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Editorial/Editoriale

Occupational cancer and reproductive outcomes in the semiconductor industry: the need for an international epidemiologic study

Tumori professionali ed effetti riproduttivi nell'industria dei semiconduttori: la necessità di uno studio epidemiologico internazionale

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Summary

Occupational health of semiconductor workers has been the subject of only a few, limited investigations, all in developed countries. Findings of reproductive problems and increased risk of several cancers have not been adequately followed up by larger, more definitive studies. Industry and government have failed to take the initiative to protect workers before the industry was exported to many regions of the world. There is a compelling need for a large, international epidemiologic study of the semiconductor industry and its workforce. Eur. J. Oncol., 14 (2), 69-78, 2009

Key words: **semiconductor, industry, occupational health, reproductive, cancer**

Riassunto

La salute dei lavoratori dell'industria dei semiconduttori è stata oggetto di rare e limitate indagini, tutte condotte in paesi industrializzati. Le osservazioni di effetti sulla riproduttività e di un aumentato rischio di numerosi tumori non sono state adeguatamente seguite da ampi e più conclusivi studi. L'industria e il governo hanno mancato di prendere l'iniziativa per proteggere i lavoratori prima che l'industria fosse esportata in numerose aree del mondo. C'è un bisogno improcrastinabile di un ampio studio epidemiologico internazionale nell'industria dei semiconduttori e della sua forza lavoro. Eur. J. Oncol., 14 (2), 69-78, 2009

Parole chiave: **semiconduttore, industria, salute ambienti di lavoro, riproduttivo, cancro**

Introduction

The semiconductor chip industry amounts to well over $200 billion per year. These high-technology devices are crucial to the manufacture and sales of about $1 trillion in electronic products each year, and underlie a large part of the world economy. The semiconductor industry now employs so many

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workers worldwide that any increase in the risk of occupational health problems should be a matter of broad and deep public health concern. Many of the older technologies and equipment are exported to newly industrialized countries as newer technologies are installed in the more highly developed industries of Japan, the United States, and Europe. Asia has become the world's preferred location for electronic equipment manufacturing. China manufactures more than a third of all electronic products used in the world today. This dramatic global redistribution of high-technology manufacture to poorer countries is accompanied by a disturbing ignorance of or disinterest in occupational and environmental health in the host countries (1). Many developing countries begin to manufacture high-technology products before they have instituted programs to regulate and enforce occupational and environmental health standards. When they do so, they unwittingly assume long-term costs of workers' health care, compensation, and environmental remediation that their countries can hardly afford (2).

Occupational Health

Health issues in the semiconductor industry have not received adequate public health attention anywhere in the world. Many known reproductive toxicants and carcinogens have been and still are used in the manufacture of semiconductor chips, and some very worrisome findings have been reported; yet no broad epidemiological study has been conducted to define possible risks in a comprehensive way. There is particular concern about the many workers, mostly in countries that are still industrializing, who have inherited jobs that use chemicals, technologies, and equipment that are no longer in use in developed countries. Since most such countries lack cancer registries and have inadequate reproductive and cancer reporting mechanisms, industry efforts to control exposures to carcinogens are of particular importance.

The semiconductor industry is complex and diverse, with many technologies and manufacturing processes. The manufacturing settings share many characteristics, but no two are exactly the same. Thousands of different chemicals and other materials have been used (3). The industry also presents problems of radiation exposures as well as a variety of occupational stressors, including unresolved ergonomic issues (4). However, because of the rapid development of this industry and its penchant for secrecy, the health hazards of chip manufacturing are poorly understood by workers, their physicians, and the general public. What was once thought to be a "clean" industry is actually one of the most chemical-intensive industries ever conceived. Moreover, manufacturing is done in a "cleanroom" in which air contaminated with chemicals is recirculated giving rise to multiple chemical exposures of a largely female workforce of childbearing age. The term cleanroom refers to the removal of dust in the manufacturing facility to protect the chip from damage during production, but dust removal does not alter the ambient concentrations of chemical fumes and vapors.

