Priorities for Development of Research Methods in Occupational Cancer

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Occupational cancer research methods was identified in 1996 as 1 of 21 priority research areas in the National Occupational Research Agenda (NORA). To implement NORA, teams of experts from various sectors were formed and given the charge to further define research needs and develop strategies to enhance or augment research in each priority area. This article is a product of that process. Focus on occupational cancer research methods is important both because occupational factors play a significant role in a number of cancers, resulting in significant morbidity and mortality, and also because occupational cohorts (because of higher exposure levels) often provide unique opportunities to evaluate health effects of environmental toxicants and understand the carcinogenic process in humans. Despite an explosion of new methods for cancer research in general, these have not been widely applied to occupational cancer research. In this article we identify needs and gaps in occupational cancer research methods in four broad areas: identification of occupational carcinogens, design of epidemiologic studies, risk assessment, and primary and secondary prevention. Progress in occupational cancer will require interdisciplinary research involving epidemiologists, industrial hygienists, toxicologists, and molecular biologists. ***Key words:*** **cancer research, National Occupational Research Agenda, occupational health, research priorities.**
Environ Health Perspect **111:1–12 (2003). [Online 29 November 2002]**
doi:10.1289/ehp.5537 available via *http://dx.doi.org/*

In 1996, the National Institute for Occupational Safety and Health (NIOSH) engaged more than 500 organizations and individuals, representing labor, industry, government, and academia, in a process to identify occupational safety and health research priorities for the United States. This process identified 21 priority research areas that became the National Occupational Research Agenda (NORA) (NIOSH 1996). One of these priority areas is occupational cancer research methods. The term "research method" has been defined to include the range of methods, tools, approaches, and strategies that are used in, or enable, the conduct of occupational cancer research. The primary reason to focus on occupational cancer research methods is that, while there has been an explosion of efforts to develop methods for cancer research, these methods have not been widely applied to resolve important issues in occupational cancer, such as the carcinogenicity of substances classified by the International Agency for Research on Cancer (IARC) in Groups 2A and 2B (probably and possibly carcinogenic to humans), certain mixed-exposure circumstances, and particulates. To implement the agenda, a team of researchers and public health professionals from industry, labor, academia, and government deliberated on how the methods of occupational cancer research can be augmented, strengthened, developed, and applied to the key issues in occupational cancer research today. This article contains the findings of that group, as enhanced by peer reviews.

The goal of this article is to identify those methodologic enhancements that are particularly applicable to occupational cancer research and that would help generate reliable data to support decisions impacting worker health.

Focusing on the methods of occupational cancer research is important for a number of reasons. First, a substantial number of cancer deaths are related to occupational exposure. At least 4% (24,000) of the approximate 600,000 deaths from cancer each year in the United States is thought to be the result of exposures in the workplace (Doll and Peto 1981). Other estimates range as high as 10% (Landrigan and Markowitz 1989; Leigh et al. 1997). If the 4% estimate for deaths is the same for cancer morbidity, an estimated 48,000 new cases of cancer each year have occupational causes. This is an important contribution to the human cancer burden, exceeded only by the contribution of cigarette smoking and diet. The burden of recognized occupationally related cancer falls especially on the minority of workers in blue collar jobs in high-exposure industries—mining, construction, manufacturing, and certain parts of the service sector—so that the 4% or 10% averaged over the full population is multiplied several-fold in these high-exposure groups (Doll and Peto 1981; Landrigan and Markowiz 1989; Leigh et al. 1997). Estimates of the number of cancers related to occupational exposures are based on cancer sites such as lung and bladder, which are recognized as having a substantial occupational component, and do not account for any additional contribution that workplace exposures play in cancers of other sites. These limitations contribute to underestimates of the true impact of occupational cancer.

The second reason to enhance occupational research methods is the need to identify occupational carcinogens before widespread human exposure occurs. Although all known carcinogens that have been studied adequately in experimental animals have produced positive results (Fung et al. 1995), less than 2% of chemicals in commerce have been adequately tested for carcinogenicity. Improved methods are needed to prioritize chemicals for testing, including computational and toxicologic approaches to predicting carcinogenic potential. In particular, experimental approaches must be adapted for evaluation of the carcinogenicity of materials that are mixtures and to exposure circumstances that include mixtures of chemicals.

A third reason it is important to enhance methods for occupational cancer research is that there is ongoing workplace exposure to chemicals and exposure circumstances for

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Mention of company names or products in this article does not constitute endorsement by the National Institute for Occupational Safety and Health or other agencies, institutions, or individual authors.

Received 11 February 2002; accepted 18 June 2002.

which there is some evidence of carcinogenicity. Of particular concern are exposures classified by IARC in Groups 2A and 2B as possibly or probably carcinogenic to humans. In addition, there are numerous occupations for which an elevated risk of cancer has been documented, but for which the causative agent has not been definitively identified, including painters, rubber workers, dry cleaners, printing processes, and welding (IARC 2001). Although occupational exposures to many known human carcinogens (other than tobacco smoke) have been reduced in industrialized countries, Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs) do not exist for all potential human carcinogens, and existing PELs for almost all agents and substances listed as "reasonably anticipated to be human carcinogens" in the *Ninth Report on Carcinogens* [National Toxicology Program (NTP) 2001] are based on acute effects and are higher than would be allowed if regulated based on carcinogenicity. Moreover, historically the single chemical approach has been taken to assess carcinogenicity. New methods and strategies are especially needed to identify carcinogenic agents in workplace environments where simultaneous or sequential exposures to multiple agents exist, as is the case in most workplace environments. Improvements are needed in both toxicologic and epidemiologic methods to detect the effects of low-level carcinogen exposures, exposures to complex mixtures or multiple chemicals, and potential interactions between occupational and nonoccupational risk factors.

An important reason to enhance occupational cancer research is that occupational cohorts often provide the best opportunity to estimate risks associated with lower, but much more widespread, environmental exposure to carcinogens. Evidence from twin studies (Lichtenstein et al. 2000) indicates that environmental factors may be a major contributor to the development of cancer, and the workplace is still a principal location for environmental exposure to potentially carcinogenic substances. Because occupational studies may allow individual exposures to be estimated, data from occupational studies are especially important for quantitative risk assessment. Studies in occupational groups provide a unique opportunity to understand gene–environment interaction and other aspects of the mechanisms by which environmental exposures cause human cancer. Occupational studies may also provide a unique opportunity to investigate the relationship between endocrine disruptors and cancers of the reproductive organs.

Finally, more emphasis is needed on methods for preventing occupationally related cancer, whether it is associated with exposure to carcinogens or attributable to other occupational factors. Design of processes to minimize workplace exposures to potential carcinogens is central to prevention of occupational cancer due to chemicals and particulates. In designing strategies for occupational cancer prevention, attention should also be focused on nonchemical risk factors. For example, white collar and clerical workers have a 1.7-fold excess risk of colon cancer related to their sedentary work, a risk factor that may be amenable to intervention strategies (Hsing et al. 1998). Moreover, complex interactions may occur between occupation and lifestyle factors such as diet, alcohol consumption, and smoking, which contribute to differential cancer risks by occupation. Theoretical examples of positive interactions include *a*) induction of P450 2E1 by ethanol and nicotine, which leads to an increased rate of metabolism of certain chemicals (e.g., vinyl chloride) to DNA-reactive intermediates (e.g., chloroethylene oxide) (Ghissassi et al. 1998; Howard et al. 2001); *b*) inactivation of DNA repair processes or inactivation of the *p53* gene, which will increase the carcinogenic risk for agents (e.g., aflatoxin) modulated by these proteins (Deman and Van Larebeke 2001). Prevention research methods should emphasize the overall reduction of cancer risks through modification of both occupational and nonoccupational risk factors.

