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THE ROLE OF EPIDEMIOLOGY IN ASSESSING THE HEALTH EFFECTS OF METALS

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Introduction

The process of assessing the health effects of human exposure to metals, or any other substance, often requires consideration of data available from a number of study disciplines. In this regard, one must consider the health effects data available from a variety of disciplines including results from epidemiologic, clinical, industrial hygiene and animal toxicologic research. Whereas each of these study approaches offers certain advantages, each also has certain limitations. Consequently, exclusive reliance upon any single approach does not provide all or even most of the needed answers to the many occupational and environmental health questions which are raised.

As no single study approach can provide all or even most of the needed health information, so must a specific approach, such as epidemiology, consider the results of studies involving a number of populations exposed to common materials. Such is frequently the case where workers are exposed to chemicals inside a plant and where residents of communities contiguous to the plant are similarly exposed, though usually to a lesser degree. In such instances, studies of workers in the plant can frequently provide valuable clues as to effects upon residents in adjacent communities. That is, occupational health data can be considered the sentinels of the effects of chemicals among the general population. Conversely, studies of the general population can at times provide clues as to health effects among workers exposed to similar substances.

One of the well recognized advantages of the epidemiologic approach is that it offers the potential to determine effects of long-term, low-level exposures to chemicals in man under actual conditions of exposure, i.e., as they occur in the "real world." However, one of the major problems in epidemiologic research, either in the workplace or the community, often involves the difficulty in quantifying present exposures and, more frequently, the even greater difficulty in adequately determining previous exposures. For this reason, it is usually not possible to obtain accurate dose-response information of pollutant effects using epidemiology alone, particularly when one is concerned about effects which may develop many years following onset of exposure. In contrast, whereas more accurate dose-response information can be derived from toxicologic studies using experimental animals, an investigator must consider the question of how to extrapolate results from experimental animals to man and how to extend the results from observed higher dose levels to lower dose levels. Clinical studies, which involve exposure of volunteers for brief periods to known concentrations of single or simple mixtures of pollutants, are limited by the toxicity of the materials which can be administered and by the fact that results from only a few individuals must be extrapolated to the entire population. Clinical studies are not very useful for determining chronic effects which frequently result from long-term low-level exposures.

However, when all three study approaches are utilized in a coordinated way, the benefits of each individual approach may frequently be maintained and many of the methodological weaknesses of a given approach may be overcome.

The remainder of this paper illustrates the above points and discusses (1) the usefulness of toxicologic data in predicting long-term effects of chemicals in man, in turn providing clues for epidemiologic studies, (2) the usefulness of occupational studies as sentinels of toxic effects among the general population, and (3) the potential of community studies to provide clues as to effects of chemicals upon workers.

The value of animal studies in predicting a cancer risk for man has been corroborated by numerous examples in which epidemiologic studies in man have confirmed the results observed in animals. Illustrations of such corroboration include vinyl chloride, β-naphthylamine, benzidine, 4 aminodiphenyl, and bis (chloromethyl) ether. There are, of course a large number of chemicals which have been shown to be carcinogenic in animals but for which epidemiologic evidence for cancer in humans is generally weak or nonexistent. In these instances, one must carefully examine available epidemiologic studies to determine whether they were sufficiently well designed to detect an increased cancer risk and whether their data have been properly evaluated or given full consideration.

Beryllium

Beryllium, for example, is a substance which has shown positive responses for cancer in multiple species of experimental animals. In fact, few substances give so consistent a carcinogenic response in so many animal species as beryllium. Additionally, numerous studies have repeatedly shown beryllium to be carcinogenic by most routes of administration, i.e., inhalation; intravenous, intraperitoneal, subcutaneous, and intratracheal.

As early as 1946, Gardner and Heslington[1] reported the induction of osteosarcoma in rabbits following intravenous injection of zinc beryllium silicate or beryllium oxide. The intravenous administration of zinc silicate, zinc oxide, and silicitic acid to rabbits, however, failed to elicit this carcinogenic response. Over the years osteosarcoma has been induced in rabbits by these same and other beryllium compounds using intravenous or intramedullary administration. In 1951, Dutra et al.[2] reported the induction of osteosarcoma in one of six rabbits following inhalation of beryllium oxide dust.

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Vorwald[3] in 1966 reported that rats developed pulmonary neoplasia following inhalation of beryllium sulfate. Similar findings have also been observed in rats by other investigators using this same and other compounds of beryllium[4-6]. As recently as 1972, Groth[7] reported the induction of pulmonary cancer in rats injected intratracheally with several beryllium compounds.

Beryllium has also been shown to be carcinogenic to primates[2,8]. Vorwald[3], in 1966, reported the induction of pulmonary cancer in monkeys exposed by intrabronchial and/or bronchopleural implantation of beryllium oxide and by inhalation of beryllium sulfate.

