Carcinogens in the Workplace

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When international age-adjusted cancer incidence rates first became available in the early 1960's, patterns prevalent in the low risk countries of Africa and Asia were compared by Higginson\(^1\) with those prevailing in the United States' white population or in the western European countries. The total incidence of cancer in a hypothetical population at minimal risk was calculated by summing the lowest age-adjusted rate for each site from the most appropriate country. Ugandans, Nigerians, and the South African blacks, for example, were at lowest risk for cancers of the lung, stomach, large intestine, corpus uteri and kidney. The Singapore registry recorded the lowest rates for cancers of the pancreas, urinary bladder and breast. Conversely, the rate for primary hepatocellular carcinoma was highest in Mozambicans and in the South African blacks, whereas it was lowest in the United States white and black populations. Carcinoma of the nasopharynx was highest in Singapore. Higginson estimated that the age-adjusted cancer incidence in the hypothetical population at minimal risk was one-fifteenth of that in the males, and one-ninth of that in the females of high risk countries. A preliminary analysis indicated that the hypothetical cancer incidence was one-third of that observed in the United States white population. From these geographical differences, it was postulated that 70-90 percent of human cancers are likely to be due to environmental factors and, by implication, preventable after extrinsic factors are identified.

Studies of various migrant populations have measured shifts in cancer mortality and incidence as groups move from one part of the world to the other. If genetic factors were primarily responsible for the international differences in risk, then the prevailing rates among population groups that migrate should remain relatively fixed. However, the evidence to date indicates that the risks of cancer in organs of the digestive (i.e., stomach and large intestine) and reproductive (i.e., breast, corpus uteri and ovary) systems were displaced from the rates prevailing in the country of origin toward those experienced by indigenous residents of the host country.\(^3\)
In a monograph published in 1975, it was estimated that we already have the knowledge to prevent 30 to 40 percent of the common cancers in the United States. Current “best” estimates of the percentage of all human cancers that may be attributed to occupational exposure range between one and five percent. A more extreme assessment of the causal fraction due to occupational exposure may pertain to uncommon types of cancer (e.g., angiosarcoma of the liver, mesothelioma of the pleura or peritoneum, scrotal cancer), or in the instance of squamous cell carcinomas of the lower urinary tract in men. Among men 20-74 years of age, approximately 20 percent of bladder cancers are related to occupational exposure.

Industrial agents may not necessarily be confined to the workplace, but may spread by polluting ambient air or water in the general environment. Current estimates from the Environmental Protection Agency (EPA) indicate that there are as many as 50,000 chemical substances, excluding pharmaceuticals and food additives, in common use. In the past 10 years, the production of synthetic organic chemicals in the United States has increased more than 2.5 times over that of previous years, although relatively few of the new compounds have been studied adequately for carcinogenic potential. Standards of Threshold Limit Values (TLV's) of exposure have been promulgated for only a small number (less than 500) chemicals to which workers are exposed. Although new regulatory approaches are urgently required for occupational carcinogens, the present conservative posture of the federal agencies is to view human carcinogenicity of industrial chemicals as a relatively uncommon phenomenon.

**Historical Overview**

“...workers in certain arts and crafts sometimes derive from them grave injur-ies, so that where they hoped for a subs-istence that would prolong their lives and feed their families, they are too often re-paid with the most dangerous diseases...”

From De Morbis Artificum Diatriba, Bernardino Ramazzini, 1700

Up until the late Middle Ages, the impact of the occupational environment on the manual worker had not received careful attention by practitioners of medicine. Because expanding commercial enterprise during the 15th century increased the demands for gold, silver, iron, copper and lead, the miners and metal workers were among the earliest occupational groups to be studied. The first publication concerning an occupational disease was prepared in 1472 by Ulrich Ellenbog, a German physician from Augsburg. The pamphlet was entitled, *On the Poisonous, Evil Vapors and Fumes of Metals*, and described the irritating effects of the fumes of lead and mercury experienced by goldsmiths. In 1556, *De Re Metallica* was published by Georgius Agricola, who prepared a comprehensive treatise on the accidents and diseases prevalent among the miners and smelters of gold and silver. He attributed their chronic lung disease (“miner’s asthma”) to the inhalation of dust, and recommended the use of facial masks and the need for adequate ventilation.

With the publication in 1700 of the first edition of *De Morbis Artificum Diatriba* (Discourse on the Diseases of Workers), Bernardino Ramazzini founded occupational medicine. His book was a comprehensive survey of existing knowledge of the nature of diseases believed to be caused by a particular craft or work setting. Physicians were instructed to go beyond traditional Hippocratic practice and inquire of the work activity of each patient. The patterns of disease or health within a given population were now to be viewed in the broad context of social class.

The first clinical report of occupational chemical (hydrocarbon) carcinogenesis has been attributed to Percivall Pott who described in a brief essay in 1775 cancer of the scrotum among chimney sweeps in England. The condition was acknowledged in the trade as the “soot wart,” because it was assumed to be due to chronic exposure to soot. As Pott wrote, “The disease in these people seems to derive its origin from a lodging of soot in the rugae of the scrotum...” Although this treatise, which appeared in Pott’s book...
Chirurgical Observations, has been regarded as a seminal paper in preventive oncology, there was no explicit discussion of the compelling need for careful personal hygiene and laundering of work clothes.

Domestic soots contain hydrocarbons and tars which arise from the incomplete combustion of carbonaceous materials such as wood, coal and oil. It is of interest that the incidence of scrotal or "soot cancer" in England was reported to be significantly higher than in Scotland and Germany. The geographic differences in risk were not registered precisely, but were of sufficient magnitude to require consideration of the unique features of exposure and life style of the English sweeps. Such factors in England included earlier substitution of coal for wood, employment of young children who would crawl through flues rather than pulling up the debris without working from within them, and marked differences in personal washing practices.12,13

Henry Earle, a grandson of Percivall Pott, observed in 1823 that only a small proportion of the exposed individuals would manifest disease more than 20 years after their work experiences. He conjectured about "constitutional predisposition...which renders the individual susceptible to the action of soot." Thus, the "soot cancer" in chimney sweeps was serving to stimulate biologic concepts about external factors, predisposing host factors, tissue susceptibilities, and the latency of chemical carcinogenesis.

The expanding industrial revolution after 1850 created an increasing need of lubricating oils for machines. Volkman, Bell and Butlin reported during the latter half of the 19th century that scrotal cancer occurred in tar, paraffin and shale oil workers. These derivatives of coal tar were also shown to be carcinogenic to the skin and vulva. Butlin also raised the troublesome prospect of inhaled and ingested domestic soots giving rise to internal cancers. In 1915, the Japanese workers, Yamagiwa and Ichikawa, produced cancer on a rabbit's ear by painting it with tar. Later, similar results were produced in other animal species using soot, coal tar pitch, anthracene oil and creosote derivatives of coal tar. Cook and Kennaway in the 1930's isolated benzo(a)pyrene, a potent, polycyclic hydrocarbon carcinogen, from coal tar.14

Epidemiologic Methods
For Determining Risks
Among Exposed Workers

"The proper study of mankind is man."
From Essay on Man, Alexander Pope, 1734

Evaluation of the risk of cancer in response to suspect environmental agents rests in part on the evidence derived from observational, epidemiological studies. The initial suggestion of a relationship between an agent and a disease often emanates from animal experiments or case reports in patients with a common exposure, or from both. Animal experimentation anticipated the subsequent confirmation by epidemiologists of the hazards of occupational exposure to 4-aminobiphenyl and other aromatic amines, vinyl chloride, bis(chloromethyl) ether and other alkylating alpha-haloethers, and mustard gas.15-18 Astute clinical observation initiated epidemiologic research confirming the high risk features of nickel refining, woodworking in the furniture industry and other trades exposed to wood dust, manufacturing of leather goods such as the shoe industry, and the mining of uranium and fluor spar.19,20 Identification of the risks of occupational exposure to the inorganic arsenicals has been pursued by epidemiologists in the absence of satisfactory experimental models.18

Epidemiology is concerned with identifying patterns of distribution of human diseases. Rates of incidence and mortality are reviewed in the context of time trends, geography, and personal characteristics. This descriptive profile of a disease serves to guide the pursuit of etiologic factors that are likely determinants of a specific pattern.