More effective prevention of occupational cancers can be accomplished by improving the methods used in occupational cancer research. Needs or gaps in occupational cancer research methods have been identified in four broad areas: identification of occupational carcinogens, design of epidemiologic studies, risk assessment, and primary and secondary prevention.

Identification of Occupational Carcinogens

Animal testing of chemicals for carcinogenic effects. Approximately 80,000 chemicals are available in world commerce (Fisher 1998), and, on average, 2,000 new ones are introduced each year. Testing in laboratory animals is the main tool used for identification of potential human carcinogens. Historically, for many chemicals, initial evidence of cancer in experimental animals has subsequently been confirmed by definitive human studies (Huff 1993; Tomatis 1979). Despite the utility of testing in laboratory animals to identify potential carcinogens and the potential to use positive testing results to minimize or eliminate human exposure, it is estimated that fewer than 2% of chemicals in commerce have been adequately tested for carcinogenicity.

In the United States, chemicals are tested for carcinogenicity by government agencies and private organizations under a variety of circumstances. In some cases, manufacturers of chemicals, acting alone or in cooperation with other companies under the auspices of a trade association or similar group, may conduct carcinogenicity tests. Major manufacturers of some chemicals with high commercial value such as fuel oils (Nessel et al. 1998, 1999), solvents (Green et al. 1997), or pesticides (Yano et al. 2000) have conducted carcinogenicity tests voluntarily. For pesticides, the U.S. Environmental Protection Agency (EPA) may require carcinogenicity testing in order to demonstrate that pesticides do not pose a human cancer risk. The U.S. EPA's Office of Pesticide Programs testing requirements are in the Code of Federal Regulations (CFR) 40, parts 150–189, "Protection of the Environment." When new chemicals are introduced into the U.S. marketplace, the Toxic Substances Control Act (TSCA) requires a manufacturer or distributor to submit a premanufacture notice to the U.S. EPA 90 days before marketing. Under section 5 of TSCA, the U.S. EPA may order additional testing, which may include cancer bioassays, if the agency finds there is not enough information to determine whether the material "poses an unreasonable risk to health or the environment." Section 4(a) of TSCA gives the U.S. EPA the authority to require testing by industry of chemicals already in commerce. TSCA also provides for the Interagency Testing Committee (ITC) to review chemicals in commerce for adequacy of toxicologic data and designates those chemicals that require further testing, including cancer bioassays. In practice, the U.S. EPA uses a tiered testing approach of gene toxicity testing and subchronic testing. The agency reviews these data as well as exposure data before requiring carcinogenicity testing. At the present time, the U.S. EPA has developed voluntary testing programs in which chemical companies submit data on specified toxicologic end points to the agency (U.S. EPA 2002a, 2002b).

When chemical companies carry out cancer tests on chemicals that come under the jurisdiction of TSCA and those tests yield positive results, the results must be submitted to the U.S. EPA. Submission of the data is required under section 8(e) of TSCA. That section also requires submission of positive results in cancer tests of chemicals being evaluated for pesticide effects but not yet registered with the U.S. EPA, as well as new chemicals being prepared for marketing. Health and safety data submitted under TSCA section 8(e) cannot be claimed confidential, and those data are available to the public.

The NTP is the interagency program responsible for chemical testing and development of methodologies for testing. The NTP carries out bioassays of chemicals, and NTP's long-term (usually 2-year) bioassays evaluate carcinogenic potential, as well as examine

other end points of toxicity and possible mechanisms for toxic effects. In general, chemicals are selected for testing when *a*) there is significant human exposure, *b*) evidence suggests potential carcinogenicity, *c*) bioassays can be properly conducted with a relevant exposure route, and *d*) results will be applicable for hazard identification, quantitative risk assessment, or regulatory action. A significant limitation is that while workers are often exposed to mixtures of chemicals, NTP bioassays typically test one chemical at a time. However, initiatives have begun to test relevant mixed exposures in a laboratory setting (Bucher and Lucier 1998).

It is clear that we need to increase and improve carcinogenicity testing of chemicals to which workers are exposed. Improved testing of workplace chemicals will require *a*) better characterization (qualitative and quantitative) of workplace exposures; *b*) efforts to replicate (or simulate) occupational exposure circumstances in experimental studies where appropriate (this recommendation does not relate to dose but rather to route of exposure, physical and chemical form, and common co-exposures); and *c*) development of improved experimental and computational (structure–activity) methods that reduce uncertainty in the identification and characterization of potential human carcinogens in a cost-effective manner.

Exposure characterization. Establishing that a significant number of workers or members of the general population are or may be exposed to a carcinogen is central to a rationale for cancer testing. For the past 20 years, the NIOSH National Occupational Hazard Survey (NOHS) and National Occupational Exposure Survey (NOES) (conducted in 1972–1974 and 1981–1983, respectively) have been driving forces behind the testing of many occupational agents. Those surveys are the only comprehensive assessments of the number of workers potentially exposed to chemical agents in general industry. However, these databases are outdated and of questionable usefulness because they indicate only the potential number of workers exposed to an agent through its production or use. The survey results do not provide information on the extent of exposure associated with industrial processes or other sources (e.g., combustion by-products). Due to these limitations, the existing NIOSH surveys leave critical gaps in estimates of exposed populations today and in the near future (Lucier and Schecter 1998). Recognizing this, NIOSH plans to update the NOES with hazard surveillance in high-risk industries and occupations (Boiano and Hull 2001).

To adequately estimate the number of workers potentially exposed to specific chemicals or mixtures, methods are needed to combine available information about chemical production and potential release into the workplace environment with data on employment, job categorization, and manufacturing processes. Research is also needed to characterize occupational exposures to aid in the design of occupationally relevant exposure studies. A good example of such research is the recently established collaboration between NIOSH and the National Institute of Environmental Health Sciences to assess the inhalation toxicity of cellulose fibers. NIOSH is characterizing human exposures in the workplace by determining dose, dimension, and type of cellulose fibers. This information will serve as a basis for the NTP's experimental testing procedures.

Experimental exposures. It would be helpful for experimental studies to be conducted in a manner that reflects occupational exposure circumstances. Several issues need to be addressed in designing experimental exposures. Extrapolation to humans is facilitated when animal studies are conducted using the same routes as occur for human exposures. Complex mixtures such as welding or asphalt fumes, metal-working fluids, diesel particulate matter, and synthetic fibers are not readily characterized for the purpose of producing standardized test materials that are needed for bioassays. A worker's cancer risk may be affected by whether he or she is exposed to a single agent or has multiple (mixed) exposures. In one scenario, simultaneous exposure to a complex mixture of potential cancer-causing or modifying agents might arise from a single source, such as the combustion of organic material. Another exposure scenario may involve simultaneous or sequential exposure to two or more cancer-causing or modifying agents from separate sources. Exposure to single versus multiple agents may result in tumor induction at the same target organ and/or different ones. These scenarios reflect the need to consider potential interactive effects and to ascertain if the risk from exposure to multiple agents differs from what would be expected on an additive basis of the individual components. It is critically important to evaluate the impact of each constituent of a mixture on the other constituents' roles in the process of carcinogenesis. For example, one agent may induce or inhibit enzyme activities that affect the tissue concentration of the active intermediate of a second agent, or the first agent may inhibit critical repair processes (e.g., DNA repair), resulting in increased potency of other carcinogenic agents in the mixture. Conceivably, chemical interactions that are not evident at occupational exposure levels may result at exposure levels used in some animal bioassays.

