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Review Article

Review for Retrospective Exposure Assessment Methods Used in Epidemiologic Cancer Risk Studies of Semiconductor Workers: Limitations and Recommendations

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ABSTRACT

This article aims to provide a systematic review of the exposure assessment methods used to assign wafer fabrication (fab) workers in epidemiologic cohort studies of mortality from all causes and various cancers. Epidemiologic and exposure–assessment studies of silicon wafer fab operations in the semiconductor industry were collected through an extensive literature review of articles reported until 2017. The studies found various outcomes possibly linked to fab operations, but a clear association with the chemicals in the process was not found, possibly because of exposure assessment methodology. No study used a tiered assessment approach to identify similar exposure groups that incorporated manufacturing era, facility, fab environment, operation, job and level of exposure to individual hazardous agents. Further epidemiologic studies of fab workers are warranted with more refined exposure assessment methods incorporating both operation and job title and hazardous agents to examine the associations with cancer risk or mortality.

1. Introduction

The wafer fabrication (fab) process in the semiconductor industry involves the use of potentially hazardous chemicals such as metals, photoactive chemicals, organic solvents, acids, and toxic gases in a wide variety of combinations and workplace settings. This industry also presents risks associated with radiation exposure, shift work, and other occupational stressors, including ergonomic issues.

Several epidemiologic studies have been conducted to examine whether workers employed in wafer fab operations are subject to either increased cancer risk or mortality [1–9]. Results have been mixed, which may, in part, be due to the exposure assessment methodologies used.

Detailed and accurate exposure classification of workers is crucial for epidemiologic studies to compare the incidence and/or mortality rate among subgroups of workers. Misclassification of study participants by exposure can severely affect observed health risks of these workers. The development of groups with similar exposure distributions in fab operations, however, can be challenging because people often work in large and diverse environments with multiple operations and perform a wide spectrum of operations and tasks, resulting in complex exposure patterns. In addition, the nature of this highly competitive industry and rapid changes in technology and materials make it difficult to investigate chronic health risks, such as cancer, associated with exposures.

Given that the retrospective exposure assessment methods used to classify wafer fab workers have not been fully evaluated, we performed a systematic review of the exposure surrogates and type of estimates that have been used in epidemiologic studies to evaluate cancer risk and mortality. We also discuss recommendations for the construction of retrospective assessment strategies in future studies of fab operations.

2. Materials and methods

Epidemiologic and exposure assessment studies of silicon wafer fab operations in the semiconductor industry were collected through an extensive literature review of articles reported until the end of 2017, without limitation to the study period. The keywords used in the literature search were “semiconductor

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operations," "wafer fab operation," and "clean room environment" singly and in combination.

Retrospective exposure assessment methods used in cancer risk and mortality studies were reviewed. Reproductive toxicity and health risks other than cancer and mortality were included in this review for descriptions of the processes and examples of how exposure groups have been developed. The source of work/exposure histories and type of exposure surrogates used to classify fab workers are identified and discussed. Manufacturing of crystal ingots, chips on the fabricated wafers, and other electronic products are excluded for this study, although two studies included workers from companies that performed final assembly of the chips [3,5] and that manufactured storage devices such as disks, disk drives, and box assembly [1,2]. We summarized the type of cancer significantly associated with exposure to fab environments and the exposure metrics used to classify semiconductor workers. Semiconductor operations from wafer fab through the manufacturing of chips on the fabricated wafer are described in detail to understand well the retrospective exposure assessment each used in epidemiologic study (See the Appendices).

3. Results

In total, nine epidemiologic articles published between 1985 and 2011 evaluated mortality from all causes and various cancers or incidence of various cancers among workers in silicon wafer fab facilities of the semiconductor industry. Five cohort study groups from three countries (two from five studies in the UK, two from three studies in USA and one from Republic of Korea) were evaluated (Table 1). Work history sources and information collected and the various exposure surrogates that were used in each study to classify semiconductor workers are summarized in Tables 1 and 2, respectively. No study was performed in plants manufacturing substrates or processing wafer substrates with gallium arsenide or gallium arsenide phosphide. Health risks for workers who manufacture crystal ingot have not been evaluated.

