Review

The health impacts of semiconductor production: an epidemiologic review

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Background: Despite concerns over the harmful health effects of semiconductor production, epidemiological studies have shown mixed results.
Objectives: We aim to critically appraise epidemiologic studies to date, and to suggest future research and actions to protect workers in semiconductor industry.
Methods: Epidemiologic studies were identified through electronic database searches, review of reference lists of relevant published works, and expert consultations, and were narratively reviewed.
Results: Most evidence suggests reproductive risks from fabrication jobs, including spontaneous abortion (SAB), congenital malformation, and reduced fertility. Although chemicals have been suspected as causal agents, knowledge of the likely contribution(s) from specific exposures is still limited. Evidence of cancer risk seems to be equivocal. However, the available studies had serious limitations including healthy worker effects (HWEs), information bias, and insufficient power, all of which are associated with underestimation. Nevertheless, excess risks for non-Hodgkin's lymphoma (NHL), leukemia, brain tumor, and breast cancer were observed.
Conclusions: Monitoring and innovative research based on international collaboration with a focus on sentinel events are required.

Keywords: Adverse reproductive outcomes, Cancer, Epidemiology, Healthy worker effect, Information bias, Semiconductor, Statistical power

Introduction

The semiconductor industry began as a parts production sector of the microelectronic industry in the 1960s. However, with the growth of the computer industry, semiconductor manufacturing has taken the linchpin of the entire microelectronics industry. Semiconductor global sales revenue reached US$307 billion as of 2011,[1] and the size of workforce is also huge; for instance, the number of employees in just two countries – South Korea (hereafter Korea)[2] and Taiwan[3] – exceeds 290 000. This industry is typically characterized by highly specialized processes, rapid technological innovation, significant chemical use, and large-scale investment to support such innovation and mass production,[4] all of which could influence workers' health and safety.

Contrary to its 'clean' image represented by 'bunny suits', semiconductor production includes a wide variety of hazards. Work processes mainly consist of three steps – wafer manufacturing, fabrication, and packaging/testing, and at each step, there are various sub-processes. In particular, the wafer-fabrication process includes material deposition, photolithography, etching, and doping, all of which include the use of hazardous materials.[5] A variety of chemicals including organic solvents, acids, and metals are heavily used. Some individual chemicals are simply irritants to skin or respiratory organs, whereas others are carcinogens, reproductive toxins, and/or neurotoxins. Air recirculation systems designed to minimize dust make workers more vulnerable to effects from these chemicals both singly and in complex combinations. Physical hazards including extremely low-frequency electronic magnetic and radiofrequency radiation are not negligible, and are known to be associated with cancer development. In addition, there exist ergonomic hazards including awkward positions, repetitive work, shift work, and job stress, most of which are not unique but common to manufacturing industries in general. The detailed explanations of work process and potential hazards in semiconductor production are found elsewhere.[6–8]

However, not enough is known regarding the full range of potential health effects of such exposures. Technical development is so fast that it is nearly impossible to examine all of them, and the widespread practices of trade secrecy within the semiconductor

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DOI 10.1179/2049396713Y.0000000050

industry make the situation worse.[4] In this context, social as well as scientific debates have become intensified regarding causality and liability for suspected occupational diseases.

In 1979, the US National Institute for Occupational Safety and Health (NIOSH) conducted a health hazard evaluation in the Signetics fabrication plant in Sunnyvale, CA, where workers claimed chronic harmful exposure to chemicals. National Institute for Occupational Safety and Health identified chemicals as 'irritant' and 'narcotic' in nature, although their concentrations were all well below the permissible exposure levels. National Institute for Occupational Safety and Health concluded that 'a larger, more systematic study' was required to characterize medical problems and determine the size of the affected workforce.[9] The next year, the California Department of Industrial Relations in the U.S. reported that semiconductor workers were exposed to many hazardous chemicals including a variety of carcinogens and repro-toxic agents.[10] Shortly thereafter, groundwater contamination near a Fairchild semiconductor factory in San Jose was revealed, which affected the drinking water in thousands of households.[4] In 1985, a chemist at the IBM research facility in San Jose tried to alert top management after five of his 12 colleagues contracted cancer.[11] However, IBM had took no action until three more victims were identified, at which point they conducted an internal investigation.[12] In the late 1990s and 2000s, a series of suits were filed against IBM by its workers and their families who were struggling for recognition of work-relatedness of the workers' cancers and their children's birth defects.[4] Across the Atlantic, some female workers employed by National Semiconductor, Scotland (hereafter, NSUK) claimed the U.S. head office was responsible for their exposure to carcinogens. In response, the UK Health and Safety Executive (HSE) launched an epidemiologic investigation.[13]

Health concerns, once confined to the US and UK, have spread to the Asian countries along with the expansion of the global supply chain in the microelectronics industry. In the early 1990s, four workers died and about 200 workers were diagnosed with lead poisoning in one Thailand HDD company, and similar incidents were repeated across India, China, Taiwan, and Malaysia.[14] In the late 1990s, groundwater contamination similar to the San Jose case was identified in Taiwan.[14] In addition, the Korean government has investigated cancer risk among semiconductor workers in response to the rising concern over cancer cluster in Samsung Electronics.[15]

In the meantime, scientific evaluation of health risks has evolved. Based on the Swedish cancer registry, Vagero and Olin[16] first reported an excessive cancer incidence in electronic workers. Using the workers' compensation data in California, LaDou identified that the semiconductor sector had higher incidence of occupational illness, in particular, systemic poisoning, while the combined rates of occupational injuries and illnesses were lower compared to private industries in total.[6,17] The first cohort study result was reported in 1985 by the UK HSE.[18] About that time, IBM began an internal investigation of the cancer cluster described above; the results were not published until 10 years later and the focus was limited to brain cancer.[19] Since then, a series of epidemiological studies were launched, most of which were motivated by the struggles and lawsuits by workers and community residents.

Although several scientific papers have been published, there is still a dearth of knowledge on the health effects of semiconductor production.[20] In this article, we critically appraise the epidemiologic studies to date, and based on our review, suggest future research and actions to protect workers in the semiconductor industry. Epidemiologic studies were collected through electronic database searches, review of reference lists of relevant published works, and expert consultations, and narrative review of them was conducted. Compared to the previous reviews,[6,12] we extend the scope, both chronological and geographical; our review includes studies conducted in Asian countries, as well as those from the UK and the US, and covers more recent publications than were available at the time of the previous reviews.[12] In addition, we place more emphasis on epidemiologic methods, and cover health problems other than cancer and reproductive outcomes.

Reproductive Health

Concerns for reproductive health first received community attention in early 1980s, when residents' drinking water was contaminated by toxic solvents leaked from the nearby semiconductor factory in San Jose and abnormal pregnancy outcomes were reported. An epidemiologic study conducted in 1983 found a risk elevation for spontaneous abortion (hereafter, SAB) and congenital malformation (especially, cardiac anomaly) in the exposed neighborhoods.[21,22] The follow-up study covering the time up to 1985 failed to replicate this finding, although risk elevation for SAB was still significant when the analysis was limited to the contamination period of 1980–1981, which could not be explained by hydrogeologic modeling of contaminated groundwater.[23] Rightfully, the finding raised a question about adverse reproductive effects on workers who dealt with the chemicals directly inside the plant.

Reproductive toxicity is an important issue in semiconductor industry, because a majority of the workforce is females of childbearing age and hazardous effects could affect offspring. In addition, reproductive outcomes may act as sentinels for detecting occupational and environmental hazards with a long latency because of their relatively short latency from exposure.[24]

Spontaneous abortion is a relatively well-documented outcome among many reproductive problems in the semiconductor industry. An early clue was presented by a Finnish study in 1980, which found particularly higher risks for SAB among electronics workers compared to other manufacturing workers as well as the general population.[25] Based on a questionnaire survey of female workers and spouses of male workers in semiconductor industry, Pastides *et al.*[26] reported that working in diffusion (RR=2.18, 95% CI 1.11–3.60) and photolithography process (1.75, 0.77–3.25) was associated with higher risk for SAB, while through a community survey Lipscomb *et al.*[27] observed that women with a solvent exposure history in electronics production during the first trimester of pregnancy were more likely to experience SAB than controls (OR=3.34, 95% CI 1.42–7.81). The Semiconductor Health Study launched by the Semiconductor Industry Association (hereafter, SIA) is the most comprehensive reproductive health study in this industry. It covered 14 US companies with silicon-based wafer-fabrication rooms, and examined SAB in both a retrospective[28–30] and a prospective way,[30,31] menstrual cycles[32] and fertility[33] in a prospective design, and male fertility through a cross-sectional survey. In particular, its prospective component measured human chorionic gonadotropin through daily urine collection for about 6 months, in order to accurately assess menstrual cycles and early fetal loss.[30] They reported elevated risks for SAB among workers in fabrication processes, especially masking and photolithography.[29–31] More specifically, ethylene glycol ether (hereafter, EGE) and fluoride-containing compounds were noted to be associated with the excess risk.[28,34] Given that the methods of outcome ascertainment were diverse across studies and sample sizes were usually small because it was not easy to recruit enough number of eligible women from even several thousand workers, such consistent results strongly suggest a causal association. In addition, the risk estimates became greater by classifying exposures more specifically, from dichotomy (fabrication vs non-fabrication) to work group such as photolithography, and to specific agents like EGE. Furthermore, the fact that risk estimates were obtained through internal comparison between workers gives more credibility to the results by minimizing the 'infertile worker effect'.[35] Two studies did not observe a significant risk elevation; of these, one case–control study was apparently subject to selection bias and insufficient statistical power[36] and another was hampered by misclassification bias (Tables 1 and A1).[37]

