Overview of Preventable Industrial Causes of Occupational Cancer

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This paper summarizes what is known about preventable causes of occupational cancer, including single agents, complex mixtures, and broad occupational associations. Epidemiologic methods have been very successful in documenting cancer risks associated with single agents. Epidemiologic data are most conclusive when an exposure–response relationship can be demonstrated. Examples of agents for which epidemiologic studies provide evidence of an exposure–response relationship include benzene and (concurrent exposure to) *ortho*-toluidine and aniline. Vinyl chloride and bischloromethyl ether are examples of associations between single agents and rare histologic types of cancer. It is more difficult to conduct epidemiologic studies to identify cancer risks associated with complex mixtures. Studies of diesel exhaust and lung cancer and metal machining oils are cited as having employed advanced industrial hygiene and epidemiologic methods for studies of complex mixtures. Elevated cancer risks have also been identified in broad occupational groups, including painters and dry cleaners. Epidemiologic case–control studies are often used to detect such associations but are limited in their abilities to detect the causal agents. Major gaps exist in knowledge of occupational cancer risks among women workers and workers of color. Because epidemiologic research measures illness and mortality that have already occurred, a positive study can be interpreted to represent a failure in prevention. The challenge we face in the next decade is to identify interventions earlier in the causal pathway (toxicologic testing, biomarkers of exposure or precancerous changes, institution of engineering and good industrial hygiene practices to reduce occupational exposure levels) so that occupational cancer can be prevented. — Environ Health Perspect 103(Suppl 8):197–203 (1995)

Key words: carcinogen, standards, occupational health, epidemiology

Introduction

It is estimated that about 4% of all cancers are due to occupation (*1*), concentrated among lung and bladder cancer. A total of 10 to 20% of lung cancers (*2*) and 21 to 27% of bladder cancers (*3,4*) are estimated to be related to occupational exposure. This paper will summarize what is known about preventable causes of occupational cancer and highlight some critical gaps in knowledge. Knowledge of occupational cancer risks will be discussed in relation to single agents, complex mixtures, and broad occupational categories.

This paper was presented at the President's Cancer Panel Conference on Avoidable Causes of Cancer held 7–8 April 1994 in Bethesda, Maryland. Manuscript received 9 March 1995; manuscript accepted 24 March 1995.

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Abbreviations: BCME, bischloromethyl ether; CI, confidence interval; U.S. EPA, U.S. Environmental Protection Agency; IARC, International Agency for Research on Cancer; NCI, National Cancer Institute; NCHS, National Center for Health Statistics; NTP, National Toxicology Program; NIOSH, National Institute for Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; PCE, perchloroethylene; ppm, parts per million; PEL, permissible exposure limit; REL, recommended exposure limit; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio; $\mu g/m^3$, micrograms per cubic meter.

Sources of Data on Occupational Carcinogens

The most comprehensive source of information about both occupational and nonoccupational carcinogens is a series of monographs published by the International Agency for Research on Cancer (IARC) (*5*). These monographs are prepared with the help of international working groups of experts. IARC has published reviews on over 1000 substances. Each review contains a brief description of the chemical and physical properties of the agent, methods and volume of production, use patterns and occurrence, summaries of experimental carcinogenicity tests, a brief description of other relevant biological data (toxicity and genetic and related effects), summaries of case reports and epidemiologic studies of cancer in humans, and an evaluation of its carcinogenicity. IARC classifies agents (or exposure circumstances) according to their carcinogenicity, which ranges from carcinogenic to humans (Group 1) to probably not carcinogenic (Group 4). Among the 100 definite and probable carcinogens, approximately 40% involve primarily occupational exposures (*6*).

Within the United States, the National Toxicology Program (NTP) publishes an annual report on carcinogens each year. This legislatively mandated document [Section 301(b) (*4*) of the Public Health Service Act] contains "a list of all substances which are known to be carcinogens or may reasonably be anticipated to be carcinogens and to which a significant number of persons residing in the United States are exposed." It also contains information on the extent and nature of exposure and each standard established by a Federal agency with respect to the substance. *The Seventh Annual Report on Carcinogens* listed 24 substances known to be carcinogenic and approximately 140 substances that are reasonably anticipated to be carcinogens (*7*).