In the British semiconductor industry, cancer incidence and cancer mortality for two cohorts have been evaluated by five studies [4,6–9]. One study identified a cohort of 1,807 workers at a semiconductor factory in the West Midlands region of England during the period of 1970–1982 [9]. The study identified a cluster of melanoma in female workers, which disappeared with a further 7 years of follow-up (1970–1989) [8]. Employment, years since first employment, and duration of employment at the facility and, in particular, in the photo masking department (indicated as a surrogate for UV exposure) were the exposure metrics. Nichols and Sorahan [7] incorporated an additional 13 years of mortality (1970–2002) and 11 years of cancer incidence (1971–2000) data on this cohort and classified them by the year of hire (pre 1940; 1940–1949; 1950–1959; 1960–1969; 1970–1979), years since first employment ($<$10, 10–19, 20-29, $\geq$30), and duration of employment in the parent company ($<$5, 5-9, $\geq$10 years). Although elevated standardized registration ratio (SRRs) were found for the rectum, pancreas, and skins cancers other than melanoma, specific associations with wafer fab jobs or work could not be associated with mortality or incident risk, because, as indicated in this article, only start and end dates of working at the factory were originally abstracted from the company records.

Another cohort group of 4,388 semiconductor workers in the UK during 1970–1999 was studied [6]. Specific years of employment and work area were available on the study participants. Only a single 10-year cut-off period was used for a latency (time since first employment) analysis. Workers were categorized by employment duration ($>$1 year), start year of employment (before 1982 or after), and ever/never having worked in the fab room. The authors found significant or nonsignificant excesses of lung [SRR = 2.7, 95% confidence interval (CI) = 1.4–4.9], stomach (SRR = 4.4, 95 % CI = 0.9–1.3), and breast cancer (SRR = 1.3, 95% CI = 0.8–2.1) in female fab workers and brain cancer (unadjusted standardized mortality ratio (SMR) = 4.0, 95% CI = 0.8–11.7) in male workers. Only lung cancer among females was found to be significantly associated with the fab room.

Accordingly, the Health and Safety Executive and the Institute of Occupational Medicine conducted a further study of this cohort, looking particularly at the work done by the women who developed the lung, breast, and stomach cancers and the men who developed brain cancer [4]. A retrospective exposure assessment was undertaken to gather more detailed exposure information about the processes, work practices, and working conditions at the NSUK plant, since it opened in 1972, from records and interviews with long-serving employees. In addition to the exposure surrogates used in study by McElvenny et al [6], exposure to International Agency for Research on Cancer (IARC) category 1 and 2 substances (i.e., arsenic and its compounds, ceramic fibers, antimony trioxide, carbon tetrachloride, trichloroethylene, chromium trioxide and chromic acid, and sulfuric acid mist), radiation sources, shift work, or a group of key chemicals (i.e., solvents, acids and toxic gases) were assessed. All the exposure assessments were binary-based because subjective estimates of intensities were not considered by the authors to be sufficiently reliable, and occupational hygiene measurements were not available for the whole lifespan of NSUK. This study found that females either first employed before and during 1982 or fab female workers working for $<$10 years since first employment were significantly associated with lung cancer incidence.

In America, three epidemiological studies were conducted at companies that manufactured semiconductors, including three IBM factories that were the subject of two studies [1,2]. The three factories manufactured silicon wafers, chips, and other electronic storage devices. The two studies used electronic work histories before 1984 and the Corporate Employee Resource Information System records for 1984 and later to identify jobs at the end of each year [10]. These were used to compile work histories from which were developed facility-specific lists of unique combinations of division code, division name, department code, department name, job code, and job name (DDJ) (and presumably year, since manufacturing era was used as an analytic variable). From these combinations, the authors developed exposure groups of similar activities, which were evaluated as always or frequently in a clean room. Each DDJ was further classified as "potentially exposed" (i.e., including any type of work other than offices) or "unexposed". Potential exposure to solvents, metals/acids/bases, nonionizing radiation, ionizing radiation, and work in a clean room was also assessed.