As a causal agent(s), most studies suspected organic solvents, in particular EGE, a well-known repro-toxin. Some experts have cautioned, however, that it is a mistake to attribute reproductive problems exclusively to EGE, and have warned that merely removing EGE from the fabrication processes may not have eliminated the reproductive risks. The first report of excess risk for SAB in semiconductor production observed that the ambient EGE concentration was far below the federal standard,[26] and other studies reporting elevated risks also found that the companies fully complied with industrial exposure regulations for EGE.[30,34] Concentrations of glycol ethers in 400 air samples from seven US semiconductor factories were also far below the regulatory limit.[38] There could be alternative explanations for excess SABs; first, there might be a different mode of exposure to EGEs other than ambient air, such as skin contact, which is not routinely monitored; second, even ambient air levels of exposure well below 'permissible exposure limits' might cause harmful effects, which would imply the need for lower regulatory limits and/or safe alternative chemicals; third, chemicals or physical hazards other than (or in combination with) glycol ethers might be responsible for excess SABs. In fact, some scientists were suspicious about the industry attributing adverse reproductive outcomes solely to EGE,

Table 1 A summary of risk estimates for spontaneous abortion (SAB) in semiconductor industry

Exposure	Design (measure)	Risk estimates (95% CI)	Source
Fab (vs non-fab)	Retrospective cohort (RR)	1.43 (0.95–2.09)	Schenker *et al.*[30]
	Prospective cohort (RR)	1.25 (0.63–1.76)	Eskenazi *et al.*[31]
	Case–control (OR)	0.58 (0.26–1.30)	Elliott *et al.*[36]
Work group			
Photolithography (vs non-manufacturing)	Retrospective cohort (RR)	1.75 (0.77–3.25)	Pastides *et al.*[26]
Photolithography (vs non-fab)	Retrospective cohort (RR)	1.67 (1.04–2.55)	Beaumont *et al.*[29]
Diffusion (vs non-manufacturing)	Retrospective cohort (RR)	2.18 (1.11–3.60)	Pastides *et al.*[26]
Etching (vs non-fab)	Retrospective cohort (RR)	2.08 (1.27–3.19)	Beaumont *et al.*[29]
Masking (vs non-fab)	Retrospective cohort (RR)	1.78 (1.17–2.62)	Schenker *et al.*[30]
Masking (vs non-fab)	Prospective cohort (RR)	1.30 (0.59–1.84)	Eskenazi *et al.*[31]
Dope/film (vs non-fab)	Prospective cohort (RR)	1.39 (0.51–1.96)	Eskenazi *et al.*[31]
Agent-specific			
EGE/fluoride high (vs non-fab)	Retrospective cohort (RR)	3.21 (1.29–5.96)	Swan *et al.*[28]
EGE high (vs no exposure)	Retrospective cohort (RR)	2.80 (1.40–5.60)	Correa *et al.*[34]

fab: fabrication; non-fab: non-fabrication; EGE: ethylene glycol ether; RR: relative risk; OR: odds ratio; CI: confidence interval.

which had already been largely phased out.[6] Little is known about the situation since the late 1990s, because no reports on SAB have been published further. Recently, Lin *et al.*[39] reported that persistent rotating shift work was associated with lighter birth weight based on a retrospective cohort study in a Taiwan semiconductor company. Further investigations are strongly warranted to identify all causal agents for SAB in semiconductor production.

Other Taiwanese studies examined hazardous effects on offspring. Two studies in retrospective cohort design reported that children born to fathers who were employed in semiconductor production during the preconception period were three times more likely to die of congenital malformation (RR=3.75, 95% CI 1.29–10.94, OR=3.26, 1.12–9.44), especially heart defects (RR=5.06, 1.58–16.19, OR=4.15, 1.08–15.95), compared to those born to non-exposed fathers.[40,41] Considering that the data lacked information on SAB and minor malformation, and we could not rule out the possibility of non-differential misclassification bias, such significant and large effects strongly suggest a causal association. Even though risk elevation for birth defects was not observed among children born to female workers employed in semiconductor production during the periconception period,[42] a retrospective cohort study of the same female cohort found an elevated risk for cancer among their children. Relative risks for all cancer and leukemia in offspring were estimated to be 2.26 (1.12–4.54) and 3.83 (1.17–12.55), respectively, which further increased by excluding a manager group. From the past labor inspection reports, the authors presumed the observed carcinogenic effect to be attributable to *in utero* exposure to organic solvents, in which presumption could not be confirmed.[43] To understand seemingly conflicting results, underlying mechanisms (i.e. mutations in germ cells before conception, and teratogenic and carcinogenic effects in fetuses) should be considered. Mutagenesis and carcinogenesis are stochastic events without any threshold, and therefore even very low exposure could lead to DNA damage, whereas teratogenesis is a threshold phenomenon with a presumptive dose–response relationship.[44] Prior to conception, male germ cells are more prone to suffer mutagenic effects because toxicity depends on cell division; spermatogenesis that takes 3 months for completion of a cycle is a continuous process from puberty on, whereas female's oogenesis is complete early during the zygote period.[45] After conception, teratogenesis is assumed to be less likely at the lower level of maternal exposure, while even very low levels of maternal exposure to carcinogens could lead to an offspring's cancer because there is no threshold in carcinogenesis.

As for fertility, prospective cohort studies with daily urine collection[30,33] and retrospective cohort studies[34,46] reported that working in fabrication process, especially photolithography or dopant/film process and EGE exposure, was associated with lower fertility[30,33,46] or elevated risk for subfertility among female workers.[34] Although Samuels *et al.*[47] reported no significant risk elevation through a cross-sectional interview survey, it seems reasonable to give more credence to the evidence from cohort studies. Moreover, these cohort studies were based on internal comparisons with less likelihood of infertile worker effect.[35]

In addition, Gold *et al.*[32] reported that fabrication workers experienced more variable menstrual cycles, although mean cycle length was not different between fabrication and non-fabrication workers. A decade later, Hsieh *et al.*[48] observed that working in a fabrication process – in particular, photoresist and diffusion process – was associated with prolonged menstrual cycles through a cross-sectional survey of Taiwanese workers. They suggested that such prolonged cycles could be one explanation for prolonged waiting time to pregnancy of fabrication workers observed in their previous study.[46]

In summary, most epidemiologic evidence to date indicates there are adverse impacts of semiconductor fabrication work on various developmental and reproductive outcomes (see Tables A1 and A2 in the appendix). Although chemical exposures – in particular to glycol ethers – were frequently suspected for causal agents, it seems clear that knowledge about the potential spectrum of specific agents contributing to and responsible for reproductive problems and their mechanisms is still very limited, making effective prevention efforts a major challenge.

Cancer

In 1985, a cohort study to examine cancer risk in semiconductor production first appeared in a scientific journal. It estimated standardized mortality ratio (hereafter, SMR) and standardized incidence ratio (hereafter, SIR) of 1807 employees at one semiconductor factory located in the West Midland, UK with reference to the general population, and concluded that the observed number of cases was close to expectation.[18] Since then, a series of epidemiologic papers have been published, all of which are from a few countries, including the UK, US, Taiwan, and Korea.