The epidemiologic methods that are concerned with testing causal hypotheses can be classified either as case-control or cohort in type (Table I). The case-control (retrospective, case history) study is most
suitable in studies of rare diseases, in "fishing" for multiple factors of uncertain significance, and for the initial exploration of a specific etiologic hypothesis. The cohort (prospective, longitudinal, follow-up) study is advantageous in that it provides a direct measure of the incidence or risk of developing a disease in individuals with a specific characteristic, and is most suitable for testing a particular hypothesis which has already been developed from prior retrospective or cross-sectional studies, or both. For practical purposes, the various caveats about sample size in cohort studies guide the epidemiologist to focus on hypotheses that involve a relatively common exposure (in more than two or three percent of individuals at risk), a relatively common cancer (incidence of 1/1,000/year), and for discerning relative risks (risk ratios) in the exposed individuals that are at least twice that of the control group.

The conduct of each epidemiologic study requires some judgment about whether or not an association is of causal significance. The Surgeon General's Report on Smoking and Health concluded an introductory discussion of judgment and causal inference with the following: "The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability."

The criteria most appropriate for evaluating an association are consistency, strength, temporal relationship, coherence and specificity. The criterion of consistency is analogous to experimental replication, but may also rest on the demonstration that diverse investigative approaches produce similar results. The strength of an association may be expressed in terms of relative risk (risk ratio, odds ratio) and population attributable risk or etiologic fraction (Table II). Coherence embraces the criterion of biologic plausibility, although it should not discourage the consideration of unorthodox, innovative hypotheses. The temporal criterion requires that the presumed cause must always precede the observed effect, whereas the criterion of specificity implies that there is a predictive pattern of effect(s) likely to occur with frequency greater than random chance if the antecedent event or complex of events were of causal significance. The methodological features of epidemiological studies of the workplace and cancer are reviewed in Table III. The important parameters include the type and "strength" of exposure, age at initial exposure, latency or the frequency distribution of the interval from first exposure to the initial diagnosis of disease, duration of exposure, intensity of exposure and its variability over the cumulating person-years at risk, and the spectrum of morbidity and mortality. In addition to the methodological issues summarized in Table III, there are other interpretive pitfalls in epidemiological research that may confound or obscure precise inferential reasoning.

Confounding refers to the extraneous influence of factors, other than the measured occupational experience, on the association with the risk of cancer. For example, social class is closely linked with occupational status, and may be more directly associated with the risk of developing or dying from various types of cancer. Social class factors may be linked with personal habits, aspects of life style that include patterns of nutrition and non-occupational environmental factors, and access to and utilization of medical care services. The observed increased risk of cancer may arise from mixed chemical and physical exposures or the interaction of occupational and non-occupational factors.

The observations emanating from epidemiological studies may be suspect because of lack of accurate exposure data and limited or incomplete follow-up from the onset of some remote exposure, even if it was of short duration. In the studies that depend upon recall, the workers may be unaware of the identity of the substances that they have handled. Routine records rarely satisfy the needs of epidemiological research, but rather what may be needed is the development of a standardized comprehensive occupational health information system with prospective monitoring throughout a defined work
| **Characteristics** | **Case-control method** |
|---------------------|------------------------|
| **Design:**         | Past                    |
| Look for past exposure(s) in cases and controls | Retro-spective |
| Select cases with specific cancer diagnosis and controls without cancer from the same or related populations |
| Cases may include all those diagnosed during a period of time in one or more hospitals, clinics or doctors’ offices, a defined population or community (or random sample of such), or a specific workplace or company of workplaces |
| **Cost:**           | Involves relatively less expense since less time and a smaller sample are required. Interviewing and the generation of new data are less costly. |
| **Time required for completion of study:** | Relatively quick results since pertinent events have already occurred. Various data sources are reviewed and the results analyzed. Data may be drawn from personal interview, clinical and hospital records, work history records, vital documents, etc. |
| **Size of study population:** | Smaller number of subjects required. The sample size depends on the prevalence of exposure to the “causal” factor(s), the relative risk of disease that one regards as important to detect, and the desired levels of Type I and II errors (see Table 1A). |
| **Usefulness in studying rare diseases:** | More useful with rare diseases since confirmed cases constitute the study group. Where the association between the factor and the disease is very strong, the number of cases of the disease needed to show a significant difference is quite small. |
| **Problems in selecting controls:** | The important problems are those related to selection of appropriate controls for cases. The source of controls as well as the characteristics on which cases and controls are matched are important considerations. The representativeness of cases in relation to the spectrum of the disease and representativeness of the controls compared to the general population are important for enabling generalization. Ideally, one should be able to identify the population from which study cases are drawn and make comparisons with controls from the same population. Since it usually is not possible to verify the comparability of cases and controls, multiple comparison groups are often used as a safeguard. These may be selected from the same hospital, neighborhood, family or workplace, and/or general population. |
| **Problems in obtaining required information:** | Information based on records may be incomplete. Patient or patient’s family may not be able to provide needed information. If possible, it is desirable to validate through independent confirmation the key items of information. |
| **Problems of bias:** | Patient recall of antecedent events may be distorted by knowledge of the disease. |
**TABLE 1 (continued)**

| Characteristics | Cohort method |
|-----------------|---------------|
| **Design:**     | Select exposed and non-exposed groups | Select exposed and non-exposed groups |
|                 | Trace through records | Concurrent surveillance |
|                 | Historical prospective | Concurrent prospective |
|                 | 1950 | current date |
| Population may be selected from a well defined geographical or administrative area, or a select group of the population (e.g., professional, occupational, veteran, unique exposure history). |
| **Cost:**       | Relatively expensive since a larger sample and a longer period of observation are involved. Most data must be recorded de novo. |
| **Time required for completion of study:** | A long followup period may be needed depending on latent period between exposure and onset of disease. A historical cohort study, whereby observations have been recorded in the past and effects reviewed in the present, frequently provides the alternative expedient. |
| **Size of study population:** | Larger number of subjects required. Apart from specifying the desired levels of Type I and II errors (see Table 1A), the sample size depends on the expected incidence of the disease among the non-exposed and the relative risk of disease that one regards as important to detect. |
| **Usefulness in studying rare diseases:** | If the incidence of a disease is low in the exposed and unexposed groups, a very large sample will be needed to show significant differences between the groups. |
| **Problems in selecting controls:** | Finding an unexposed group of controls that is comparable to the exposed or study group with respect to other personal characteristics may be difficult. |
| **Problems in obtaining required information:** | Subjects may change jobs or residence and, as a consequence, be lost to followup. In the historical approach, documentation of past exposures and tracing individuals may be incomplete. |
| **Problems of bias:** | Diagnostic criteria and methods may change over time. Participant or observer knowledge of exposure status may affect ascertainment of disease. These potential biases may be minimized by "blind" assessment of effects. Subjects may cross over from unexposed to exposed groups. Dropout rates may vary between exposed and unexposed groups. Bias may result if the degree of followup is less than 95 percent. |
force. Job titles may not connote a specific exposure, or the same title may encompass a multitude of possibly toxic agents that are likely to produce a variety of effects. Each individual worker may have moved through a number of different jobs, even within the same manufacturing industry. The task is to attempt to group the various jobs into homogeneous categories of exposure.