Beall et al [1] evaluated mortality among 126,836 employees at these three IBM facilities using the retrospective exposure assessment results developed by Herrick et al [10] The authors evaluated mortality pattern by facility, time since first exposure ($>$15 years), duration of employment ($>$5 years), manufacturing era, and process which was alone or in combination. The authors found ovarian cancer, pancreatic cancer, central nervous system cancer, breast cancer, and prostate cancer to be significantly associated with more than one of several fab environment characteristics, even though constant associations with specific fab exposure variable were not observed. An additional investigation of the same cohort focused on cancer incidence for a subset of the participants (N = 42,612 at the East Fishkill and N = 46,912 at the San Jose sites) [2]. The investigators found that workers who had a latency of $\geq$15 years at San Jose and worked for $\geq$5 years showed significant standardized incidence ratio (SIR) for prostate cancer (SIR = 1.2, 95% CI = 1.1–1.4). Constant association of fab environment with cancer risk between two studies evaluating same cohort was not detected.

Table 1
Work history information sources and exposure surrogates used in epidemiologic studies of wafer fab workers.

Authors	Country (name of plant)	Number of plants	Information sources on work history and work-related exposures	Exposure surrogates used to classify study participants
Sorahan et al (1985) [9]	UK	1	Company personnel records	Year from first employment
Sorahan et al (1992) [8]	UK	1	Company personnel records	Employment status, employment duration
McElvenny et al (2003) [6]	UK	1 (Scottish)	Four sources within company (personnel/ payroll/pension/occupational health)	Employment duration (<10/≥ 10 years), start year of employment (<and ≥1982), and plant work area (fab or nonfab areas)
Beall et al (2005) [1]	US (IBM)	3 (East Fishkill/Burlington/ San Jose*)	IBM's electronic personnel file (position/hire date and end date/location code/division name/department code/department name/ job code/job title)	Facility/years since first record of employment/ years worked/manufacturing era/type of process/potential exposure including work other than offices (yes/no)/work group
Nichols and Sorahan (2005) [7]	UK	1	Company personnel records	Year of hire/period from 1st employment/ duration of employment
Bender et al (2007) [2]	US (IBM)	2 (East Fishkill/San Jose*)	Company electronic personal files (position/ hire and end date/location code/division name/department code/department name/ job code/job title)	Facility/years since first record of employment and years worked/manufacturing era/type of process/potential exposure including work other than offices (yes/no)
Boice Jr et al (2010) [3]	US	2 large companies located in 10 cities in five states	Company electronic work history information for job and exposure classification	Occupation (fab/nonfab)/duration of employment as job title/occupation and manufacturing eras
Darnton et al (2010) [4]	UK	1 National Semiconductor UK Ltd. at Greenock	Company historical documents, interviews with long-serving employees and questionnaire	Occupation (fab/nonfab)/duration of employment)/qualitative exposure assessment: carcinogens, radiation, group of chemicals, and shift work (yes/no)/start year of employment (<and ≥1982)
Lee et al (2011) [5]	Republic of Korea	5 companies and 8 factories	No description of the methods used to collect work history data or information and to classify fab workers	Hire date (<1991, 1992–1997, 1998–2003 and ≥ 2004)/job title/duration of employment

fab, fabrication.
* Facility developed, manufactured, and packaged storage product devices such as hard disk drives, network servers, magnetic tape drivers, and micro drives.

Table 2
Exposure metrics used to classify wafer fabrication workers in epidemiologic cancer risk studies.

Authors*	Facility	Manufacturing era	Fab/nonfab	Operation	Job	A group of agents or matrix	Specific agent including carcinogen
Sorahan et al (1985) [9] *A*	One wafer fab facility	1970–1982	N/A	N/A	N/A	N/A	N/A
Sorahan et al (1992) [8] *A*	One wafer fab facility	1982–1989 (7 years of follow-up)	N/A	N/A	N/A	N/A	N/A
Nichols and Sorahan (2005) [7] *A*	One wafer fab facility	1970–2002 (13 years of follow-up)	N/A	N/A	N/A	N/A	N/A
McElvenny et al (2003) [6] *C*	One wafer fab facility	Fab/nonfab area	N/A	N/A	N/A	N/A	N/A
Beall et al (2005) [1] *B*	Wafer fab manufacture, masking and packaging (East Fishkill and Burlington‡)	1983/1984–1999 1965–1973/1974–1988/1989–1999	Classified by facility	N/A	N/A	N/A	N/A
	Hard disk drives, network servers, and micro drives (San Jose)	1965–1972/1973–1989/1990–1999	Fab† versus nonfab	N/A	N/A	N/A	N/A
Bender et al (2007) [2] *B*	Wafer fab, masking and packaging (East Fishkill and Burlington)	Early/middle/late (no specific date)	Fab	N/A	Operators & Equipment service technician/Engineers, supervisors & managers	N/A	N/A
Boice Jr et al (2010) [3]	Hard disk drives, network servers, and micro drives (San Jose‡) (34 wafer fab facilities)	Early/middle/late (no specific date)	Nonfab	Office/nonoffice	Professional or office workers; back-end workers and other workers	N/A	N/A
Darnton et al (2010) [4] *C*	One wafer fab facility	N/A	Fab	N/A	N/A	Solvent, acid, toxic gases	Antimony trioxide, arsenic & its compounds, carbon tetrachloride, chromic acid, sulfuric acid, etc
Lee et al (2011) [5]	9 wafer fab facilities and 2 fab packaging facilities	N/A	Classified by job	N/A	Classified by facility (operator, service engineer, process engineer, supervisor, utility	N/A	N/A