In the mid-1980s, IBM commissioned a research project in response to the rising concern over a suspected brain cancer cluster. Using the Corporate Mortality File containing information of tens of thousands of former and current workers, the case–control study concluded that VDT development work was unlikely to be associated with brain tumors. However, excess risk for brain tumor mortality was observed among engineers (OR = 1.7, 95% CI 1.3–3.0) and programmers (OR = 2.8, 1.1–7.0) with a tenure of 10 years or more.[19] Another case–control study in a community setting reported that electromagnetic radiation exposure increased the risk for brain tumors, especially in design/manufacture/repair/installation jobs. The authors argued that the risk might be associated with combined exposure to chemicals and electromagnetic rays.[49] However, subsequent retrospective cohort studies commissioned by IBM repeatedly reported that there was no evidence to support the association between specific work exposures and cancer.[50,51] In addition, a retrospective cohort study sponsored by the SIA concluded that potential exposure to hazardous conditions (i.e. fabrication processes) was not associated with excess risk for cancer death.[52] Meanwhile, two studies to estimate proportional mortality ratio (hereafter PMR) using the same IBM Corporate Mortality File, which became available to the plaintiffs through a court decision, found elevated risks for brain tumors in males (proportionate cancer mortality ratio (PCMR) 166, 95% CI 129–213) and hematologic malignancies in females (162, 121–218).[53,54]

In response to workers' demands, the UK HSE conducted an epidemiologic investigation on cancer risk in the NSUK located in Greenock, Scotland,[13] which was followed by successive studies to extend follow-up time and add a historical hygiene assessment.[55–57] Although the initial analysis found elevated risks for lung cancer incidence (SIR 273, 136–488) and mortality (SMR 241, 116–444) among female workers,[13] they were not found to be significant in the follow-up studies. In addition, further analysis for breast cancer in a case–control design did not find any significant risk factors. Finally, the HSE concluded that there was little evidence to support excess cancer risk among semiconductor workers.[55,57] Meanwhile, another two follow-up reports (published in 1992 and 2005) of the above-mentioned West Midland cohort study also concluded that there was no evidence of excess cancer risk among semiconductor workers, although certain types of cancer were observed more frequently.[58,59]

In Taiwan, a series of epidemiological analyses done after groundwater contamination by chlorinated solvents from the former RCA plant had been identified in 1998. The company had been operating from 1968 to 1992 in northern Taiwan, to produce remote controllers, main boards for color TVs, and IC products including semiconductor packaging. Lee *et al.*[60] reported that the mortality odds ratio for all cancer (2.07, 1.3–3.27) and for liver cancer (2.57, 1.21–5.46) were significantly higher in male residents living in the downstream community from the waste site, compared to the unexposed ones living in an upstream community.[14] The risk estimates further increased during follow-up.[60] In case of workers inside, based on the industrial hygiene reports and interviews, it was assumed that almost all workers had been exposed to organic solvents during employment. A proportionate cancer morbidity study to compare the former RCA workers with textile and other electronics workers found that breast cancer risk was significantly elevated.[14] Based on employment insurance and cancer registry data, Chang *et al.*[61] estimated SMRs of the former RCA workers with reference to the general population. They found an elevated SMR for breast cancer among female workers (114, 85–151), in particular, those with longer employment (1–5 years: 125; 5 years or more: 132), while there was no risk elevation for other types of cancers.[61] The following SIR study found no elevated risk except for breast cancer of female workers (119, 103–136).[62] These two studies concluded that there was no evidence to support excessive cancer risk from the exposure to chlorinated solvents.[61,62] Meanwhile, Sung *et al.*[63] reported that breast cancer risk was higher for those who were hired before 1974 when regulations for organic solvents were introduced (SIR 138, 111–170) or worked for more than 10 years (168, 111–242).

The only Korean epidemiologic study was conducted by the government in 2008, in the context of determining eligibility for workers' compensation which several Samsung Electronics workers claimed for their cancer development. The study included all workers from all five semiconductor companies with eight factories involved in fabrication processes in Korea. Based on the national cancer registry and mortality database, SMRs and SIRs were estimated with reference to the general population. The study concluded that risks for overall mortality and most types of cancer were smaller than that of the general population. However, the incidence of non-Hodgkin's lymphoma (hereafter, NHL) in female workers (SIR 231, 123–395) and thyroid cancer in male workers (SIR 211, 149–289) was found to be significantly elevated, which was not explained by the subsequent sub-group analysis.[15] The study team also published a case series on hematologic malignancies as a part of their investigation. It covered five cases of leukemia, one NHL case, and one aplastic anemia case, all of which involved claims for workers' compensation. Based on hygiene assessment of current work environment, review of the past monitoring records, and construction of detailed work history of the affected workers, they concluded that there was insufficient evidence of workers' exposure to occupational carcinogens.[64] However, a few months later, another case series was reported, which comprised 13 leukemia and 4 NHL cases, all of whom were fabrication workers in Samsung's Kiheung facility.[65] In this case, the authors selected cases from dozens of cases reported to a labor advocacy group, and obtained information solely from workers and their family members because they could not gain access to government and company data. The authors found that cancer developed in a relatively young worker with a short latency, and argued that the work environment was poor and chemical accidents were not uncommon, contrary to the official reports.

At the first glance, overall indications of excess cancer risk in the semiconductor industry seem to be at most equivocal. However, the results should be interpreted with caution because most studies have considerable methodological limitations, which should not be overlooked. In addition, by examining results in more detail, we could find some patterns in common.

First of all, most studies seeking to estimate SMR or SIR with reference to the general population were seriously impacted by the healthy worker effect (HWE). It is known that the HWE influences findings on cardiovascular disease while cancer findings are known to be less susceptible to this bias. The HWE is a mixed effect of different biases including (a) selection bias arising from selection process at employment or survival effect during follow-up, (b) information bias due to differential probability of case ascertainment, and (c) confounding bias such as lower smoking prevalence and higher socioeconomic status of the employed population.[66] Indeed, SMRs for mortality from all causes were significantly less than unity[15,50–52,55] except for the cases of the UK West Midland male workers[58] and the Taiwanese female workers.[61] As an extreme case, the SMR of Korean male workers was just a quarter of the expected one.[15] Except for the West Midland studies,[58] SMRs of male workers were much smaller than those of female workers, which seemed to reflect gender difference in socioeconomic position; male workers were likely to be engineers with a relatively higher education, whereas most female workers were operators. It is well known that lower socioeconomic position is associated with higher mortality. Meanwhile, SMRs for cancer were consistently greater than those for total mortality, except for Taiwanese male and female workers, although many of them were still less than unity. Taken into account such HWEs, 'near average cancer risk' could be consistent with real risk elevation over what these specific workers otherwise have experienced.[67]

In addition, selection bias was further exacerbated by the fact that vulnerable workers (i.e. migrant workers) or early retirees who quit their job before the start of follow-up were excluded from the analyses. The West Midlands studies[18,58,59] could not obtain information about the workers who quit their job before 1970, and the NSUK studies failed to follow-up non-UK nationals.[13,55,57] The US SIA studies did not include migrant workers and the workers who quit their job before 1983, and those excluded from the analysis amounted to 40.0% of total workforce.[52] Also, the Taiwanese studies[14,42,63,68] failed to include workers exposed to more hazardous conditions of earlier times. Indeed, Sung *et al.*[63] reported that breast cancer risk was greater for the period before the adoption of government regulation in 1974. The Korean employment cohort covered only the period from 1998 to 2007,[15] although mass production of semiconductors began in the early 1980s. By excluding those who worked in more dangerous or disadvantaged conditions, a bias toward the null is more likely to occur.

Another important limitation is the possibility of misclassification bias, in that most studies were based on historical data, originally constructed for administrative use, not for research. For example, the Korean employment cohort data designated 4295 out of 48 022 female workers (8.9%) in fabrication processes and 1669 out of 19 767 female workers (8.4%) in assembly processes as 'engineers', respectively.[15] However, this classification is unreliable, because while usually men with diplomas from vocational schools or colleges are recruited as engineers, it is very rare for women to be trained as and then work as engineers in Korea. Furthermore, by treating all workers employed in semiconductor industry as one group (i.e. semiconductor workers vs general population), the risk of actually exposed workers could be diluted. Through simulation, Parodi *et al.*[69] showed that such dilution effect, in particular in case of dichotomous classification, could result in considerable underestimation of risk. In fact, the Semiconductor Health Study showed that risk estimates for SAB became greater by refining classification of the exposure status down to the level of the specific agent(s).[7] This kind of non-differential misclassification bias can also lead to underestimation of risk.

Finally, false-negativity problem (type 2 error)[70] due to small sample size and short follow-up time should be considered; the UK West Midland and the NSUK studies covered only 1807 and 4339 workers, respectively,[57,58] whereas 86.9% of the Korean cohort members were born after 1970, relatively young for cancer development.[15] In fact, when the NSUK study proposal was made public, experts and labor advocates pointed out the problem of small sample size and raised a call for a nationwide or international survey,[71,72] which was never carried out.

Despite these limitations, we could observe elevated risks for some types of cancer across studies – NHL, leukemia, brain tumor, and breast cancer. Given that most studies were subject to considerable biases toward the null, more attention should be paid to such findings, even if a statistical significance was not secured or effect sizes were small.

