	Some (primarily replacing of small quantities of ink and epoxy in tools or slurries and surfactant in dispense cabinets)	Some (primarily replacing of small quantities of ink [phased out mid-2000s] and epoxy in tools or slurries and surfactant in dispense cabinets)
Manual delivery of chemicals to the Line	Some (primarily replacing of small quantities of ink and epoxy in tools or slurries and surfactant in dispense cabinets)	Some (primarily replacing of small quantities of ink [phased out mid-2000s] and epoxy in tools or slurries and surfactant in dispense cabinets)
Manual pushing and pulling of wafers or die in trays	Some (automated movement in Testing)	Some (automated movement in Testing)
Manual collection and removal of wastes from the Line	None or very little (assuming chemical waste)	None or very little (assuming chemical waste)
Enclosures of LN2 piping systems at rear of equipment	All	All
Enclosures of LN2 lines	Welded stainless steel lines	Welded stainless steel lines
Oxygen Monitoring	All	All
Excess flow control valves on LN2 system	All	All
Type of smock used in clean room	Fully encapsulating suit, hat and boots worn	Fully encapsulating suit, hat and boots worn
Ventilation of Line (through core area)	General dilution supply and relief	General dilution supply and relief
Building or fire codes for semiconductor plants	Yes	Yes
Wafer size	8" (200 mm)	8-12" (200 - 300mm)
Device geometry	<1 um	<1 um
Clean room class	1,000	1,000

Table IV. Evaluation of process changes impacting exposure potential on Line 5 from the 1990s to the 2000s.

Manufacturing Eras and Associated Characteristics	Samsung - Line 5	
Identifying Factors	**1990 - 1999**	**2000 – Present**
Manual application of chemicals, e.g., photoresist	None	None
Manual dipping of wafers in chemical baths	None (limited manual dipping of wafers in Clean for Line 3; 1 to 2 tools)	None (limited manual dipping of wafers in Clean for Line 3; 1 to 2 tools)
Manual refilling of chemicals in tools	Rare (PR bottle changes only)	Rare (PR bottle changes only)
Manual delivery of chemicals to the Fab	Rare (PR bottle changes only)	Rare (PR bottle changes only)
Manual movement of wafers (from tool to tool in enclosed wafer boxes)	All	All
Manual collection and removal of wastes from the Fab	None or very little (assuming chemical waste)	None or very little (assuming chemical waste)
Manual cleaning of metal deposition equipment	Automated clean prior to chamber clean (some local exhaust used).	Automated clean prior to chamber clean (local exhaust always used).
Enclosures of piping systems at rear of furnaces	All	All
Enclosures of toxic gas lines	Enclosed/exhausted gas cabinets and valve boxes with welded stainless steel lines.	Enclosed/exhausted gas cabinets and valve boxes with welded stainless steel lines.
Toxic gas monitoring	Select gases	Select gases
Excess flow control valves on toxic gases	Select gases	Select gases
Type of smock used in clean rooms	Fully encapsulating suit, hood, mouth cover and boots worn	Fully encapsulating suit, hood, mouth cover and boots worn
PPE: gloves 100% inspected for pin holes by manufacturer	Full implementation	Full implementation
Plenum ventilation of Fab (through core area)	Flow through design with plenum return	Flow through design with plenum return
Ethyl or methyl series glycol ethers (or acetates)	Phased out (~1992)	None
Building or fire codes for semiconductor plants	Yes	Yes
Type of photoresist	Negative & positive, predominantly positive	Negative & positive, predominantly positive
Etching and photoresist removal	Dry (very limited wet); wet cleaning performed	Dry (very limited wet); wet cleaning performed
Wafer size	8" (200mm)	8" (200mm)
Device geometry	<1 um	<1 um
Clean room class	1	1

4.1.3 Conclusions

Inspection of Tables III and IV do not show evidence that process changes which would be expected to significantly influence the potential for or magnitude of exposures occurred on line 1 or lines 3/5 between the 1990s and the 2000s. In conjunction with the absence of temporal trends in the monitoring data from 2000-2011, the lack of change in process operations indicates that the potential for and magnitude of exposure is unlikely to have varied systematically between the 1990s and the 2000s. As a result, monitored exposure levels from the 2000s are likely to be representative of exposure levels during the 1990s on Lines 1 and Line 3/5.

4.2 Exposure Reconstruction – Job Exposure Matrix

To facilitate the exposure reconstruction a job-exposure matrix for all SEGs on lines 1, 3 and 5 was populated by quantitative estimates for exposure. Exposure estimates are provided for process chemicals and by-products which were detected in industrial hygiene monitoring. The exposure levels are described by the geometric mean and geometric standard deviation of the 8 h TWA for normal operations, and of the 8 h TWA and/or task-duration TWA for maintenance tasks.

The JEM forms the basis for the exposure reconstruction of the six employees but can also be used to reconstruct exposures for any worker on lines 1, 3 or 5 whose work places them in an identified SEG.

4.3 Classification of chemical and physical agents in the workplace as carcinogens

The following chemical and physical agents were classified as known to cause the specific types of cancers (AML, ALL, or NHL) diagnosed in the cases according to authoritative sources:

- Ionizing radiation has been classified as a known carcinogen causing leukemia and solid cancers (including NHL) by the IARC , the US EPA , and the NTP
- Formaldehyde has been classified as a known carcinogen causing acute non-lymphocytic leukemia (especially AML) by the IARC (2009), and provisionally by the US EPA (2010).
- Trichloroethylene has been upgraded from a possible carcinogen to a carcinogen known to cause cancer at multiple sites (specifically, kidney cancer, NHL, and liver cancer) by the US EPA (2009). Trichloroethylene is currently classified as a probable carcinogen (Group 2A) by the IARC but this classification is more than 15 years old (IARC 1995). The IARC has recently indicated that the evidence that TCE exposure causes kidney cancer and NHL is convincing, and more limited for liver and biliary tract cancer (IARC 2009).

There were no chemicals in addition to TCE or physical agents used in processing or expected to be present in the semiconductor line environment that have been classified as a probable carcinogen (IARC Group 2A or equivalent) by authoritative sources and associated with AML, ALL, or NHL.

Extremely low frequency (“ELF”) magnetic fields have been identified by the IARC as a possible carcinogen (Group 2B) for the development of childhood leukemia (IARC 2002). The IARC

further describes the evidence that ELF magnetic fields cause childhood leukemia as limited in humans (using human epidemiological data) and inadequate in experimental animals (using animal toxicological data) (IARC 2002). There were no other chemical/physical agents used in processing or expected to be present in the semiconductor line environment that have been classified as possible carcinogens by authoritative sources.

4.4 Work History and Diagnoses for Cases

4.4.1 Case 1

Case 1 was a female employee who began working in semiconductor fabrication in October 2003. She was diagnosed with acute myelocytic leukemia ("AML") M2 (French American British ("FAB") system for classification) at age 20 in June 2005. She was diagnosed 1 year and 8 months after she began working at Samsung Electronics.

Case 1 worked at the Giyeung, Fabrication Line 3 and was hired on October 6, 2003. She took a leave of absence from Samsung that began in June 2005 and separated from the company October 31, 2006. Her duration of employment at the facility totaled 1.63 calendar years. Her work history is described in the table below:

Dates of assignment	Department	Process	Tasks
2003 Oct 6 – 2004 Dec (15)*	FAB Section 3	Diffusion, Line 3 (Bays 1, 22, 24)	Coating films semiconductor wafers; Move wafers between tools; Includes on- the-job training (2003 Oct 6-2004 Jan 6)
2004 Dec (16)* – 2005 Mar 20	FAB Section 3	Wet Clean (Bay 3)	Labeling wafer boxes and obtaining orders (Administrative)**
2005 Mar 21 – 2005 Jun 10	FAB Section 3	Wet Clean (Bay 3)	Activities included a manual task of moving carrier between liquid baths.
2005 Jun 11 – 2006 Oct 31	Sick Leave	Not applicable	Not applicable
NOTES: *Exact date of the month unknown, 15th of the month arbitrarily selected for end of assignment and 16th of the month arbitrarily selected for beginning of next job/task assignment ** Task descriptions consistent with terminology in KOSHA documentation, Samsung terminology is 'Clean Line 3 (Labeling Wafer) (Supportive).			