fab, fabrication.
"N/A" indicates that exposure surrogates were not analyzed in the classification of study participants.
* Same character (*A, B, C*) indicates the same study cohort group.
† No classification of type of fab (wafer fab and chip packaging).
‡ East Fishkill & Burlington: masking, clean rooms, test/probe/dicing/slicing/die removal/wire bonding, process equipment maintenance, research and development, other manufacturing; San Jose: head fabrication, test/dice/slice, assembly, facilities/laboratories, research & development, other manufacturing.

Another study, supported by the Semiconductor Industry Association, evaluated cancer mortality for 100,081 silicon wafer manufacturing workers who worked between 1968 and 2002 at two large US semiconductor companies [3]. This study evaluated exposures based on a retrospective exposure assessment conducted by Marano et al [11] who categorized each worker into one of five exposure groups (fab operators and equipment service technicians; fab professionals; nonfab professionals and office workers; nonfab back-end workers; and other nonfab workers) on the basis of job-department combinations of >37,000 department names and >8,600 job titles. It was not clear why process operators were grouped with equipment service technicians (i.e., maintenance workers). Fab eras were classified into three groups early-, middle-, and late-technology eras (the basis for, and the specific dates of, these eras were not provided). Boice Jr et al [3] concluded that work in the wafer fab clean rooms was not associated with increased cancer mortality overall or mortality from any specific form of cancer.

In Republic of Korea, Lee et al [5] evaluated cancer mortality (N = 113,443) and incidence (N = 108,943) in wafer manufacturing workers, including chip assembly workers, and other electronic devices. Hire date, job title in fab versus assembly operations, and duration of employment longer than 1 month provided by the employer were retrospectively assessed. Five job titles, i.e., operator, service engineer (maintenance worker), process engineer, utility workers and supervisor were used to classify workers. The incidences of non-Hodgkin's lymphoma in female operators in chip assembly manufacturing and thyroid cancer in male process engineers in the fab operation were found to be significantly increased.

A total of nine epidemiologic cancer risk studies conducted in semiconductor industries evaluated 10 types of cancer to be significantly associated: melanoma, rectum, prostate, pancreas, thyroid, breast (no. of studies = 2), brain, ovarian, lung, non-Hodgkin's lymphoma, and stomach (n = 1).

4. Discussion

To date, a total of nine studies have examined the association between cancer incidence or mortality and the fab work environment in integrated circuit manufacturing operation of the semiconductor industry. The exposure assessment in several of the studies (particularly the earlier studies) was minimal (e.g., duration of employment). More recent studies have conducted more in-depth exposure assessments, but no study has used a tiered exposure assessment approach that incorporates facility, fab environment, operation, job, and level of exposure to hazardous agents by fab era to develop similar exposure groups. Moreover, we found that to date, no epidemiologic cancer risk or mortality study of fab workers has assessed exposure to specific carcinogens quantitatively or semi-quantitatively.