If workers are exposed to a mixture, carcinogenicity studies of the mixture itself may be an efficient first step, particularly where it is uncertain which, if any, components might be carcinogenic. Testing individual components can be critical in identifying the primary carcinogenic agent or agents in the mixture, assuming that human exposure to the mixture cannot be eliminated. However, testing complex mixtures presents formidable scientific problems. When a mixture is tested, it is important that the composition of the mixture be similar to what occurs in the workplace, but this may not be easy to achieve because products of individual processes (i.e., combustion of organic materials) may vary depending on reaction parameters such as temperature, as to both identity and relative quantities of mixture constituents. An example of properly characterizing occupational exposures and reproducing these exposures under experimental conditions is an ongoing study of asphalt fume. NIOSH, in conjunction with the Asphalt Institute, is developing and testing an asphalt-fume–generating system that simulates road paving conditions to assess the toxicity and carcinogenic potential of the asphalt fume in animal inhalation studies. Comparable methodologies are needed for such mixtures as welding fumes, metalworking fluids, fibers and dusts, and combustion products. All of these complex exposures pose different problems that will require unique solutions.

Strategies must also be developed to predict potential adverse effects of mixtures (Haddad et al. 1999). This includes strategies for identifying which mixtures merit most consideration for testing and how testing should be accomplished. The value of such a strategy depends on its ability to use data from tests of one mixture to predict effects of exposure to a new but similar mixture. An alternative approach could involve the development of mechanism-based dose–response models through an iterative process of designing experiments, confirming that model.

Experimental methods and models. The chronic exposure rodent bioassay, as conducted by the NTP, is the international standard for identifying chemical carcinogens (Fisher 1998). To date, no human carcinogens have produced negative findings in this bioassay (IARC 1999a). However, in many cases, data from epidemiologic studies are not sufficient to provide direct confirmation of carcinogenicity in humans of chemicals shown to cause cancer in animals. In the absence of sufficient human data, the NTP Report on Carcinogens (NTP 2001) describes such agents as "reasonably anticipated" to cause cancer in humans, while the IARC Monograph program (IARC 1999a) describes such agents as "probably" or "possibly" carcinogenic in humans, depending on supporting data.

Data gaps in our knowledge of chemical carcinogenicity create uncertainties in quantitative extrapolations of animal findings to human risk at occupational exposure concentrations. Additional data and better risk assessment models are needed that accurately

account for interspecies, intraspecies, and interindividual differences in sensitivity, as well as differences in exposure circumstances. Quantitative information on the effects of carcinogen exposure at the cellular and molecular levels will be critical to developing biologically based dose–response models that could strengthen the scientific basis for extrapolation of animal findings to humans.

Genetically altered mice are being evaluated as possible replacements for, or adjuncts to, conventional rodents for bioassays of chemical carcinogenesis (Donehower et al. 1992; Leder et al. 1990; Yamamoto et al. 1996). Interest is high in using transgenic mice to identify cancer-causing agents because bioassays in transgenic mice may be performed more rapidly and with less expense than the conventional 2-year rodent study (Eastin 1998). Some researchers speculate that these models show preferential responses to trans-species carcinogens and are better suited to identifying human carcinogens because they already possess altered genes known to be involved in human cancers (Tennant 1998). There is also a concern about interpretation of negative results in animals that are observed for only a fraction of their potential life span. The transgenic carcinogenesis testing systems must be validated against known and probable human carcinogens if they are to provide data useful for risk assessment. These models must be shown to be responsive to agents that are likely to be weak carcinogens in humans. Also, methods are needed for estimating human risk from carcinogenicity data obtained in transgenic mice.

In the past decade, interest has grown in developing computer programs that use structure–activity relationships to identify potential carcinogens. These systems rely on two general approaches (Richard 1998). The first approach, which examines statistical correlations between structure and activity, is used by the computer programs TOPKAT (Accelrys, Burlington, MA) and CASE/MULTICASE (Multicase Inc., Beachwood, OH). The second approach, which is knowledge-based and relies on expert judgment for developing program rules, is used by DEREK (Lhasa Limited, Leeds, UK), OncoLogic (Logichem, Inc., Boyertown, PA), and METEOR (Lhasa Limited). Although these methods show considerable promise, predictions must be demonstrated to approach the reliability of animal testing if the methods are to be used to reach conclusions about the carcinogenicity of chemicals. A model approach is the NTP challenge to predict the results of 2-year rodent-cancer studies in progress (Bristol et al. 1996, 1997; Wachsman et al. 1993). Such efforts should be expanded, and modeling methods should be more unified in their approach. Chemicals shown to be potentially carcinogenic based on structure–activity relationships, shown to be positive in short-term tests, or predicted to be negative based on computer models should be tested in long-term animal studies to validate these approaches and to obtain dose–response data.

An important enhancement to current efforts to identify potential carcinogens is to develop a data resource that provides users with information on chemical structure–activity relationships and toxicologic testing results (Richard 1998). Often, toxicologic test results are not published in the peer-reviewed literature and are not accessible to those building and evaluating predictive models. The possibility of establishing such a data resource should be explored, with attention to methodologic issues such as minimal technical requirements for studies to be included and confidentiality concerns related to proprietary research.

Epidemiologic Study Methods

Over the years, epidemiology has played the leading role in associating exposures to chemicals with development of cancer in humans. Historically, clinicians were the first group to recognize occupational cancers. Early reports identified elevated scrotal cancer in chimney sweeps (Pott 1775), lung cancer in uranium miners (Harting and Hesse 1879), and urinary bladder cancers in dye industry workers (Rehn 1895). In the early to mid-1900s, methods evolved for conducting epidemiologic cohort studies (Samet and Munoz 1998), and were applied to the analysis of mortality in occupational cohorts. Early occupational cohort studies documented the association of exposure to β-naphthylamine and benzidine with bladder cancer (Case et al. 1954), arsenic with lung and skin cancer (Hill and Faning 1954), and asbestos with lung cancer and mesothelioma of the chest or peritoneum (Doll 1955).

In parallel with the development of methods to elucidate the relationships between chemical exposures and cancer in humans, the foundation for study of chemical carcinogenesis in animals was established in the early twentieth century (Cook et al. 1932; Kennaway 1934; Yamagiwa and Ichikawa 1915). In 1968, a formal animal bioassay program was established at the National Cancer Institute, and by 1978, 356 chemicals had been entered into testing (Epstein 1979). The development of experimental models for carcinogenesis and the passage of the Occupational Safety and Health Act in 1970 stimulated tremendous activity in occupational cancer epidemiology in the 1970s and 1980s. While case reports and reports of workplace "cancer clusters" continued to provide impetus for epidemiologic studies, positive findings in animal bioassays stimulated increasingly systematic efforts to identify occupational cohorts for study. Occupational cohorts often provided the best opportunity to evaluate the risk of cancer from chemicals that have been found to be animal carcinogens because personnel records allowed identification of persons who had been employed decades earlier, and occupational exposures were often orders of magnitude higher than those experienced elsewhere.

Occupational cohort studies initiated in the 1970s and 1980s were invaluable in documenting the effects in humans of exposure to asbestos, benzene, beryllium, bis-chloromethyl ether, vinyl chloride, and other widely used chemicals and environmental contaminants (IARC 1987). More recently, population-based case–control studies began to focus on occupational factors (Siemiatycki et al. 1987). These studies have provided data on potential interactions between occupational and nonoccupational exposures and allowed estimation of the proportion of lung, bladder, and other cancers that can be related to occupational factors (Doll and Peto 1981; Silverman et al. 1989a, 1989b; Simonato et al. 1988).