Properly designed epidemiological studies may serve to identify the absence of risk. The validity of any inference about minimal or no risk may be determined by the adequacy of exposure and follow-up information. The ability to detect significant differences in risk will depend in part upon a statistically adequate sample that will enable the determination of differences in risk if they do indeed exist. However, a limitation of the epidemiologic method may be its insensitivity to measure, in retrospect, single or complex low level chemical exposures that give rise to small increases in risk. In addition, because of the long latency period, the orientation is post hoc and not predictive or applicable to new chemicals that are in the process of being introduced into the workplace.

**Principles of Non-Human Testing for Chemical Carcinogenicity:**

**The Relevance of Animal and in Vitro Studies for Predicting Human Risks**

Current methods for estimating the risk of human cancer from long term exposure to low doses of chemical carcinogens involve extrapolating from animal experiments conducted at doses high enough and of sufficient duration to produce tumors in an appreciable fraction of the animals tested. The process of extrapolation or of using animals as surrogates for people involves various assumptions and caveats:

a) chemicals that cause cancer in one or more species of mammalian animal may be capable of causing cancer in humans;
b) the dose-response curve assumed for man may be analogous to that demonstrated in the most sensitive animal model;

c) although it is conceivable that at certain dose levels even potent carcinogens will not produce tumors in humans, a subthreshold dose or "safe" level cannot be determined with certainty by animal assays;

d) higher dose levels of a chemical carcinogen may increase the incidence of commonly occurring or unusual cancers, or of the number of primary cancers per animal, or shorten the latency period; and,

e) target organ(s) for tumors observed in experimental animals may not necessarily predict the type(s) of tumor induced in humans.39

The prediction of the carcinogenic potential of chemicals in humans by animal bioassay required careful selection of suitable animal species, rigorous experimental procedures, meticulous pathological examination and optimal numbers of experimental and control animals. At least two animal species, both sexes, and several dosage levels should be employed. Although the choice of animal for routine testing should take into account the manner in which the chemical is metabolized in humans, more commonly the test animals used, and in particular the mouse, rat and hamster, are selected initially in the absence of comprehensive knowledge of pertinent aspects of human metabolism. There may be significant differences in the responses of various species to a given class of carcinogen. For example, an aromatic amine, such as 2-naphthylamine, may give rise to tumors of the bladder (human, monkey, dog, hamster), or liver (mouse), while having no apparent effect on other species (rat, rabbit). The fact that aromatic amines induce tumors in excretory organs has led to the concept that it is the N-hydroxylated metabolite, and the species-specific capacity for metabolic activation, that are responsible for the induction of cancer.40
Since the rate of occurrence of most cancers is related to the lifespan of a given species, bioassay systems have been concentrated on small rodents with an average lifespan of two or three years, and the longer lived animals such as the dog and monkey have been used for specialized studies. At present, chronic toxicity studies begin with weanling animals and are maintained at desired dose levels for a natural lifetime. The period of experimental observation should not be less than two years for rats and hamsters, or 18 months for mice. Where studies are concerned with the effects of exposure to the fetus, or during the perinatal period, then the protocol should be modified appropriately.

The route and mode of administration of repeated exposures should reflect, whenever possible, the natural human experience. Artificial portals of administration require careful assessment of systemic levels of exposure, and whether or not tissue injury and degeneration are due to the prolonged presence of injected or implanted chemicals.\(^1\)\(^2\)

The appropriateness of using very large or maximum tolerated doses in rodents is a source of controversy and confusion. The dose levels are selected on the basis of mortality and partial suppression of normal weight gain when compared with untreated controls. The justification for the routine use of a maximum tolerated dose is that it maximizes the sensitivity of the experimental system to detect the tumorigenic effects of "weak" carcinogens that would have been missed at lower dose levels within the relatively brief lifespan of rodents, and enables limitation on the number of animals generally recommended for testing. At the much lower dose levels which may correspond to common human exposures, several thousands of animals may be needed to estimate any increased carcinogenic risk.

In determining in advance the required sample size, the investigator must consider the spontaneous incidence of organ-specific cancers and mortality due to intercurrent (non-neoplastic) diseases that is to be expected in the unexposed control group. The sensitivity of the experiment or the magnitude of the difference in tumor incidence between experimental and concurrent control groups (this may include a separate vehicle control group), and the degree of confidence required to detect such a difference, should be determined in advance. The higher the expected incidence of spontaneous cancers or the smaller the difference in cancer incidence that is being sought, the larger the required sample size.

Under a given set of experimental conditions, has the agent been shown to be carcinogenic, and was there a "safe" dose, below which there was no indication of increased risk? As described by Cornfield,\(^41\) the Environmental Protection Agency has defined the "no observed effect level" as the "level (quantity) of a substance administered to a group of experimental animals at which those effects observed or measured at high levels are absent, and at which no significant difference between the group of animals exposed to the quantity and an unexposed group of control animals, maintained under identical conditions, is produced." The basic problem in risk assessment for carcinogenic substances occurs when extrapolation is attempted downward from the observed range of experimental effects to an assumed safe level through the application of mathematical assumptions which achieve linear dose-response effects. Most mathematical models deny the assumption of a uniform threshold, or that there is a level of exposure below which there is no possible carcinogenic response for the entire population at risk. The procedure for estimating human risk consists of extrapolation of experimental results achieved at high dose levels to much lower dose levels within the species tested, and then extrapolation of these estimated risks at low doses to risks in humans at comparable levels.\(^44\)\(^47\)

Bioassay by in vivo animal studies of the many thousands of chemicals that are constantly entering the workplace and general environment would be an overwhelming and costly task. Short term in vitro screening tests for mutagenicity and malignant transformation are being developed to facilitate the estimation of po-
TABLE 3

METHODOLOGICAL FEATURES
OF OCCUPATIONAL STUDIES

**Issue:** "Sign" cancer.
**Commentary:** Suspect an occupational agent when cancers of uncommon site or histology appear in space-time clusters, particularly when some cases are diagnosed under age 80 years.
For example, mesothelioma, pleura and peritoneum (asbestos)\(^{14}\), angiosarcoma, liver (vinyl chloride monomer)\(^{14}\), adenocarcinoma, nasal cavity and paranasal sinuses (isopropyl oil, chromium, nickel, woodworkers in furniture industry, boot and shoe workers)\(^{15-19}\), squamous carcinoma, scrotum (soot, lubricating oils)\(^{11}\), oat cell carcinoma, lung (chloromethyl ether, chloromethyl methyl ether)\(^{15-23}\), acute leukemia, including erythroleukemia (benzene)\(^{14}\), rubber workers)\(^{25}\), osteogenic sarcoma (radium watch dial painters)\(^{16}\).

**Issue:** Interval since onset of exposure.
**Commentary:** The latent period between first exposure and onset of disease may vary between 5–50 years. The calculation of latency or the median interval of time of onset of disease, and the approximated confidence limits about the median, should be corrected for the spontaneous occurrence of cancer, particularly for the more common types of cancer. Factors that may influence latency include the type and strength of exposure, interaction with mixed or multiple chemical exposures (including cigarettes) and individual (host) factors. The instantaneous risk of disease or death may not be constant over time and, therefore, a life table analysis may be more appropriate than cumulating person-years of experience, irrespective of the time since first exposure\(^{25}\).