The goal of an exposure assessment is to be as accurate and precise as possible. Any exposure group developed should have the same exposure distribution to all agents to which the individual participant is exposed. Unfortunately, this approach is not always possible because of the lack of information or specificity of jobs, tasks, or operations as they relate to the study participants. Measurements of exposure, or even use of chemicals, may be poorly documented or may not even be available, even though a couple of studies reported airborne level of chemicals. Boice Jr et al [3] reported that over 98% of the air chemical samples were below occupational exposure limits from 12,300 long-term and short-term personal samples collected for over 60 different chemicals during the years 1978–2004. The fast-paced changes in the technology, the complex work environment and operations, and the large number of hazardous agents, add to the complexity of the assessment. It is especially challenging to construct retrospective exposure profiles over the long latency period for most cancers. Thus, it is incumbent on the assessor to collect as much information as possible and to carefully evaluate how best to use that information.

Hammond et al [12] developed a three-tiered approach to their exposure assessment to reflect increasing specificity of exposures in wafer fab operations, (first, fab vs. nonfab; second, five work groups; and third, agent-specific exposure ranking or qualitative exposure level) for a reproductive study of fab operation workers. They used a cluster analysis to group workers similarly exposed to a series of agents, who then were investigated for reproductive effects and exposure patterns of these agents across jobs. These patterns were identified because there was considerable overlap and similarity in exposures across the groups due to the proximity of the operations and re-circulated air.

We present here a paradigm of how an exposure assessment could look for the semiconductor industry, which modifies the approach used by Hammond et al [12]. All fab workers could be basically classified into (1) fab and nonfab within facility, by (2) type of operation, (3) job title within the wafer fab operation, and (4) various exposure agents and be stratified by manufacturing era. Unique groups of workers with the same types and distribution of exposures should be grouped together, where possible. Because, however, of the possibly substantial overlap of jobs, tasks, or chemical use, the proximity of operations with different agents, and the recirculation of contaminated air from other operations, development of specific and unique highly detailed groups may not be possible. Therefore, the approach used by Hammond et al [12] (i.e., hierarchical cluster analysis or a principle components analysis) may be useful in developing broad exposure groups with similar patterns of exposure rather than multiple groups exposed to different specific chemicals. This approach has the additional advantage of allowing the evaluation of possible synergistic effects. Alternatively, to account for different groups of workers with overlapping exposures, a different set of groups may need to be developed for each specific exposure. This latter approach would be challenging, given the many agents of interest in the industry. In any case, a more detailed approach than what has been used in current cancer studies of the semiconductor industry is needed to better characterize cancer risks. Evaluating risk on a crude level of exposure as has been done in several studies (e.g., manufacturing era or duration of employment) may lead to misclassification of exposure, which could lead to dilution of risks and the inability to detect an association that actually exists.

4.1. Type of facility

There are three types of manufacturing environments in a semiconductor manufacturing facility i.e., manufacture of blank silicon wafers, fabrication of integrated circuit (IC) on silicon wafer (fab operation), and separation and packing of chips on the wafers (chip assembly) (Fig. A1 in Appendices). Characteristics of the operations, the chemicals used, and hazardous agents generated differ considerably among these three types of environments, with the number and amount of chemicals used in the fab operation substantially outweighing other two operations. No studies have evaluated health effect of workers who manufactured blank silicon wafers. Boice Jr et al [3] and four UK studies studied only silicon wafer manufacturing facilities, while both silicon wafer and chip operations and other electronic storage devices (disk and disk drives or ferrite cores) were included in three studies (Table 2) [1,2,5]. Therefore, the processes and chemicals in the nine studies discussed here differed, which may be one reason why epidemiologic findings have differed.

4.2. Fab versus nonfab

After the broader categorization of facility type, the next assessment tier that should be considered is to determine whether study participants worked inside or outside of the fab environment. Of the nine studies reviewed, three studies that did not examine differences of cancer risk among fab and nonfab workers due to the lack of sufficient exposure information [7–9]. Cancer risk by exposure to fab environment was evaluated by several exposure classifications: such as office worker versus manufacturing workers [5], fab versus nonfab workers [3], ever exposure versus unexposed to fab [1,2].