By the late 1990s, a widespread perception existed that the scientific and public health importance of investigations of workplace-related cancer had diminished. This perspective likely stemmed in part from the belief that most major occupational carcinogens have already been identified. However, the absence of epidemiologic data for many animal carcinogens (including some common workplace exposures) suggests that this conclusion may be premature (Blair et al. 1999). Epidemiologic studies remain critically important in the prevention of occupational cancer, and studies in occupationally exposed groups have significant potential to contribute to the understanding of risks from carcinogenic chemicals for the general population. The development of better tools for conducting epidemiologic studies is needed to identify exposed populations for study, measure exposure–response relationships, and identify, validate, and utilize measurable intermediate outcomes (early disease biomarkers) rather than cancer incidence or death from cancer.

The strengths and limitations of occupational cancer epidemiology were highlighted by Karstadt (1998), who reviewed IARC evaluations of carcinogens, as presented in the IARC Monographs. As of 1999, occupational studies had led to IARC's classification of 38 chemicals with industrial uses as Group 1 (known human carcinogens). In addition, many other industrial chemicals are in IARC Groups 2A and 2B, "probably" or "possibly" carcinogenic to humans, respectively, which usually indicates they have "sufficient" evidence for carcinogenicity in animals, but less than sufficient evidence from human studies.

Many of the industrial agents classified in Groups 2A and 2B have been the subject of

unsuccessful searches for cohorts amenable to epidemiologic study, with lack of success attributable to inadequate cohort size, latency, or exposure information. Many industries use structurally related chemicals, and a great deal of substitution of chemicals has occurred over time. For example, in the dye manufacturing industry, it has been difficult to identify a cohort exposed to an aromatic amine such as *o*-toluidine but not exposed historically to known bladder carcinogens such as β-naphthylamine or more recently to benzidine-based dyes. Assembling cohorts for studies of chemicals, such as dry cleaning solvents, that are used in small businesses has also been difficult. Several occupational groups, including painters, hairdressers, and dry cleaners, are known to have increased risks of cancer, but the link between cancer and specific chemicals for these groups has not been definitely established.

Exposure assessment. Exposure assessment plays a central role in occupational cancer epidemiology. An exposure–response relationship within a cohort is powerful evidence that an agent is carcinogenic. Exposure assessment presents a major challenge because the exposure period of interest is usually 10–50 years before the onset of cancer. In many industries, quantitative exposure data are available only for recent decades. Retrospective exposure assessment requires precise knowledge about how production processes and exposure controls changed over time. Detailed exposure assessment may not be feasible for many studies, either because of insufficient historic exposure data or because work histories and job titles are not sufficiently detailed. For these reasons, many epidemiologic studies of occupational cancer have been able to analyze outcomes only by duration of employment or by assignment to specific jobs or departments, which are qualitative surrogates for exposure data (Stewart and Herrick 1991). Even when quantitative exposure–response data are generated, variability of exposure among workers in an exposure group, and among exposures for an individual worker day-to-day, present obstacles to observing exposure–response relationships.

Development of methods for reconstructing retrospective (historical) exposures in cohort and case–control studies was a focus of research in the 1990s. Progress was made in that area, as exemplified by a number of cohort studies for which historical exposure estimates have been successfully developed and used in exposure–response analyses, including studies of dioxin (Piacitelli et al. 2000; Steenland et al. 1999), acrylonitrile (Blair et al. 1998; Stewart et al. 1998), formaldehyde (Blair et al. 1990; Gardner et al. 1993), diatomaceous earth (Checkoway et al. 1997), benzene (Hayes et al. 1997; Rinsky et al. 1987), vinyl chloride (Simonato et al. 1991), and 1,3-butadiene (Macaluso et al. 1996). High-quality historical exposure reconstruction is technically demanding and time-consuming. Investigators at NCI and NIOSH are attempting to develop standardized methods for retrospective exposure assessment in cohort studies, but to what degree those methods will be suited to the wide variety of exposures and exposure circumstances across the industrial spectrum is still unclear (Stewart et al. 1999).

Retrospective exposure assessment in population-based case–control studies is difficult because often the only data available are job title, type of industry, and dates of employment, as reported by a study subject or the survivor of a deceased subject. However, data collection methods in case–control studies have improved in the past 20 years to allow collection of more exposure information (Gerin et al. 1985; Stewart et al. 1996). Newer assessment methods enable researchers to estimate exposures to individual chemicals or groups of chemicals over a working lifetime or during specific periods of employment. These approaches involve a combination of asking detailed questions tailored to specific jobs (job-specific modules) and applying expert knowledge to develop exposure estimates.

In the future, epidemiologic studies (whether cohort or case–control) are likely to rely on data generated from exposure estimation models whenever actual measurements of exposure are unavailable, unreliable, or otherwise limited in utility. The models will incorporate factors called "determinants of exposure," which should increase the accuracy and reliability of exposure estimates. Research is needed to identify which determinants of exposure are important under which circumstances, and to use empirical data to validate exposure estimates based on models. Because the exposure estimates in case–control studies are largely based on questionnaire responses, additional research is needed on the validity and reliability of questionnaires used in the collection of occupational history information.

Exposure assessment is particularly difficult for substances that may be absorbed through the skin. Although air concentrations of chemicals are routinely measured, quantitative information from which to determine dermal exposure potential is either limited or nonexistent for most chemicals and workplaces. Even when data on surface contamination levels are available, those data are difficult to correlate directly with human exposure. Methods for detecting dermal contact with chemicals, such as patch samples attached to work clothing and hand wash samples, are often of limited utility because they are difficult to relate to absorbed dose and may interfere with estimation of exposure through all routes by biological monitoring. Moreover, few data are available on the potential for absorption through intact or broken skin of a large number of chemicals used in industry. Strategies are needed to identify which potential occupational carcinogens can be absorbed through the skin, especially those for which skin absorption may represent a major exposure route. Methodologic needs include structure–activity models, well-validated *in vitro* and *in vivo* test systems to predict skin penetration in humans, and methods to measure the extent of dermal absorption of chemicals in the work environment (Boeniger and Lushniak, 2000).

The need is especially pressing for better methods to quantify the total dose received by workers through all routes of exposure to workplace chemicals. Development of biological markers of exposure, as well as an understanding of metabolism of occupational chemicals in humans, will be critical to improving dose estimation for chemicals with significant dermal absorption potential.

Scientists had hoped that biological markers of exposure would contribute to historic exposure reconstruction over a working lifetime, but to date their utility in this regard has been limited. Most biological markers do not reflect exposures acquired over long periods of time. Many chemicals have relatively short half-lives in humans, and even those that bind to hemoglobin or DNA in various tissues are present only for the life span of the target cell. A fruitful approach has been to use specimen banks holding historic blood specimens to provide data for retrospective exposure analysis for substances with longer half-lives, such as organochlorines (Hoyer et al. 2000; Ward et al. 2000; Wolff et al. 2000) as well as non-Hodgkin lymphoma (Rothman et al. 1997).

Epidemiologic study designs. Retrospective cohort studies have played an important role in identifying occupational carcinogens, but identifying suitable populations for such studies is often not possible. Even for widely used chemicals, identifying study populations with adequate sample size, good work-history records, and a minimum of confounding exposures may be difficult. The problem of limited population size may in some cases be overcome by conducting multinational studies with data collection standardized across countries and combined into one large cohort for analysis. The Environmental Epidemiology Unit at IARC has coordinated a number of these types of studies; recent examples include studies of workers exposed to phenoxy herbicides, chlorophenols, and dioxins (Kogevinas et al. 1997), styrene (Kogevinas et al. 1994), and and vinyl chloride (Ward et al. 2001). Better methods must be developed for identifying occupational groups suitable for cohort studies using existing databases compiled for other purposes, and accessing and utilizing information from labor and industry organizations.