In case of NHL, the IBM workers with longer tenure showed elevated SMRs; those workers employed for 5 years and 10 years or more were 125 (95% CI 98–158) and 122 (88–165), respectively.[50] While the SMRs estimated from the US SIA were below unity, the point estimate was greater in fabrication workers than non-fabrication workers (86 vs 61).[52] The Korean study found elevated SMRs, in particular, of female workers (250, 68–640),[15] although they were not statistically significant. The PMR study based on IBM Corporate Mortality File found elevated risks among both males (150.4, 136.5–165.8) and females (139.5, 110.7–176).[53] Meanwhile, SIRs were not significantly elevated except for the case of Korean female workers (231, 123–395).[15] However, we could still find a certain trend that longer employed or exposed groups were more likely to show larger point estimates of SIR; in the IBM East Fishkill plant, SIRs of total workers and those employed for 5 years or more were 94 and 98, respectively, whereas SIRs of workers unexposed, ever-exposed, and exposed for 5 years or more were 80, 100, and 109, respectively. Also, in the IBM San Jose plant, SIRs for total workers and those employed for 5 years or more were 91 and 110, respectively, although they failed to show statistical significance (Table 2).[51]

As for leukemia, elevated risk was observed among the Korean females (SMR 137, 55–281)[15] and the IBM workers (PCMR of males: 113.3, 102–116; females: 113.7, 89.6–144.4). Risk elevations were seen prominent in manufacturing jobs (PCMR of females: 165.8, 101.6–270.8).[53] In addition, a longer tenure was associated with a larger point estimate; in the IBM study, SMRs of total workers, those employed for 5 years, and those employed for 10 years or more were 85, 95, and 103, respectively,[50] while the SIA study reported smaller SMRs for fabrication workers.[52] Although there were small increases of point estimates among IBM San Jose workers,[51] we could not find any consistent pattern regarding SIRs, except that risk estimates of female workers were greater than those of male workers in gender-stratified analysis (Table 3).

Elevated SMRs for brain tumor were more frequently observed in the US studies – both the IBM (108, 87–132)[50] and the SIA (111, 84–145).[52] In addition, the IBM PMR study showed statistically significant excess risk (PMR of males: 191.8, 173.2–212.3; females: 132, 100.8–173.8).[53] Although the SIR estimates seemed equivocal, longer employment or exposed status was associated with risk elevation in the IBM East Fishkill site; SIRs of workers

Table 2 A summary of risk estimates for non-Hodgkin's lymphoma (NHL) in semiconductor industry

Population	Measure	Attributes	Risk estimates (95% CI)	Source
Mortality				
US IBM	SMR	Total	99 (82–119)	Beall *et al.*[50]
		Employed for 5+ years	125 (98–158)	
		Employed for 10+ years	122 (88–165)	
	PMR	Males	150 (137–166)	Clapp[53]
		Females	140 (111–176)	
	PCMR	Males	136 (123–149)	
		Males, manufacturing	126 (98–163)	
		Females	122 (97–154)	
		Females, manufacturing	144 (86–240)	
US SIA	SMR	Total	69 (48–97)	Boice *et al.*[52]
		Non-fab workers	61 (37–95)	
		Fabrication workers	86 (47–144)	
Korea	SMR	Males	133 (43–309)	Lee *et al.*[15]
		Females	250 (8–640)	
Incidence				
US IBM	SIR	East Fishkill, total	94 (74–118)	Bender *et al.*[51]
		East Fishkill, employed for 5+ years	98 (69–136)	
		East Fishkill, unexposed	80 (43–137)	
		East Fishkill, exposed	100 (76–128)	
		East Fishkill, exposed for 5+ years	109 (72–157)	
		San Jose, total	91 (69–117)	
		San Jose, employed for 5+ years	110 (76–154)	
		San Jose, unexposed	116 (77–168)	
		San Jose, exposed	74 (50–106)	
		San Jose, exposed for 5+ years	84 (46–141)	
Korea	SIR	Males	93 (45–171)	Lee *et al.*[15]
		Females	231 (123–395)	

SMR: standardized mortality ratio; SIR: standardized incidence ratio; PMR: proportionate mortality ratio; PCMR: proportionate cancer mortality ratio; CI: confidence interval.

Table 3 A summary of risk estimates for brain cancer in semiconductor industry

Population	Measure	Attributes	Risk estimates (95% CI)	Source
Mortality				
US IBM	SMR	Total	108 (87–132)	Beall *et al.*[50]
		Employed for 5+ years	114 (82–154)	
		Employed for 10+ years	119 (77–174)	
	PMR	Males	192 (173–212)	Clapp[53]
		Females	132 (101–174)	
	PCMR	Males	162 (146–179)	
		Males, manufacturing	166 (129–213)	
		Females	109 (83–142)	
		Females, manufacturing	119 (65–219)	
US SIA	SMR	Total	111 (84–145)	Boice *et al.*[52]
		Non-fabrication workers	127 (90–172)	
		Fabrication workers	83 (45–139)	
UK West Midlands	SMR	Total	83 (17–143)	Nichols and Sorahan[58]
UK NSUK	SMR	Males	189 (39–552)	Darnton *et al.*[55]
		Females	n.a.	
Taiwan RCA	SMR	Males	48 (1–266)	Chang *et al.*[61]
		Females	91 (33–199)	
Korea	SMR	Males	92 (25–235)	Lee *et al.*[15]
		Females	34 (1–187)	
Incidence				
US IBM	SIR	East Fishkill, total	94 (65–132)	Bender *et al.*[51]
		East Fishkill, employed for 5+ years	94 (52–158)	
		East Fishkill, unexposed	77 (28–168)	
		East Fishkill, exposed	101 (67–147)	
		East Fishkill, exposed for 5+ years	116 (60–203)	
		San Jose, total	91 (56–139)	
		San Jose, employed for 5+ years	126 (67–215)	
		San Jose, unexposed	102 (47–193)	
		San Jose, exposed	87 (45–152)	
		San Jose, exposed for 5+ years	164 (75–311)	
UK West Midlands	SIR	Total	50 (6–81)	Nichols and Sorahan[58]
UK NSUK	SIR	Males	209 (57–535)	Darnton *et al.*[57]
		Females	n.a.	
Taiwan RCA	SIR	Males	n.a.	Sung *et al.*[63]
		Females	107 (59–180)	
Korea	SIR	Males	137 (62–259)	Lee *et al.*[15]
		Females	22 (1–122)	

SMR: standardized mortality ratio; SIR: standardized incidence ratio; PMR: proportionate mortality ratio; PCMR: proportionate cancer mortality ratio; CI: confidence interval.

unexposed, ever-exposed, and exposed for 5 years or more were 77, 101, and 116, while in the San Jose site, they were 102, 87, and 164, respectively (Table 4).[51]

Excess risk for breast cancer was prominent among the Taiwanese workers (SMR 114, 85–151), and it further increased with longer tenure.[61] Also, the IBM PMR study showed significantly greater PMR (137, 125–150) and PCMR (115, 106–125).[53] As for incidence, although the IBM East Fishkill site showed elevated SIR, there was scarcely a consistent pattern to imply a plausible association.[51] In the UK, SIRs were elevated for the NSUK (123, 90–163), in particular, among fabrication workers (135, 96–184),[55] while there was no similar results in the West Midlands.[58] Similar to the mortality pattern, the Taiwanese female workers showed an elevated SIR (109, 96–122). The relative risk increased further among workers employed for 10 years or more (168, 111–242) and those hired before 1974 when the government regulations for chemicals were introduced (138, 111–170).[63] Such findings seem to be highly plausible, in accordance with expectation (Table 5).

In spite of 'reasonable doubt' about elevated cancer risks, we should be still cautious in determining causal association. As Boffetta *et al.*[73] commented, multiple comparisons by sub-group analyses could raise the likelihood of false-positivity by chance. In addition, lack of specific *a priori* hypotheses and insufficient adjustment for important confounders like tobacco use could contribute to false-positivity.[73] Many findings we mentioned are based on a series of sub-group analysis, usually without *a priori* hypotheses. Therefore, we could not rule out the possibility of false-positivity. However, considering that dilution effects are common in studies based on historical data, cases of substantial confounding (even smoking) are actually rare in occupational epidemiology,[74] potential biases in the studies we examined are consistently toward the null, and their statistical powers are limited, it is unlikely that the danger of false-positivity surpasses that of false-negativity.

To summarize, epidemiologic evidence to date does not seem to strongly support a causal association between semiconductor production work and overall cancer risk. However, most studies were subject to

Table 4 A summary of risk estimates for leukemia in semiconductor industry

Population	Measure	Attributes	Risk estimates (95% CI)	Source
Mortality				
US IBM	SMR	Total	85 (69–105)	Beall *et al.*[50]
		Employed for 5+ years	95 (69–127)	
		Employed for 10+ years	103 (69–147)	
	PCMR	Males	113 (102–126)	Clapp[53]
		Males, manufacturing	88 (63–121)	
		Females	114 (90–144)	
		Females, manufacturing	166 (102–271)	
US SIA	SMR	Total	77 (54–107)	Boice *et al.*[52]
		Non-fabrication workers	82 (52–122)	
		Fabrication workers	69 (34–123)	
UK West Midlands	SMR	Total	96 (20–282)	Nichols and Sorahan[58]
Taiwan	SMR	Males	44 (5–159)	Chang *et al.*[61]
		Females	54 (23–107)	
Korea	SMR	Males	39 (8–114)	Lee *et al.*[15]
		Females	137 (55–281)	
Incidence				
US IBM	SIR	East Fishkill, total	70 (49–98)	Bender *et al.*[51]
		East Fishkill, employed for 5+ years	62 (35–103)	
		East Fishkill, unexposed	79 (34–157)	
		East Fishkill, exposed	70 (46–102)	
		East Fishkill, exposed for 5+ years	70 (36–123)	
		San Jose, total	103 (73–142)	
		San Jose, employed for 5+ years	115 (71–175)	
		San Jose, unexposed	107 (59–180)	
		San Jose, exposed	104 (66–156)	
		San Jose, exposed for 5+ years	114 (56–200)	
UK West Midlands	SIR	Total	121 (39–283)	Nichols and Sorahan[58]
Taiwan	SIR	Males	n.a.	Sung *et al.*[63]
		Females	78 (49–117)	
Korea	SIR	Males	69 (30–137)	Lee *et al.*[15]
		Females	128 (61–236)	

SMR: standardized mortality ratio; SIR: standardized incidence ratio; PMR: proportionate mortality ratio; PCMR: proportionate cancer mortality ratio; CI: confidence interval.

considerable limitations including HWEs, information bias, and insufficient statistical power, all of which are associated with underestimation of risk. In this context, data interpretation solely based on statistical significance could result in a faulty conclusion. At a minimum, the evidence to date suggests that excess risk may be present for NHL, leukemia, brain tumor, and breast cancer in the semiconductor industry, and further studies should be undertaken.