4.4.2 Case 2

Case 2 was a female employee who began working in semiconductor fabrication in January 1995. She was diagnosed with acute myelocytic leukemia (AML) M3 variant (FAB classification) at age 30 in July 2006. This subtype of AML is also known as acute promyelocytic leukemia ("APL"). She was diagnosed 11 years and 6 months after she began working at Samsung Electronics.

Case 2 worked at the Giyeung, Fabrication Line 3 and was hired on January 17, 1995. She took a 3 month leave of absence from Samsung that began in March 2006. She worked for approximately one month after returning from her leave. Her duration of employment at the facility totaled 11.55 calendar years. Her work history is described in the table below:

Dates of assignment	Department	Process	Tasks
1995 Jan 17 – 2001 June (15)*	FAB Line 3	Sputter (Bays 6 & 9)	Move wafers between tools Includes on-the-job training (1/17/1995-4/14/1995)
2001 June (16) – 2004 June (15)*	FAB Line 3	CVD (Bays 11 & 14)	Move wafers between tools
2004 June (16)* - 2005 Mar (15)*	FAB Line 3	Ordering Task	Print labels and label wafer carriers
2005 Mar (16)* - 2005 Aug (15)*	FAB Line 3	Wet Etch (Bay 3)	Activities included a manual task to clean films on wafers: Wafer carrier with a handle put in and removed from liquid baths.
2005 Aug (16)* - 2006 Mar (15)*	FAB Line 3	Diffusion (Bay 22)	Move wafers between tools
2006 Mar (16)* -2006 June (15)*	Maternity Leave	--	
2006 June (16)* - 2006 Jul (15)*	FAB Line 3	Wet Etch (Bay 3)	Activities included a manual task to clean films on wafers: Wafer carrier with a handler put in and removed from liquid baths.
2006 July 15	Separated		
NOTES: *Exact date of the month unknown, 15th of the month arbitrarily selected for end of assignment and 16th of the month arbitrarily selected for beginning of next job/task assignment			

4.4.3 Case 3

Case 3 was a male employee who began working for Samsung Electronics in semiconductor fabrication in June 1997. He was diagnosed with acute lymphocytic leukemia ("ALL") pre-B cell type at age 30 in October 2004. He was diagnosed 6 years and 11 months after he started working at Samsung Electronics.

Case 3 began working at Giyeung Fabrication, Line 5 and was hired on June 11, 1997. He was re-assigned to Line 1 on August 22, 2002. He took a leave of absence from Samsung that began in April 2005. His duration of employment at Line 5 was 5.19 years and his duration of employment at Line 1 was 2.67 years for a total duration of 7.86 calendar years. His work history is described in the table below:

Dates of assignment	Department	Process	Tasks
1997 Jun 11 – 2002 Aug 21	Line 5	CMP	Preventive maintenance activities. Case 3 spent approximately 25% of his job time in the office. Includes on-the-job training (1997 Jun 11 – 1997 Aug 26).
2002 Aug 22 – 2005 Apr 22	Line 1	Back-Lap	Preventive maintenance activities. Case 3 spent approximately 30-35% of his job time in the office. Performed a tool installation in 2002 Aug.
2005 Apr 23 – 2005 Jul 22	Leave of Absence	--	--

4.4.4 Case 4

Case 4 was a female employee who began working in semiconductor assembly and packaging in December 2004. She was diagnosed with acute myelocytic leukemia ("AML") variant M1 (FAB classification system) at age 20 in September 2007. She was diagnosed 2 years and 9 months after she started working at Samsung Electronics.

Case 4 began working at Onyang Assembly and Packaging on December 27, 2004. She took a leave of absence from Samsung on November 9, 2007. Her work history is described in the table below:

Dates of assignment	Department	Process	Tasks
2004 Dec 27 – 2007 Nov 8	Assembly Line 1 QE Inspection	Front process, Mold, Tin, Trim/Form, PVI	Process inspection. Tasks included: use of X-ray, Cool & Hot test, visual inspection. Included on job training (12/27/2004-1/15/2005)
2007 Nov 9	Sick Leave		

4.4.5 Case 5

Case 5 was a female Samsung employee diagnosed with acute myelocytic leukemia ("AML") M3 (FAB system) at age 36 in May 2005. She was diagnosed 14 years and 4 months after she started working at Samsung Electronics.

Case 5 began working at Onyang Assembly and Packaging (Line 1) on January 14, 1991. She separated from Samsung on January 31, 1996. Her work history is described in the table below:

Dates of assignment	Department	Process	Tasks
1991 Jan 14 – 1996 Jan 31	Packaging and Assembly Line 1	Marking, Solder, Trim/Form	Tasks included: moving wafers between tools, visually inspect products, and mold cleaning with air gun. Used TCE-wetted swabs to clean product. Included on job training and employment at Bucheon and Giheung facilities.
1996 Jane 31	Resigned		

4.4.6 Case 6

Case 6 was a male former Samsung employee diagnosed with diffuse large B-Cell lymphoma at age 38 in October 2008. He was diagnosed 15 years and 5 months after he started working at Samsung Electronics.

Case 6 began working at the Onyang Assembly and Packaging facility (Line 1) on May 24, 1993. He separated from Samsung Electronics on 1998 December 31. He worked at Samsung Electronics for a total of 5.67 calendar years. His work history is described in the table below:

Dates of assignment	Department	Process	Tasks
1993 May 24 – 1998 Dec 31	PKG Line M (extant)	Plating in finish process	Maintenance of wafer load/unload piece of TIN tools. Make-up task of TIN tools included: cleaning tool interior, and filling and replacing consumables. Make-up tasks accounted for 50% of work time. Heating plating chemicals accounted for 30% of work time. Office work accounted for 20% of work time.
1998 Dec 31	Resigned		

4.5 Reconstructed exposures for carcinogens known to cause the diagnosed cancers in the cases

4.5.1 Case 1

Case 1 was assigned to SEGs based on the work history of Case 1 described in Section 4.4.1.

No overtime was reported for Case 1 in the KOSHA Personal Epidemiological Investigation Report. ENVIRON assumed Case 1 worked 8 h per day, 6 days per week for 50 weeks per year for the calculation of equivalent work years, where a work year is equal to 2000 hours of work per calendar year. Review of the process chemicals and by-products to which Case 1 had potential exposure while working on Line 3 did not identify potential exposure to AML-causing agents in the SEGs where Case 1 was employed. Therefore, there were no reconstructed exposures for AML-causing agents.

4.5.2 Case 2

Case 2 was assigned to SEGs based on the work history of Case 2 described in Section 4.4.2.

No overtime was reported for Case 2 in the KOSHA Personal Epidemiological Investigation Report. ENVIRON assumed Case 2 worked 8 h per day, 6 days per week for 50 weeks per year for the calculation of equivalent work years, where a work year is equal to 2000 hours of work per calendar year. Review of the process chemicals and by-products to which Case 2 had potential exposure while working on Line 3 did not identify potential exposure to AML-causing agents in the SEGs where Case 2 was employed. Therefore, no exposures were reconstructed for the evaluation of AML risk.