In the United States, the agencies mandated to ensure the health and safety of the working population are the Occupational Safety and Health Administration (OSHA) within the Department of Labor, and the National Institute for Occupational Safety and Health (NIOSH) within the Centers for Disease Control and Prevention. OSHA, the agency charged with promulgating and enforcing occupational health standards, has standards for 24 carcinogens (Table 1). These standards specify not only the permissible exposure limit (PEL) for the concentration of the substance in air but also other requirements for labeling, personal protective equipment, and medical screening. OSHA standards require

Table 1. Potential occupational carcinogens recognized by NIOSH.

Acetaldehyde	Gasoline
2-Acetylaminogluorene (O)[a]	Heptachlor
Acrylamide	Hexachlorobutadiene
Acrylamide	Hexachloroethane
Acrylonitrile (O)	Hexamethyl phosphoric triamide (HMPA)
Aldrin	Hydrazine
4-Aminodiphenyl (O)	Kepone
Amitrole	Methoxychlor
Aniline and homologs	Methyl bromide; class, monohalomethanes
o-Anisidine	Methyl chloride
p-Anisidine	Methylhydrazine
Arsenic, inorganic (O)	Methyl iodide; class, monohalomethanes
Arsine	Methyl hydrazine; class, hydrazines
Asbestos (O)	4,4'-Methylenebis(2-chloroaniline) (MBOCA)
Asphalt fumes	Methylene chloride
Benzene (O)	4,4'-Methylenedianiline (MDA) (O)
Benzidine (O)	α-Naphthylamine (O)
Benzidine-based dyes	β-Naphthylamine (O)
Beryllium	Nickel, metal, soluble, insoluble, and inorganic; class, nickel, inorganic
Butadiene	Nickel carbonyl
tert-Butyl chromate; class, chromium,	Nickel sulfide roasting
Cadmium dust and fume (O)	4-Nitrobiphenyl (O)
Captafol	*p*-Nitrochlorobenzene
Captan	2-Nitronaphthalene
Carbon tetrachloride	2-Nitropropane
Chlordane	*N*-Nitrosodimethylamine (O)
Chlorinated camphene	Pentachloroethane; class, chloroethanes
Chlorodiphenyl (42% chlorine); class, polychlorinated biphenyls	*N*-Phenyl-β-naphthylamine; class, β-naphthylamine
Chlorodiphenyl (54% chlorine); class, polychlorinated biphenyls	Phenyl glycidyl ether; class, glycidyl ethers
Chloroform	Phenylhydrazine; class, hydrazines
Chloromethyl methyl ether (O)	Propane sultone
bis(Chloromethyl) ether (O)	β-Propiolactone (O)
β-Chloroprene	Propylene dichloride
Chromium, hexavalent [Cr(VI)]	Propylene imine
Chromyl chloride; class, chromium, hexavalent	Propylene oxide
Chrysene	Radon
Coal tar pitch volatiles; class, coal tar products	Rosin core solder, pyrolysis products (i.e., formaldehyde, acetaldehyde, malonaldehyde)
Coke oven emissions (O)	Silica, crystalline cristobalite
DDT (dichlorodiphenyltrichloroethane)	Silica, crystalline quartz
Di-2-ethylhexyl phthalate (DEHP)	Silica, crystalline tripoli
2,4-Diaminoanisoleo	Silica, crystalline tridymite
O-Dianisidine-based dyes	Silica, fused
1,2-Dibromo-3-chloropropane (O)	Soapstone, total dust silicates
Dichloroacetylene (DBCP)	Tremolite silicates
p-Dichlorobenzene	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) (dioxin)
3,3' -Dichlorobenzidine (O)	1,1,2,2-Tetrachloroethane
Dichloroethyl ether	Tetrachloroethylene
1,3-Dichloropropene	Titanium dioxide
Dieldrin	*o*-Tolidine-based dyes
Diesel exhaust	*o*-Tolidine
Diglycidyl ether (DGE); class, glycidyl ethers	Toluene diisocyanate (TDI)
4-Dimethylaminoazobenzene (O)	Toluenediamine (TDA)
Dimethyl carbamoyl chloride	*o*-Toluidine
1,1-Dimethylhydrazine; class, hydrazines	*p*-Toluidine
Dimethyl sulfate	1,1,2-Trichloroethane; class, chloroethanes
Dinitrotoluene	Trichloroethylene
Dioxane	1,2,3-Trichloropropane
Environmental tobacco smoke	Uranium soluble compounds
Epichlorohydrin	Vinyl bromide; class, vinyl halides
Ethyl acrylate	Vinyl chloride (O)
Ethylene dibromide	Vinyl cyclohexene dioxide
Ethylene dichloride	Vinylidene chloride (1,1-dichloroethylene); class, vinyl halides
Ethylene oxide (O)	Welding fumes, total particulates
Ethyleneimine (O)	Wood dust
Ethylene thiourea	Zinc chromate; class, chromium
Formaldehyde (O)	
Gallium arsenide	

[a]O, Occupational Safety and Health Administration.

companies to reduce exposures to specified levels. In addition to the comprehensive standards for the 24 carcinogens, OSHA may have PELs limiting occupational exposure to potential carcinogens based on other health effects.