Other Health Outcomes

Although most attention has been paid to cancer and reproductive outcomes, other health problems have been also reported in semiconductor industry.

Respiratory abnormalities are one of them. Using pulmonary function test, Luo *et al.*[75] found that Taiwanese male fabrication workers, mostly process/maintenance/equipment engineers, were four times more likely to experience restrictive pulmonary abnormality compared to non-fabrication workers. Given that there were no definite abnormalities in chest x-rays and physical examinations, and pulmonary function abnormality was not observed among female operators, it is plausible to posit that the maintenance engineers had intermittent short-term peak exposures that could have resulted in mild pulmonary dysfunction.[75] Based on a cross-sectional questionnaire survey in the US, McCurdy *et al.*[76] reported that upper (prevalence 71%, RR=1.08, 1.03–1.13) and lower respiratory symptoms (41.5%, RR=1.12, 1.01–1.22) were more frequent among fabrication workers compared to non-fabrication workers. Moreover, there was a dose–response relationship between prevalence of upper respiratory symptoms and hours per day in the fabrication room, and photolithography or furnace jobs were significantly associated with symptoms. In addition, complaints of persistent wheezing were 1.9 times more likely among fabrication workers.[76]

The same study also reported that dermatologic problems were more frequently observed among fabrication workers (RR=1.19, 1.04–1.35) and specifically, methanol and isopropanol were suspected as causal agents. Alopecia was also more common among fabrication workers (RR=1.73, 1.16–2.54), although the causative agents could not be identified.[76] Previously, Pastides *et al.*[26] reported that female workers in photolithography were more likely to experience skin rashes compared to the other workers (13.4 vs 5.7%, prevalence ratio=2.38, 1.13–4.89). Various skin problems among electronics workers have been documented. Adams[77] and Koh *et al.*[78] presented a comprehensive review of dermatologic hazards potentially involved in specific electronics

Table 5 A summary of risk estimates for female breast cancer in semiconductor industry

Population	Measure	Attributes	Risk estimates (95% CI)	Source
Mortality				
US IBM	SMR	Total	95 (80–112)	Beall *et al.*[50]
		Employed for 5+ years	100 (73–134)	
		Employed for 10+ years	102 (65–154)	
	PMR	Total	137 (125–150)	Clapp[53]
	PCMR	Total	115 (106–125)	
		Manufacturing	97 (79–120)	
US SIA	SMR	Total	92 (75–112)	Boice *et al.*[52]
		Non-fabrication workers	109 (89–136)	
		Fabrication workers	65 (42–95)	
UK West Midlands	SMR	Total	47 (25–81)	Nichols and Sorahan[58]
UK NSUK	SMR	Total	104 (50–192)	Darnton *et al.*[55]
Taiwan RCA	SMR	Total	114 (85–151)	Chang *et al.*[61]
		Employed for 1–4 years	125 (n.a.)	
		Employed for 5+ years	132 (n.a.)	
Korea	SMR	Total	84 (10–302)	Lee *et al.*[15]
Incidence				
US IBM	SIR	East Fishkill, total	104 (89–120)	Bender *et al.*[51]
		East Fishkill, employed for 5+ years	114 (88–145)	
		East Fishkill, unexposed	115 (89–145)	
		East Fishkill, exposed	98 (81–117)	
		East Fishkill, exposed for 5+ years	94 (65–133)	
		San Jose, total	102 (87–119)	
		San Jose, employed for 5+ years	94 (69–125)	
		San Jose, unexposed	109 (87–136)	
		San Jose, exposed	97 (77–121)	
		San Jose, exposed for 5+ years	80 (48–125)	
UK West Midlands	SIR	Total	78 (59–102)	Nichols and Sorahan[58]
UK NSUK	SIR	Total	123 (90–163)	Darnton *et al.*[55]
		Fabrication workers	135 (96–184)	
		Non-fabrication workers	81 (33–167)	
Taiwan RCA	SIR	Total	109 (96–122)	Sung *et al.*[63]
		Employed for 10+ years	168 (111–242)	
		Hired before 1974	138 (111–170)	
		Hired after 1974	99 (85–114)	
Korea	SIR	Total	77 (44–126)	Lee *et al.*[15]

SMR: standardized mortality ratio; SIR: standardized incidence ratio; PMR: proportionate mortality ratio; PCMR: proportionate cancer mortality ratio; CI: confidence interval.

industry processes including semiconductor production – irritants such as solvents, soldering fluxes, hydrofluoric acid, and epoxy resin; allergens such as epoxy resin, colophony, metals, and anti-static agents; and others including fiberglass, use of protective equipment, and low humidity.

Musculoskeletal problems associated with poor ergonomic conditions including awkward posture and long working hours were also reported,[79–81] and are not unique to the semiconductor industry. Mental health problems have been reported in the microelectronics industry but are not specific to semiconductor production. Cases of mass psychogenic illness in electronics plants were found to be associated with stress from uncomfortable physical environments[82] and repetitive work demanding a high degree of concentration[83] rather than specific chemical exposures. One review concluded that the so-called 'mass psychogenic illness' seemed to be triggered by objective stressors such as low level of chemical odors and insect bites, and transmitted by psychological factors within groups.[84] In fact, neuropsychological impairments were more frequently observed among former electronics workers who worked with organic solvent compounds compared to a control group,[85] and the clinical pattern derived from the MMPI questionnaire was similar to that observed in organic solvent toxicity.[86] On the other hand, a Japanese[87] and Taiwanese study[88] each reported a high level of job stress among workers in microelectronics. Recently, serial cases of suicide in the Foxconn plants in southern China raised the worldwide concern over the working conditions of microelectronics workers, mostly poor young workers who migrated from rural homes to industrial cities. Although the company attributed the tragedy to 'immaturity and fragile' state of mind of the young rural migrants, labor advocates argued that harsh working conditions such as intense work stress and labor rights abuses were associated with the incidents.[89]

All of these reports suggest that exposure to chemical and physical hazards in semiconductor production could impair skin and respiratory organs, and that the scope of new research needs to be expanded to other types of hazards such as job stress, ergonomic conditions, and mental health issues.

Discussion

Although considerable concerns over adverse health outcomes among semiconductor workers continue to be expressed, it is not yet possible to reach firm conclusions based on definitive evidence. In reality, we observed that many studies have varying degrees and types of limitations, most of which could bias the risk toward the null. In this context, we could summarize our findings as follows; first, there is a relatively clear association between reproductive abnormalities and fabrication work. Second, in spite of seemingly equivocal results, cancer studies provide reasonable grounds for us to suspect excess cancer risk in this industry, in particular, for hematologic malignancy, brain tumors, and breast cancer. Third, dermatologic and respiratory problems due to chemical exposures are relatively common, and ergonomic and psychosocial problems are shared with other industries. However, the specific causative agents or mechanisms are yet to be identified in this field.

Based on our review, we suggest some points for further research and actions regarding health and safety of workers in semiconductor production.