Semiconductor chip manufacturing is a light industry in which there are fewer injuries than in heavier manufacturing. Nonetheless, semiconductor manufacturing has been shown to present a particular problem with occupational illnesses. The U.S. Bureau of Labor Statistics (BLS) reports poisoning disorders for workers with ingestion or absorption of toxic substances. In 2003, BLS reported that the rate of occupational illnesses caused by poisoning was 0.4 (per 10,000 full-time workers) for all private industry, and slightly higher at 0.5 for all manufacturing industry. The rate of poisoning disorders for electronic components manufacturing, including semiconductors, was 3.0, and it was 6.0 for semiconductor and related device manufacturing (5). Skin disorders and respiratory conditions also occur at elevated rates in the semiconductor industry (6-8). These occupational illnesses may reflect the widespread use of toxic materials in the industry.

Reproductive Health Studies

Since a high proportion of semiconductor workers were women of childbearing age, the risk of adverse reproductive outcomes was examined among workers at a Massachusetts semiconductor company. Personal interviews were conducted with manufacturing workers, spouses of male workers, and an

internal comparison group of non-manufacturing workers (9). Elevated rates of spontaneous abortion were observed for women working in cleanrooms (31.3 abortions per 100 pregnancies for photolithographic workers, 38.9 for diffusion workers, and 17.8 for unexposed women). No other significant differences in reproductive outcome were identified. The authors stressed the tentative nature of their findings and called for more definitive studies.

IBM, then and now one of the world's largest semiconductor manufacturers, engaged the School of Hygiene and Public Health at Johns Hopkins University to study reproductive problems among IBM employees. The retrospective portion of the study, conducted at facilities in New York and Vermont, was reported in 1992. It showed an increased rate of spontaneous abortion among women who worked in two specific cleanroom areas (10). Birth defects, cancer, and other health measures were not studied, for reasons that have not been made public. The semiconductor industry has failed to conduct studies of birth defects, despite the fact that most production workers are women of childbearing age.

The Semiconductor Industry Association (SIA) engaged researchers at the University of California, Davis to conduct a retrospective cohort study of 6,088 women. In this group there were 904 eligible pregnancies ascertained by completion of a detailed telephone interview, and 113 of these resulted in a spontaneous abortion eligible for inclusion in the analysis. The crude risk ratio for women working in fabrication areas *vs* non-fabrication areas was 1.45 (95% CI 1.02-2.05). This reduced slightly to 1.43 (95% CI 0.95-2.09) after adjustment for various potential confounders. This study provides the most compelling demonstration to date of the need for serious study of reproductive risks associated with semiconductor manufacturing work (11).

This excess occurred in settings where industrial hygiene air measurements were widely reported to be in compliance with current occupational standards. The two studies that found high miscarriage rates in workers recorded solvent levels substantially below their respective exposure standards. This fact suggests several possibilities, none of them welcome: that present standards are inadequately protective, that routes of exposure not included in the standards are important, that the relevant agents were not measured, that agents are acting in unexpected synergy, or that the reports are incomplete. Both IBM and the SIA pointed to former use of glycol ethers as the cause of the elevated miscarriage rates. When challenged to repeat the studies now that glycol ethers have supposedly been removed from the plants, the semiconductor industry began stonewalling discussion and study of the reproductive health issue, a refusal to cooperate that continues to this day.

In 1999, the Health and Safety Executive (HSE) of the United Kingdom published the results of a study of spontaneous abortion at National Semiconductor (NSUK) in Greenock, Scotland (12). The publication was criticized internationally as "a poorly designed and ultimately uninformative study, with too small a study population to yield any statistically reliable results" (13, 14). The selection process used in the study failed to produce a representative sample of semiconductor cleanroom workers. Most of the test subjects had jobs outside the high-risk work areas, which would dilute any real effects, perhaps to a level where they could not be demonstrated.

Many scientists were struck by the conclusions reached by the HSE in its inconclusive study of spontaneous abortion at the NSUK plant in Scotland. The HSE stated that, "*We found no reason to suggest that any further specific action on the part of the industry in Great Britain is indicated, nor have we identified any issues which currently warrant further research in the British semiconductor industry*" (12). This familiar behavior of industry, to take an equivocal study result and call it a negative study, then use the result to deny the need for further investigation, has not been challenged by any major national enforcement arm of government.

There is ample reason for concern about reproductive toxicity among semiconductor workers but no definitive study has been reported. The absence of studies that include birth defects among measured reproductive outcomes is a serious omission. Such a study is sorely needed. Given these problems in industrialized countries, with the newest technologies and facilities, it is even more important to study reproductive health in workers who use older technologies and chemicals no longer used in developed countries.