NIOSH, the agency charged with conducting occupational health research and issuing recommendations, has identified 131 substances as potential occupational carcinogens (Table 1). Many of these substances were identified by NIOSH as potential occupational carcinogens based on animal data alone. NIOSH recommends that exposure to these substances be reduced to the lowest feasible concentration (*8*). While NIOSH-recommended exposure limits (RELs) are not legally enforceable, they serve as technology-forcing goals in reducing exposure.

Occupational cancer epidemiology in the United States is conducted by a number of Federal agencies, including NIOSH, the National Cancer Institute (NCI), and the National Institute for Environmental Health Sciences (NIEHS), as well as academic institutions. Many of these agencies also have toxicology programs that evaluate chemicals for carcinogenicity. Although animal studies are critically important in the identification of potential occupational carcinogens and the interpretation of epidemiologic study results, this paper will focus on data from epidemiologic studies.

Single Agents as Preventable Causes of Occupational Cancer

Identification of single agents as preventable causes of occupational cancer is most frequently done by retrospective cohort studies. These studies require the identification of sizable populations exposed historically to the agent of interest in the absence of other potential carcinogens. The populations are followed for cancer mortality and/or incidence, allowing a 20- to 40-year latency period for cancers to develop.

The confirmation of an agent as an occupational carcinogen is most persuasive when an exposure–response relationship is demonstrated. Exposure–response may be evaluated in the overall cohort, or in a nested case–control study when it is more efficient to characterize exposure in only a portion of the cohort. Data can be used in risk assessments to estimate the reduction in risk associated with a decrease in exposure.

An example of a study demonstrating an exposure–response relationship is a

study of rubber hydrochloride workers potentially exposed to benzene at two plants (*9,10*). A total of 1165 white men with at least 1 ppm-day exposure to benzene between January 1, 1940, and December 31, 1965, were included in the study. Air monitoring data for benzene were available from the two plants as early as 1946. Based on these data, a matrix was developed linking each job title with an estimate of the time-weighted average benzene exposure. Linking this matrix with the individual job histories allowed calculation of the cumulative lifetime exposure (ppm-years) for each individual. Table 2 summarizes the results of the standardized mortality ratio (SMR) analysis, in which a pattern of higher risk with higher cumulative exposure was observed. This data set was used by OSHA in 1987 to demonstrate that the 1 ppm PEL for benzene would prevent a significant risk of material health impairment (*11*).

In studies in which historical industrial hygiene data are unavailable, duration of exposure is sometimes used as a surrogate for dose. In a study of bladder cancer incidence among workers exposed concurrently to the aromatic amines *ortho*-toluidine and aniline in a rubber chemicals manufacturing plant, no historical industrial hygiene data were available (*12*). Investigators used duration of employment as a surrogate for dose, and found a striking relationship (Table 3).

Strong associations also have been established for certain chemicals that cause rare types of cancer. For example, workers exposed to vinyl chloride have died from liver cancer at a rate seven times that expected; most of the deaths were due to angiosarcoma of the liver (*13*), a histologic type that accounts for under 1% of liver neoplasms diagnosed in the United States (*14*). The carcinogenicity of bischloromethyl ether (BCME) was first recognized by the occurrence of three cases of small cell lung cancer among 45 workers from the same facility in a Philadelphia chemical plant (*15*). Summarizing the data to date, Steenland et al. (*2*) found that in a total of 3332 workers exposed to BCME studied worldwide, 98 lung cancer cases were observed and 24.1 were expected (SMR = 4.1). Studies have typically exhibited a marked dose response and a histologic specificity for small cell tumors (*2*).

Table 2. Standardized mortality ratios (SMRs) for leukemia among workers exposed to benzene in a rubber hydrochloride plant.