When suitable retrospective cohorts cannot be identified, alternatives should be considered, including prospective cohort studies, case–control studies, and studies using intermediate markers as end points. Prospective cohort studies are particularly useful for studying exposures that are difficult to ascertain from records or from recall. This design allows for periodic collection of both exposure and health outcome data and potential banking of biologic specimens. Nested case–control studies may be conducted within prospective cohort studies and may be particularly efficient in studies where costly analyses of biological specimens are needed. This design is amenable to studying the relationship between genetic factors, exogenous exposures, and cancer outcome.

Prospective cohort studies are expensive and time consuming, but they may be cost effective, especially as multiple outcomes can be evaluated. Few examples exist of prospective cohort studies established primarily for evaluating effects of occupational exposures on cancer occurrence. One such investigation is the Agricultural Health Study, which is a cohort of more than 90,000 North Carolina and Iowa pesticide applicators and their spouses (Alavanja et al. 1996). This study focuses on a narrowly defined occupational group [commercial and private pesticide applicators (farmers) and farmers' spouses] and provides considerable statistical power to examine the association between development of cancer and exposure to numerous agricultural chemicals. Additionally, buccal cavity cells are being collected for use in studying genetic factors.

General population case–control studies of associations between cancer and occupation can be advantageous in terms of cost, feasibility, and time needed to carry out the investigation. Case–control studies can be incidence based, typically feature more accurate cancer diagnoses than cohort mortality studies, include small as well as large workplaces, and provide opportunities to assess a broad spectrum of risk factors and how they interact with each other (Blair et al. 1999). Case–control studies also provide better opportunities to collect biological samples because, unlike most retrospective cohort studies, many involve direct contact with study subjects. These specimens are particularly useful in assessing genetic polymorphisms because constitutive DNA will not be affected by disease status.

The principal limitation in case–control studies has been the reliance on data from questionnaires to assess occupational exposures. Methodologic research is needed to improve exposure estimation in case–control studies. Also, better methods must be developed for rapid case ascertainment for studies of cancers with poor survival because proxy interview information may be especially poor for workplace exposure information. Methods also are needed for evaluating the potential for and correcting response bias in case–control studies and for assessing disease and treatment effects on biologic measures of exposure.

Case–control studies to evaluate relationships between cancer occurrence and occupational exposures must be large enough to have adequate statistical power to detect associations for less common occupations and exposures. Consequently, multicenter studies are often necessary to obtain a large enough sample in a reasonable time frame. International studies have made important contributions by allowing sufficient statistical power to examine less common histologic types (Fortuny et al. 1999) and exposure–response relationships in great detail (Agudo et al. 2000). One way to increase the efficiency of case–control studies of cancer is to study multiple sites under a similar protocol and use a common control group.

Cross-sectional studies and early biologic effect (intermediate effect) biomarkers. Cross-sectional studies of intermediate end points in healthy worker populations exposed to known or suspected carcinogens have been carried out for many decades. The goals of such studies are to provide mechanistic insight into the early biologic effects of a given exposure and at the same time, either implicitly or explicitly, to evaluate the potential future risk to study subjects, at least at the group level. Given that cancer incidence and mortality data have limited utility for cancer prevention because they are discernable only after workers have been exposed, disease has developed, and people have died, cross-sectional studies of intermediate end points in healthy workers can play an important role in the timely evaluation of carcinogenic risk. IARC has given credence to the results of such studies in its more recent evaluations of several suspect occupational carcinogens. For example, human genotoxicity data were used by IARC to upgrade ethylene oxide to a known human carcinogen (IARC 1994).

A wide variety of intermediate end points have been studied in occupational studies of workers exposed to a long list of chemical agents. These include biological markers of DNA damage (e.g., DNA adducts in peripheral white blood cells or other accessible targets such as exfoliated urothelial cells (Groopman and Kenslar 1999; Wild and Pisani 1998) and chromosomal damage (e.g., chromosomal aberrations in cultured peripheral lymphocytes (Tucker et al. 1997). Intermediate markers may reflect biologic changes further downstream from exposure that result in altered structure or function, such as elevated p53 in blood of vinyl chloride workers (Trivers et al. 1995). Although much of this work has focused on biomarkers that reflect genotoxic effects, increasingly studies are evaluating potential carcinogens that may exert their action through more subtle mechanisms, such as alteration of immune function or the hormonal milieu. At the same time, new biotechnology approaches that can be applied to accessible tissue of healthy workers exposed to agents of concern hold the promise of providing more extensive insight into cytogenetic and somatic mutation patterns, changes in mRNA expression, and alterations in the type and levels of proteins. Applying these new methods, both in experimental systems and where appropriate in exposed worker populations, to the study of potential occupational carcinogens should be a high priority.

Although cross-sectional studies can be useful in providing mechanistic insight into the early biologic effects of particular compounds in exposed workers, their direct application to the risk assessment process is far more challenging. For an intermediate end point to play a role in the later process, particularly at the semiquantitative or quantitative level, evidence must be provided that the biologic marker reflects processes that are on the causal pathway or that are good surrogates for events occurring on the causal pathway from the exposure to disease.

Both prospective animal studies and human studies can be used in this process. Priority should be given to methods for incorporating intermediate markers into long-term bioassays because these studies involve prospective followup of relatively large numbers of laboratory animals. At the same time, opportunities should be sought to evaluate the quantitative relationship between intermediate markers and subsequent cancer risk in humans through calculation of the etiologic fraction of the disease attributable to particular levels of the biomarker (Schatzkin et al. 1990; Schulte and Rothman 1998).

Validation of biomarkers in humans often requires following large populations for long periods. For some biomarkers, the temporal criterion can be satisfied by analyzing banked biological specimens in cohorts whose cancer incidence can be ascertained through linkage to outcome registries or other procedures (however, this cannot be done for some important markers that must be analyzed in fresh tissue). Although the issue of validation of intermediate effect biomarkers is not unique to occupational groups, worker populations under medical surveillance (because of their high risk of certain cancers) may offer opportunities to evaluate the predictive ability of intermediate biomarkers. Unfortunately, there has been little work on evaluating the relationship between intermediate biomarkers and cancer risk in occupational groups or in the general population. One exception is a series of general population cohort studies that provided evidence that chromosomal aberrations in peripheral lymphocytes are associated with increased risk of subsequently

developing cancer (Bonassi et al. 2000; Hagmar et al. 1998; Liou et al. 1999).

A recent study combined data from two of these cohorts and showed that the relationship between chromosomal aberration frequency and cancer risk did not differ by smoking status or in regard to exposure to various occupational carcinogens (Bonassi et al. 2000). This finding suggests that chromosomal aberration frequency integrates a variety of genotoxic exposures as well as genetic susceptibility and might be a general marker of cancer risk. These original findings need to be confirmed and extended (the number of cases was too small to estimate cancer site-specific risks with precision). In addition, this type of research needs to be supported to develop a wider range of valid intermediate biomarkers that can be used in cross-sectional studies of workers exposed to various types of suspected carcinogens. Also, further work is needed to identify and evaluate intermediate biomarkers that may be specific for particular exposures and for specific cancer sites and to prioritize biomarkers for developmental and validation studies.