4.5.3 Case 3

Case 3 was assigned to SEGs based on the work history of Case 3 described in Section 4.4.3 .

No overtime was reported for Case 3 in the KOSHA Personal Epidemiological Investigation Report. ENVIRON assumed Case 3 worked 8 h per day, 6 days per week for 50 weeks per year for the calculation of equivalent work years, where a work year is equal to 2000 hours of

work per calendar year. Review of the process chemicals and by-products to which Case 3 had potential while working on Line 1 did not identify potential exposure to agents classified as a carcinogenicity hazard for leukemia in general, or ALL specifically. Therefore, no exposures were reconstructed for the evaluation of ALL risk.

4.5.4 Case 4

Case 4 worked in QE Inspection on Line 1: The work tasks for Case 4 fall into five different SEGs.

Overtime was reported for Case 4 in the KOSHA Epidemiologic Investigation Report: In addition to the regular work shift, which ENVIRON assumed to be 8 h per day, 6 days per week for 50 weeks per year, Case 4 worked 4 h overtime 12-13 days per month. ENVIRON assumed Case 4 worked 4 h overtime 13 days per month, 12 months per year.

A review was conducted for the process chemicals, by-products, ionizing radiation and formaldehyde to which Case 4 had potential exposure while working on Line 1.

According to the KOSHA Epidemiologic Investigation Report for Case 4, the equipment use record indicated Case 4 worked for 30 months in the X-ray room, 5.8 days per month. This corresponds to a total of 1392 h (over 2.5 years), and equals 0.70 equivalent 2000 h work years. ENVIRON measured ionizing radiation in the QE Inspection room to be 7×10^{-5} to 1×10^{-4} mSv/h. For the exposure reconstruction, the maximum measured value was used. The maximum dose received in one calendar year (5.8 days per month for 12 months per year, or 557 h) is computed to be:

$$1 \times 10^{-4} \text{ mSv/h} \times 557 \text{ h/yr} = 0.0056 \text{ mSv}.$$

The cumulative dose of ionizing over the 30 months of performing the X-ray task is estimated to be:

$$1 \times 10^{-4} \text{ mSv/h} \times 2000 \text{ h/yr} \times 0.70 \text{ yr} = 0.14 \text{ mSv}.$$

After accounting for the time Case 4 spent in the X-ray room, the remaining duration of her employment was divided equally among the five SEGs. In equivalent 2000 h work years, Case 4 was assumed to spend 0.73 work years in each of the five SEGs.

Formaldehyde was measured by ENVIRON in the Worker Exposure Characterization Study in the Packaging – Tin Plating Line 1 SEG. A total of 10 industrial hygiene samples were collected: As 8 h TWA, these data are approximately lognormally distributed with GM = 0.0058 mg/m^3 and GSD = 1.19. For this lognormal distribution, the arithmetic mean ("AM") is 0.0059 mg/m^3 (0.0048 ppm) and the 75th percentile of the distribution is 0.0065 mg/m^3 (0.0053 ppm). The median is equal to the GM, 0.0058 mg/m^3 (0.0047 ppm). Considering the equivalent work years, the mean cumulative exposure to formaldehyde for Case 4 is estimated to be 0.0043 mg/m^3-yr (0.0035 ppm-yr).

4.5.5 Case 5

Case 5 was assigned to SEGs based on the work history of Case 5 described in Section 4.4.5.

Overtime reported for Case 5 in the KOSHA Epidemiologic Investigation Report included 4 h overtime on regular work days and 8-12 h on other days, with only 2-3 days off work per month. ENVIRON assumed that Case 5 worked 12 h per day, 28 days per month. From this assumption, Case 5 was estimated to work 10.16 work years, where one work year equals 2000 h/yr. Review of the process chemicals and by-products to which Case 5 had potential exposure (while working on Line 1 did not identify potential exposure to any AML-causing agents. Therefore, no exposures were reconstructed for the evaluation of AML risk.

4.5.6 Case 6

Case 6 worked on Line 1 and was assigned to SEGs based on the work history of the individual. Case 6 was estimated to be potentially exposed to trichloroethylene as a result of processes conducted in the adjacent process areas where TCE-wetted swabs were used. Potential exposures incurred as the result of work tasks performed by other, nearby workers are termed "by-stander" exposures.

Overtime reported for Case 6 in the KOSHA Epidemiologic Investigation Report included 4 h overtime on regular work days and 8-12 h on holidays three times per month. ENVIRON assumed that Case 6 worked 12 h per day, 28 days per month. Case 6 reported spending 20% of the work day doing office work: ENVIRON assumed that there was no potential for exposure during the time Case 6 performed office work. Excluding the time spent in the office, Case 6 was assumed to spend 9.6 h per day in the process areas. Given 9.6 h per day, 28 days per month and 12 months per year, Case 6 was determined to spend an equivalent of 9.14 work years in the process areas.

Trichloroethylene use was discontinued in April 1995, such that Case 6 had potential exposure to TCE for 1.93 calendar years. Considering over-time, and time-spent in the office, Case 6 spent 9.6 h per day in the process areas. Over 1.93 calendar years, this time in the process areas equals 3.11 equivalent 2000 h work years.

Review of the process chemicals and by-products to which Case 6 had potential exposure due to specific work activities on Line 1 did not identify potential exposure to any NHL-causing agents. Therefore, no exposures were reconstructed for the evaluation of NHL risk for direct exposure resulting from Case 6 work activities.

However, Case 6 had potential exposure to TCE as a by-stander to work activities in adjacent process areas. The work activity utilizing TCE involved the wetting of swabs with TCE, which were then used to clean products. This activity was conducted in the Marking and Trim/Form process areas, which have a separate ventilation system from the Tin-Plating process area in which Case 6 worked. The potential exposure of Case 6 to TCE, therefore, was incurred by Case 6 walking through the process areas with TCE use. No monitoring data were available for TCE for this, or any task in the available datasets. As a result, a mathematical model was used to predict the exposures to Case 6 as a by-stander to this TCE use. The mathematical model is described in detail separately. The model estimated by-stander exposures to be 2.10 mg/m^3

(0.40 ppm) as an 8 h TWA, based on 100 min duration of TCE use. ENVIRON assumed that Case 6 spent 30 min in the process areas with TCE use, such that the potential exposure of Case 6 is 0.13 mg/m^3 (0.058 ppm) as an 8 h TWA. Based on 3.11 work years of potential exposure, the cumulative dose is estimated to be 0.405 mg/m^3-yr (0.076 ppm-yr).

4.6 Exposure characterization in epidemiological studies used to inform weight-of-evidence for carcinogenicity classification

Based on the process area and SEGs to which the individual cases were assigned, the following carcinogens – known to cause at least one of the specific types of cancer diagnosed in the six cases – were used in processing, anticipated to be present as a by-product, or otherwise measured and detected in the SEGs to which one or more of the cases were assigned:

- Ionizing radiation was measured for all process areas on Line 1 including areas associated with the Packaging-Molding and Packaging-Tin Plating SEGs. In addition, an x-ray inspection instrument located the QE Inspection room was used periodically by Packaging-Molding and Packaging-Tin Plating employees. The x-ray inspection instrument was used to closely examine product from the two SEGs to identify certain defects that could impact the product's functionality. The equipment was used in a closed configuration that ensured that shielding to prevent ionizing radiation leakage from the instrument was in place prior to operation through the use of interlocks. Ionizing radiation is classified as carcinogenic to humans and is widely recognized by authoritative sources to cause all types of leukemia except chronic lymphocytic leukemia, and also solid tumors, including lymphoma;

- Formaldehyde was detected in the Line 1 Packaging-Molding and Test-MBT SEGs. Although formaldehyde was not used at Samsung and not anticipated to be present as a by-product, its presence is not entirely unexpected because it is a common indoor air contaminant. Formaldehyde is classified as carcinogenic to humans and is recognized by authoritative sources to cause nasopharyngeal cancer and AML. There is currently no convincing evidence that it causes other types of cancer, including non-Hodgkin's lymphoma.
- Trichloroethylene was used in the Packaging-Trim/Form and Packaging-Marking SEGs during 1991 to 1995. Samsung discontinued use of TCE as a solvent in April 1995. Trichloroethylene is anticipated to be classified as carcinogenic to humans via all routes of exposure by the US EPA in the fourth quarter of 2011, after undergoing a 10 year review process (US EPA 2009). TCE is currently classified as a probable human carcinogen (Group 2A) by the IARC (1995); nevertheless, the IARC has recently described the evidence that TCE exposure causes "site-specific cancers" in humans as "convincing" (IARC 2009) and noted that many epidemiological studies have been published since the 1995 review. Consistent with the US EPA (2009) review, the IARC identified the evidence as strongest for kidney cancer, and also noted associations between TCE exposure and non-Hodgkin's lymphoma and liver cancer (IARC 2009).