Benzene exposure, ppm/year	Observed deaths	Expected deaths	SMR
0.001–40	2	1.83	1.09
40–200	2	0.62	3.22
200–400	2	0.17	11.86
>400	3	0.04	66.37
Total	9	2.66	3.37

Adapted from Rinsky et al. (*10*).

Table 3. Standardized incidence ratios (SIRs) for bladder cancer among workers exposed to *ortho*-toluidine and aniline in a rubber chemicals manufacturing plant.

Years in department	Number of persons	Observed cases	Expected cases	SIR
< 5	584	0	0.75	–
5–9.99	51	1	0.11	8.8
> 10	73	6	0.22	27.2
Total	708	7	1.08	6.5

Adapted from Ward et al. (*12*).

Because it is possible to develop evidence for a causal relationship between the specific agent and the cancer excess, single-agent carcinogens can be effectively controlled. Twenty-three of the 24 carcinogens regulated by OSHA, including benzene, asbestos, BCME, and vinyl chloride, are single-agent exposures.

Complex Mixtures as Preventable Causes of Occupational Cancer

Many occupational exposures involve complex mixtures rather than chemically specific substances. Diesel exhaust is an example of a complex mixture that is carcinogenic in animals (*16*) and is considered a probable human carcinogen by IARC and NIOSH. Levels of occupational exposure are difficult to quantify because until recently there was no air sampling method specific to diesel exhaust (*17*). In 1988, a review of the carcinogenicity of diesel exhaust concluded that the epidemiologic evidence was limited by the difficulty in defining and quantifying exposure, the relatively short time between initial exposures and analysis of risk in some studies, and the need to control for cigarette smoking (*18*).

Recent epidemiologic studies have improved on earlier research. Smoking data have been collected and an attempt has been made to measure diesel exposure currently and then extrapolate back to historical levels. For example, Steenland et al. (*19*) conducted a nested case–control study of lung cancer deaths within the Teamsters Union. Interviews with next of kin were conducted to determine smoking history; both Teamster Union records and next-of-kin interviews were used to determine work history. Odds ratios for jobs with diesel exposure were compared with those without. Long-term (>35 years) truck drivers of primarily diesel trucks had an odds ratio of 1.89 (95% confidence interval [CI] = 1.04–3.42); individuals whose main job was truck mechanic had an odds ratio of 1.69 (95% CI=0.92–3.09), which was not related to length of exposure. An industrial hygiene survey (*17,20*) used elemental carbon as a marker of diesel exhaust. This survey estimated that air concentrations of elemental carbon in the work area of mechanics averaged 26.6 $\mu g/m^3$, while air concentrations in the cabs of long-haul trucks averaged 5.1 $\mu g/m^3$. Background levels in residential areas average 1.1 $\mu g/m^3$.

There are approximately 1.5 million U.S. workers exposed to diesel exhaust, principally in the trucking and construction industry. Steenland et al. (*2*) estimated that approximately 800 of the 100,000 lung cancer cases diagnosed among U.S. males each year are attributable to occupational diesel exposure. Diesel exposures among long-haul truck drivers, the largest occupational group exposed to diesel emissions, are being reduced by U.S. Environmental Protection Agency (U.S. EPA) regulations for allowable truck emissions. However, truck mechanics and railroad workers may continue to have substantial exposures.

Another example of complex mixtures that have been recognized as potentially carcinogenic are cutting and lubricating oils. These products are thought to be responsible for the excesses of cancer of the scrotum, bladder, and digestive tract that have been observed among workers in the machining and metalworking occupations. In a recent example, a case–control study of occupational causes of bladder cancer found an elevated risk among drill press operatives (Table 4) that was related to length of exposure (*3*). In 1981, NIOSH estimated that there were 6 million workers in nonagricultural industries exposed to

Table 4. Number cases and controls and relative risks (RR), according to duration of employment in the occupation of drill press operator, white males.

Duration, year	Cases	Controls	RR	Trend test, *p*
< 5	22	33	1.0	0.008
5–9	14	14	1.8	
10 +	12	9	2.4	

From Silverman et al. (*3*).

mineral oils, 2 million to lubricating oils, 1 million to cutting oils, and 1 million to motor oils. The complexity and diversity of cutting oils, however, make it difficult to determine the actual carcinogenic exposure.

