

Identification of cancer risks from chemical exposures — An epidemiologic program at the Swedish National Institute of Occupational Health

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In the United States (US), occupational cancers have been estimated to contribute to 2–8 % of all cancers (1), and the Swedish Cancer Committee has made similar estimates for Sweden. Do such estimates of magnitude motivate further research efforts into occupational cancer? Even a low estimate of 2 % of all cancers would mean 700 incident cases and 400 deaths annually in Sweden, which is far more than, eg, the fatalities caused by occupational accidents in Sweden. It would be just as absurd to claim that one should stop studying — and taking actions against — fatal accidents as it would be to stop studying — and preventing — fatal occupational diseases.

It has also been argued that occupational cancers are of little importance because the influence on the general cancer morbidity would be negligible even if all these cancers were prevented. A similar reasoning for therapeutic attempts to prolong the life of cancer victims would be outrageous. Indeed, small improvements in the survival time due to improved cancer therapy is often praised and most welcome for that particular group of patients although such improvements hardly influence the national statistics on cancer morbidity or mortality. Identifications of cancer risks are just as welcome for the occupational groups concerned, and the elimination of the risk is often definite rather than relative.

On the basis of this rationale the Swedish National Institute of Occupational Health is continuing its research program for the identification of new potential cancer hazards and the follow-up of old hazards that might prevail from lower exposures.

Soot and combustion gases

The first study on soot and combustion gases concerned chimney sweeps, and already in the first publication (14) highly excessive risks were demonstrated for several cancer sites — lung, esophagus, and liver — to such a degree that the overall cancer mortality was increased by approximately 50 %. The latest updates and cancer incidence studies (8, 9) have con-

firmed most of the preliminary results, and, in addition, have demonstrated an increased bladder cancer risk. However, the increased liver cancer risk now seems questionable due to several imprecise notifications on the death certificates which became obvious during the scrutinization of the cancer registry reports.

Recently a manuscript by Gustavsson on a Scandinavian cohort study of 176 men employed at least one year between 1920 and 1986 at a waste incineration plant was submitted for publication. There was a two- to threefold increase in the risk for lung cancer (nine observed deaths), depending upon whether national or local rates were used for calculating the expected numbers, and a standardized mortality ratio of 130 (34 deaths) for ischemic heart disease.

Also in progress are a study on 350 gas workers, another on 700 diesel-exposed bus garage workers, and finally a follow-up of the mortality outcome for 1 000 fire fighters in Stockholm, in which the number of extinguished fires since the 1920s is being used as the measure of exposure.

Cooperation is being sought for a more advanced analysis of the exposure situation at different work sites, and there is also hope to initiate mechanistic research concerning the repeatedly observed excess deaths from ischemic heart disease among workers exposed to soot and combustion gases.

Metals

Recently a study was submitted for publication on the mortality of 1 876 hard metal workers with at least five years' occupational exposure to cobalt (13). The overall mortality was lower than expected from the national average, but the risk for lung cancer was doubled in a subcohort of workers exposed long-term (seven deaths), and there was a standardized mortality ratio of 140 for ischemic heart disease among long-term and highly exposed workers (21 deaths). The average exposure levels were low for the majority of the workers in these companies, as only few were employed in the 1940s and 1950s. The highly exposed group was estimated to have been exposed to an 8-h time-weighted average concentration of cobalt of 0.01–1 mg/m³.

To my knowledge this is the first epidemiologic cancer study on cobalt exposure without other important

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confounding exposures. Future follow-up, inclusion of workers exposed short-term (less than five years), and the cancer incidence findings will be interesting. There are unusually many old exposure data from this industry, and the situation seems well adapted for exposure modeling based on toxicologic principles for internal dose in the critical organs. There are plans for cooperation with US investigators with access to industrial groups of hard metal workers in US companies.

In 1985 the results on cancer mortality among 522 Swedish workers exposed to cadmium for at least one year in a nickel-cadmium battery plant were published which demonstrated indications of increased risks of lung and prostate cancers (3). The results from another small cohort of cadmium smelting workers are now available (2), but they do not add very much information, as the group was small and the exposure data somewhat weak. There were four deaths from prostate cancer versus 2.5 expected and 2 from lung cancer versus 2.9 expected. However, other metal workers in the same township had definitely decreased risks from lung and prostate cancer. In conclusion, there seems to be some support for an increased risk of lung and prostate cancer in the Swedish cadmium cohorts, and further follow-ups are in progress.