As a result of this consistent evidence of carcinogenic effects caused by beryllium compounds in animals and of the generally assumed negative, though admittedly limited epidemiologic evidence to date, beryllium has often been cited as an example of a compound which is carcinogenic only in experimental animals. Reexamination of the available epidemiologic evidence, however, raises questions on concluding that beryllium is not a carcinogen for man.

For example, a study by Bayliss[9] which observed that excess respiratory tract cancers did not occur among 4,000 workers exposed to beryllium might lead one at first to negate the possible role of beryllium in human cancer. However, the majority of workers in this study had not been followed more than 15 years since onset of exposure to beryllium, a latency period which is not long enough to demonstrate a related risk of lung cancer.

Hardy et. al.[10] in 1967 reported on the complications of beryllium disease among 535 individuals entered into the Beryllium Case Registry during 1952-1966. Of 14 subjects known to have subsequently developed cancer among this group, three were diagnosed as having primary cancer of the bone. The observation of three such cases was striking since the International Agency for Research on Cancer of the World Health Organization[11], has estimated that no more than 0.1 case of bone cancer would have been expected to occur among these 535 individuals.

In 1970, Mancuso[12] reported on the relation of duration of beryllium exposure and beryllium-induced bronchitis and pneumonitis to the etiology of lung cancer among beryllium production workers. Among 142 cases of beryllium-related bronchitis and pneumonitis identified during 1940-1948, six deaths due to lung cancer subsequently occurred for an age-adjusted lung cancer mortality rate of 284.3 per 100,000 population. This rate contrasted with 77.7 for all white males employed in the same beryllium production facility during 1937-1948, and led Mancuso to conclude that "prior chemical respiratory illness does influence the subsequent development of lung cancer among beryllium workers."

These observations constitute a continuum, starting with experimental bioassys for carcinogenesis, through epidemiological studies in man which is highly consistent and supportive of the position that beryllium is not only carcinogenic to animals but can be carcinogenic in man as well. Although additional evidence is certainly needed before any definitive conclusions can be made, it is evident that had epidemiologists and clinicians followed through sooner on the strongly suggestive body of evidence from experimental animals, the question of beryllium carcinogenicity for man might already be fully resolved.

Molybdenum

The role that molybdenum may play in gout offers a second example of animal studies which have provided valuable clues to epidemiologists. A number of these studies has shown molybdenum to affect the xanthine oxidase-uric acid metabolic pathway. By comparison, an epidemiologic study from the Russian province of Ankavan, where dietary molybdenum intake ranges from 10-15 mg per day due to high natural levels, has shown elevated blood xanthine oxidase activity and increased uric acid concentrations in the blood compared to controls living in an area with lower molybdenum exposure[13]. A high percentage (31%) of the examined population from the Ankavan province was diagnosed to have a gout-like disease. These animal data combined with the community study provide substantive evidence for the need to evaluate workers exposed to molybdenum for a possible increased prevalence of gout. This is an example not only of toxicologic data providing clues for epidemiologic research, but also of a community study providing clues as to a possible occupational health problem.

Arsenic

A recent example of complementary epidemiologic studies of both workers and residents in contiguous populations exposed to industrial emissions involves inorganic arsenic.

As reviewed by Blejer and Wagoner[14], nine out of eleven epidemiologic studies reported from 1948 to 1975 have shown, initially or upon reassessment, significant excess mortality from respiratory cancer among diverse occupations exposed to various inorganic arsenicals. Two of the nine studies showed concomitant, significant excess mortality from lymphatic cancer; and another, from skin cancer. Additionally, two of these studies revealed a dose-response relationship between arsenical exposure and lung cancer. In the first, reported in 1969, the relationship was semi-quantitative with a possible interactive role by sulfur dioxide or other contaminants[15]. The other demonstrated an increased lung cancer mortality risk[16], apparently at arsenic concentrations above 1 $\mu g/m^3$, when the total dosage was recalculated as the 8-hour time weighted average daily exposure over a 40-year working life[14]. However, these and related data did not reveal a definite no-effect exposure level. Arsenic is an example where an animal model for lung cancer has not yet been found.

A recent study by Blot and Fraumeni[17] of residents of counties with copper, lead, or zinc smelting and refining industries, but not of counties where other nonferrous ores are processed, showed significantly increased lung cancer rates for white males and females based upon data compiled from 1950 to 1969. These findings could not be attributed to differences in geographic region, population density, urbanization, socioeconomic status, or other manufacturing process. The authors concluded that exposure of residents to community air contaminated with industrial emissions containing inorganic arsenic may have contributed to these excesses of mortality from lung cancer. A study by Milham[18] showing excess arsenic absorption among children residing near a smelter in Tacoma, Washington provides additional bases for concern.