A major epidemiologic study was conducted to examine the risks associated with the three major classes of machining fluids: straight oils (cutting oils), which are naphthenic or paraffinic mineral oils; soluble oils, which contain emulsifying agents to suspend the oil drops in water; and synthetic oils, in which synthetic chemicals are substituted for oils (*21*). This cohort mortality study included more than 45,000 workers from three plants, almost 1 million person-years of follow-up, and over 10,000 deaths. An analysis of three subcohorts ever exposed to straight oils (n=13,967), soluble oils (n=23,488) and synthetic fluids (n=8446) suggested associations of exposure to straight oil with rectal, laryngeal, and prostatic cancers. For each of these cancers, the SMR for those ever exposed to straight oils was elevated, there was some indication in the poisson modeling of a trend in risk with increasing duration of exposure, and the association was consistent across plants (Table 5) (*22*). No cancer excesses were associated with soluble oil exposure. There was some evidence of an association between pancreatic cancer and exposure to synthetic fluids. In a separate set of analyses, investigators examined risk of several cancers in relation to quantitative estimates of cumulative exposure to specific types of machining fluids; some analyses were limited to grinding occupations. These analyses demonstrated an exposure-response relationship for exposure to straight oils and laryngeal cancer, for grinding operations and esophageal cancer, and for exposure to straight oils and rectal cancer. The rate ratio for rectal cancer increased in a monotonic fashion up to 2.9 (95% CI=1.3–5.0) in the highest exposure category.

This study was unique both in terms of its massive size and extensive exposure characterization. The exposure characterization required that type of machining fluid used be assigned to each job-department–plant–calendar-year combination after review of plant purchasing and industrial hygiene records and interviews with plant personnel. Estimates of total machining fluid aerosol were based on current measurements of total aerosol collected by the investigators in assembly, machining, and grinding operations in the three study plants and historical air sampling data collected by the company as well as on extensive interviews with plant personnel (*23*). One of the reasons it was possible to conduct such a detailed exposure assessment was that the study was jointly sponsored by the General Motors Corporation and the United Autoworkers Union and therefore investigators had full access to company records, facilities, and knowledgeable personnel.

In summary, studies of complex mixtures may require more refined methods of exposure assessment than studies of single agents. In the diesel studies, a method of monitoring for a component of diesel exhaust not present in cigarette smoke, manufacturing emissions, or wood smoke was developed. In the machining fluids study, a detailed historical reconstruction was used to characterize exposure to different types of machining fluids. Development of better exposure assessment techniques is at the cutting edge of occupational epidemiology.

Table 5. Relationship between duration of exposure to straight-oil and risk of rectal, laryngeal, and prostatic cancer.

Cause of death	Exposure to straight-oil, years	Number of deaths due to cause of death	Rate ratio	95% CI
Rectal cancer	—	16	1.0	
	>0–0.99	5	0.93	0.34–2.56
	1.00–2.49	6	1.20	0.47–3.08
	2.50–7.49	9	1.64	0.72–3.76
	>7.50	21	3.17	1.62–6.24
Laryngeal cancer	—	13	1.0	—
	>0–0.99	6	1.26	0.48–3.32
	1.00–7.49	8	1.02	0.41–2.49
	>7.50	11	2.02	0.86–4.75
Prostatic cancer	—	64	1.0	—
	>0–0.99	16	0.83	0.48–1.43
	1.00–2.49	21	1.27	0.77–2.09
	2.50–7.49	24	1.26	0.78–2.03
	>7.50	40	1.52	1.01–2.29

CI, confidence interval. Adapted from Tolbert et al. (*22*).

In addition to their utility in mixed-exposure situations, sophisticated exposure assessment techniques are needed to determine a quantitative exposure–response relationship for single-agent studies. For example, Greife et al. (*24*) used 2350 air-sampling data points collected at 21 companies, to develop and validate a statistical model to estimate ethylene oxide exposure for a retrospective cohort mortality study in the medical supplies industry. Stewart et al. (unpublished data) developed a complex exposure assessment strategy for a cohort mortality study of workers exposed to acrylonitrile. The study included eight plants that had started production between 1952 and 1965, but seven of the eight started taking air samples only in the late 1970s, and even after that time there were no air sampling data available for most of the jobs. A variety of techniques were used, including a ratio method, which estimated exposure for unmonitored jobs by assuming that the ratios of similar jobs at different plants would be similar, and a homogeneous exposure group method based on combining jobs with similar exposures.