**Issue:** Dose-response relationship.
**Commentary:** Unfortunately, crucial retrospective dose data are often not available. The dose-rate may have varied over time; therefore duration of exposure may not be equivalent among workers unless interval exposure levels, duration and age are considered concomitantly. There are methods to summarize linear and nonlinear components of the dose-response relationship.

**Issue:** Synergism.
**Commentary:** Is the risk associated with a particular exposure additive or multiplicative (interactive) with known causes of the disease? Examples of interactions between known causes of the same disease are few in the epidemiologic studies of occupational carcinogenesis (e.g., cigarette smoking in asbestos workers or uranium miners)\(^ {25,26}\). Further research is needed on this important issue, for example, with respect to cigarette smoking and known occupational causes of lung and lower urinary tract cancers. Demonstration of synergism has important implications for industrial hygiene, selective screening and counseling of individual workers.

**Issue:** Why not use the general population as the only control group in a cohort study?
**Commentary:** Although most cohort studies of occupational mortality use the general population as a standard for deriving the expected number of deaths, pre-employment selection ("healthy worker" bias) affects the comparative experience. Age-standardized mortality ratios (SMR)\(^ {15-23}\) in general are 60–90 percent of the standard in the working population. The selection factors are particularly in evidence when reviewing mortality due to cardiovascular, chronic respiratory and infectious diseases, but less striking for malignant neoplasms. The effect is higher in the employed blacks\(^ {14}\). A suggested remedy is to develop reference working populations from other published cohorts of workers, a 10 percent sample of social security recipients (Longitudinal Employer—Employee Data File)\(^ {25}\), and/or internal comparisons within the study cohort stratified by degree of exposure, age, sex, race, geographic area of residence and tobacco smoking history.

\(^ {a}\) The standardized mortality ratio (SMR) has been widely used in occupational studies for the evaluation of overall and cause-specific mortality. It is derived from the ratio of observed number of deaths to those expected based upon the age, sex, race, geographic area, calendar period, cause-specific mortality of a standard population. An SMR of less than 100 indicates that for the aggregate of person-years there were fewer deaths than expected, while an SMR above 100 implies the opposite. The SMR, which is distinctive from a summary estimate of relative risk, has been evaluated critically in recent years.
ential human risk. In vitro methods under controlled biologic conditions should afford the advantages of validity, reliability, rapidity and economy. Selective testing of suspect chemical agents should be guided by knowledge of structure and metabolism, electrophilic reactivity of each compound and metabolites, genetic effects and extent of human exposure.48-52

There is a high degree of correlation qualitatively between mutagenic and carcinogenic activity as revealed in a wide variety of in vitro assay systems. A method that has attracted considerable interest uses several Salmonella typhimurium histidine-dependent tester strains engineered by Ames and McCann,13,34 although other bacteria, fungi, plants, insects and mammalian cells are also being used. In the study by Ames and colleagues, 90 percent of a selected battery of chemicals known to be carcinogenic in one or more animal species were detected as mutagens; almost all chemicals known to be carcinogenic in humans were mutagenic in the Salmonella microbial-rat liver microsome system. About 13 percent of chemicals considered currently to be non-carcinogenic showed some degree of mutagenicity. The sensitivity of various bacterial strains to develop frameshift mutations or base-pair substitutions, which result in reverting the characteristic of histidine dependency, is enhanced through the addition of a mammalian liver microsome system, and selecting strains without lipopolysaccharide in the cell wall or without an effective system for repairing altered DNA. A positive in vitro test for mutagenicity would serve to identify chemical agents that require long term animal testing and, if extensive human exposure has occurred, appropriate epidemiologic studies should be conducted.55,56

The close correlation between mutagenic and carcinogenic properties implies that a primary mechanism in malignant transformation involves alteration of the genome. Meselson and Russell57 are even suggesting in their preliminary studies that there is a quantitative relationship between the carcinogenic action of a compound in laboratory animals and its mutagenic activity in the microbial system.

However, the universality of the somatic mutation theory of the origin of cancer has been challenged in its application to higher (eukaryotic) organisms. Whether or not epigenetic mechanisms are of greater fundamental importance in the multistage process of human carcinogenesis does not necessarily detract from the utility of using non-mammalian systems for identifying chemical agents with potentially chronic toxicologic effects in humans.58 In addition, because of species differences in metabolism and detoxification of various classes of chemical compounds, in vitro assays for malignant transformation and mutagenic activity that use mammalian cells should be employed in conjunction with the microbial systems.59,60

Workplace Exposure to Known or Suspected Carcinogens

Of the many commercially produced substances which have been reported to be tumorigenic in one or more in vivo test systems, only a limited number are of importance in clinical occupational medicine. These agents are listed in Table IV. Key animal studies of tumorigenicity are noted, particularly where these tests rather than observations in human populations are the primary basis for concern over the agent's carcinogenic potential. For example, the carcinogenic potential for several of the aniline-derived agents was so dramatically demonstrated by animal studies that widespread human exposure was averted.

The extent of occupational exposure to the agents listed in Table IV varies widely. For some, such as asbestos and ionizing radiation, the work settings and job activities in which exposure may occur are extensive, diverse, and sometimes unexpected. For other agents, however, the potential for hazardous exposure is relatively circumscribed.

The route of absorption of an agent is determined both by its physical properties and by the circumstances of exposure. Inhalation of vapors and fumes is the most frequent route of exposure, while the skin is a potential route of absorption for both liquids and gaseous agents. Inadvertent
ingestion occurs with agents in a solid phase, such as metallic dusts or salts of certain compounds.

The mean latency period, i.e., the average interval between onset of exposure and development of a neoplasm, most often falls between 10 and 20 years, although the range may be considerably wider. There is considerable variability in latency in individual cases, perhaps reflecting intensity and duration of exposure as well as ill-defined host biological factors. Estimates of the relative risk of developing a neoplasm following exposure also vary. Patterns of exposure in different groups of workers exposed to a common agent may differ greatly. The heterogeneity of exposure group, the duration and completeness of follow-up achieved, and the size of the exposed group vary from study to study. These factors influence the magnitude and precision of estimates of relative risk and account for the sometimes broad range of such estimates.

For the most part, when cancer develops as a result of exposure to an occupational carcinogen, it is predictably confined to a limited number of target organs or tissues; in animal studies, the same organs or tissues may not necessarily be affected by the same agent (Table IV). Seventeen agents among those listed have been included under the Federal Standard for Carcinogens; this indicates that all contact with the agent should be avoided or reduced to the lowest possible level.

Current Concepts of Prevention and Control of Occupational Cancers

"The Congress declares...its purpose and policy...to assure so far as possible every working man and woman in the Nation safe and healthy working conditions..."