Dust

Several studies have found an association between exposure to quartz and lung cancer, particularly among patients with silicosis (5). A difficulty in the interpretation of several epidemiologic investigations considering the relationship between silica exposure and lung cancer has been that the individuals were often exposed to other known lung carcinogens, such as polycyclic aromatic hydrocarbons in the foundry industry or ionizing radiation in mining. However, no such confounding carcinogen exposures are known in the ceramic industry, and therefore a lung cancer incidence study has been undertaken among 280 male ceramic workers with silicosis notified to the Swedish Silicosis Registry. During the study period 1958–1983 a doubled risk for lung cancer (nine cases) was observed in comparison with expected numbers based on national rates (22). The findings are supported by the results of an Italian study (4) and of animal studies as well (6, 18). Whether the increased risk is caused by quartz dust per se, due to impairment of important lung functions, or by some other fibrosis-related mechanism remains unresolved.

A study is also being carried out on 1 500 workers who insulate one-family houses with man-made mineral wool and who have never been exposed to asbestos.

Finally, a follow-up of a cohort of asbestos cement workers and another cohort of asbestos-exposed railroad mechanics (20, 21) is being extended.

Chemical manufacturing

For about 10 years a few small cohorts of workers exposed to ethylene oxide have been followed. These studies were initiated by some cases of leukemia in a plant with sterilizing equipment (16). In the last published follow-up, eight cases of leukemia and six cases of stomach cancer were identified in comparison with the 0.8 and 0.65 cases expected, respectively (15). The three small cohorts, comprising 539 men and 170 women, were recently followed for three more years (11). A few more blood and lymphatic malignancies and stomach cancers had occurred, and the risk increase seemed to be fivefold for these malignancies. However, nine of the ten stomach cancers had occurred in a chemical industry with very mixed exposures, and no excess has been demonstrated in the other two cohorts. The epidemiologic (12) and toxicologic data (17) strongly indicate a causal relationship between ethylene oxide and the induction of malignancies, even at low-level and intermittent exposure.

In 1986 two different cohort studies were published, one on rubber workers and another on workers exposed to polychlorinated biphenyls. They clearly illustrate the variety of cohorts that are being worked with. The mortality and incidence of cancer was studied among 8 734 workers from two Swedish rubber manufacturing companies (7). The study period was 1952–1981. No significant risk excesses were detected when the results were analyzed without consideration of employment time and latency period. However, the mortality from ischemic heart disease and the incidence of lung cancer were increased when the study period was limited to 40 or more years since first employment. Some of the excess risks found in other cohorts of rubber workers were observed, like bladder cancer, while the number of observed cases of leukemia corresponded well with the number expected in contrast with the results of several US studies of rubber workers. The reason is probably that benzene was banned from Swedish industry before 1950.

Another interesting finding in this study was that immigrants from Finland had an increased total mortality (31 observed versus 16 expected) when the Swedish national statistics were used as reference, while no such excesses were observed for immigrants from non-Scandinavian countries. This result should receive further attention in the future.

In the other study 142 male capacitor workers exposed to polychlorinated biphenyls were followed for 18 years (10). The only remarkable finding was one person who had developed two rare tumors, a slow growing mesenchymal tumor, and a malignant lymphoma. This finding was noteworthy as both types of malignancies have been associated with chlorinated phenoxy acid herbicides and chlorophenols, compounds that are chemically related to polychlorinated biphenyls.

Disadvantages and advantages for occupational cancer epidemiology in Sweden

Occupational epidemiology in Sweden has certain restrictions but also some advantages. The main disadvantage is that the occupational groups are predominantly small, ie, the confidence intervals for the risks of less common cancer sites are usually broad unless the excesses are drastic. There are also few historic exposure measurements, and the possibilities are limited for retrospective exposure assessment. However, these latter two disadvantages are also found in most other countries.

Some of the major advantages are (i) reasonable validity and high report frequency to the cancer registry, established in 1958 (19), (ii) negligible loss of follow-up (usually less than 1 %) due to high traceability through individually unique 10-digit personal identification numbers, (iii) reasonable rules for confidentiality and record matching, and (iv) usually good cooperation from both employers and trade unions and access to all workplaces.

Record-linkage studies and multicenter collaboration

Many record-linkage studies between the 1960 census and the cancer and mortality registers have been published, but not by the National Institute of Occupational Health. However, these linked registers can also be used for efficient case-referent studies. Individual cases and referents can be identified and relatives contacted, after proper permission, and the exposure frequency will be high in these occupational cohorts. Recently a case-referent investigation using this technique to study lung cancer among slaughterhouse workers has been published (7).

Due to the satisfactory situation for cancer studies in Sweden, and to compensate for our small material sources, the Institute collaborates with institutions in other countries. Swedish investigators participated in the joint European study on man-made mineral fibers, and, at the moment, cooperative projects are under way with the International Agency for Research on Cancer on, eg, workers exposed to styrene, workers exposed to vinyl chloride, and welders.

Concluding remarks

No one would dispute the historical importance of the identification and prevention of such occupational cancer hazards as soot, asbestos, aromatic amines, shale oil, benzene, arsenic, chromium, ionizing radiation, or combustion gases. Indeed, most of these hazards still exist in most countries, and some are increasingly used in newly industrialized countries. Unless prevented and checked, they will continue to cause huge numbers of victims.