4.6.1 Ionizing radiation

All types of ionizing radiation are classified as known to cause cancer by the IARC, US EPA, and other authoritative sources. Ionizing radiation is recognized for causing cancers at multiple

sites, including all types of lymphohematopoietic cancers except for chronic lymphocytic leukemia ("CLL") (Ghissassi 2009). Therefore, it is well accepted that exposure to ionizing radiation at high doses causes AML.

The epidemiological evidence for high doses of ionizing radiation exposure to cause lymphohematopoietic cancers (as well as other cancers) is strong and indisputable. Much of the evidence used to inform risk assessments of low dose ionizing radiation comes from nearly 87,000 survivors of the atomic bombings in Japan, known as the Life-Span Study ("LSS") cohort, who were exposed to high doses of ionizing radiation (NRC (NAS), 2006). Other supporting evidence is provided by cohorts exposed to ionizing radiation during medical treatment for cancers and occupational cohorts of nuclear workers. The BEIR VII relied on mortality data for the period 1950-2000 for the LSS cohort to estimate leukemia risks from ionizing radiation at low doses (NRC (NAS), 2006). The BEIR VII also analyzed data from other supporting studies and found the results to be compatible with the BEIR VII model. Nevertheless, the doses received by the LSS cohort were significantly higher on average than those seen in a 15 country multisite study of nuclear workers (Cardis et al. 2005). This study is the largest study to date of workers exposed to low doses of ionizing radiation. Approximately 90% of a total of 407,391 nuclear workers employed in one of 154 facilities received cumulative doses less than 50 millisievert (mSv) and less than 0.1% received cumulative doses greater than 500 mSv. The average cumulative dose for the cohort was 19.4 mSv. The excess relative risk ("ERR") of leukemia in the cohort was 1.98 (95% CI 0 – 8.47) per sievert (1000 mSv). Based on the results in this study, Cardis et al. (2005) conclude that a small excess risk of leukemia (excluding chronic lymphocytic leukemia) exists even at low doses received in occupationally-exposed radiation workers.

Study	**Exposure Characterization**	**Dose measurement [1]**	**Risk estimates [2] (95% CI)**
407,391 nuclear workers employed in one of 154 facilities in 15 countries Cardis et al. 2005	Cumulative doses (mSv) 90% of workers received cumulative doses < 50 mSv Less than 0.1% received cumulative doses > 500 mSv average cumulative dose=19.4 mSV	 per 1 Sv 100 mSv	 ERR=1.98 (0–8.47) RR=1.20 [3]
NOTES: Abbreviations: ERR=excess relative risk, RR=Relative Risk, Sv=sieverts, mSv=millisieverts [1] Bone marrow dose. [2] Risk estimates are for leukemia excluding chronic lymphocytic leukemia. [3] Relative risk (RR) is calculated based on a linear relative risk Poisson regression model, RR=1+β*Z where Z is the cumulative dose equivalent in sieverts (Sv) and β=ERR			

In contrast, the highest levels of workplace exposure to ionizing radiation measured at the Samsung facilities (0.0001 mSv/h or 0.2 mSv per year assuming constant doses over 2000 hours per year) were below the reported range of average annual exposures worldwide to natural radiation sources (mean 2.4 mSv, range 1 – 10 mSv) (NRC (NAS), 2006).

4.6.2 Formaldehyde

The IARC classifies formaldehyde as a Group 1 carcinogen (known human carcinogen). Formaldehyde has been listed as a Group 1 carcinogen since 2006 based on human evidence of nasopharyngeal cancer since 2006. In 2010, the IARC added leukemia, particularly myeloid leukemia, to the list of cancers caused by formaldehyde exposure (IARC 2009, Baan, 2009).

The conclusion that formaldehyde exposure causes leukemia remains controversial. In 2010, the US EPA classified formaldehyde as carcinogenic to humans by inhalation for nasopharyngeal cancer, leukemia (primarily AML), and Hodgkin's lymphoma in its draft external review for the Integrated Risk Information System program (EPA 2010). The National Academies, National Research Council ("NRC")recently reviewed the draft external review for formaldehyde and concluded that the US EPA assessment failed to support the conclusion that formaldehyde exposure causes leukemia (NRC (NAS), 2011). The committee had several substantive criticisms of the draft risk assessment including: the EPA grouped all types of leukemias and lymphomas despite evidence that these represent diverse cancers that are not closely related and the EPA speculated extensively with respect to how formaldehyde reacts in the body but did not provide adequate evidence in its assessment that formaldehyde causes leukemia (NRC, 2011).

Baan et al. (2009) summarized the proceedings for the recent IARC meeting and singled out one epidemiological study (Hauptmann et al. 2009), published since the previous IARC assessment (IARC, 2006), as increasing the epidemiological evidence for formaldehyde to cause leukemia, particularly myeloid leukemia.. Hauptman et al. (2009) reported that embalming was significantly associated with an increased risk for myeloid leukemia; significant trends were reported for cumulative years of embalming (P trend=0.020) and for increasing surrogates of peak formaldehyde exposure (P trend=0.036). Beane Freeman et al. (2009) reported no excess deaths due to myeloid leukemia, with 44 cases observed and 49 cases expected (SMR = 0.90; 95% CI 0.67-1.21) among the formaldehyde-exposed. Nevertheless, myeloid leukemia was weakly and not statistically significantly associated with peak formaldehyde exposure and average exposure (P trend=0.13 and P trend=0.43, respectively). Peak exposure was defined as short term exposure, typically less than 15 minutes, exceeding the 8-hr TWA for the job category. No association was observed between myeloid leukemia and cumulative formaldehyde exposure.

Study Population	Exposure Characterization	Exposure estimates	Risk estimates [1] (95% CI)
Funeral home directors and embalmers Hauptmann et al. 2009	Cumulative formaldehyde exposure	> 9253 ppm-hrs (4.7 ppm-yrs) (> 11,365 mg/m^3-hrs) (> 5.8 mg/m^3-yrs [2])	OR=3.1 (1.0 – 9.6)
	Years of employment in embalming	> 34 years	OR=3.9 (1.2 – 12.5)
	Number of embalmings	> 3068	OR=3.0 (1.0 – 9.2)
	Peak formaldehyde exposure	> 9.3 ppm (> 11.4 mg/m^3)	OR=13.1 (1.4–116.9)
25,619 workers employed in formaldehyde-producing and -using industries Beane Freeman et al. 2009	Peak formaldehyde exposure	≥ 4 ppm (≥ 4.9 mg/m^3)	RR=1.78 (0.87 – 3.64)
	Average exposure	≥ 1 ppm (≥ 1.2 mg/m^3)	RR=1.61 (0.76 – 3.39)
	Cumulative exposure	≥ 5.5 ppm-yrs (≥ 6.8 mg/m^3-yrs)	RR=1.02 (0.48–2.16)

NOTES:
Abbreviations: OR=Odds Ratio, RR=Relative Risk, CI=Confidence Interval
[1] Risk estimates are for myeloid leukemia
[2] Conversion of ppm-hrs to ppm-yrs (mg/m^3-hrs to mg/m^3-yrs) assumes 1950 working hours per year.