Lead

Lead has been shown to produce kidney cancer when administered to experimental animals[11]. Data from the U.S. Cancer Mortality by County from 1950-1969 show that the rate of kidney cancer among males, but not females in Shoshone County, Idaho, site of a lead, zinc, and cadmium smelter, is elevated (100%) compared to the state of Idaho[19]. The recent data showing increased absorption of lead among residents near this same smelter are also relevant. Landrigan, et al.[20], have dem-

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onstrated that 99% of 1-9-year-old children living within 1.6km of the smelter had blood lead levels of 40 µg/100ml or greater indicating increased absorption, and 22% had levels of 80 µg/100ml or more. The prevalence of elevated blood lead levels decreased with increased distance of residence from the smelter. Free erythrocyte protoporphyrin levels also increased with blood lead levels, and 17% of children with lead levels of 80 µg/100ml or greater were anemic. While there was no overt neurologic toxicity, toxic effects of lead were found based upon decreased nerve conduction velocity in children with blood lead levels of 40 µg/100ml or greater. A study by Cooper and Gaffey[21] has shown increased mortality from lung cancer among workers in lead smelters suggesting the need to evaluate lung cancer mortality among workers in and residents near this smelter.

Cadmium

The first indication of potential cancer risk in man from cadmium dates back to Potts in 1965[22]. He reported eight deaths from a group of 74 workers exposed for over 10 years to cadmium oxide dust generated in the manufacture of alkaline batteries. Potts noted that three of the deaths were due to carcinoma of the prostate, one was due to carcinoma of the bronchus, and one was due to carcinomatosis.

Kipling and Waterhouse[23] in 1967 studied 248 cadmium workers who had been exposed for a minimum of one year to cadmium oxide. They found a high incidence of prostatic carcinoma (4 cases) compared to 0.58 cases which would have been expected. Other studies by Humperdinck[24], Holden[25], and Friberg[26], however, failed to find excess cancer mortality among men occupationally exposed to cadmium.

These data in part prompted Lemen, et. al.[27], to initiate a mortality study of workers exposed to cadmium. The smelter selected for study began production in 1880 as a lead smelter. It switched to arsenic production at the end of World War I and ceased that production in 1925 to begin production of cadmium. The smelter is currently engaged almost exclusively in the production of cadmium metal and compounds. Some production of lead occurs, but this represents only a one or two-man operation. An industrial hygiene study at the plant conducted by the state of Colorado's Department of Health in 1960 showed that cadmium air concentrations in the plant ranged from 3 to 210 $\mu g/m^3$. The latest analyses of samples taken in 1973 indicated cadmium air concentrations in the premeld department of 90 and 75 $\mu g/m^3$, and in the retort department of 1,105 $\mu g/m^3$ while arsenic levels were only 1.1 $\mu g/m^3$, 0.3 $\mu g/m^3$, and 1.4 $\mu g/m^3$, respectively. Exposure at this smelter was therefore primarily to cadmium oxide with relatively low concentrations of arsenic.

To evaluate the mortality experience of the workers at this smelter, Lemen, et. al., ascertained occupational histories from company employment files. The cohort under study was restricted to 292 males who had achieved three years employment in the plant between January 1, 1940, and December 31, 1969. As of August 1, 1975, 180 cohort workers were alive, 92 dead and 20 untraced. For analysis purposes those untraced were considered alive, thus making cause-specific results conservative. Total person-years in the study were 6,968. The total of 92 deaths observed compared to 99.32 expected deaths based upon U.S. white male rates matched for age, sex, and race.

Malignant neoplasms, however, accounted for 27 of the observed deaths whereas only 17.57 would have been expected ($p<0.05$). Twelve of the 27 cancer deaths were due to lung cancer ($p<0.05$) and four deaths were due to prostatic cancer ($p<0.05$).

These results which can be considered conservative, show significantly increased mortality due to total malignancies, lung cancer, and prostatic cancer among cadmium smelter workers. These results confirm earlier reported studies and strongly implicate cadmium exposure as a contributing cause to lung and prostatic cancer.

Conclusions

Occupational and environmental epidemiologic studies can provide useful and complementary health information. At times, however, there has been reluctance to consider both study approaches when addressing a given problem. Although the setting of exposure standards for the general population considers a number of factors not usually addressed in setting exposure standards for workers, this does not mean that studies of workers and communities cannot be interrelated to achieve better assessment of the effects of chemicals upon human health. In this regard, data available from a variety of disciplines including epidemiologic, clinical, industrial hygiene, and animal toxicologic research can provide valuable information.

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