First of all, careful monitoring should be strengthened and expanded across countries. The problems we reviewed are not just a legacy of the past; technical developments have not caused them to disappear. To begin with, it should be noted that many of the study cohorts were so young that further follow-up is needed for health outcomes with long latency such as cancer. In addition, as the recent investigation in the contaminated neighborhoods in Taiwan showed, toxic chemicals persist in the ground at dangerous levels even now.[90,91] In addition, although considerable improvements have been achieved in health and safety measures, there are still many unknown hazards in the workplace, and protection and prevention measures are far from perfect. The UK HSE inspection of semiconductor-manufacturing plants in 2002 found that occupational health provisions varied across companies and many of them failed to meet legal compliance for health surveillance.[92] Also, when the Korean government agency identified 424 chemical ingredients out of 509 chemicals used in one company, only 10% of them were monitored. Further, it should be noted that unexpected by-products could be generated under conditions of high energy plasma, high temperature, UV radiation, and/or ion emission; in fact, formaldehyde, arsenic, and ethylene oxide gas, which are supposedly not used in the processes themselves, are still generated from photolithography and/or ion implantation processes.[5] In addition, the evidence reveals that seemingly complete controls cannot guarantee safe work places. For instance, risks for SAB were elevated even where the suspected agent – glycol ethers – was tightly controlled at far below the permissible exposure limits as evidenced by air sampling.[30,34] Decreased numbers of leukocytes were observed among male engineers working within a fully automated clean room.[93] In addition, genotoxic effects (increased frequency of micronuclei in leukocytes) were identified among exposed workers though their urine and airborne concentrations of chemicals yielded results consistent with air levels below regulatory standards.[94] Sometimes, alternative materials to replace toxic chemicals were proven to be also harmful; for example, propylene glycol ether introduced as a substitute for EGE was also found to be hazardous.[95] Furthermore, it should be noted that along with the expansion of the global supply chain, developing countries such as China, Eastern Europe, and South America are rising as a new production base, which have less resources, weak regulations, and insufficient surveillance systems.[4] It is possible that materials that are banned or processes that are tightly controlled in developed countries are not strictly followed there. All of these facts indicate that strengthening monitoring and surveillance must be emphasized more than ever.

Regarding etiological studies, we believe that simple replication of current studies using the same design would not give much help and therefore alternative strategies should be taken.

First, for cancer epidemiology, international collaboration research is imperative. Based on larger samples with sufficient statistical power, detailed subgroup analysis would be available. In fact, we have little knowledge of whether dose–response relationships are linear or an approach assuming constant risk over time is appropriate. Estimates of specific rates according to age of diagnosis, exposure timing, and exposure duration would add an important clue for causal inference. Also, different timing of regulation or introduction of new chemicals from one country to another could provide valid counterfactual conditions for making internal comparison. As LaDou and Bailar[12] proposed, the International Agency for Research on Cancer needs to take the initiative.

In addition, information on unusual events in one country needs to be shared across countries even prior to publication of scientific papers. By doing so, further research could be organized if necessary, and warning signals could be acted upon in accord with the precautionary principle. For example, when some Korean workers afflicted with multiple sclerosis or amyotrophic lateral sclerosis claimed workers' compensation, no scientific papers were found to support the work-relatedness of semiconductor production, though a number of papers have reported strong associations between organic solvent exposure and multiple sclerosis.[96] Later, we learned that the IBM PMR study also found elevated risks for these conditions and compensation claims by some electronics workers with multiple sclerosis had been resolved, all of which were not mentioned in the original article with a focus on cancer.[53,97] As with individual case reports, this sort of information could be instructive for constructing health surveillance systems or launching new epidemiologic studies.

Special focus should be placed on sentinel events such as hematologic abnormalities, reproductive aberrations, and dermatologic and respiratory disorders. For example, leukocyte abnormalities among fabrication engineers[93] and excess risk for SAB[26,28–30,34] or congenital malformations in offspring[40,41] could be relevant to risks of cancer development. Skin[78] or respiratory abnormalities[75,76] could be a clue to reveal the presence of workplace hazards. They are characterized by relatively short latency between exposure and case development, and events are relatively common compared to cancer. Accordingly, primary data collection is readily available and internal comparison based on exact exposure classification is possible, which could minimize information bias, HWEs, and insufficient statistical power. In the case of the Semiconductor Health Study, daily urine collection and diary was done for 6 months among 400 workers, which was quite expensive and labor-intensive method, but the compliance was fairly good.[98] Such studies seem to be readily feasible in Korea and Taiwan where a large number of young females are working.

In the meantime, barriers that hamper further epidemiological studies and surveillance should be identified. In general, semiconductor manufacturing needs huge capital investment and its impact on national economies is considerable, especially in some countries; for example, in Korea, semiconductor products generated 6.5% of real GDP and about 10% of total export revenues in 2010.[2] Therefore, it is not unusual that national economic strategies are deeply involved in promoting this industry, privileged conditions are provided for them,[2,3] and trade unions rarely exist.[4] In this context, both domestic and transnational companies have overwhelming power to control workers, working conditions, and even research itself. For instance, under the name of trade secrets, Samsung rejected the call from the workers' advocates to disclose industrial hygiene assessment reports, which were eventually made public through parliamentary inspection.[99] IBM resisted the disclosure of its Corporate Mortality File until forced by a court decision to release it,[4] and then tried to prevent the publication of a scientific paper derived from analyses of its contents.[11,100,101] Moreover, workers suffer from the widespread adoption of outsourcing, subcontracting, and temporary work arrangements, in which they are more likely to be denied labor rights and excluded from regulatory protection.[102] In such conditions, the records of employment or work environment tend to be kept poorly, and therefore it is more difficult to identify work history or track exposure status for the purpose of assessing work-relatedness.[103] Gender inequality also needs to be considered. The majority of manufacturing workers in the semiconductor industry are females, with this pattern based on the gender stereotype; females' physical make-up is considered more suitable for such jobs and females, especially young and from poor families, are thought to be docile, motivated, and obedient to management.[104] The fact that chemicals that have been strictly controlled for their reproductive toxicity in the printing industry where skilled and unionized male workers dominate are still used in the microelectronics shows that unequal power relations based largely on gender affect the working environment differentially.[105] In such a context, it is highly probable that passive surveillance works poorly and identification of health problems among workers is difficult as well as incomplete. In order to overcome these barriers, concealment of health and safety information under the guise of trade secrets needs to be strictly restricted on a legal basis and workers' participation in health and safety programs and/or epidemiologic investigations should be substantially guaranteed.

In conclusion, it seems clear that workers in semiconductor manufacturing, and in particular within the fabrication process, have been exposed to hazardous conditions contrary to the misconception of 'clean' image of this industry. These hazardous conditions are developing to a different extent across countries. However, there is still a significant gap in knowledge about health problems with long latency and rare incidence, while the causal association is strongly supported in the case of reproductive abnormalities. Monitoring and innovative research based on international collaboration is indispensable, while protective measures based on the available evidence should be immediately exercised under the precautionary principle.

Disclosure Statement

There is no conflict of interest.

Acknowledgements

Earlier versions of this paper were presented at the Korea Society of Occupational and Environmental Medicine Annual Meeting (2011) and the American Public Health Association Annual Meeting (2012), and the authors are grateful to the commentators for their helpful comments. M.-H. Kim was supported by the Health Equity Research Fund of the People's Health Institute and the National Research Foundation of Korea grant funded by the Korean Government (NRF-2010-330-B00133).

Appendix

Table A1 Summary of study findings on adverse developmental outcomes in semiconductor industry

Authors	Year	Area/company	Subjects (design)	Out come	Main findings	Funding
Pastides *et al.*	1988	US (MA)/ DEC	1984–1986, retrospective cohort of 471 female workers and 273 spouses of male workers Photo and diffusion vs non-manufacturing	SAB	RR: photolithography 1.75 (0.77–3.25), diffusion 2.18 (1.11–3.60) – consistent findings even in multiple logistic regression analysis to adjust for potential confounders	n.a.
Dean *et al.*	1989	US (CA)	1980–1981, cross-sectional study through interview and medical records 228 exposed vs 274 unexposed female residents 145 live births in the exposed area vs 182 ones in the unexposed	SAB (congenital anomaly)	Prevalence of SAB: exposed 21.5% vs unexposed 11.0% OR for SAB: 2.3 (1.3–4.2) (consistently elevated risks across validation methods) RR for congenital malformation 3.1 (1.1–10.4)	Public
Swan *et al.*	1989	US (CA)	1981–1983, cross-sectional study through interview, vital statistics, and medical records Exposed vs unexposed communities (by time-period)	Congenital anomaly	Prevalence of anomaly: exposed period – exposed area 0.56% vs unexposed 0.26%, unexposed period – exposed area 1.7% vs unexposed 3.2% RR: exposed period 2.2 (1.2–4.0), unexposed period 0.5 (0.2–1.7) Discrepancy between spatial distribution of anomaly and hydrogeologic modeling	Public
Wrensch *et al.*	1990	US (CA)	1980–1985, retrospective cohort study through interview and medical records of 1105 community living women Exposed vs non-exposed communities (by time-period)	SAB	OR: 1980–1981 original subjects 3.5 (1.2–10.3), new subjects 0.3 (0.1–1.1); 1982–1985 original 1.0 (0.5–1.9), new 1.3 (0.6–2.9)	Public
Lipscomb *et al.*	1991	US (CA)	1980–1985, cross-sectional study through interview of 1038 community living women Solvent exposure vs non-exposure	SAB	OR: first trimester exposure 3.34 (1.42–7.81), regular exposure 4.44 (1.86–10.58)	n.a.
Shusterman *et al.*	1993	US (CA)	Case–control study based on questionnaire, pathology records, and birth certificates Electronics (semiconductor fab, printed circuit board, assembly) vs community residents	SAB	OR: 0.94 (0.58–1.5) Risk elevation in diffusion, parts encapsulation, soldering, flux terminal (statistically not significant)	n.a.
Schenker *et al.*	1995	US/SIA	1986–1989, historical cohort study of 904 women through interview and medical records 1989–1991, prospective cohort study of 402 women through 6-month daily urine collection, diaries, and interview Fab vs non-fab comparison	SAB	RR: retrospective fab 1.43 (0.95–2.09) – esp. masking 1.78 (1.17–2.62), prospective fab 1.25 (0.63–1.76) Dose–response relationship in photoresist and developer solvents	SIA, public
Eskenazi *et al.*	1995	US/SIA	1989–1981, prospective cohort study through 6-month daily urine collection, diaries, and interview 152 fab vs 251 non-fab workers	SAB	RR: fab 1.25 (0.63–1.76), dopant and thin film 1.39 (0.51–1.96), and masking 1.30 (0.59–1.84)	SIA, public
Beaumont *et al.*	1995	US/SIA	1986–1989, historical cohort through interview and medical records 447 fab vs 444 non-fab pregnancies	SAB	RR: fab 1.43 (0.95–2.09), masking 1.78 (1.17–2.62), etching 2.08 (1.27–3.19), and photo 1.67 (1.04–2.55)	SIA
Swan *et al.*	1995	US/SIA	1986–1989, historical cohort through interview and medical records: 447 fab vs 444 non-fab pregnancies	SAB	RR: EGE and fluoride high exposure 3.21 (1.29–5.96) – dose–response relation with EGE Fab workers without exposure 0.98 (0.55–1.69)	SIA
Correa *et al.*	1996	US (NY, VT)/IBM	1980–1989, retrospective cohort through interview and plant records of 378 female workers and 375 spouses of male workers EGE exposure: no vs low vs med vs high	SAB	RR: female worker high exposure 2.8 (1.4–5.6) – dose–response relation, no association in spouses Suspected dermal contact of EGE (low level of air concentration)	IBM, public