Cancer Studies

Semiconductor workers may be subject to a risk of occupational cancers in parallel with the risks of occupational reproductive effects. A 1983 report evaluated the general cancer incidence pattern in the electronics industry (15). It used the Swedish Cancer Environmental Registry, which was created by linkage of the 1960 census to the Swedish Cancer Registry of 1961 to 1973. The control population contained more than 3 million individuals. The total risk estimates were 1.15 for men and 1.08 for women, but the relative risk estimates for lung, bladder, and malignant melanoma were significantly increased, to 1.52, 1.22, and 1.35, respectively. A subpopulation of workers in the electronics industry was further examined with regard to cancers of the mouth, pharynx, and respiratory system. Among males the incidence of lung tumors was moderately but significantly elevated (RR=1.36). There were 13 cases of pharyngeal cancers giving a risk estimate of 3.0. In a subgroup composed of workers who largely held assembly jobs, there were 5 nasal cancers, representing a risk increase of more than fourfold.

Studies in the United States

In the 1980s, IBM commissioned a study of cancer whose results were held from publication by the company and its contract academic researchers. The study was finally published in 1996, and was for some reason limited to a report only of brain cancer mortality among IBM workers. The contract researchers at the University of Alabama, Birmingham (UAB), utilized the IBM Corporate Mortality File, which is a record of deaths for all U.S. employees of IBM over a period of more than 30 years. The study reported a significant association between working at IBM in a "technical job" for ten years or more and dying of brain cancer. Apart from this disconcerting finding, the study had severe limitations, prompting the authors to state that information about specific exposures in the work environment, such as electromagnetic fields (EMF), ionizing radiation, or chemical agents, was not available. Some of the observed associations are difficult to interpret because exposure information pertaining to division and job groups is lacking (16).

Despite its weaknesses, the IBM study was consistent with an earlier study that found that mortality from brain cancer among male electronics workers increased with duration of employment. The risk of dying from brain cancer was highest among electrical and electronics workers with long-term work histories – specifically of 10 years or more – and with probable exposure to solders and organic solvents (17). This study, published in 1987, found that the risk of astrocytic tumors among electronics manufacture and repair workers was increased tenfold among those employed for 20 or more years. The authors pointed out that, "*Numerous solvents used throughout the electrical and electronics industry are known neurotoxins, causing peripheral neuropathy, central nervous system depression, and neurobehavioral dysfunction*". The authors discussed radiation exposure, but had no industrial hygiene data from which exposure risks could be assessed.

In 2003, a suit against IBM involving two plaintiffs with cancer came before a jury in San Jose, California. In the course of legal discovery, attorneys for the plaintiffs asked for employee health records. The court granted access to the same Corporate Mortality File that IBM had provided to UAB investigators for their earlier study (16). Attorneys for the plaintiffs asked epidemiologists Richard Clapp of Boston University School of Public Health to study the IBM Corporate Mortality File. Clapp found patterns of mortality in the IBM workforce consistent with occupational exposures to solvents and other carcinogenic materials used in IBM manufacturing processes. The files contained data on decedents between 1969 and early 2001, and the US population was used as controls. The final number of records used in the Clapp study was 31,941, including 27,272 males and 4,669 females. There had been 7,697 cancer deaths in men, where 7,206 would have been expected (PMR=106.8; 95% CI=104.8-108.8; 99%CI=104.2-109.5). Among the females, there were 1,667 cancer deaths compared to 1,454 expected (PMR=114.6; 95% CI=110.3-119.1; 99% CI=108.9-120.6) (18).

Proportionate mortality ratios (PMRs) for many cancer sites were found to be significantly elevated in both IBM males (cancers of the large intestine,

pancreas, kidney, testis, thyroid, central nervous system (CNS), and all lymphatic and hematopoietic tissues, and melanoma) and females (cancers of the lungs and bronchus, breast, other female organs, CNS, and all lymphatic and hematopoietic tissues). The types of cancers that increased the most were consistent with the findings of other studies of semiconductor workers and studies of workers in other industries exposed to the same chemicals. Key findings were the excess deaths due to brain, breast, kidney, lymphatic and hematopoietic cancers and melanoma. PMRs are not as informative as other statistical techniques, but stronger evidence was not available because IBM would not provide data beyond mortality files.