The formaldehyde exposures estimated for Case 4 have a mean 0.0059 mg/m^3 (0.0048 ppm) as an 8 h TWA, which yielded a mean cumulative exposure estimate of 0.0043 mg/m^3-yr (0.0035 ppm-yr). These exposures are much lower than the exposures associated with increased risk of myeloid leukemia in the epidemiological studies used to inform the classification of formaldehyde as a Group 1 carcinogen that causes myeloid leukemia. In addition, the mean 8 h TWA for formaldehyde measured in the Packaging-Tin Plating SEG where Case 4 worked (0.0059 mg/m^3 or 5.9 µg/m^3) is within the range reported in ambient outdoor air (mean = 3.44 µg/m^3, range: 0.7–45.03 µg/m^3) in the United States (US EPA, 2010). In addition, the exposure estimated for Case 4 is less than the dose expected from smoking one cigarette: The median yield of formaldehyde in the mainstream smoke of cigarettes is 49.5 µg (range: 12.2 – 105.8 µg) per cigarette (IARC, 2004).

4.6.3 Trichloroethylene

Trichloroethylene is currently classified as a Group 2A carcinogen (probably carcinogenic to humans) (IARC, 1995); however, this classification was based on existing evidence from 16 year ago. In a recent external draft toxicological review of TCE for the Integrated Risk Information System (IRIS), the US EPA has classified TCE as carcinogenic in humans by all routes of exposure (EPA, 2009), a classification equivalent to IARC Group 1 (the final assessment is expected to be released later this year). The US EPA (2009) describes the epidemiological evidence of a causal association between TCE exposure in humans and kidney cancer as convincing and the epidemiological effects of a causal association between TCE exposure and non-Hodgkin's lymphoma as "compelling" but less convincing than for kidney cancer. The evidence for liver cancer and biliary tract cancer is limited.

These target effects are consistent with those described in a recent IARC technical report that identified gaps and needs to resolve the carcinogenicity of TCE, as well as several other Group 2A and 2B substances (IARC, 2009). The IARC (2009) concluded that the epidemiological literature as a whole "provides convincing evidence of a causal association between TCE exposure in humans and site-specific cancers, particularly in the kidney." The IARC also discussed epidemiological studies that have shown increased risks of NHL associated with TCE exposures. Since the last review of its carcinogenicity by IARC (1995), five case-control studies (Hardell et al., 1994; Persson and Fredrikson, 1999; Wang et al., 2009; Seidler et al., 2007 Costantini et al., 2008), two cohort studies (Hansen et al., 2001; Rasschou-Nielsen et al., 2003), and a meta-analysis (Mandel et al., 2006) have been published that show associations between TCE exposure and non-Hodgkin's lymphoma (NHL). Several studies found increased risks and/or increased risks with increasing TCE exposure (Wang et al., 2009; Seidler et al., 2007; Hansen et al., 2001; Rasschou-Nielsen et al., 2003). Raaschou-Nielsen et al. 2003 showed increasing risks with duration of employment. Although a surrogate of exposure was used in this study to calculate risks, a related study showed that during the time period of the study, TCE concentrations decreased based on data collected from Danish regulatory agencies at 150 companies during the years 1947–1989 (n=1,075 air measurements): geometric mean (GM)=329 mg/m^3 [61 ppm] for period 1947-1959; GM=260 mg/m^3 [48 ppm] for 1960–1969; GM=53 mg/m^3 [10 ppm] for 1970–1979 (see Raaschou-Nielsen et al. 2002). The IARC (2009) reported that a significant increased risk (summary relative risk estimate [SRRE]=1.59, 95% CI: 1.21–2.08) among TCE subcohorts in the highest quality studies was found in the meta-analysis (Mandel et al., 2006). Nevertheless, Mandel et al. (2006) noted several limitations of the study data included in their meta-analysis that prevent a causal interpretation between TCE exposure and non-Hodgkin's lymphoma. These limitations included variability in results in the highest quality studies (heterogeneity), limited exposure assessments, lack of exposure-response trends, and inconsistent findings in epidemiological studies of exposure and NHL.

Studies that informed the weight-of-evidence classification for TCE to cause NHL and which included estimates or indicators of exposure to TCE are described below for comparison purposes:

Study	Exposure Characterization	Metrics	Risk estimates (95% CI)
40,049 blue-collar workers at TCE-using companies in Denmark, 1964–1997	Subcohort with expected highest exposure levels, n=14,360 (First employed before 1980, worked one year or more) [1]		
	Duration of employment	1 – 4.9 yrs	SIR=1.5 (1.1–2.1)
Rasschou-Nielsen et al. 2003		≥ 5 yrs	SIR=1.6 (1.1–2.2)
	Year first employed	Before 1970	SIR=1.6 (1.1–2.3)
		1970 – 1979	SIR=1.5 (1.0–2.1)
Case-control study of 710 lymphoma cases in Germany	Cumulative exposure (parts-per-million-years) (ppm-yrs)	> 35 ppm-yrs (> 188.1 mg/m^3-yrs)	$OR_{All\ lymphoma}$=2.1 (1.0–4.8) *P-trend=0.14*
		> 35 ppm-yrs (> 188.1 mg/m^3-yrs)	$OR_{B\text{-}cell\text{-}NHL}$=2.3 (1.0–5.3) *P-trend=0.08*
Seidler et al. 2007			

NOTES:
SIR=Standardized Incidence Ratio
OR=Odds Ratio
[1] During this time period, TCE concentrations decreased based on data collected from Danish regulatory agencies at 150 companies during the years 1947–1989 (n=1,075 air measurements): geometric mean (GM)=329 mg/m^3 for period 1947-1959; GM=260 mg/m^3 for 1960–1969; GM=53 mg/m^3 for 1970–1979 (see Raaschou-Nielsen et al. 2002)

The reconstructed cumulative exposure estimated for Case 6 to TCE was 0.405 mg/m^3-yr (0.076 ppm-yr). This cumulative exposure is three-orders of magnitude lower than the exposure estimates associated with increased risk for NHL in the epidemiological studies that were used to inform the weight-of-evidence with respect to the classification of TCE to cause NHL.

4.7 Risk Calculations Based on Reconstructed Exposures

Individual lifetime risk of AML from exposure to ionizing radiation and leukemia were calculated for Case 4. Individual lifetime risk of NHL (combined with risk of kidney cancer and liver and biliary tract cancer) based on lifetime exposure to trichloroethylene was estimated for Case 6.

4.7.1 Risk of Leukemia from Exposure to Ionizing Radiation for Case 4

According to the BEIR VII preferred model, the lifetime attributable risk of incident leukemia (any kind except CLL) is 20 cases of leukemia per 10 mSv for a woman age 18 to 65 years old. To provide a conservative estimate of risk, we assumed Case 4 received a maximum biological dose of 0.056 mSv of ionizing radiation per year for the ages when she worked during her adult life. Her estimated risk of being diagnosed with leukemia would be 1.5 per 100,000 (about 1 in 66,500) and her estimated risk of dying from leukemia would be 1.2 per 100,000 (about 1 in 81,600). The actual risk for a woman exposed to a dose of 0.056 mGy per year for 3 years between ages 18 and 20 would be lower. Her estimated risk of being diagnosed with leukemia would then be 1.2 per 1,000,000 and her estimated risk of dying from leukemia would be less than 1 in 1,000,000.