Table A1 Continued

Authors	Year	Area/company	Subjects (design)	Out come	Main findings	Funding
Elliott *et al.*	1999	UK	1987–1993, nested case–control study of 36 cases and 80 controls Fab vs non-fab	SAB	OR: fab 0.58 (0.26–1.30) No evidence of elevated risk (even in EGE exposure)	Public
Lin *et al.*	2008	Taiwan	1980–1994, 5702 live births from 6834 male workers Retrospective cohort study based on national birth/death registry and labor insurance data Exposure: employed in semiconductor production during 2 months prior to conception vs not	Child death	OR: congenital anomaly 3.26 (1.12–9.44), heart anomalies 4.15 (1.08–15.95) Possible link between paternal preconception exposure of semiconductor manufacturing and an increased risk of congenital anomalies, especially of the heart	Public
Lin *et al.*	2008	Taiwan	1980–2000, 24 223 live births from 27 610 female workers Retrospective cohort study based on national birth/death registry and labor insurance data Exposure: employed in semiconductor production during pre/post 3 months of conception vs not	Child death	OR: congenital anomaly 0.56 (0.13–2.40) in 1980–1994 and 0.88 (0.37–2.11) in 1995–2000 No significant risk elevation	Public
Sung *et al.*	2008	Taiwan	1978–2001, 40 647 first singleton babies from 40 647 female workers Retrospective cohort study based on cancer registry (1979–2001) – 639 051 person years (PYs) Exposure: employed in semiconductor production during pre/post 3 months of conception vs not	Child cancer	Exposed cases 11, unexposed cases 36 RR for all cancer: total 2.26 (1.12–4.54), $\leqslant$6 years of education 3.05 (1.20–7.74), 7–9 years of education 2.49 (2.49–4.94), excluding manager group 2.32 (1.15–4.66) RR for leukemia: total 3.83 (1.17–12.55), excluding manager group 3.92 (1.20–12.86) Suspicious role of organic solvents exposure	Public
Lin *et al.*	2011	Taiwan	1997–2007, retrospective cohort study of 440 female workers with 158 live births Rotating shift work: none vs intermittent vs persistent	Birth weight	Mean birth weight (g): none 3271.4 ± 395.4>intermittent 3251.3 ± 460.9>persistent 2998.5 ± 381.2 ($P<0.01$) OR for lightest quintile of birth weight: persistent shift 4.3 (1.1–16.8) Significantly elevated risk for lighter birth weight in female workers	n.a.
Sung *et al.*	2009	Taiwan	1973–1992, 13 592 live births from 7202 male workers Retrospective cohort study based on national birth/death registry and labor insurance data Exposure: employed in semiconductor production during 3 months prior to conception vs not	Child death	RR: infant mortality 5.06 (2.33–11.0) (>10 years work) and 2.81 (1.44–5.51) (1–10 years) RR: congenital malformation 3.75 (129–10.94) and cardiac defect 5.06 (1.58–16.19) Suspicious role of organic solvents' exposure	Public

SAB: spontaneous abortion; OR: odds ratio; RR: relative risk; SIA: Semiconductor Industry Association; EGE: ethylene glycol ether.

Table A2 Summary of study findings on adverse reproductive outcomes in semiconductor industry

Authors	Year	Area/company	Subjects (design)	Outcome	Main findings	Funding
Gold *et al.*	1995	US (CA, UT)/SIA	1989–1991, prospective cohort study through 6-month daily urine collection, diaries, and interview 152 fab vs 250 non-fab workers	Menstrual cycle (days)	Mean cycle length: fab 34.8 $\pm$ 1.7 vs non-fab 32.5 $\pm$ 1.4 (P=0.97) Mean standard deviation: ion implant 6.68 $\pm$ 1.28, photo 5.72 $\pm$ 1.24 vs non-fab 4.1 $\pm$ 1.16 (P=0.013 and 0.019) RR for cycle<24 days: supervisors 2.46 (1.19–3.63), photo 1.83 (0.94–2.88)	SIA, public
Hsieh *et al.*	2005	Taiwan	1997, cross-sectional study through questionnaire 473 fab vs 133 non-fab workers	Menstrual cycle	OR for long menstrual cycle: fab 2.0 (1.0–3.9), etching 0.9 (0.4–2.2), thin film 2.0 (0.8–4.9), photo 4.4 (1.7–11.4), diffusion 3.8 (1.3–11.6) vs non-fab OR for short menstrual cycle: fab 1.5 (0.5–4.7), etching 1.4 (0.4–4.7), thin film 1.4 (0.3–5.8), photo 1.6 (0.6–9.4), diffusion 1.3 (0.2–8.6) vs non-fab Suspicious role of multiple chemical exposure in photo process	Public
Samuels *et al.*	1995	US/SIA	1984–1989, cross-sectional study of male workers through interview 241 fab (165 births) vs 447 non-fab workers (300 births)	Fertility	RR for fertility: fab 0.98 (0.80–1.19) RR for previous conceiving difficulty: furnace/thin film/ion implant workers 1.79 (1.09–2.94) *Failure to control for maternal factors	SIA
Schenker *et al.*	1995	US/SIA	1989–1991, prospective cohort study of 402 women through 6-month daily urine collection, diaries, and interview 1989–1990, cross-sectional survey of 1637 female and 1536 male workers Fab vs non-fab comparison	Fecundability, infertility	FR: fab 0.51 (0.27–0.95), dope/film 0.32 (0.11–0.90), mask 0.75 (0.37–1.55) OR for infertility: male fab 1.17 (0.79–1.74), female fab 1.09 (0.72–1.46)	SIA, public
Eskenazi *et al.*	1995	US/SIA	1989–1991, prospective cohort study of 402 women through 6-month daily urine collection, diaries, and interview 152 fab vs 251 non-fab workers	Fecundability	OR for fecundability: fab 0.59 (0.32–1.09) OR for clinical pregnancy: fab 0.43 (0.19–0.90) Lowest fecundability group: dopant and thin film, or exposed to glycol ether	SIA, public
Correa *et al.*	1996	US/IBM	1980–1989, retrospective cohort of 378 female workers and 375 spouses of male workers (561 and 589 pregnancies) through interview and plant records Focus on EGE: no vs low, med, and high exposure	Subfertility	RR: female worker's high exposure 4.6 (1.6–13.3) – dose–response relation RR: spouse's high exposure 1.7 (0.7–4.3) Suspected role of EGE exposure	IBM, public
Chen *et al.*	2002	Taiwan	1990–1997, retrospective cohort study of 173 female workers Fab (EGE) vs non-fab comparison	Waiting time to pregnancy	RR for fecundability: photo 0.77 (0.45–1.32), EGE exposure 0.59 (0.37–0.94) RR for clinical pregnancy: fab 0.22 (0.05–0.96), EGE exposure 0.37 (0.11–1.19) Suspected role of EGE exposure on ovarian function	Public

RR: relative risk; SIA: Semiconductor Industry Association; OR: odds ratio; FR: fecundability ratio; EGE: ethylene glycol ether. *Confidence intervals and p-values are presented where present in the original studies. Presentation of CI and p-values are preferred to the use of arbitrary dichotomy - 'significance vs. non-significance'. No information in these table means it was lacking in the original papers.