IBM then retained the epidemiologists at the University of Alabama who had conducted their prior cancer study to look at the cancer incidence and cancer mortality at three IBM sites. The healthy worker effect was evident in lower than expected mortality overall. Employees had total cancer incidence rates that were lower than the general population rates overall and those of subgroups with many years since starting work and relatively long duration of employment. "*These deficits reflected employees' low incidence rates of most cancers related to smoking, alcohol and nutritional deficits. When compared with the general population, some employee subgroups had small increases in several cancers, including melanoma of the skin and cancers of the colon, breast, prostate, and thyroid*". The UAB researchers begin their paper by stating "*Because it was not known whether semiconductor workers have been exposed to carcinogenic agents and because previous epidemiological studies have not provided evidence that exposures in the industry are associated with cancer, we did not evaluate hypotheses on specific agents and cancers as part of the present research*". They end the paper by concluding that, "*The results of the study do not provide any strong evidence of a causal association between employment factors and cancer*" (19).

There was no use by investigators of the company records of either work assignments or worker exposures to carcinogens. In discussing their study, the authors suggested that, "*Another improvement would be the use of more quantitative exposure rankings based upon actual measurements of exposure, which could be accomplished by historical records of industrial hygiene measurements of airborne contaminants, as well as the archived records of chemical use for the three facilities. As IBM has maintained these records, a quantitative reconstruction of historical exposures to agents known or suspected to be carcinogens may be possible. Although this reconstruction was outside the scope of the current project, it could be incorporated in a future investigation*" (20).

The UAB researchers published another paper using the same database as an additional investigation focused on cancer incidence rather than on mortality. They compared the incidence rates of cancer for 89,054 men and women workers at IBM facilities in East Fishkill, New York and San Jose, California with general population rates. Employees had total cancer incidence rates that were lower than the general population rates overall and those of subgroups with many years since starting work and relatively long duration of employment. "*These deficits reflected employees' low incidence rates of most cancers related to smoking, alcohol and nutritional deficits. When compared with the general population, some employee subgroups had small increases in several cancers, including melanoma of the skin and cancers of the colon, breast, prostate, and thyroid*" (21).

At the East Fishkill plant in New York, work in process equipment maintenance was associated with central nervous system cancer (8 observed, SIR = 192, 95% CI 83 - 379; RR 1.5, 95% CI 0.6 - 3.5), as in the prior mortality study. The excess was concentrated in employees with greater than 15 years since starting and greater than 5 years worked (4 observed, 0.8 expected). "*Incidence results for CNS cancer at East Fishkill and for prostate cancer at San Jose warrant further consideration because of work group associations seen for these cancers in the companion mortality study*" (21).

The past two years of legal delays gave IBM and its consultant epidemiologists the opportunity to conduct and publish favorable studies of the IBM Mortality File, and to present the results in the most acceptable manner possible to IBM employees and to the public. During this time, IBM lost no opportunity to challenge and to denigrate independent attempts to assess its commitment to occupational

health and safety. The actions of IBM and of Elsevier Science point up the need for speedy government action to obtain studies, independent of industry control or influence, of many workplace hazards and a wider commitment of all journals, editors, and their publishers to ensure that research findings that may affect public health or social justice reach both the scientific community and the public as rapidly as possible (22).

Studies in the United Kingdom

In 2001 the HSE announced the results of its study of cancer rates in a small sample of workers at the National Semiconductor (NSUK) plant at Greenock, Scotland. It has never been made clear why the study was conducted in Scotland rather than in England where there is a much larger semiconductor industry, or why the study was done in an American plant rather than a UK plant. Nonetheless, that study found that the overall mortality rate from all causes of death was lower among NSUK employees than it was for Scotland as a whole, though the total incidence of cancer cases was about the same as for Scotland as a whole. However, HSE identified a higher than expected incidence of three particular types of cancer among women in the work force, and one type in men. There were 11 cases of lung cancer in women, two to three times as many as expected. Information on smoking was not available to HSE's investigators, but semiconductor production workers are not allowed to smoke on the job, and their general rate of smoking may be substantially lower than in the general population. There were three cases of stomach cancer in women, four or five times as many as expected. There were 20 cases of breast cancer among women, five more than would have been expected. Ten of the cases had a latency of less than 10-years, with ages at diagnosis ranging from 31 to 60. There were three deaths from brain cancer among men, about four times as many as would be expected. Three cases had a latency of less than 10 years. No important excesses of other types of cancer investigated were identified (23).