4.7.2 Risk of Leukemia from Exposure to Formaldehyde for Case 4

Based on the mean exposure value of 0.0059 mg/m^3 (5.9 µg/m^3 or 0.0048 ppm) as an 8-hr TWA for formaldehyde, the mean reconstructed cumulative exposure for Case 4 was 0.0043 mg/m^3-yrs (4.3 µg/m^3-yr) [0.0035 ppm-yr)]. The lifetime average equivalent concentration (based on 70 years) was 0.02 µg/m^3 [1.6×10^{-5} ppm]. Therefore, the lifetime extra cancer risk associated with

formaldehyde exposure was 0.95 x 10^{-6} for Case 4. This risk can be interpreted as follows: If an individual were to continuously breathe air containing formaldehyde at an average of 0.02 µg/m^3 [1.6 × 10^{-5} ppm] over an entire lifetime (70 years), that person would hypothetically have less than one in 1,000,000 increased chance of developing leukemia from breathing formaldehyde in air, or less than 1 extra leukemia in 1,000,000 persons.

4.7.3 Risk of non-Hodgkin's Lymphoma from Exposure to Trichloroethylene for Case 6

Based on the maximum modeled exposure estimate of 0.13 mg/m^3 (130 µg/m^3 or 0.058 ppm) as an 8-hr TWA, the reconstructed cumulative exposure for Case 6 was 0.405 mg/m^3-yr (405 µg/m^3-years or 0.076 ppm-years). The lifetime average equivalent concentration (based on 70 years) was 1.98 µg/m^3 [0.000368 ppm]. The upper bound inhalation unit risk for three cancers (kidney, lymphoma, and liver cancer) combined is 4.1 x 10^{-6} per µg/m^3 [2.2 x 10^{-2} per ppm]. Therefore, the lifetime extra risk for developing any of the three cancers (kidney, lymphoma, and liver cancer) associated with TCE exposure is 8.1 x 10^{-6}. This is interpreted as follows: if an individual were to continuously breathe air containing TCE at an average of 1.98 µg/m^3 (0.000368 ppm) over an entire lifetime (70 years), that person would hypothetically have no more than a 1 in 123,300 increased chance of developing any one the following cancers from inhalation of TCE: kidney cancer, non-Hodgkin's lymphoma, or liver cancer. Because this is a lifetime extra cancer risk for three cancers combined, this estimate overestimates the increased chance of developing lymphoma specifically (or kidney cancer specifically or liver cancer specifically). In fact, the EPA adjusted the inhalation unit risk value for kidney cancer incidence (1.02 x 10^{-6} per µg/m^3 [5.49 x 10^{-3} per ppm]) based on the relative contributions to extra risk for cancer incidence from TCE exposure using relative risk estimates for each of the three cancers reported in an epidemiological study (Rasschou-Nielsen 2003). As a result, the lifetime extra risk estimate may be overestimated by a factor of 2 (US EPA 2009).

5 Summary of Findings and Risks

5.1 Finding for Case 1

Case 1 did not work in an area where a chemical/ agent classified by authoritative bodies as a known or probable carcinogen with potential to cause **acute myelocytic leukemia** was measured and detected in the work environment. Therefore, ENVIRON did not reconstruct exposures to carcinogens and could not calculate an excess lifetime risk for Case 1. On this basis, there is no evidence that workplace exposures to known or suspected carcinogens increased the risk of AML for Case 1.[9]

5.2 Finding for Case 2

Case 2 did not work in an area where a chemical/agent classified by authoritative bodies as a known or probable carcinogen with potential to cause **acute myelocytic leukemia** was measured and detected in the work environment. Therefore, ENVIRON did not reconstruct exposures to carcinogens and could not calculate an excess lifetime risk for Case 2. On this basis, there is no evidence that workplace exposures to known or suspected carcinogens increased the risk of AML for Case 2.

5.3 Finding for Case 3

Case 3 did not work in an area where a chemical/agent classified by authoritative bodies as a known or probable carcinogen with potential to cause **acute lymphocytic leukemia** was measured and detected in the work environment. Therefore, ENVIRON did not reconstruct exposures to carcinogens and could not calculate an excess lifetime risk for Case 2. On this basis, there is no evidence that workplace exposures to known or suspected carcinogens increased the risk of ALL for Case 3.

5.4 Finding for Case 4

The likelihood that workplace exposure to ionizing radiation increased the risk of **acute myelocytic leukemia** for Case 4 is very low. This finding is based on the following:

- Case 4's workplace dose relative to background dose levels was low. The highest levels of workplace exposure to ionizing radiation measured at the facility (0.0001 mSv/h or 0.2 mSV per year assuming a constant dose received over 2000 hours per year) were below the range of average annual exposures worldwide to natural radiation sources (mean 2.4 mSv, range 1 – 10 mSv) (NRC of NAS), 2006).
- The average annual estimated dose to ionizing radiation for Case 4 was 0.056 mSv. This is substantially below the average doses reported in radiation workers (mean = 19.4 mSv) in epidemiological studies that have quantified exposures in relation to excess risks of leukemia.[10]

9 Case 1 worked for fewer than two years. In general, the minimum latency (time since first exposure to diagnosis) for AML is two years and is based on leukemia developing after use of chemotherapeutic agents to treat a primary cancer. The latency interval varies according to type of cancer and the specific chemical or agent of interest.

10 Epidemiological studies measuring ionizing radiation in the semiconductor industry in relation to excess risk of cancer have not been conducted.

- ENVIRON calculated an increased risk of being diagnosed with leukemia from the estimated annual dose (0.056 mSv) received in the workplace is 1.5 per 100,000 (about 1 in 66,500) and her estimated risk of dying from leukemia would be 1.2 per 100,000 (about 1 in 81,600).

The likelihood that workplace exposure to formaldehyde increased the risk of AML for Case 4 is very low. This finding is based on the following:

- Reconstructed cumulative exposures for Case 4 were 0.0043 mg/m3-yrs [0.0035 ppm-yrs]. This estimate is substantially below cumulative exposure estimates (5.83 mg/m3-yrs [4.75 ppm-yrs] and > 6.76 mg/m3-yrs [>5.5 ppm-yrs]) associated with increased risk estimates reported in epidemiological studies (Hauptmann 2009; Beane Freeman 2009) considered by authoritative bodies in their weight-of-evidence evaluation that resulted in the classification of formaldehyde as a carcinogen known to cause AML by the IARC (Baan 2009) and the US EPA (US EPA 2010).
- ENVIRON calculated an excess lifetime risk for developing AML associated with Case 4's estimated cumulative formaldehyde exposure of 0.95×10^{-6}. The excess lifetime risk of acute myelocytic leukemia from her workplace exposure to formaldehyde was below the upper bound on the range of residual cancer risks (i.e. excess lifetime cancers risks between 1×10^{-6} and 1×10^{-4}) considered and typically allowed by the US EPA when setting regulatory policy.

5.5 Finding for Case 5

Case 5 did not work in an area where a chemical/ agent classified by authoritative bodies as a known or probable carcinogen with potential to cause **acute myelocytic leukemia** was measured and detected in the work environment. Therefore, ENVIRON did not reconstruct exposures to carcinogens and could not calculate an excess lifetime risk for Case 5. On this basis, there is no evidence that workplace exposures to known or suspected carcinogens increased the risk of AML for Case 5.