Table A3 Summary of study findings on cancer in semiconductor industry

Author	Year	Dataset and follow-up	Comparison	Measure	Main findings	Fund
US (IBM)						
Beall *et al.*	1996	Corporate Mortality File: 1975–1989 (10 331 deaths) 146 brain tumor cases vs 591 controls	Case vs control (VDT exposure)	OR	No significant association between VDT and brain tumor Technician employed for 10+ years 1.7 (1.0–3.0), programmer 2.8 (1.1–7.0)	IBM
Beall *et al.*	2005	Employment cohort: 1965–1999 (126 836 workers in NY, VT, CA) Death registry: 1965–1999 (2 055 328 person years (PYs), 6579 deaths)	External: VT, NY, CA population Internal: exposed vs unexposed (Cox regression)	SMR, RR	SMR: overall death 65 (64–67), all cancer 78 (75–81) RR (ever-exposed): stomach cancer 1.9 (1.0–3.7), ovarian cancer 2.1 (1.0–4.4)	IBM
Bender *et al.*	2007	Employment cohort: 1965–1999 (89 054 workers in NY, CA) Cancer registry: 1976–1999 (NY), 1989–1999 (CA) (861 521 PYs, 2860 cancer cases)	External: NY, CA population Internal: exposed vs unexposed (Cox regression)	SIR, RR	SIR: all cancer NY 81 (77–85), CA 87 (82–92), prostate CA 115 (103–128) RR: no consistent findings	IBM
Clapp	2006	Corporate Mortality File: 1969–2001 (31 941deaths in VT, CA, MN)	US population	PMR, PCMR	PMR for all cancers: male 107 (105–109), female 115 (110–119) PCMR: male manufacturing – brain 166 (129–213), kidney 162 (124–212), melanoma 179 (131–244), pancreas 126 (101–167); female manufacturing – kidney 212 (116–387), hematologic 162 (121–218)	Plaintiff
Clapp *et al.*	2008	Corporate Mortality File: 1969–2001 (115 cancer deaths in NY)	NY population	PCMR	PCMR: male melanoma 367 (119–856), lymphoma 220 (101–419), kidney 165 (45–421), brain 190 (52–485); female breast 126 (34–321)	Plaintiff
US (SIA)						
Boice *et al.*	2010	Employment cohort: 1968–2002 (100 081 workers in CA, TX, NM, OR, AZ) Death registry: 1983–2007 (2664 deaths)	External: CA, TX, NM, OR, AZ population Internal: fab vs non-fab (Cox regression)	SMR, RR	SMR: overall death – fab 54 (51–57), non-fab 54 (51–56); all cancer – fab 74 (66–83), non-fab 72 (66–79) RR for all cancer: fab 0.98 (0.9–1.1), operators/technicians 0.97 (0.8–1.1)	SIA
West Midlands, UK						
Sorahan *et al.*	1985	Employment cohort: 1970–1979 (1807workers) Death registry: 1970–1982 (52 deaths) Cancer registry: 1970–1981 (49 cases)	SMR: England and Wales population SRR: West Midlands population	SMR, SIR	SMR: overall death 71*, all cancer 91 (male 174, female 67) SIR: all 103 (male 168, female 88)	n.a.
Sorahan *et al.*	1992	Death registry: 1970–1989 (107 deaths) Cancer registry: 1970–1988 (93 cases)	SMR: England and Wales population SRR: West Midlands population	SMR, SIR	SMR: overall death 72*, all cancer 79 (male 129, female 65*) SIR: all cancer 96 (male 140, female 87)	n.a.
Nichols *et al.*	2005	Death registry: 1970–2002 (319 deaths) Cancer registry: 1970–2001 (239 cases)	SMR: England and Wales population SRR: West Midlands population	SMR, SIR	SMR: overall death male 99 (79–122), female 74 (65–85), all cancer male 112 (75–161), female 69 (55–86); breast cancer 47 (25–81) SIR: all cancer male 130 (95–173), female 94 (82–109); male rectum 284 (104–619); female pancreas 226 (108–415), melanoma 221 (110–396)	n.a.

Table A3 Continued

Author	Year	Dataset and follow-up	Comparison	Measure	Main findings	Fund
Greenock, Scotland, UK (National Semiconductor i.e. NSUK)						
McElvenny *et al.*	2003	Employment cohort: 1970–1999 (4388 workers) Death registry: 1970–2000 (55 014 PYs, 71 deaths) Cancer registry: 1970–1998 (45 901 PYs, 123 cases)	Scotland population (adjusted for deprivation)	SMR, SIR	SMR: overall death male 40 (27–59), female 75 (54–101); all cancer male 47 (17–102), female 110 (69–164); female lung cancer 241 (116–444) SIR: all cancer male 99 (64–147), female (83–145); female lung 273 (136–488), stomach 438 (90–1280), breast 134 (82–206); male brain 401 (83–1172)	Public
Darnton *et al.*	2010	Death registry: 1970–2007 (84 733 PYs, 145 deaths) Cancer registry: 1970–2006 (80 456 PYs, 238 cases)	Scotland population (adjusted for deprivation) Nested case-control	SMR, SIR, OR	SMR: overall death male 45 (34–57), female 73 (58–90); all cancer male 43 (23–76), female 101 (73–136); female lung 157 (88–258), stomach 362 (99–926) SIR: all cancer male 90 (69–116), female 102 (85–122); female lung 144 (82–234), breast 123 (90–163), stomach 312 (101–729); male brain 338 (69.7–987) OR: no significant risk factors	Public
Darnton *et al.*	2012	Death registry: 1970–2007 (84 733 PYs, 145 deaths) Cancer registry: 1970–2006 (80 456 PYs, 238 cases)	Nested case-control 21 breast cancer cases vs 83 matched controls	OR	No consistent evidence of any relationship with occupational exposures	Public
Taiwan						
Chang *et al.*	2003	Employment cohort: 1973–1997 (86 868 workers) Death registry: 1985–1997 (1 022 094 PYs, 1257 deaths, 316 cancer cases)	Taiwan population	SMR	Overall death: male 79 (71–87), female 113 (105–120) All cancer: male 65 (50–83), female 100 (88–114)	Public
Chang *et al.*	2003	Employment cohort: 1978–1997 (52 835 workers) Death registry: 1985–1997 Cancer registry: 1979–1997 (829 cases)	25 596 textile and 17 960 electronic workers	PCMR	Males: liver 1.8 (1.0–3.1) (vs electronic workers) Females: stomach 1.7 (1.1–2.4), liver 1.8 (1.1–2.9), uterus 4.4 (2.8–6.6) (vs electronic workers), breast cancer 1.2 (1.0–1.4)	Public
Chang *et al.*	2005	Employment cohort: 1973–1997 (86 868 workers) Cancer registry: 1979–1997 (998 cases)	Taiwan population	SIR	All cancer: male 78 (65–92), female 105 (98–112) Female breast cancer 119 (103–136)	Public
Sung *et al.*	2007	Female employment cohort: 1973–1997 (63 982 workers) Cancer registry: 1979–2001 (1 403 824 PYs, 1572 breast cancers)	Taiwan female population	SIR	All cancer 96 (91–101) Breast cancer: all workers 109 (96–122), employed for +10 years 168 (111–242), hired before 1974 138 (111–17), hired before 1974 and employed for 10+ years 162 (102–242)	Public

Table A3 Continued

Author	Year	Dataset and follow-up	Comparison	Measure	Main findings	Fund
South Korea						
Lee *et al.*	2011	Employment cohort: 1998–2008 Death registry: 1998–2008 (113 443 workers, 267 deaths) Cancer registry: 1998–2007 (108 933 workers, 346 cases)	Korean population	SMR, SIR	SMR: all death male 25 (21–29), female 66 (55–80); all cancer male 44 (32–58), female 79 (51–118); NHL male 133 (43–309), female 250 (68–640); leukemia male 39 (8–114), female 137 (55–281) SIR: all cancer male 86 (74–98), female 88 (74–103); thyroid male 211 (149–289), female 99 (76–127); NHL male 93 (45–171), female 231 (123–395); leukemia male 69 (30–137), female 128 (61–236)	Public

OR: odds ratio; SMR: standardized mortality ratio; RR: relative risk; SIR: standardized incidence ratio; PMR: proportionate mortality ratio; PCMR: proportionate cancer mortality ratio; SRR: standardized rate ratio; NHL: non-Hodgkin's lymphoma. *Confidence intervals and p-values are presented where present in the original studies. Presentation of CI and p-values are preferred to the use of arbitrary dichotomy - 'significance vs. non-significance'. No information in these table means it was lacking in the original papers.

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