The HSE study not only used a very small group of employees; a substantial fraction of them had little or no exposure to the chemicals of concern. The HSE investigators simply defined all NSUK Greenock employees as subjects, thereby seriously limiting the opportunities to demonstrate increased cancer risks in the workers who were occupationally exposed. HSE also excluded contractors, in particular contract cleaners, who were known to have worked in the most exposed areas. The short latency periods may simply reflect the still short periods of employment in the expanding semiconductor industry. If so, the burden of disease may be found to be much greater and more severe when longer work histories are available.

The small sample size and weak study design were of concern to many of us who reviewed the HSE study proposal (24). Still, the results substantially reinforce the concerns that prompted the investigation and suggest a work-related cause for several kinds of cancer. It is remarkable that four apparent excesses in cancer were found in a study with a weak design, few heavily exposed workers, and a total of only 71 deaths. However, the relative risks are still subject to very wide uncertainty, and the range of effects (including other cancers and other causes of death) may be substantially larger or smaller than present data indicate. Cancer is fairly common at three of the sites reported (excepting brain), and important but small increases in less common sites could have been missed simply because the study was too small to detect them. The somewhat reduced total mortality (presumably a healthy worker effect), with a near-average cancer registration rate, suggests the possibility of some real elevation in the cancer risks over what these workers might otherwise have experienced.

After promising to do a major study of semiconductor manufacturers throughout the United Kingdom, the HSE retreated to propose another small study of a single company in Scotland. Objections addressed to HSE by worker advocates were ignored (25). In April 2006, after more than five years of procrastination, HSE announced that it was going to conduct a study, but that the study would be limited to NSUK, and look specifically at only the four cancers found to be at elevated rates in its former study (26). Minutes of the Microelectronics Joint Working Group from November 22, 2005 give a disturbing picture of the questionable HSE commitment to conduct a definitive research study

of cancer in the semiconductor industry. Commenting on the recently published IBM study by Bender *et al* (21) the following was recorded at the meeting, "*HSE epidemiologists do not think that these findings undermine the decision to take forward NSUK II: we cannot avoid investigating the lung cancer finding: the IBM finding for breast cancer is for mortality only - this is now an eminently "treatable" cancer and we need to see the more relevant data on cancer incidence: the finding for CNS cancers supports our decision to do the case-only study on brain cancers*" (27).

The group of scientists and clinicians who had written to Dr. Osman of HSE about their dismay with the planning and conduct of the original HSE study, wrote again on May 12, 2006 to state that they were, "*deeply concerned about the HSE proposal to study the cancer incidence in semiconductor workers, and suspicious that the agency is operating under undue political pressure to obtain equivocal or negative results (28). No serious scientist would agree with your statement to the Greenoch Telegraph regarding the decision to study just four cancers in a very small study population. One cannot assume that the four cancers elevated in the HSE study in Scotland are the only cancer risks. In the case of occupational cancer [reported in the first HSE study], the very limited data available are a reason for worry. Though the findings are not conclusive, it is clear that more detailed studies are urgently needed to determine whether or not there is a workplace risk, and if so to determine its specific nature and size. The HSE continues to ignore calls for a larger and more definitive cancer study. Following the first HSE cancer study, NSUK stated in a press release that, 'there was no scientific evidence of increased cancer risk for employees working at our facility' (29). This is the very outcome that we warned against when the study was proposed that a small, poorly designed study with little chance of definitive findings would be used to argue against doing it right (24). We strongly encourage the HSE to reexamine its plan to study cancer in semiconductor workers and to submit its study design for review and comment by unbiased scientists in a public process*" (28).