Host factors and gene–environment interactions. In 1775, Sir Percival Pott described a high frequency of scrotal cancer among chimney sweeps exposed to coal tar, establishing one of the first links between occupational exposure and cancer. Less well known is the hypothesis put forward several decades later that because not all chimney sweeps exposed to soot developed this cancer, constitutional factors might also play a role in the etiology of this condition (Waldron 1983). As the genetic basis for biological responses to environmental and occupational exposures is becoming increasingly understood, it is clear that interindividual variation in susceptibility and the genetic repair process may play roles in the development of occupational as well as nonoccupational cancers (Ishibe and Kelsey 1997; Nakajima and Aoyama 2000).

Advances in genetic research are being propelled ever more rapidly through the use of new tools derived from the Human Genome Project. For example, a completed first draft of a working transcript of the human genetic code was recently announced (U.S. Department of Energy 2001). The Human Genome Project will ultimately provide a working transcript of the human genetic code. A large part of the subsequent effort will be to define human disease susceptibility in terms of DNA sequence variation. Armed with the tools furnished by the genome project, epidemiologic studies will be able to more efficiently investigate genetic susceptibility to disease. The analytical tools to evaluate genetic parameters are available. Robotics and test design [TaqMan (Applied Biosystems, Foster City, CA), Gene-Chip (Affymetrix, Inc., Santa Clara, CA), and automated DNA sequence determination] have made it possible to carry out rapid analysis of large numbers of samples using "high sample through-put" testing schemes.

There are several reasons that incorporating the study of common genetic polymorphisms into epidemiologic studies should enhance our understanding of the relationship between occupational exposure and cancer. First, application of genetic risk factors into studies of cancer (or validated intermediate end points) caused by known occupational carcinogens can provide a powerful approach to understanding the basic biological mechanisms of disease and may lead to better techniques for cancer prevention. Second, evaluation of the relative risk for suspect exposures within subgroups defined by biologically important genetic variants may clearly identify carcinogens that have small, equivocal risks in the overall worker population and may lead to more meaningful risk assessment and implementation of policies and standards that protect the most vulnerable members of the workforce. Third, the demonstration that polymorphisms in genes that carry out exposure-specific metabolic functions interact with complex mixtures to cause cancer may help clarify which components of such mixtures are the key carcinogens. Finally, by identifying genetic polymorphisms associated with a given cancer, one may generate insights into the potential carcinogens acted upon by these gene products (Rothman et al. 2001).

For the same reasons that studies in occupational groups were useful for identifying human carcinogens, occupational groups with established or potential cancer risks may provide ideal populations in which to investigate the effects of genetic susceptibility to environmental carcinogens. However, conducting workplace-based studies related to genetic susceptibility to occupational carcinogens requires consideration of ethical, legal, and social issues. Legitimate concerns have been raised on the part of workers and their advocates about the potential ramifications of genetic susceptibility research for employment discrimination, workers' compensation, and insurability (Samuels 1998). Complex questions arise concerning the ability of researchers to safeguard the confidentiality of genetic data. These are serious concerns that must be addressed in each study. At the same time, it is unlikely that genetic information concerning workplace cancer risk will ever be sufficiently informative to be relevant to the individual for use in genetic testing per se. This is because, based on studies carried out to date and on theoretical grounds, such common polymorphisms pose small to modest relative risks and are likely to have very low absolute risks (i.e., penetrance) (Rothman et al. 2001). Rather, the incorporation of genetic susceptibility markers into epidemiologic studies will have its most significant impact in the development of better laboratory model systems, toxicogenomics and proteomics, improved risk assessment, intervention and prevention, and ultimately ensuring that the workplace is safe for all workers.

Methods to evaluate occupational cancer among women and minorities. In 1997, approximately 60 million women and 10 million nonwhite men were employed outside the home in the United States, accounting for 46% and 7%, respectively, of the employed civilian workforce (Bureau of Labor Statistics 2001). Most epidemiologic research on occupational cancer, however, has focused on white men (Zahm et al. 1994). Although we assume risks identified in white men also pertain to women and minorities, studying women and minorities specifically is important for several reasons. The frequent occurrence of mammary and reproductive tumors in rodent bioassays (Dunnick et al. 1995; Griesemer and Eustis 1994) indicates these sites may be particularly susceptible to occupational carcinogens. Women and minorities may respond differently to occupational exposures than white men because of anatomic, metabolic, genetic, or other differences. They may also experience hazardous occupational exposures in recently developed industries, such as electronics, that have not yet been fully evaluated for cancer risks among white men. Women and minorities may have workplace exposures different from those of white men. Most exposure measurement data have been generated from studies of men, and few studies have estimated variability in exposure measurements based on sex, race, ethnicity, or related variables. The same external exposure may result in different internal dose because of sex-specific absorption, distribution, kinetic, and metabolic rates (Greenberg and Dement 1994) or may vary between racial and ethnic groups because of differences in the frequency of metabolic polymorphisms. Studying exposure variability by sex, ethnicity, and race may help to design intervention and prevention strategies and to more accurately estimate exposure for epidemiologic studies.

Epidemiologic research on occupational cancer among women and minorities has been hampered by methodologic problems. The most important obstacle is that, in general, only a small number of women and minorities are employed in jobs of interest in any given study. Although many industrial cohorts assembled for study of potential occupational carcinogens in the past have included few women because of historic employment patterns, some hazardous occupations now have large female workforces.

Every effort should be made to fully use the data on women and minorities in all

study populations, including existing studies that have substantial numbers of women and minorities but do not have sex- and race-specific analyses. To overcome methodologic problems associated with small numbers of women and minorities in specific job categories or industries, studies of occupational cancer among women and minorities should focus on exposures to individual chemicals or mixtures of chemicals across job categories and industries. Whether sex, race, and ethnicity should be taken into account in exposure assessment must be evaluated. If so, appropriate methodologies should be developed.

Setting priorities for epidemiologic studies in worker populations. One approach to setting priorities for cancer studies in occupational cohorts has been to target exposures classified by IARC in Groups 2A and 2B for which there is widespread human exposure. Recent changes in criteria for evaluation of animal bioassay data by IARC and other agencies suggest an additional priority area for epidemiologic research. The IARC Monograph program, the NTP, and the U.S. EPA have developed criteria by which tumors arising in certain organs or through certain hypothesized mechanisms in animals are judged not to be relevant to humans. Use of these criteria by IARC, for example, has resulted in chemicals for which there is "sufficient evidence for carcinogenicity in animals" being classified in Group 3, "not classifiable as to carcinogenicity in humans" (Karstadt and Haseman 1997). For some of these chemicals, including diethylhexyl phthalate (IARC 2000) and atrazine (IARC 1999b), direct information on the biological activity in humans has been limited. Methods should be developed to examine relevant intermediate end points in humans to verify or refute assumptions about mechanism, as well as to evaluate cancer risks in exposed populations.

Methods for studying the association between parental occupation and childhood cancer in offspring. Since the early 1980s, several reports have been published on the relationship between parental occupational exposures and the risk of childhood cancer in offspring (Colt and Blair 1998; Kristensen et al. 1996; Savitz and Chen 1990). These studies, which have been mostly case–control in design and focused on paternal occupation, have reported associations between a variety of occupations and exposures and diverse cancers. Relatively consistent associations have been noted for motor vehicle-related occupations, painters, metal workers, solvent workers, and pesticides applicators and the risk of childhood cancers such as leukemia and central nervous system tumors (Colt and Blair 1998; Daniels et al. 1997; Savitz and Chen 1990; Zahm and Ward 1998). However, current epidemiologic evidence is insufficient to determine the causal relationship, if any, between parental occupation and risk of cancer in offspring. The major limitation has been the ascertainment and evaluation of occupational exposures. Recent case–control studies have been able to evaluate more etiologically homogeneous subgroups due to larger study sizes and use of biologic and molecular markers (Robison et al. 1995). The use of job-specific modules for the collection of work histories and other advances discussed earlier are being used to improve the quality of exposure assessment in case–control studies of childhood cancer as well. In addition to incorporating more refined methods to estimate occupational exposures, future studies should use sensitive techniques to detect the effects of occupational chemical exposures on the placenta, fetus, and germ cells; for example, assays of DNA damage by fluorescence *in situ* hybridization. Advancement in this area will require multidisciplinary research by epidemiologists, industrial hygienists, toxicologists, and molecular biologists.