4.3. Wafer manufacturing era within the fab environment

Many epidemiologic studies account for changes in processes and chemicals over time. Some consider annual changes whereas others consider time periods or eras. Changes in the semiconductor industry have occurred quickly and often, and therefore identifying changes and the specific year they were implemented is challenging. One approach may be to base era on the diameter of the wafer. As the size of the wafer increased over time, the level of automation increased, not just for the handling of the wafers but also for other components of the process, including the level of manual handling of chemicals, e.g., photo resister (PR), dipping of wafers in chemical baths, refilling of chemicals in tools, delivery of chemicals to the fab, pushing and pulling wafers, collection and removal of wastes from the fab, and cleaning of metal deposition. Thus, the level of automation substantially varied among three categories of wafer sizes and may generally be classified as no automation for <3.25 inch wafers, some automation for 3.25–5 inch wafers, and substantial automation for 5–12 inch wafers [10].

As found by Herrick et al [10], the fab technology, the wafer size, the circuit width on the chip, and work characteristics have changed over time and differed greatly not only from plant to plant but also within plant. Therefore, Herrick et al [10] classified the fab era into three categories (1963–1973, 1974–1983, and 1984–1999) based on the information on the year the fab facility was built or upgraded, process type and wafer size, clean room class (how clean the clean room had to be), the extent of manual work and handling of chemicals by workers, the level of personal protective equipment required, and several other characteristics. More details of each of these eras can be found in their report [10]. Marano et al [11] followed a similar approach, but no information was provided to compare with Herrick et al's eras.

Assessing participants by duration of employment will not necessarily account for differences in exposures over time. Although a participant with long duration must have worked in earlier years, participants with short duration may have worked either in earlier or later years. As a result, the correlation between exposure levels and duration of employment may not be high [13]. Years since first employment provides some indication of era, but the cut-points used in the analysis may not be related to changes in era, which could result in participants in different eras being grouped. Combining duration and first employment is likely to have a similar limitation. Without knowing the characteristics of the processes over time, comparison of study results cannot be accurately made.

4.4. Type of operation within the fab environment

No study has evaluated mortality or cancer risk among classified fab workers based on the type of fab operation (e.g., oxidation), even though the fab environment comprises several operations and job titles with different exposure characteristics (Table A1-A3 in *Appendices*). Marano et al [11] noted that breaking the fab operation into five finer operations (e.g., oxidation) was considered but not deemed possible due to the rapid changes to job and department titles. Herrick et al [10] combined fab operations but separated the masking operation. Beall et al [1] found several cancers associated with different parts of the process developed by Hsieh et al [14] who found significant associations with prolonged menstrual cycles in female workers among particular fab operations, such as photolithography and diffusion compared to nonfab workers. Although such associations do not necessarily mean causality, they do suggest that exposures generated from different operations could result in different health effects.

To subdivide fab workers into various exposure groups with distinctly different exposure profiles, the characteristics of the various operations and jobs or tasks in the fab environment must be evaluated. However, because of close proximity of operations, often similar exposures due to narrow boundaries among several fab operations, and frequent re-circulation of air that is mixed from multiple processes, it may be very difficult to identify fab workers with different exposure profiles. For example, the boundaries among diffusion, thin film, metallization, ion implantation, epitaxy, and chemical vapor deposition (CVD) process groups were reported in one study to be less fixed than the boundaries between these process groups and the set of masking, photolithography, and etching process groups [12]. This pattern, of course, may vary among plants and even within plant. Hammond et al [12] assigned the ion implantation, epitaxy, and CVD in the "diffusion" or "thin films or metals" process groups in their study because of proximity of work location and similarity of the operations. Thus, it may be necessary to combine fab operations with similar exposure characteristics due to the proximity of operation, work practices, and ventilation characteristics. Exposure differences among fab operations with fully automated operations may not be substantial. In contrast, in fab manufacturing eras where manual handling was done, classification of fab workers by type of fab operation should be considered.

4.5. Type of job within the fab environment

Five studies conducted in the UK did not evaluate job title at all (Table 2). As shown in Table 1, exposure agents and levels can be different across job titles. There may be particular challenges in evaluating job title [11]. One unfortunate trend identified in this industry, as has been found in other industries, is the evolution of specific job titles to more general job titles. Associated with this trend may be the rotation of individuals among what were formerly multiple jobs. Although this trend may actually make exposure assessment easier, it may make it impossible to relate a health outcome to a single causative agent.