The Occupational Safety and Health Act of 1970

A sound foundation for an occupational health program is based in part upon instituting engineering and hygienic measures that control or limit contamination by toxic substances in the working environment. In parallel with these industrial control measures, a prospective medical program of periodic general health examination and "targeted" clinical and laboratory medical surveillance (e.g., sputum and urine cytology, liver function tests, pulmonary function studies and reporting of pulmonary symptoms or skin lesions) is an essential component of an occupational health program. These procedures should serve to enhance the safety of the working environment. Each preventive measure should be evaluated carefully as to its potential effectiveness in diminishing subsequent incidence, morbidity and mortality due to the various types of cancer and precursor diseases. The rationale for control strategies emanates from the best available epidemiologic information and extrapolation from animal research.¹³⁴,¹³⁵

In the United States, control of carcinogens in the workplace prior to the 1970's involved using engineering controls and personal protective devices to minimize exposure, and substituting less toxic materials whenever possible. The Occupational Safety and Health Act of 1970 authorized the Occupational Safety and Health Administration (OSHA) within the United States Department of Labor to enforce maximum allowable concentrations or Threshold Limit Values (TLV's) of exposure to carcinogens. A TLV refers to a time-weighted average level of airborne concentration of a substance in the working environment below which it is believed that nearly all workers may be repeatedly exposed, day after day, with no adverse effects. The American Conference of Governmental Industrial Hygienists has since established threshold limits for more than 400 suspect substances.¹³⁶

In addition, the recommendation of standards to OSHA by means of scientific "criteria documents" is the responsibility of the National Institute for Occupational Safety and Health (NIOSH), which is an agency of the Center for Disease Control of the United States Public Health Service. The official position of NIOSH is that it is not currently possible to demonstrate precise tolerance levels of exposure to chemical carcinogens, and, there-
### TABLE 4
INDUSTRIAL AGENTS ASSOCIATED WITH CANCER

#### A. Federally Regulated Carcinogens

| Agent                        | ANIMAL STUDIES | CLINICAL AND EPIDEMIOLOGIC STUDIES | Comments (pertinent references) |
|------------------------------|----------------|------------------------------------|---------------------------------|
| Asbestos fibers              | Rat p.o.       | Multiple Lung, mesothelioma         | Lung cancer synergism between asbestos and cigarette smoking. Because of rarity of mesothelioma in absence of asbestos exposure, relative risk estimate has limited meaning. The number of potentially exposed workers is some 1.6 million. Current estimates of proportionate mortality in heavily exposed workers are lung cancer (20-25%), mesothelioma (7-10%) and gastrointestinal cancers (8-9%). (61-63). |
|                             | Rat Inh.       |                      |                                 |
|                             | Rat, ham-      |                      |                                 |
|                             | ster, rabbit   |                      |                                 |
|                             | rat, rabbit    |                      |                                 |

**Occupation:** Asbestos miners; asbestos textile makers; auto brake repairers; cement mixers; construction workers; cutters and layers of water pipes; insulation cord makers; insulators; shipyard workers.

- Coke oven emissions (aromatic hydrocarbons including benz(a)pyrene)
- 3,3'-dichlorobenzidine and its salts
- 4-dimethylaminoazobenzene
- 4,4'-methylene-bis-(2-chloroaniline) (MOCA)
- \(α\)-naphthylamine
- \(β\)-naphthylamine

**Occupation:** Coke oven workers

**Occupation:** Pigment makers, polyurethane workers

**Occupation:** Elastomer makers, epoxy resin workers, polyurethane foam workers

**Occupation:** Chemical synthesizers, dye makers, rubber workers

**Occupation:** Research workers*
| Compound                        | Species | Route | Site(s)                                      | Tumor(s) | Description                                                                                                                                 |
|--------------------------------|---------|-------|----------------------------------------------|----------|--------------------------------------------------------------------------------------------------------------------------------------------|
| 2-acetylaminofluorene          | Rat     | p.o.  | Liver                                        | Skin     | Early appreciation of carcinogenic potential averted commercial production. (68)                                                        |
|                                | Dog     | p.o.  | Bladder, liver                              | Skin     |                                                                                                                                            |
|                                | Guinea pig | p.o. | Negative                                    | Skin     |                                                                                                                                            |
| Occupation: Research workers*  |         |       |                                              |          |                                                                                                                                            |
| 4-aminophenyl                  | Mouse   | p.o.  | Bladder, liver                              | Lung     | Formerly used as a rubber anti-oxidant and as a dye intermediate. No longer commercially produced. Fifty-three bladder tumors in 315 exposed workers; 1 case occurred with only 133 days of exposure. (71, 72) |
|                                | Dog     | p.o.  | Bladder                                     | Skin     |                                                                                                                                            |
| Occupation: Dihyphenylamine workers; research workers* |         |       |                                              |          |                                                                                                                                            |
| 4-nitrophenyl                  | Dog     | p.o.  | Bladder                                     |          | No documented cases in humans. Exposure to 4-nitrophenyl always occurs concurrently. (66)                                                |
| Occupation: Research workers*  |         |       |                                              |          |                                                                                                                                            |
| Benzidine and its salts        | Mouse   | s.c.  | Liver, ear duct, intestine                   | 16       | Bladder Medical personnel using benzidine to test for occult blood. (73–75)                                                                 |
|                                | Dog     |       | Bladder                                     | 14       |                                                                                                                                            |
| Occupation: Biochemists; dye workers; medical laboratory workers; organic chemical syntheses; plastic workers; rubber workers; wood chemists |         |       |                                              |          |                                                                                                                                            |
| β-propiolactone                | Rodents |       | Skin papilloma and sarcoma, stomach, liver  | Lung      | No skin cancer cases documented in humans. (76)                                                                                           |
|                                |         |       |                                             | Skin     |                                                                                                                                            |
| Occupation: Acrylate plastic makers; chemists; disinfectant workers; plastic makers; resin makers; viridical agent makers |         |       |                                              |          |                                                                                                                                            |
| Vinyl chloride                 | Rat     | Inhalation | Skin, lung, osteo- | Lung       | Full potential risk of cancer and of hepatobiliary tract disease in humans is not yet established. (16, 77) |
|                                |         |       | chondroma                                    | ?Skin    |                                                                                                                                            |
| Occupation: Organic chemical syntheses; polyvinyl resin makers; rubber workers |         |       |                                              |          |                                                                                                                                            |
| Chloromethyl methyl ether (CMME) | Mouse | Skin, s.c. | Carcinoma, sarcoma          | Lung      | Small cell carcinomas. Human exposures generally involve both CMME and BCME. (76–80)                                               |
| Occupation: Organic chemical syntheses |         |       |                                              | Skin     |                                                                                                                                            |
| Bis (chloromethyl) ether (BCME) | Mouse | Skin, s.c. | Olfactory esthesioneuroepitheloma, lung adenoma, papilloma, carcinoma, fibrosarcoma | Lung      | Small cell carcinoma. (81)                                                                                                               |
|                                | Rat     | s.c.  |                                             |          |                                                                                                                                            |
| Occupation: Ion exchange resin makers; laboratory workers; organic chemical syntheses; polymer makers |         |       |                                              |          |                                                                                                                                            |
| Ethyleneimine                  | Rat     | s.c.  | Sarcoma, kidney                            | Lung      | No documented human cases. (82)                                                                                                           |
|                                | Mouse   | p.o.  | Liver, lung                                 | Skin     |                                                                                                                                            |
| Occupation: Effluent treaters; organic chemical syntheses; paper makers; polyethyleneimine makers; textile workers |         |       |                                              |          |                                                                                                                                            |
| N-nitrosodimethylamine         | Rat     | p.o., inhalation | Liver, kidney                            | Lung      | Carcinogenic in 7 animal species. No information on chronic effects in humans. (83, 84)                                               |
|                                |         |       |                                              | Skin     |                                                                                                                                            |
| Occupation: Dimethyldrazine makers; nematocide makers; solvent workers |         |       |                                              |          |                                                                                                                                            |