Surveillance. Improved methods could enhance the ability of surveillance programs to detect occupationally related cancer. Cancer surveillance systems have been developed by a few large companies. A useful resource for occupational cancer surveillance is the National Occupational Mortality Surveillance System (NOMS), which has coded occupation and industry on death certificates in 27 states over a 10-year period. These data have been used to explore occupational associations with health outcomes (Burnett and Dosemeci 1994; Loomis and Savitz 1991; Cocco et al. 1999a, 1999b; Krstev et al. 1998) and to investigate etiologic associations (Loomis et al. 1994). Methods should be explored to conduct occupational cancer surveillance through cancer registries because it has several advantages. These include the ability to detect associations with less fatal cancers and to examine associations with histological subtypes. Methods should be developed for hospitals to collect and code occupational data in a standardized way to facilitate data collection by cancer registries. In addition, cancer surveillance by specific companies could be enhanced by methods to use information routinely collected for insurance purposes, with appropriate attention to privacy and confidentiality.

Improvements in Risk Assessment

Risk assessment is a process that uses available scientific information on the properties of an agent and that agent's effect on biological processes to evaluate the potential for harm as a consequence of exposure to that agent. Occupational cancer risk assessment might be considered a more specific application of the process, focusing on whether a particular workplace exposure would result in cancer.

Risk assessments in general are organized into four components: hazard identification, exposure–response assessment, exposure assessment, and risk characterization. The first three components answer the questions of whether an occupational insult may cause cancer, at what exposure level this may occur, and what occupational exposure level exists in the population. Risk characterization integrates the exposure response and current exposure in a population to produce a numeric estimate of the risk. There are specific components of the process that might be particularly important for occupational cancer risk assessment.

Better integration of animal and human studies. Too often, animal and human research are not formally or effectively linked to address unknown factors in occupational cancer. Ideally, animal and human studies should be better coordinated using results of each to inform the other. At present, the most important need, paradoxically, is to explore in laboratory studies the markers and mechanisms of agents for which the carcinogenicity in humans is well established. The relationships between laboratory indices and human effects will establish the paradigm for future hazards identified in laboratory studies. The ability to identify similar biological pathways, or modes of action, in different species will be critical to this process. For example, markers of intermediate cancer-related end points, metabolism, or noncancer related toxicity can be examined interactively in animal and in human studies, then confirmed in large-scale human studies. Approaches should also be developed to foster collaboration between scientists who study cancer in humans and scientists who carry out cancer studies in animals. When exposure–response data are available from human studies, they should be used in the risk assessment process (Samet et al. 1998).

Incorporating mechanistic information in cancer risk assessments. Risk assessment models that link advances in knowledge of the cancer process from both experimental and epidemiologic studies into an overall assessment should be further developed and validated. Currently, little modeling of animal bioassay data, and even less modeling of human data, incorporate these advances. Furthermore, human and animal studies are modeled separately; both types of models are relatively simplistic, and in general are not even consistent with each other. Federal regulatory agencies typically fit animal cancer bioassays with risk assessment models in which the chemical's risk is additive to background and not a function of age, whereas human studies are most often fit with relative-risk models, in which the relative risk due to chemical exposure is usually a function of age and other covariates. Better integration of animal and human cancer incidence and mechanism studies is needed, as well as better

biologically based models that incorporate this information. These models might be viewed to some extent as extensions of the original Armitage and Doll (1954) multistage model for cancer (inherently a relative-risk model), and should incorporate information, such as target tissue dosimetry, specific oncogene activation, tumor-suppressor gene deactivation, and promoter mechanisms, as available.

The use of multistage theory as a starting point and the incorporation of gene activation/deactivation and similar information highlights the importance of developing and validating models that specify the target organ, with corresponding time-dependent estimates of target organ dose. This would require further research into historical background rates and physiologically based pharmacokinetic (PBPK) models, respectively.

It is also important to take into account interindividual variations in susceptibility and sensitivity to cancer induction, especially when such variations have a genetic basis. The explosion of genetic information in recent years may allow for risk assessments based on a combination of susceptibility information and exposure data. Also needed are new approaches to using data on mechanism of action to reduce uncertainties in cancer risk assessments. These approaches should include sensitivity analysis to identify model parameters that need experimental data to reduce major uncertainties in occupational risk assessments.

In addition to genetic differences in sensitivity, cultural or individual behavioral factors may affect a person's exposure or response to occupational carcinogens. New cancer risk assessment models should account for such differences. For example, models are needed to account for interactions between occupational respiratory carcinogens and cigarette smoking, a personal risk factor which is present in 30% of the U.S. population and is estimated to account for approximately 40% of U.S. cancer mortality and more than 90% of U.S. lung cancer mortality. Similarly, alcohol consumption has been associated with esophageal and liver cancer, so studies of chemicals thought to affect those organs should look at potential synergistic effects of alcohol. Models considering potential interaction between workplace exposure to initiating and promoting substances, or in the human diet or with infectious agents, should also be considered. The development of these models may require data from a testing program that includes joint administration of tobacco smoke, alcohol, a diet (i.e., high fat, enriched with fiber or vitamins) along with the carcinogens being tested. Cancer risk assessment models should also be developed for chemical mixtures or production processes most common in industry or involving the most people. Alternative models, and the hypotheses underlying them, should be validated to ensure that they produce more reliable estimates of risk than the standard models.

Just as new cancer models need to be developed and validated, regulatory agencies need to develop guidelines for their application consistent with regulatory policies and authority. Ultimately, the utility of risk assessments will be judged on how well they lead to effective risk management and cancer prevention decisions. More research is needed on how this type of information is communicated to managers, decision makers, and the public, how it is used, and how it can be improved (Paustenbach 1995).

Prevention

Methods for primary prevention. Primary prevention of cancer can be accomplished in two ways: by avoiding the introduction of carcinogenic agents into the environment and by eliminating or drastically reducing exposure to carcinogenic agents that are already in the environment (Tomatis et al. 1997). For many industrial processes, reduction of exposure to carcinogenic agents in the workplace can be achieved using established technology, while for others, more innovative methods are needed and should be a priority for future research. There should be greater emphasis on designing industrial processes to eliminate exposure to potential carcinogens. For example, chemists and engineers should plan "safe" reactions and processes at the research stage before reactions are scaled up for pilot plant and, ultimately, full-scale production. Such planning requires knowledge of the possible carcinogenicity of by-products and intermediates, as well as the desired product, and should take advantage of advances in computer modeling and prediction of toxicologic potential. Research on less hazardous substitutes for processes that produce or otherwise involve carcinogens should be directed by considerations of cancer risk to workers as well as chemical or engineering needs.

As a number of known and suspected carcinogens are already in use, research is needed to develop methods to reduce exposure to these carcinogens. This is part of the public health approach that recommends that engineering controls to reduce or, preferably, eliminate exposure, should be the primary prevention strategy (Weeks et al. 1991). Although this approach has been implemented in a number of industries, further research is needed to develop practical and affordable engineering controls to reduce exposures to carcinogens. Despite the desirability of such engineering controls, use of personal protective equipment may be needed in some settings. Research on more effective and practical personal protective equipment is thus needed. Efforts to reduce occupational exposure should be coupled with efforts to eliminate transport of toxic substances outside the workplace.