It may be practical to combine multiple job titles, such as operators, from several fab operations based on the characteristics of fab work environment including proximity of operation, generality of operation works, level of automation, health hazards exposed, and air circulation pattern. As a minimum, however, it may be possible to distinguish operators from maintenance workers. Such differentiation may be important because although the frequency with which operators handle wafers and chemicals has decreased due to automation, maintenance work still requires hands on work to clean, repair, or change parts of process equipment, pumps, and exhaust ducts, which fab operators generally do not perform. For example, periodic maintenance of the ion implanter includes changing and cleaning of the ion source head, the manipulator, and the beam-line setup cap. The used parts or equipment are removed from the ion implanter, packed in a plastic bag, brought to the cleaning room, and cleaned there using various techniques such as brushing, blowing and bead blasting, etc.

Four studies have studied the association of cancer risk or mortality by job type alone [5] or in combination with other exposure surrogates such as facility, employment, or exposure duration [1–3] and manufacturing era [3]. The number of analytic groups has been limited (generally around 5–10), but this may, in part, be due to the difficulty in distinguishing uniquely exposed groups.

The classification of jobs performed in the fab operation, in particular, maintenance work, differed in these studies. A distinction in exposure between operators and maintenance workers was not considered in the study of Boice Jr et al [3], although the authors indicated that the two groups had different exposures and different patterns of exposure. Table 2 also shows how exposure patterns arising from performing maintenance work may be distinctly different from those of operators. Herrick et al [10] and Lee et al [5] each developed a unique maintenance group separate from the operators, but no further division within maintenance was made. To date, no cancer risk and mortality study has broken out the types of maintenance workers specific to the fab operation and the characteristics of the maintenance work. This differentiation by type of maintenance work, however, is not easy to link to study participants, especially for cancer studies that cover several decades, because often only "maintenance" is specified in work history records. It is especially difficult to assess more detailed characteristics, such as the frequency of preventive maintenance, brake maintenance and warranty maintenance work on the study participant level due to the irregular work schedule. Most companies probably lack maintenance work records that identify maintenance frequency and maintenance exposures over the time period necessary for cancer investigations. For example, in Republic of Korea, each maintenance worker is typically assigned to a specific fab operation or to specific utility equipment without a difference in job title. Thus, these workers often have the same job title but perform maintenance tasks with varying durations and frequencies in different processes and hence typically have different exposures to different agents.

In one exposure study of automated fab operations, most of the maintenance work with high exposure potential was generally outsourced to external workers, who typically performed one specific maintenance task in a specific operation [15,16]. In Republic of Korea, there are generally different companies that are contracted to perform various types of maintenance tasks either inside or offsite of the plant. Currently, faulty parts or equipment is generally sent to an external company for repair. This situation, i.e., various types of maintenance jobs are outsourced to external workers employed by many different employers, may make follow-up for an epidemiological study difficult. There is no description as to whether external workers were included as study participants in the studies reviewed here. In a Korean study [5], cancer risks for external workers were not evaluated (personal communication), although they were believed to be involved in several types of maintenance jobs in the plants.

How to classify maintenance workers could be one of the most challenging parts of an epidemiological study of fab workers. Investigators of one study of cancer and acrylonitrile interviewed workers to determine how much time specific maintenance workers spent in the acrylonitrile units [17]. It is even more challenging to trace workers who were employed at an external company. Many supervisors might have risen through the ranks of the production jobs and thus had, in the past, performed one or more of fab operations or maintenance, which should be considered for exposure classification. Complete work histories, therefore, may be particularly important for this group.

4.6. Exposure to individual specific agent or agent group including carcinogens

The usefulness of job titles, departments, and dates as analytic variables is generally limited without quantitative estimates of exposure to specific agents. Thus, in the last recommended tier, participants classified should be assessed for either (preferably) exposure to a specific agent or (often more practically) to an agent class (e.g., chlorinated solvents). Hundreds of chemicals are used in the fab environment, and fab workers may be exposed concurrently to multiple agents. Yet to date, no individual chemical agent has been assessed to evaluate cancer risk or mortality in a fab operation, although exposure to two physical agents, i.e., X-rays and shift work, and a general class of agents (carcinogens) was assessed in one study [4]. This assessment, however, was dichotomous exposure (ever, never) to the specific agent or agent class without hierarchically combining the assignment with the type of operation and job title.