*Early recognition of carcinogenic potential averted extensive commercial production. Most current exposures are in limited investigational settings.
### TABLE 4 (continued)

**INDUSTRIAL AGENTS ASSOCIATED WITH CANCER**

#### B. Agents for which Epidemiologic and/or Animal Studies Suggest Carcinogenic Potential

| Agent           | ANIMAL STUDIES | CLINICAL AND EPIDEMIOLOGIC STUDIES | Comments (pertinent references) |
|-----------------|----------------|-------------------------------------|----------------------------------|
| **Benzene**     | *Mouse* s.c., skin unsuccessful attempts to produce leukemia experimentally. | **Lung** 6–14 2.5 **Skin** | Aplastic anemia and/or leukemia and/or thrombocytopenia. Erythroleukemia. Acute leukemia established, and with acute leukemias highly suspect. (85-87) |
| **Soots, tars, oils** (mixtures of aromatic hydrocarbons including benz(a)pyrene) | *Skin* 9–23 1.3 *Lung* 23 | *Skin, scrotum* Lung Bladder | Precise risk varies with nature of mixture and nature and route of exposure. Creosote, a complex mixture of phenolic and aromatic compounds, may act as a tumor promoter. (88-90) |
| **Isopropyl oil** | *Mouse* s.c., inhalation | **Lung** 10 20 **Respiratory tract** | Ethmoid sinus (91) |
| **Organochloride pesticides** | *Aldrin* Rat Mouse p.o. Negative or inconclusive | *Aramite* Rat Mouse p.o. Liver Biliary tract | Aldrin is metabolized to Dieldrin. Use of Aldrin and Dieldrin have been discontinued in the U.S. and many other countries. Human studies of Aldrin, Aramite, DDT and Dieldrin are too limited to be conclusive. No epidemiologic studies are available for Heptachlor or Mirex. (98) |
| **DDT** | *Mouse* Rat guinea pig Dog, monkey p.o. p.o. p.o. Negative | **DDT** | Inconclusive |
| **Dieldrin** | *Mouse* Rat Dog, monkey p.o. p.o. | **Dieldrin** | Negative Inconclusive |
| **Heptachlor** | *Rat* p.o. | **Heptachlor** | Inconclusive |
| **Mirex** | *Mouse* p.o. | **Mirex** | Liver |

**Occupation:** Adhesive makers; asbestos product-impregnators; benzene hexachloride workers; burnishers; carbolic acid makers; chemists; chlorinated benzene workers; detergent makers; dry-battery workers; dye makers; furniture finishers; glue makers; linoleum makers; maleic acid makers; nitrobenzene makers; petrochemical workers; putty makers; rubber makers; styrene makers; welders; artificial leather makers and shoe workers.

**Occupation:** Cable layers; coal, gas, coke and petroleum industry workers; coal tar and pitch workers; electrical equipment workers; fabric proofers; net fixers; optical lens grinders; waterpoofers, wharfmen, wood preservers.
| Substance                  | Species | Route | Tumor Site | Comments |
|---------------------------|---------|-------|------------|----------|
| Polychlorinated biphenyls | Mouse   | p.o.  | Liver      | Skin     |
|                           | Rat     | p.o.  | Liver      | Skin     |
|                           |         |       |            |          |
|                           |         |       |            |          |
|                           |         |       |            |          |

Occupation: Cable coaters, capacitor producers, dye makers, electrical equipment makers, herbicide makers, investment casting processors, lacquer makers, paper treaters, plasticizer makers, resin makers, rubber workers, textile flame proofers, transformer workers, wood preservers

Twelve thousand persons estimated to have occupational exposures. Wider environmental exposures. Deliberate effects on mammalian reproduction. Human studies are too limited to permit conclusions as to carcinogenic potential. Ingestion in humans has produced a syndrome consisting of chloracne, brown pigmentation of skin and nails, transient visual disturbances, swelling of eyelids with eye discharge, and gastrointestinal symptoms with liver abnormalities and jaundice. (92–97)

| Aniline       | Multiple | p.o. | Negative | Lung | Skin |
|---------------|----------|------|----------|------|------|
| Occupation:   | Acetanilide workers, bromide workers, coal tar workers, disinfectant makers, dye workers, ink workers, leather workers, lithographers, nitrilene workers, perfume makers, photographic chemical makers, plastic workers, printers, rocket fuel makers, rubber workers, tetryl makers, varnish workers |

No adequate data to indicate carcinogenicity of aniline in animals or humans. Probably only aniline derivatives and not the parent compound are bladder carcinogens in humans. (99)

| Auramine      | Rat      | p.o. | Liver    | Lung  | 19.3 | 4.6 | Bladder |
|---------------|----------|------|----------|-------|------|-----|---------|
| Mouse         | p.o.     | Liver|          | Skin  |      |     |         |
| Occupation:   | Dye makers |

| Magenta      | Rat      | s.c. | Local sarcomas | Lung  | 23   |     | Bladder |
|--------------|----------|------|-----------------|-------|------|-----|---------|
| Occupation:  | Dye makers |

| Chloroprene  | Mouse    | s.c., ingestion | Negative | Lung | Skin |
|--------------|----------|-----------------|----------|------|------|
| Rat          | p.o.     |                 |          |      |      |
| Occupation:  | Duprene makers, Neoprene makers, rubber makers |

Used only in the manufacture of artificial rubber. Structurally similar to vinyl chloride. Studies in humans too limited to permit conclusions concerning carcinogenicity. (101, 102)

| Trichloroethylene | Rat | p.o. | Liver | Lung | Skin |
|-------------------|-----|------|-------|------|------|
| Mouse             | p.o. |      |       |      |      |
| Occupation:       | Anesthetic makers, caffeine processors, cleaners, degreasers, disinfectant makers, dry cleaners, drug makers, dye makers, electronic equipment cleaners, fat processors, glass cleaners, mechanics, metal cleaners, oil processors, perfume makers, printers, resin workers, rubber cementers, shoe makers, soap makers, solvent workers, textile cleaners, tobacco denicotinizers, varnish workers |

No human studies available. Some 283,000 U.S. workers exposed. (84, 103)

| Carbon tetrachloride | Mouse    | p.o., inhalation | Liver | Lungs | Skin |
|                      | Rat, Hamster |           |       |       |      |
| Occupation:          | Chemists, degreasers, fat processors, firemen, fluorocarbon makers, grain fumigators, ink makers, insecticide makers, lacquer makers, metal cleaners, propellant makers, refrigerant makers, rubber workers, solvent workers, wax makers |

Positive dose-response relationship in mice. No epidemiologic studies available. Clinical reports of hepatomas following acute intoxication. (84, 104)

| Chloroform      | Mouse   | p.o. | Liver |      |     |
|-----------------|---------|------|-------|------|-----|
| Occupation:     | Chemists, drug makers, fluorocarbon makers, lacquer workers, polish makers, silk synthesizers, solvent workers |

Studies in humans too limited to assess carcinogenicity. (84, 105)

| Acrylonitrile   | Rat     | p.o., inhalation | CNS, Zymbal gland, breast | Lung  | 20–25 | 3 (all sites) | Colon, lung |
|-----------------|---------|------------------|---------------------------|-------|-------|--------------|-------------|
| Occupation:     | Acrylic fiber makers, fumigators, plastic product resin makers, textile workers |

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TABLE 4 (continued)
INDUSTRIAL AGENTS ASSOCIATED WITH CANCER