5.6 Finding for Case 6

The likelihood that workplace exposure to trichloroethylene increased the risk of non-Hodgkin's lymphoma for Case 6 is very low. This finding is based on the following:

- Reconstructed cumulative exposure for Case 6 was 0.405 mg/m^3-yrs [0.076 ppm-yrs] and substantially below the cumulative exposure estimate (188.1 mg/m^3-yrs [35 ppm-yrs]) reported in an epidemiological study that quantified exposures (Seidler 2007) in relation to elevated NHL risk. This study was considered by the US EPA in its weight-of-evidence evaluation that resulted in the classification of TCE as a known carcinogen (US EPA, 2009).
- ENVIRON calculated an excess lifetime risk for developing any of three cancers (kidney, lymphoma, and liver cancer) associated with TCE exposure of 8.1×10^{-6}. The model for the US EPA risk assessment is based on human exposure data for kidney cancer and adjusted based on the relative potency of TCE to cause one of three types of cancer (kidney cancer, NHL, and liver cancer) using epidemiological data (US EPA 2009). As a

result, the excess lifetime risk for occurrence of NHL alone would be lower than the calculated excess lifetime risk for the three cancers combined. In addition, the excess lifetime risk of these three cancers from Case 6's estimated workplace exposure to trichloroethylene was within the upper bound on the range of residual cancer risks (i.e., excess lifetime cancers risks between 1×10^{-6} and 1×10^{-4}) considered and typically allowed by the US EPA when setting regulatory policy.

6 Summary and Conclusions

This study is the first to quantify historical exposures to chemical and physical agents in semiconductor fabrication, packaging and assembly lines in Korea. The job exposure matrix developed in this study, which utilizes similar exposure groups and statistical descriptions of industrial hygiene monitoring data, can be applied more broadly to other employees in the same work areas and used for subsequent epidemiological studies. The use of quantitative exposure estimates in an epidemiologic study would represent a significant advancement of improvement, as previous studies have only used qualitative exposure characterizations (e.g. broadly job title categorizations, and employment duration). On the other hand, well-conducted epidemiological studies to date have not found any consistent evidence of increased rates of cancers among semiconductor workers.

In this study, the exposure reconstruction was used to more precisely estimate past exposures to agents classified as having potential to cause the specific cancers diagnosed in six employees who allege that their cancers were caused by workplace exposures. Based on these reconstructed exposures, ENVIRON calculated their excess lifetime cancer risks for lymphohematopoietic cancers using standard methods. In addition, ENVIRON reviewed epidemiological studies that estimated risks in relation to quantified exposures and which authoritative bodies cited in their weight-of-evidence evaluations of carcinogenicity to determine whether the reconstructed exposures were comparable to exposures where relevant cancer risks have been reported to be increased.

Based on a review of the estimated exposures, risk calculations and comparisons to quantified exposures in publications referenced by authoritative bodies, ENVIRON concludes the following:

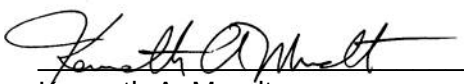
- Without exception, the six subject employees either were not exposed to measurable concentration of any of the relevant carcinogens, or were exposed to extremely low levels of these agents – none consistent with the increased risks seen at much higher levels in the literature
- Specifically, chemicals/agents classified by authoritative bodies as known or suspected to cause the specific types of cancer were not measurable (i.e., had not been used and/or had been measured but were not detected) in the work environment for four employees (Cases 1, 2, 3 and 5).
- For two employees (Cases 4 and 6) potentially exposed to carcinogens (ionizing radiation and formaldehyde for Case 4 and trichloroethylene for Case 6) during their employment, estimated cumulative exposures and/or doses were minimal and substantially below (by one or more orders of magnitude) exposures reported in epidemiological studies that demonstrated increased risks of specific types of lymphohematopoietic cancers using quantified exposures.
- For these same two employees, excess lifetime risks for developing their diagnosed cancers as a result of exposure to known or suspected carcinogens in their workplace were below the upper bound on the range of residual cancer risks (i.e., excess lifetime cancer risks between 1×10^{-6} and 1×10^{-4}) considered acceptable by the US EPA when

setting regulatory policy. Therefore, the probability that workplace exposures to these agents increased the risk of the diagnosed cancers of Case 4 (acute myelocytic leukemia) and Case 6 (non-Hodgkin's lymphoma) is very low.

- Therefore, for these six employees, reconstructed historical exposures to agents known or suspected to cause leukemia or lymphoma were absent (Cases 1, 2, 3, and 5) or insufficient (Cases 4 and 6) to conclude that these workplace exposure caused or contributed to their cancer risks. In other words, absent their exposures at Samsung, their risks would have been unchanged.

Final Report: Exposure Reconstruction and Risk Opinion for Six Employees Diagnosed with Hematopoietic Cancers

Author/Lead Investigator



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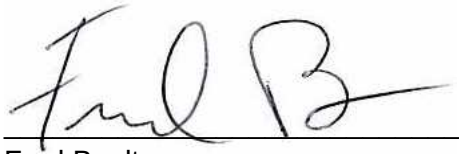

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7 References

ACGIH. 2011 TLVs and BEIs: Threshold Limit Values for Chemical Substances and Physical Agents. 2011.

Adami, H. O., D. Hunter, et al. Textbook of Cancer Epidemiology. Second, 1-748. 2008. NewYork, Oxford University Press.

Alexander, DD, Mink, PJ, et al. 2007. The non-Hodgkin lymphomas: a review of the epidemiologic literature. Int J Cancer. 120 Suppl 12: 1-39.

American Cancer Society. Leukemia--Acute Lymphocytic. http://www.cancer.org/Cancer/Leukemia-AcuteLymphocyticALLinAdults/DetailedGuide/index. American Cancer Society. Last update 10-29-2010a. [Accessed February 23, 2011].

American Cancer Society. Leukemia--Acute Myeloid (Myelogenous). http://www.cancer.org/Cancer/Leukemia-AcuteMyeloidAML/DetailedGuide/index. American Cancer Society. Last update 12-7-2010b. [Accessed February 22, 2011].

Armstrong TW, Boelter FW, Rasmuson JO. 2009. Exposure Reconstruction. In: *Mathematical Models for Estimating Occupational Exposure to Chemicals*, 2nd Ed. Keil CB, Simmons CE, Anthony TR (Editors). AIHA Press, Fairfax, VA p. 157-186.

Baan R, Grosse Y, Straif K, et al. 2009. A review of human carcinogens: Part F: chemical agents and related occupations. Lancet Oncol;10:1143-1144.

Beall, Colleen, Bender, Thomas J, et al. 2005. Mortality Among Semiconductor and Storage Device Manufacturing Workers. Journal of Occupational & Environmental Medicine. October 2005 - Volume 47 - Issue 10 - pp 996-1014.

Beane Freeman LE, Blair A, Lubin JA, et al. 2009. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute cohort. J Natl Cancer Inst 101:751-761.

Bender, TJ, Beall, C, et al. 2007. Cancer incidence among semiconductor and electronic storage device workers. Occup Environ Med. 64: 30-36.

Boice, JD, Jr., Marano, DE, et al. 2010. Cancer mortality among US workers employed in semiconductor wafer fabrication. J Occup Environ Med. 52: 1082-1097.

Cardis E, Vrijheid M, Blettner M, et al. 2005. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. Brit Med J 331:77.

Constantini AS, Benvenuti A, Vineis P, et al. 2008. Risk of leukemia and multiple myeloma associated with exposure to benzene and other organic solvents: Evidence from the Italian multicenter case-control study. Am J Ind Med 51:803-811.

Darnton, A., S. Wilkinson, et al. 2010. A further study of cancer among the current and former employees of National Semiconductor (UK) Ltd., Greenock. Health and Safety Executive; Institute of Occupational Medicine United Kingdom.