Herrick et al [10] assessed relative dichotomous exposures to general classes of chemical (solvents, metals/acids/bases) and physical agents (ionizing and nonionizing radiation) by work group (e.g., masking). The ranking scheme was "0" if the agent class was absent or present in very small amounts or at few locations in the environment or facility or if the activities associated with the agent did not require work in clean rooms; "1" if the agent was extensively used in the work environment or facility, or if the activities associated with the agent were frequently/always conducted in clean room; and "2" if the agent was present in the environment or facility but in fewer locations, smaller amounts or lower concentrations than experienced by the work groups classified as "1" or if the activities were occasionally carried out in clean rooms [10]. This classification, however, was not used in the evaluation of cancer risk or mortality of fab workers.

As indicated above, based on the circumstances, such as a fab operator's low and concurrent exposure to multiple agents in well-controlled situations in the fab environment, it may not be possible to evaluate the level of agent-specific exposures for each fab worker or job. In particular, agent-specific evaluations present several challenges, including selection of the target agents based on fab-specific information, due to the complexity in exposure characteristics of fab operation. The low levels of exposure reported in this industry make estimating exposure levels challenging. Bayesian techniques are available for censoring up to 80% and should be considered [18]. Alternatively, guidelines to assessing exposures based on workplace characteristics have been identified and appear to be able to provide reasonable exposure estimates [19].

4.7. Job-specific questionnaire

Most epidemiologic studies conducted in semiconductor industry have used work history information provided by the companies to classify fab workers (Table 1). One study relied extensively on a job-specific questionnaire (JSQ) that was administered to workers who were familiar with the processes and chemicals used in the fab environment to obtain information on the patterns of work, the chemicals and other equipment used in the various jobs and processes, and the changes in jobs, conditions, and working practices over time [4].

JSQs also can be administrated to individuals who held specific jobs or worked in an area of interest to supplement the work histories and can be designed to determine each individual's process group, time spent near various devices, and tasks, including frequency and chemicals used (e.g., dopants or positive or negative photoresist). In the fab operation, JSQs can be useful to assess specific exposure characteristics of maintenance workers who perform various types of manual work either regularly or irregularly. In general, current and former workers can also provide supplemental information on job activities, use of personal protective equipment, and accidental gas leaks and spillage of chemicals that may better reflect what actually happened than what is available in records. Investigators have found that workers can remember other workers' tasks, even for long time periods such as those in cancer studies [17].

To supplement retrospective exposure assessment with exposure surrogates and refine the predictive value and specificity of exposure estimates in the very complex fab process, JSQs for fab workers may need to be developed to reduce misclassification. One such questionnaire is available from the National Cancer Institute (http://dceg.cancer.gov/tools/design/questionnaires/occupational-history-exposures/non-hodgkin-lymphoma-study-occupational-history).

JSQ should include type of facility, type of operation, and type of job by employment duration so that semiconductor workers can be classified similarly in terms of exposure to semiconductor environments. In particular, key questions for cancer risk studies with semiconductor workers should include the location of the facility, type of operation, and type of job by work duration. The name of the facility where workers were employed is used to estimate manufacturing era. The type of maintenance job should be specified, e.g., regular preventive, warranty, and irregular maintenance. Responses to this JSQ can be used not only to estimate retrospective exposure to operations and jobs in the semiconductor industry but also to associate with the risk of all causes of death and risk of disease, including cancer. The JSQ we developed and applied to this health study of semiconductor workers has been reported elsewhere [20].

In conclusion, we found that to date, no epidemiologic cancer risk or mortality study of fab workers has assessed exposure to individual specific carcinogens quantitatively or semi-quantitatively. Although exposure surrogates used in those studies included employment duration, manufacturing eras, ever worked in a fab operation, and on occasion, job title and broad classes of hazards, these may not sufficiently address the issue of variability of exposure within each classified fab work group and thus result in misclassification and dilution of health outcome associations. Misclassification due to crude exposure assessments may be one reason for the lack of inconsistency across study findings. To provide more insight into the complexities of the semiconductor industries and to improve exposure assessment for future cancer studies, a means to possibly distinguish different exposure subgroups within fab workers should be applied for fab exposure classification, such as a JSQ. Further epidemiologic studies that address the limitations of the retrospective exposure assessments of the previous fab workers are warranted to examine the association of fab work and environment with cancer risks or mortality.

Conflict of interests

The author declares no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.shaw.2018.05.005.

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