B (continued). Agents for which Epidemiologic and/or Animal Studies Suggest Carcinogenic Potential

| Agent               | Animal Studies | Target organs and tissues | Clinical and Epidemiologic Studies | Comments (pertinent references) |
|---------------------|----------------|---------------------------|-----------------------------------|---------------------------------|
| Ethylene dichloride (1,2-dichloroethane) | Rat, mouse | p.o. | Stomach, blood vessels, skin, breast, uterus, lung | Route of absorption: Lung 10-25 Latency (years): 37 Risk: Respiratory tract | No human studies available. An estimated 10 billion pounds are produced annually in the U.S. About 2 million workers are exposed, including 34,000 with full-time occupational exposure. (106) |
| Occupation: Adhesive makers, agricultural workers, Bakelite processors, camphor workers, chemical makers, dry cleaners, exterminators, furniture finishers, gasoline blenders, grain fumigators, insecticide makers, metal degreasers, ore upgraders, petroleum refinery workers, plastic workers, solvent workers, textile cleaners |
| Mustard gas         | Mouse | i.v., inhalation | Lung adenoma | Route of absorption: Lung 43 average (21-49) Latency (years): 500 Risk: Nasal cavity and nasal sinuses | Military exposures not associated with substantial risk of respiratory cancer. (108, 109) |
| Occupation: Japanese mustard gas workers |
| Wood dust           | s.c. | Local sarcomas | Lung | Route of absorption: Lung 40-55 Latency (years): 8 Risk: Nasal cavity and nasal sinuses | Hard wood dusts. (19, 110) |
| Occupation: Cabinet makers, carpenters, furniture makers, instrument makers, sawmill workers, wood workers |
| Leather dust        |  |  |  | Route of absorption: Lung 15-35 Latency (years): 2.3-8 Risk: Nasal cavity and nasal sinuses | Excess lung cancer has been reported in association with use and production of inorganic trivalent arsenic-containing pesticides as well as metal smelting operations. (112-114) |
| Occupation: Boot and shoe manufacturers and repairers |
| Arsenic             | Mouse, rat | p.o., p.o. | Negative, Negative | Route of absorption: Lung Skin Skin Oral 40-55 15-35 2.3-8 | Excess risk of lung cancer was demonstrated in the chromate-producing industry, particularly during the 1930's and 1940's. Risk in other occupational settings with lower intensity exposures may not be substantially increased. (115-117) |
| Occupation: Alloy workers, aniline color makers; arsenic workers; Babbit metal workers; brass makers; bronze makers; ceramic enamel makers; ceramic makers; copper smelters; drug and dye makers; enamellers; fireworks makers; gold refiners; herbicide makers; hide preservers; insecticide makers; lead shot makers; lead smelters; leather workers; painters; paint makers; petroleum refinery workers; pigment makers; printers; printing ink workers; rodenticide makers; semiconductor compound makers; silver refiners; taxidermists; textile printers; tree sprayers; type metal workers; water weed controllers; weed sprayers |
| Chromium and chromates | Rat | Chromate pellets implanted in bronchial mucosa | Squamous and adenocarcinoma of the lung | Route of absorption: Lung Skin Oral 40-55 15-35 2.3-8 | Excess risk of lung cancer was demonstrated in the chromate-producing industry, particularly during the 1930's and 1940's. Risk in other occupational settings with lower intensity exposures may not be substantially increased. (115-117) |
| Occupation: Anodizers; copper etchers; electroplaters; gas workers; lithographers; metal workers; oil purifiers; photoengravers; photographers; process engravers; stainless steel workers; textile workers; welders |
| Substance          | Animal(s) | Route | Tumor Type | Lymph Nodes | Trachea | Esophagus | Lung | Nasal Passages | Oral | Respiratory Tract | Digestive Tract | Skin | Developing Site | Other Sites | Latency Period | Incidence |
|--------------------|-----------|-------|------------|-------------|---------|-----------|------|---------------|------|------------------|----------------|------|-----------------|------------|---------------|-----------|
| Beryllium          | Mouse, rabbit, monkey, rat | Inhalation | Bone sarcoma | Lung | Lower limit of 10-15 years | Lung | The character of the work operation is particularly important—heating, surface grinding, machining, or any work that can produce fumes or finely divided dusts must be considered potentially hazardous. Three epidemiologic studies have shown marginal excesses in relative risk. Further research is needed to clarify the relationship with duration and intensity of exposure, latency, and the contribution of pulmonary berylliosis and tobacco smoking. |
| Iron oxides (iron ore, haematite) | Hamster, mouse, guinea pig | Inhalation | Inhalation | Negative, Negative | Oral | Lung | 10+ | 2-5 | Respiratory tract | Ingestion of dusts. Recognized excess risk of lung cancer confined to underground haematite miners. (118, 119) |
| Lead               | Rat       | p.o., parenteral | Kidney | No evidence for carcinogenicity in humans. Carcinogenic doses of lead in animals far exceeds levels tolerated by humans. (120, 121) |
| Nickel and compounds | Rat, Rat | Inhalation | Lung | Sarcomas | 27 average (5-40) | 4.9-10.5 | Lung | A number of animal inhalation studies using powdered nickel alone or with other inhalants such as nickel carbonyl vapor have been inconclusive. The risks of respiratory cancer have decreased significantly in workers first exposed since 1925, after which important preventive measures to reduce exposure to dusts and fumes were first implemented. (122, 123) |
| Selenium and compounds | Rat       | p.o. | Liver | Skin | Lung | Oral | No known carcinogenic effect in humans. Protective effect against large bowel cancer has been proposed. (124) |
| Ionizing radiation | Multiple | Irradiation | Skin, breast, thyroid, bone, lung | 2-25 | 3.7-9.5 | Leukemia | Most leukemias are acute, some chronic myeloid. (125, 126) |

Occupation: Alloy workers and users (with aluminum, copper, nickel, and steel); electronic tube makers; fluorescent lamp makers (up until 1949); gas mantle workers; metalurgists; miners and extractors of ore (mainly beryl); nuclear reactor workers; plastic and ceramic workers; rocket and aerospace research workers.

Occupation: Arc cutters; Bessemer operators; electric arc welders; flame cutters; friction saw operators; metalizers; seam welders; stainless steel makers; steel foundry workers.

Occupation: Battery workers; brass foundry workers; ceramic makers; gasoline additive workers; glassmakers; imitation pearl makers; insecticide makers; lubricant makers; match makers; painters; plumbers; soldiers; storage tank cleaners.

Occupation: Battery makers; ceramic makers; chemists; dyers; enamblers; foundry workers; gas platers; ink makers; magnet makers; Mond process workers; oil hydrogenators; organic chemical synthesizers; paint makers; petroleum refinery workers; spark plug makers; textile dyers; varnish makers.

Occupation: Arc light electrode makers; copper smelters; electric rectifier makers; glass makers; organic chemical synthesizers; pesticide makers; photographic chemical makers; pigment makers; plastic workers; pyrite roasters; rubber makers; semiconductor makers; sulfuric acid makers; textile workers.