Many potential risks and hazards can more easily be identified and studied in the Nordic countries than in other countries where longitudinal studies might be impossible to perform. Although the exposure levels might be low and the numbers small, point risk estimates with broad confidence intervals are certainly better than no data at all.

References

1. Doll R, Peto R. The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. Oxford University Press, Oxford 1981.
2. Elinder C-G. Mortality and cancer incidence among cadmium exposed workers [in Swedish]. Swedish Work Environment Fund, Stockholm 1986. (Reports of the Swedish Work Environment Fund no 934).
3. Elinder C-G, Kjellström T, Hogstedt C, Andersson K, Spång G. Cancer mortality of cadmium workers. *Br J Ind Med* 42 (1985) 651—655.
4. Forastiere F, Lagorio S, Michelozzi P, Cavarani F, Arca M, Borgia P, Perucci C, Axelson O. Silica, silicosis and lung cancer among ceramic workers: A case referent study. *Am J Ind Med* 10 (1986) 363—370.
5. Goldsmith DF, Winn DM, Shy CM, ed. Silica, silicosis and cancer. Prager Publishers, New York, NY 1986. (Cancer research monographs, volume 2).
6. Groth DH, Stettler LE, Platek SF, Lal JB, Burg JR. Lung tumors in rats treated with quartz by intratracheal installation. In: Goldsmith DF, Winn DM, Shy CM, ed. Silica, silicosis and cancer. Prager Publishers, New York, NY 1986, pp 243—253. (Cancer research monographs, volume 2).
7. Gustavsson P, Fellenius E, Hogstedt C. Possible causes of increased lung cancer incidence among butchers and slaughterhouse workers. *Scand J Work Environ Health* 13 (1987) 518—523.
8. Gustavsson P, Gustavsson A, Hogstedt C. Excess mortality among Swedish chimney sweeps. *Br J Ind Med* 44 (1987) 738—743.
9. Gustavsson P, Gustavsson A, Hogstedt C. Cancer excess in Swedish chimney sweeps. *Br J Ind Med* (in press).
10. Gustavsson P, Hogstedt C, Holmberg B. Mortality and incidence of cancer among Swedish rubber workers, 1952—1981. *Scand J Work Environ Health* 12 (1986) 538—544.
11. Gustavsson P, Hogstedt C, Rappe C. Short-term mortality and cancer incidence in capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). *Am J Ind Med* 10 (1986) 341—344.
12. Hogstedt C. Epidemiologic studies on ethylene oxide and cancer — An update. In: Bartsch H, Hemminki K, O'Neill I, ed. Detection methods for DNA-damaging agents in man: Applications in cancer epidemiology and prevention. International Agency for Research on Cancer, Lyon (in press). (IARC scientific publications).
13. Hogstedt C, Alexandersson R. Mortality among hard-metal workers in Sweden. *Scand J Work Environ Health* 13 (1987) 177—178. (Abstract).
14. Hogstedt C, Andersson K, Frenning B, Gustavsson A. A cohort study on mortality among long-time employed Swedish chimney sweeps. *Scand J Work Environ Health* 8 (1982): suppl 1, 72—78.
15. Hogstedt C, Aringer L, Gustavsson A. Epidemiologic support of ethylene oxide as a cancer causing agent. *J Am Med Assoc* 255 (1986) 1575—1578.
16. Hogstedt C, Malmquist N, Wadman B. Leukemia in workers exposed to ethylene oxide. *J Am Med Assoc* 241 (1979) 1132—1133.
17. International Agency for Research on Cancer. Allyl com-

- pounds, aldehydes, epoxides and peroxides. Lyon 1985, pp 189—226. (Monographs on evaluation of carcinogenic risk of chemicals to humans, volume 36).
18. Johnson NF, Smith DM, Sebring R, Holland LM. Silica-induced alveolar cell tumors in rats. *Am J Ind Med* 11 (1987) 93—107.
 19. Mattsson B. Cancer registration in Sweden: Studies on completeness and validity of incidence and mortality registers. Department of Oncology and Cancer Epidemiology, Karolinska Hospital, Stockholm 1984. (Doctoral dissertation).
 20. Ohlson C-G, Hogstedt C. Lung cancer among asbestos cement workers: A Swedish cohort study and a review. *Br J Ind Med* 42 (1985) 397—402.
 21. Ohlson C-G, Klaesson B, Hogstedt C. Mortality among asbestos-exposed workers in a railroad workshop. *Scand J Work Environ Health* 10 (1984) 283—291.
 22. Tornling G, Hogstedt C, Westerholm P. Lung cancer incidence among Swedish ceramic workers with silicosis. International Agency for Research on Cancer, Lyon (in press).