This is not at all what was recommended to HSE by its own experts. The London School of Hygiene and Tropical Medicine provided the HSE with an analysis of what would be required to assess the risk of cancer in UK semiconductor workers. Their report strongly favored a large study multiple locations. "*The HSE studied cancer risks in workers from one semiconductor manufacturing plant in Greenock but, because of the small numbers in the study, the results are difficult to interpret. There is therefore an interest in the feasibility of studying a larger cohort, from across the UK semiconductor industry. The power of such a study would be related to both the numbers of workers and the length of their employment in the industry. An epidemiologist and an occupational hygienist visited each of eight plants selected because they had the largest workforces and were longest established. We found that, given suitable clearance to access the company records, it would be feasible to amass a cohort of at least 12,000 current and ex-workers. This would allow comparison of mortality or cancer incidence both with external reference rates and between workers involved or not involved directly in wafer fabrication*" (30).

UK researchers, in yet another small endeavor, studied the mortality and cancer morbidity experienced by a cohort of 1,807 male and female employees from a semiconductor factory in the West Midlands. Overall mortality was close to expectation in males [SMR 99, 95% CI 79-122] and significantly below expectation in females (SMR 74, 95% CI 65-85). Incidence of all sites of cancer was somewhat elevated in males but close to expectation in females. Significantly elevated standardized registration ratios (SRR) were found in males for cancer of the rectum, in females for cancer of the pancreas and malignant melanoma, and in males and females combined for cancer of the rectum and malignant melanoma. Detailed work history and industrial hygiene data were unavailable for analysis (31).

Present Status

Recognizing the need for an international approach to health and safety in the semiconductor industry, John C. Bailar sent the following proposal to the World Health Organization's International Agency for Research on Cancer (IARC), "*It is critically important to the workers, the companies, the*

communities, and the industry worldwide that the health issues in semiconductor manufacture, especially the cancer risks, be resolved quickly and correctly. For this reason I appeal to the International Agency for Research on Cancer to consider a large and definitive study of cancer in semiconductor workers. The complex exposures that take place in cleanrooms and elsewhere in the semiconductor companies require the knowledge and experience that IARC has used to such good effect in other studies of multiple exposures. And the reluctance of the industry to clean its own house requires the authority and credibility of IARC" (32).

Paolo Boffetta responded that IARC would delay action and, "*wait to see the outcome of the SIA study*" (33).

The Boffetta response was the result of an SIA announcement that, "*It will proceed with a retrospective epidemiologic study to investigate whether or not wafer fabrication workers in the U.S. chip industry have experienced higher rates of cancer than non-fabrication workers* (34). The SIA awarded a contract to Vanderbilt University to conduct a retrospective epidemiological study to determine whether there is an increased cancer risk among wafer fabrication workers compared to other semiconductor industry workers and the general population (35). SIA reported that the multimillion-dollar study will review records of approximately 85,000 workers who worked in wafer fabrication facilities of member companies during the past 30 years. Researchers at the Vanderbilt University-Ingram Cancer Center will conduct the study. They expect to report results to the SIA in the spring of 2009. Researchers from Vanderbilt University are now in the middle of an intensive data collection phase. Their focus is on the collection of employment and related records on current and former employees of member companies, as well as on industrial hygiene and related data.

Recent research

Research into the reproductive and carcinogenic effects of semiconductor materials continues to point to the need for employee exposure monitoring, and definitive studies of exposure effects in workers. Many of the agents used as dopants are highly toxic and, in several cases, are now identified as known or probable human carcinogens. Indium arsenide, indium phosphide, and aluminum gallium arsenide, show clear evidence of carcinogenic potential in studies in Taiwan (36-38). Cancer risk, estimated by the level of inhaled arsenic, is higher than the allowable risk based on US EPA's acceptable risk limits. These and many other dopant materials are reproductive toxicants. No research has been conducted on the possibility of increased risk to workers when toxic dopants are used in combination with solvents and other organic chemicals in the workplace. Female workers with exposure to trichloroethylene and/or mixtures of solvents, first employed prior to 1974, may have an excess risk of breast cancer (39). There is limited evidence on the hypothesis that maternal occupational exposure near conception increases the risk of cancer in offspring (40).

Conclusion

Open questions about the health risks of semiconductor manufacturing, including the full range of cancers as well as birth defects and other reproductive health outcomes must be settled once and for all. It is important to open this industry to further health research in the United States, the United Kingdom, Japan, Germany, Ireland, Malaysia, China, Korea, Taiwan and the many other countries where these manufacturing processes are now in general use.

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