Day GA, Esmen NA, Hall TA. 1999. Sample size-based indication of normality in lognormally distributed populations. Appl Occup Environ Hyg 14: 376-383.

Deschler, B, Lubbert, M. 2006. Acute myeloid leukemia: epidemiology and etiology. Cancer. 107: 2099-2107.

ECETOC. Framework for the Integration of Human and Animal Data in Chemical Risk Assessment. Technical Report 104, 1-130. 2009. Brussels.

Ghissassi FE, Baan R, Straif K., et al. 2009. A review of human carcinogens: Part D: radiation. Lancet Oncol 10;751-752.

Grulich, AE, Vajdic, CM. 2005. The epidemiology of non-Hodgkin lymphoma. Pathology. 37: 409-419.

Hansen J, Raaschou-Nielsen O, Christensen JM, et al. 2001. Cancer incidence among Danish workers exposed to trichloroethylene. J Occup Environ Med 43:133-139.

Hardell L, Eriksson M, Degerman A. 1994. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. Cancer Res 54:2386-2389.

Hauptmann M, Stewart PA, Lubin JH, et al. 2009. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. J Natl Cancer Inst 101:1696-1708.

Herrick RF, Stewart JH, Blicharz D, et al. 2005. Exposure assessment for retrospective follow-up studies of semi-conductor- and storage device-manufacturing workers. J Occup Envion Med 47:983–995.

Hoar (1983/198) Job exposure matrix methodology. J Toxicol Clin Toxicol; 21: 9-26.

Ignacio and Bullock. 2006. *A Strategy for Assessing and Managing Occupational Exposures*, 3rd Ed. AIHA Press, Fairfax, VA.

International Agency for Research on Cancer (IARC). 1995. Monographs on the Evaluation of Carcinogenic Risks to Humans. Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals. Volume 65. Lyon, France, International Agency for Research on Cancer.

International Agency for Research on Cancer (IARC). 2002. Monographs on the Evaluation of Carcinogenic Risks to Humans. Non-Ionizing Radiation, Part 1: Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields. Volume 80. Lyon, France, International Agency for Research on Cancer.

International Agency for Research on Cancer (IARC). 2004. Monographs on the Evaluation of Carcinogenic Risks to Humans. Tobacco Smoke and Involuntary Smoking. Volume 83. Lyon, France, International Agency for Research on Cancer.

International Agency for Research on Cancer (IARC). 2006. Monographs on the Evaluation of Carcinogenic Risks to Humans. Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxypropan-2-ol. Volume 88. Lyon, France, International Agency for Research on Cancer.

International Agency for Research on Cancer (IARC). 2009. Identification of research needs to resolve the carcinogenicity of high priority IARC carcinogens. IARC Technical Publication 42. Lyon, France, International Agency for Research on Cancer.International Agency for Research on Cancer (IARC). Monographs on the Evaluation of Carcinogenic Risks to Humans. http://monographs.iarc.fr/ENG/Classification/index.php. Last update 2011. Accessed on 5-6-2011.International Agency for Research on Cancer (IARC). Monographs on the Evaluation of Carcinogenic Risks to Humans. http://monographs.iarc.fr/ENG/Classification/index.php. Last update 2011. Accessed on 5-6-2011.

International Agency for Research on Cancer (IARC). Cancer Incidence in Five Continents Vol. IX. [IX]. 2007. Lyon, France, International Agency for Research on Cancer.

Korean National Cancer Center. Annual Report of Cancer Statistics in Korea in 2008. http://www.ncc.re.kr/english/infor/kccr.jsp. Korean National Cancer Center. Last update 2010.

Lee H-E, Kim E-A, Park J, Kang S-K. 2011. Cancer mortality and incidence in Korean semiconductor workers. Saf Health Work;2:135-147.

Lenhard, R., R. Osteen, et al. The American Cancer Society's Clinical Oncology. 2001. Atlanta, American Cancer Society.

Mandel JH, Kelsh MA, Mink PJ, Alexander DD, et al. 2006. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review. Occup Environ Med 63:597-607.

National Cancer Institute. What You Need To Know About Leukemia. http://www.cancer.gov/cancertopics/wyntk/leukemia. National Cancer Institute. Last update 11-25-2008. Accessed on 2-22-2011.

National Research Council (NRC) of the National Academies. 2006. Health risks from exposure to low levels of ionizing radiation: Biological Effects of Ionizing Radiation (BEIR) VII, Phase 2. Washington, DC, National Academy of Sciences.

National Research Council (NRC) of the National Academies. 2011. Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (Prepublication Copy, April 2011). Washington, DC: National Academies Press.

National Toxicology Program (NTP). 2004. 11th Report on Carcinogens. National Toxicology Program.

Nichols, L, Sorahan, T. 2005. Cancer incidence and cancer mortality in a cohort of UK semiconductor workers, 1970-2002. Occup Med (Lond). 55: 625-630.

Occupational Safety and Health Research Institute (OSHRI) of the Korean Occupational Safety and Health Agency (KOSHA). 2009. Epidemiological investigation reports for cases. KOSHA.

Persson B, Fredrikson M. 1999. Some risk factors for non-Hodgkin's lymphoma. Int J Occup Med Environ Health 12:135-142.

Raaschou-Neilsen O, Hansen J, Thomsen BL, et al. 2002. Exposure of Danish workers to trichloroethylene, 1947–1989. Applied Occup Environ Hyg 17:693-703.

Raaschou-Neilsen O, Hansen J, McLaughlin JK, et al. 2003. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. Am J Epidemiol 158:1182-1192.

Rothman, KJ, Greenland, S. 2005. Causation and causal inference in epidemiology. Am J Public Health. 95 Suppl 1: S144-S150.

Schottenfeld, D. and J. F. Fraumeni. Cancer Epidemiology and Prevention. Third, 1392-1416. 2006. New York, Oxford University Press.

Seidler A, Möhner M, Berger J, et al. 2007. Solvent exposure and malignant lymphoma: a population-based case-control study in Germany. J Occup Med Toxicol 2:2. Shields, PG. 2006. Understanding population and individual risk assessment: the case of polychlorinated biphenyls. Cancer Epidemiol Biomarkers Prev. 15: 830-839.

Skibola, CF. 2007. Obesity, diet and risk of non-hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev. 16: 392-395.

St.Jude Children's Research Hospital. Disease Informations: Leukemias / Lymphomas: Acute Promyelocytic Leukemia (APL). http://www.stjudeschildrenshospital.org/stjude/v/index.jsp?vgnextoid=9c0c061585f70110VgnVCM1000001e0215acRCRD&vgnextchannel=bc4fbfe82e118010VgnVCM1000000e2015acRCRD. St.Jude Children's Research Hospital. Last update 2011. Accessed on 23 February 2011.

U.S. Environmental Protection Agency (US EPA) 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Washington, DC: Office of Research and Development, US Environmental Protection Agency, EPA/600/8-90/066F.

U.S. Environmental Protection Agency (US EPA). 2009. Toxicological Review of Trichloroethylene in support of Summary Information on the Integrated Risk Information System (IRIS). External Review Draft, October 2009. Washington, DC: US Environmental Protection Agency.

U.S. Environmental Protection Agency (US EPA). 2010. Toxicological Review of Formaldehyde – Inhalation Assessment in support of Summary Information on the Integrated Risk Information System (IRIS). External Review Draft, June 2010. Washington, DC: US Environmental Protection Agency.

Wang R, Zhang Y, Lan Q, et al. 2008. Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women. Am J Epidemiol 169:176-185.

Zhang L, Steinmaus C, Eastmond DA, et al. 2009. Formaldehyde exposure and leukemia: A new meta-analysis and potential mechanisms. Mutation Research;681:150-168.