Occupation: Aircraft workers; atomic energy plant workers; biologists; cathode ray tube makers; ceramic workers; chemists; dental assistants; dentists; dermatologists; drug makers; drug sterilizers; electron microscope makers; electron microscopists; electrostatic eliminator operators; embalmers; fire alarm makers; food preservers; food sterilizers; gas mantle makers; high voltage television repairmen; high voltage vacuum tube makers; high voltage vacuum tube users; industrial fluoroscope operators; industrial radiographers; inspectors using, and workers in proximity to, sealed gamma ray sources (cesium-137, cobalt-60, and iridium-192); klystron tube operators; liquid level gauge operators; luminous dial painters; machinists; fabricated metal product workers; military personnel; nurses; oil well loggers; ore assayers; pathologists; petroleum refinery workers; physicists; physicists; pipeline oil flow testers; pipeline weld radiographers; plasma torch operators; plastic technicians; prospectors; radar tube makers; radiologists; radium laboratory workers; radium refinery workers; research workers; television tube makers; thickness gauge operators; thorium-aluminum alloy workers; thorium-magnesium alloy workers; thorium ore producers; tile glazers; uranium dye workers; uranium mill workers; uranium miners; veterinarians; X-ray aides; X-ray diffraction apparatus operators; X-ray technicians; X-ray tube makers.
### TABLE 4 (continued)
### INDUSTRIAL AGENTS ASSOCIATED WITH CANCER

**B (continued). Agents for which Epidemiologic and/or Animal Studies Suggest Carcinogenic Potential**

| Agent | ANIMAL STUDIES | CLINICAL AND EPIDEMIOLOGIC STUDIES | Comments (pertinent references) |
|-------|----------------|-----------------------------------|--------------------------------|
| Non-ionizing radiation (Ultraviolet) | Mouse | Skin | Skin | 5-50 | 2.5 | Skin | Basal cell and squamous cell. (127) Malignant melanoma. |
| Occupation: Agricultural workers; bacteriologists; bath attendants; beauty salon workers; brick masons; cattlemen; chemists; construction workers; dentists; farmers; fishermen; food irradiators; gardeners; graphic illustrators; greenskeepers; horticultural workers; laboratory workers; lamp testers; landscapers; lithographers; lumberjacks; maintenance workers; meat curers; metal casting inspectors; microscopists; military personnel; movie projectionists; nurses; oil field workers; open-pit miners; opticians; optometrists; outdoor maintenance workers; paint and color testers; paint curers; physicians; physicists; physiological optics workers; photo-bacteriologists; phototherapy technicians; pipeline workers; plasma torch operators; plastic curers; policemen (including crossing guards); postalmen; printers; production workers in chemical processing; railroad track workers; road workers; seamen; ski instructors; space simulator workers; sportsmen; surveyors; textile inspectors; tissue culture workers; tobacco irradiators; vitamin D synthesis workers; welders; welder foremen; wood curers. |
| **RADIOACTIVE ORES AND METALS** | | | | | |
| Uranium/radon | Rat | Inhalation | Lung | Lung | 10-38 | Small cell carcinoma of the lung | Inhalation of radon daughters with irradiation of bronchial tree. (126, 128–133) |
| Occupation: Underground miners | | | | | |
| Radium | Oral | 10-50 | 82 | Bone sarcoma | Leukemia and lymphoma Colon | Ingestion of radium-containing paint by women watch dial painters occurred up to about 1929. (28) |
| Occupation: Luminescent watch dial painters | | | | | |

### About the Table

Two groups of agents have been selected for inclusion in Table 4. The first—Part A of the Table—is a group of regulated substances for which standards have been issued by the Occupational Safety and Health Administration (OSHA), in which they are labeled chemical carcinogens. Requirements for handling these substances are delineated in the standards set by OSHA in order to provide the maximum amount of protection to employees from exposure to the carcinogens. The list of regulated carcinogens is growing as standards are agreed upon for control of other suspected carcinogens.

The agents included in Part B of the Table are selected from a much larger group of commercially produced substances for which there is a dynamic pool of documentation of carcinogenic effects. This second group of substances includes agents for which there is concern over potential occupational carcinogenicity. In some cases, carcinogenic effects have been observed in animal models; in other cases there are suggestive epidemiologic studies. The evidence of carcinogenicity for these agents varies considerably from an agent such as arsenic, which can certainly cause skin cancer but for which a standard is still pending, to aniline which is no longer suspect as a probable carcinogen.
fore, "exposure to any known or suspected carcinogen must be reduced to the lowest level possible by whatever means available."137, 138

The 1976 NIOSH Registry of Toxic Effects of Chemical Substances contains over 22,000 substances, and these include over 1,900 for which at least one in vivo laboratory test was positive for carcinogenicity. Currently, OSHA has issued TLV's for 17 chemical carcinogens (Table IV):

- asbestos fibers
- coke oven emissions
- 3,3'-dichlorobenzidine (and its salts)
- 4-dimethylaminoazobenzene
- 4,4'-methylene-bis-(2-chloroaniline)
- α-naphthylamine
- β-naphthylamine
- 2-acetylaminofluorene
- 4-aminodiphenyl
- 4-nitrobenzophenyl
- benzidine and its salts
- β-propiolactone
- vinyl chloride
- chloromethyl methyl ether (CMME)
- bis-chloromethyl ether (BCME)
- ethyleneimine
- N-nitrosodimethylamine

In a 1972-1974 survey conducted by NIOSH, it was estimated that approximately one percent of the total work force, or 880,000 employees, were exposed to one or more of the 17 regulated carcinogens.139 This estimate of exposure for the total work force appears too low when compared with that reported recently for asbestos workers; namely, the Department of Health, Education and Welfare stated that 1.5 to 2.5 million currently employed workers may be exposed to asbestos.140 As shown in controlled studies in humans and/or laboratory animals, a chemical carcinogen increases the risk of cancer in relation to the duration and intensity of exposure. The National Cancer Advisory Board Subcommittee on Environmental Carcinogenesis' report suggested that the occurrence of only benign neoplasms in experimental animals signifies that the agent should be considered "a potential human health hazard which requires further evaluation."141 A parallel increase in the incidence of benign and malignant tumors in the same tissue would underscore the evidence for carcinogenicity of the test substance. Other scientists would argue that the distinction between "tumorigen" and "carcinogen" as a basis for public health practice is not defensible.142 Furthermore, whereas environmental threshold limits have been proposed for carcinogens in the workplace, the assumption of zero tolerance has been advanced for the consumption of carcinogenic food additives under the Delaney Amendment to the Food, Drug and Cosmetic Act.143, 144 It is apparent that controversy will persist as long as there is insufficient scientific information to establish "safe" levels of exposure or to conceptualize acceptable levels of risk.

Since it is difficult to determine the "safe" level of human exposure to any suspect carcinogen with any degree of confidence, the concepts of "acceptable risk" and "risk-benefit analysis" are emerging in counterpoint to the issue of a "risk-free" workplace. In essence, this has been the philosophy of the Environmental Protection Agency, which is charged with enforcing the Toxic Substances Control Act of 1976.145 The Subcommittee on Environmental Carcinogenesis of the National Cancer Advisory Board summarized the judgmental nature of risk-benefit analysis as follows: "In those cases in which a compound has been proved to be carcinogenic remains the decision to what extent the possible risks to man are counterbalanced by the possible social, economic or medical benefits of that substance. Scientists must play a major role in these decisions by providing and interpreting the available data. The final decision, however, must be made by society at large through informed governmental regulatory and legislative groups."146

OSHA has recommended that environmental chemical carcinogens should be categorized generically, based upon the epidemiological and experimental evidence for tumorigenicity and mutagenicity.147 The assessment of risk to a community of workers and to society in general goes beyond the application of criteria for
predicting human carcinogenicity. For example, a priority for more stringent regulation should be assigned on the basis of tumorigenic potency and number of workers exposed, particularly if a seemingly safe substitute material could be introduced. The socioeconomic consequences of complying with regulatory action is a separate but essential feature of the process of decision-making.\textsuperscript{147,148}

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