Occupational Groups at High Risk for Cancer

In addition to identification of carcinogenic agents, associations between employment in particular occupations/industries and cancer have been identified by mortality surveillance projects and by case–control interview studies. A large mortality surveillance database has been created by NIOSH, NCI, and the National Center for Health Statistics (NCHS) by funding state health departments to code industry and occupation on death certificates. A total of 28 states are included for 2 years or more from 1979 to 1990, yielding a total of over 5,000,000 records (*25*). This database is available on public use tapes, not only to Federal agencies, but also to non-government researchers. In recent years, NIOSH researchers have utilized this database to examine cancer mortality among women (*25*) and occupational risk factors for breast cancer (*26*), and NCI researchers have used it to examine cancer mortality among farmers (*27*).

In case–control studies, the occupational histories of persons with cancer are compared with the occupational histories of persons without cancer. Usually the information on occupations and exposures is gathered by interview with the patient (or control) or the next of kin. The disadvantages of these types of studies are that

the information on occupational exposures is usually less specific than in cohort studies, and if the cases and controls are derived from the general population, it will be difficult to detect associations with rare exposures or occupations. The advantages of case–control studies are that nonoccupational risk factors such as smoking can be taken into account and entire lifetime occupational histories can be considered. Often the results of case–control studies are used to suggest cohort studies to perform. Much of our knowledge about risks associated with particular occupations is derived from surveillance efforts and case–control interview studies.

Painters have been shown to have increased risks of lung cancer and cancers of the esophagus, stomach, and bladder in many studies, while excesses of leukemia and cancers of the buccal cavity and larynx were observed less consistently (*28*). In 1989, IARC concluded that there is sufficient evidence for the carcinogenicity of occupational exposure as a painters. Thousands of chemical compounds are used in paint products as pigments, extenders, binders, solvents, and additives, some of which are recognized to be potential human carcinogens(*28*). Painters are employed in numerous industries, including heavy machine manufacturing, construction, automobile refinishing, and fine arts (*28*). In some of these applications, worker exposure may be controlled by standards related to specific components of the paint or solvents used (for example, chromium compounds, lead, toluene). Because there is little epidemiologic data to associate the elevated cancer risks in painters to specific exposures, it is not known whether standards put in place in the last 10 to 20 years will protect painters from the elevated cancer risks experienced by earlier cohorts. It is estimated that 500,000 individuals are employed as painters in the United States.

Workers in the dry-cleaning industry are also known to have elevated cancer risks. Unlike many broad occupational associations, the risks of dry cleaning have been documented primarily by cohort studies. Studies have reported elevated rates for urinary tract (*29–31*), bladder (*32,33*), esophageal (*29,33*), pancreatic (*32,34*), colon (*33*), and lymphatic (*29*) cancers among dry-cleaning workers. In most of these studies, it could not be determined to which specific solvent or solvents each worker was exposed. Historically, solvents used in dry cleaning include carbon tetrachloride, petroleum solvents (Stoddard solvent), trichloroethylene, and perchloroethylene (tetrachloroethylene, PCE).

Approximately 500,000 people work in the dry-cleaning industry in the United States. Perchloroethylene is used by over 90% of all dry-cleaning plants (*35*). IARC has concluded that there is sufficient evidence for the carcinogenicity of perchloroethylene in animals (*5*) based on positive bioassay results in two species of animals. Stoddard solvent, a petroleum-based mixture of alkane and aromatic hydrocarbons, is used by about 10% of all dry-cleaning plants. The OSHA PEL for both solvents is 100 ppm as an 8-hr time-weighted average exposure. NIOSH considers perchloroethylene a potential occupational carcinogen and recommends that exposure be reduced to the lowest feasible levels. The NIOSH-recommended exposure level (REL) for Stoddard solvent is 67 ppm.

NIOSH investigators have identified an excess of esophageal cancer among a small cohort (n=625) of dry-cleaning workers exposed only to perchloroethylene (*33*). The SMR for esophageal cancer among workers with >5 years of exposure and >20 years of latency was 7.17 (95% CI = 1.92–19.8). NIOSH and NCI researchers recently have conducted a nationwide search for epidemiologic study cohorts exposed only to perchloroethylene or Stoddard solvent.

To summarize, occupational groups at high risk for cancer are readily identified by surveillance and case–control studies and may in addition be documented by cohort studies, particularly of unions representing occupational groups. It has been difficult to take preventive action because the specific causal agents are not known.