The importance of dermal exposures in the workplace is increasingly being recognized. Research is needed to prevent such exposures, including primary source reduction, engineering controls, and better protective equipment. For example, the use of whole-body protection and gloves to prevent dermal exposure may be associated with adverse effects (heat stress, dermatitis), and substantial gaps exists in knowledge about the efficacy of their use to prevent dermal exposure.

As most carcinogens exhibit a dose–response relationship, a simple corollary is that low exposures are likely to result in low excess risk and that lowering of exposure levels will result in a reduction of risk (Tomatis et al. 1997). Research is necessary to evaluate the translation of knowledge on carcinogenicity and methods to reduce exposure to preventive measures and the efficacy of such measures. Methods development needs include tools to evaluate organizational decision making with regard to exposure controls, as well as improved tools to evaluate the protective effects of exposure reduction, including biomarkers of exposure and intermediate effect.

Methods for secondary prevention. More than 3 million U.S. workers are estimated to have potential occupational exposure to agents and mixtures substances classified by IARC as Group 1 (carcinogenic to humans) or Group 2A (probably carcinogenic to humans) and by the NTP as known human carcinogens or reasonably anticipated to be human carcinogens [estimates of the numbers of workers exposed are derived from NOES data reported in the *Ninth Report on Carcinogens* (NTP 2000)]. Countless more have had such exposures in the past. Secondary interventions may be applicable for some workers with potential exposure to occupational carcinogens. The study of populations at increased risk of cancer due to workplace exposures to carcinogens can provide important information about cancer prevention strategies. Conducting medical intervention studies in occupational rather than in general population cohorts can reduce the number of subjects needed to obtain adequate statistical power (because of higher incidence of disease in the worker group), as well as facilitate identification of potential subjects and stratification on potential risk (exposure) characteristics. Also, causal relationships and underlying mechanisms might be more clearly identified when focusing on groups with similar exposures.

Despite what would appear to be great advantages of using high-risk cohorts in intervention research and the potential to develop effective preventive strategies for occupationally related cancer, only a limited number of such studies have been done (Tomatis 2000). Traditional and molecular epidemiologic

studies can help identify high-risk cohorts in which secondary prevention interventions could be most effective (Perera 2000; Schulte et al. 1998). Consideration should be given to how best to incorporate such high-risk populations into future occupational cancer research. In order for high-risk persons to initiate appropriate secondary prevention, they must be made aware of their risks and options. Although NIOSH has made pioneering efforts in the notification of high-risk cohorts, much occupational cancer research may still be performed without provisions for notifying cohort members of the study's findings, and only limited data are available on the impact of notification programs or the design of notification materials (Boal et al. 1995). Evaluative research is needed to ensure that the goals of notification, to inform and to provide recommendations for reducing risk, are being achieved by existing programs.

Once cohort members are notified, more specific interventions need to be examined, particularly the use of chemicals to suppress the carcinogenic process (i.e., chemoprevention). This area deserves additional, albeit cautious, investigation in high-risk occupational cohorts. In particular, proposed interventions should be based on specific, demonstrated, biological principles to increase the likelihood of a positive effect. Studies should incorporate intermediate biomarkers that can monitor the effect on key steps in the biological pathways leading to cancer. Levels of mutant p53 protein in serum of workers exposed to vinyl chloride may represent such a marker (Trivers et al. 1995).

Although research in occupational cohorts has great promise to yield information about the efficacy of medical screening and intervention to reduce cancer risk, as well as scientific knowledge about the carcinogenesis of agents, these cohorts should be viewed as vulnerable populations. Researchers following high-risk cohorts should take special care to balance the rights and medical surveillance needs of participants with the objectives of the research (Samuels 1998). Ethical issues related to such studies need critical and ongoing attention, especially in relation to the implications of new research findings in prospective studies.

Table 1. Recommendations to enhance occupational cancer research methods.

Area	Recomendations
Identification of occupational carcinogens	Improve workplace exposure assessment and characterization for prioritization of carcinogenicity testing Improve simulation of occupational exposure circumstances for experimental studies Develop new strategies for predicting and testing the adverse effects of mixtures Develop and validate experimental and computational methods for better hazard identification and characterization of exposure–response relationships Accelerate testing of priority compounds for carcinogenicity
Epidemiologic research in occupational cancer	Improve methods to: Characterize extent of occupational and environmental exposures by all routes Identify populations for study Estimate levels of exposure retrospectively Conduct surveillance of occupationally related cancer Identify, validate, and utilize biological markers as surrogate end points Determine the relationship between maternal and paternal occupational exposure and cancer in offspring Increase emphasis on: Prospective studies with collection of biological samples and use of archival samples Multicenter case–control studies Applying advances in genetic research to better understand the etiology of occupational cancer and the basis for interindividual differences in susceptibility Studies of occupational cancer in women and minorities
Improvements in risk assessment for occupational carcinogens	Develop approaches to foster collaborations between human and animal researchers by: Improving communication and interaction Integrating modes and mechanisms Set national priorities Develop and validate risk assessment models by incorporation of modes and mechanisms of action (biomarkers): Use biologically based risk models for hypothesis framing and testing Use mechanisms to reduce uncertainty factors Study sensitive subpopulations and lifestyles Explore improved methods of communicating risk assessment information to risk managers, decision makers, and the public
Prevention of occupational cancers	Emphasize methods for primary prevention through elimination or reduction of exposure to suspected carcinogens, which will include: Greater emphasis on front-end designs to reduce exposures in industrial processes Research on effective prevention of primary exposures Research on effective communication of prevention strategies Enhance methods for secondary prevention through: Intervention research in high risk occupational cohorts that includes screening studies, early diagnosis and treatment (chemoprevention) Inclusion of high-risk occupational cohorts in future cancer research Evaluate high-risk notification and intervention programs Address ethical issues of secondary prevention studies

Conclusions

Four areas of methodologic development have been identified to enhance occupational cancer research and prevention. These include new ways to identify carcinogens, strengthen epidemiologic research and risk assessment, and strategies for prevention. Recommendations in each of these areas are shown in Table 1. In particular, further work is needed on methods to address cancer risks from chemical mixtures. The major theme of the recommendations is that traditional approaches to occupational cancer research can be strengthened by the integration of human, animal, and other biological data in planning research and conducting risk assessments. Research on occupational cancer needs to be approached as an interdisciplinary process. Less expensive ways of screening new substances for potential carcinogenicity must be developed and applied before or early in their commercial use. The Ames-Salmonella test works reasonably well for genotoxic agents; screening for nongenotoxic agents is problematic. The increasing difficulty in finding populations with suitable exposure history and characteristics for inclusion in epidemiologic studies requires refinement in exposure assessment and consideration of study designs that use intermediate biomarkers to examine mode of action in humans, as well to estimate exposure and detect early disease.

Research is also a needed on better applications of existing or new knowledge for primary prevention. In this article we focus on chemical agents, fibers, and particulates, which along with ionizing radiation are considered the primary causes of occupational cancer. Additional review is needed to address the individual and interactive roles of other physical agents, as well as biological agents and psychological factors related to work. Some of these other potential risk factors have

not been addressed in this article because of the limited information available. The aging of the U.S. workforce will result in an increased incidence of cancer. The role that work plays in affecting the availability and use of diagnosis, treatment, and rehabilitative services should be a focus for research.

More effective prevention of occupational cancers can be accomplished by improving the methods used in occupational cancer research. In this article we have suggested an agenda for those improvements.

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