Summary and Recommendations

Although the cancer policies of OSHA and NIOSH do not require adequate epidemiologic evidence to regulate an occupational carcinogen, in the past human studies have been the most potent drivers for regulatory action. Increasingly, NIOSH and OSHA, as well as the U.S. EPA and other regulatory agencies, have emphasized the importance of animal studies in making regulatory decisions. Techniques of risk assessment have developed substantially over the past decade, and OSHA has used risk assessments based on animal data in developing several recent regulatory actions (butadiene, methylene chloride) (*36,37*). Some may question the use of animal studies in identifying potential human carcinogens (*38*), but a recent review article demonstrated that 25 to 30% of agents, substances, or chemicals that have been causally or strongly associated with cancer in humans were first identified as being carcinogenic in experimental animals (*39*). Moreover, it is hoped that increased understanding of the molecular mechanisms of cancer induction will allow the design of even more predictive animal models in the future (*39*).

A related area of research that may reduce the gap between experimental models and identification of cancer risks in human populations is molecular cancer epidemiology. This has been defined to include the estimation of internal dose through biological monitoring of the concentration of chemicals or their metabolites in blood, urine, or other tissue; the estimation of biologically effective dose through measurement of the amount of carcinogen that has interacted with cellular macromolecules including DNA and protein adducts; the detection of early biologic effects such as sister chromatid exchange, DNA hyperploidy, or oncogene activation; and the identification of genetic factors in susceptibility (*40*). Such measures of exposure, susceptibility, and cellular damage may be helpful in correlating carcinogenic effects between species, investigating chemical-specific exposures and effects in mixed-exposure situations, and identifying biological changes in populations whose average or maximum latency is too short for cancer to be manifest. Eventually studies may be designed to demonstrate a direct relationship between specific indicators of cellular damage and increased cancer risk, thus increasing the value of the indicator in detecting potential human carcinogens.

Nonetheless, traditional epidemiologic studies will continue to be important in identifying and confirming occupational cancer risks. Traditional techniques of occupational epidemiology (retrospective cohort study with retrospective exposure assessment) are very effective in dealing with single-agent exposures. Creative epidemiologic and industrial hygiene techniques have been utilized to investigate occupational risks associated with complex mixtures and to determine quantitative estimates of exposure–response. These efforts tend to be very costly because they require large populations and extensive exposure assessment activities. In contrast, although much is known about associations

between particular occupations and cancer risk, there has been less progress in identifying the specific causal agents. New methods are currently being developed to allow the identification of causal agents via case–control interview studies. Identification of the causal agents would facilitate prevention by allowing intervention to be targeted at the exposures of concern. The cancer risks associated with broad occupational categories are important because they affect a large number of people.

In addition to epidemiologic and industrial hygiene research to identify the causal agents responsible for elevated cancer risks in certain occupations or associated with exposure to complex mixtures, there is a great need for information about occupational cancer risks among women and minority workers (*41,42*). Studies of occupational cancer risks among female workers are particularly needed to examine risks of hormonally related cancer. Few studies of breast cancer, the most common incident cancer among U.S. women, have addressed occupational and environmental chemical exposures, and many cancer studies of industrial cohorts have excluded women (*43*). Although there is no reason to believe that minority and nonminority workers might have a differential responses to occupational carcinogens, there is substantial evidence for differential assignment of minority and nonminority persons to higher exposure jobs within the same industry which results ultimately in differential mortality patterns. For example, an observation of higher lung cancer risk among black steelworkers was one of the factors leading to the identification of coke oven emissions as potent human carcinogens (*44*).

In addition to the importance of occupational cancer research to the prevention of cancer associated with occupation, occupational studies are important in the identification of carcinogens that may increase cancer in the general population. Many chemicals for which the cancer risks are best studied in the occupational environment are of concern because of their presence in consumer products or in the environment. Examples include formaldehyde, which is present in wood products, benzene, which is present in gasoline, methylene chloride, which is used in wood stains, paint thinners, and a variety of other consumer products, and a number of pesticides to which the general population may be exposed residentially and through food residue (*7*).

In conclusion, because epidemiologic research measures illness and mortality, situations that have already occurred, a positive study can be interpreted as a failure in prevention. The challenge of the next decade will be to identify potential interventions earlier in the causal pathway (toxicologic testing, biomarkers of exposure or precancerous changes, institution of engineering and good industrial hygiene practices to reduce occupational exposure levels) so that occupational cancers can be prevented.

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