Cancer and the Workplace

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Introduction

Although occupationally related cancers make up only a small fraction of all cancers, many environmental carcinogens have first been discovered in occupational settings. The estimate typically found in the scientific literature is that about two to eight percent of all human cancers are of occupational origin.[1] However, by averaging the unexposed population in with the exposed, such estimates tend to obscure the heavy toll that occupational cancer can take on specific populations of exposed workers. Among persons actually exposed to carcinogens at work, risk estimates are much higher. For instance, Morabia et al[2] have put the attributable risk for lung cancer at 9.2 percent for men employed in occupations characterized by exposure to established carcinogens. For bladder cancer, the population attributable risk from occupational exposures may exceed one case in five for men[3] and one in ten for women.[4]

Indeed, despite the relatively small "contribution" that occupational cancer

makes to the total cancer burden, recognition and concern for cancers related to workplace exposures have been central themes in control of environmental carcinogens. There are several good reasons for this. One is the unique nature of the workplace, which serves as a focal point in which large numbers of people may be exposed to high concentrations of chemicals or other hazardous situations. Another is that the very nature of work creates a cohort for the kinds of epidemiologic studies described below that can help establish a cause-effect relationship between an environmental exposure and cancer. It is because of the exposures to large doses and the opportunities to implement effective procedures for risk assessment and control in the workplace that the study of occupational cancer plays so important a role in the control of cancer in general.

Finally, perhaps the most important reason to identify occupational carcinogens and to elucidate their role in cancer causation is that occupational cancers are, for the most part, entirely preventable through appropriate engineering, personnel practices, and strict governmental protective legislation.

The ultimate goal of collecting, evaluating, and disseminating data on carcinogenicity of occupational exposures is to develop strategies for prevention of disease. The most efficient strategy relies on primary prevention, that is, identification and elimination of sources of expo-

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sure. Secondary prevention through screening of asymptomatic illness plays a lesser role, but may still be valuable in specific workplaces. Recent advances in molecular biology have led to identification of tests that can identify workers exposed to various carcinogens. Such tests, however, are at present extremely expensive, and their predictive value is no greater than that of traditional industrial hygiene workplace evaluations. Occupational screening may have its greatest usefulness as a tool for educating workers to potential hazards in the workplace.

Identifying Human Carcinogens

Despite the fact that more than six million chemicals have already been identified and registered with the Chemical Abstracts Service and more than 50,000 are estimated to be regularly used in commerce, probably fewer than 1,000 chemicals or exposure situations have been scrutinized as to their potential for cancer causation.[5] Even so, the literature on evaluation of cancer risks for even this small fraction of known exposures is massive and not altogether consistent for many specific substances. Estimation of actual cancer risks to humans requires careful sifting and evaluation of large quantities of data from many different studies. Since the early 1970s, an extensive effort has been made to systematize the available data on cancer risks. A comprehensive methodology for assessment of human cancer risks has been developed by the International Agency for Research on Cancer (IARC) that draws on data from a variety of disciplines.

The IARC methods, which are widely regarded as definitive, rely on the judgment of internationally recognized experts. Groups of scientists with expertise in various disciplines are convened to discuss and summarize the literature on individual carcinogens, groups of related carcinogens, or in some cases entire industries. These critical evaluations are ul-

timately presented as monographs, each of which contains a critical evaluation of the carcinogenicity of one or more target exposures. The evaluations take into account many different types of information, including data from epidemiology, experimental studies on rodents and other laboratory animals, in vitro studies where appropriate, and other relevant data including toxicity, metabolism, genotoxicity, and metabolic studies.

According to the IARC, "Each monograph consists of a brief description of the chemical and physical properties of the agent; methods for its analysis; a description of the methods and volumes of production and use; data on occurrence and human exposure; summaries of case reports and epidemiologic studies of cancer in humans; summaries of experimental carcinogenicity tests; a brief description of other relevant biologic data, such as toxicity and genetic effects, that may indicate its possible mechanism of action; and an evaluation of its carcinogenicity."[6] Because the IARC periodically revises its evaluations to reflect accumulation of new data and evolution of methods of assessment, the information in these monographs is generally current and forms the basis of the summary tables in this paper.

Categories of Carcinogenicity to Humans

The IARC classifies the evidence for carcinogenicity of specific exposures into four categories: sufficient, limited, or inadequate evidence of carcinogenicity or evidence suggesting lack of carcinogenicity. Sufficient evidence of carcinogenicity implies that a causal relationship has been established between exposure to the agent, mixture, or exposure circumstance and human cancer and that chance, bias, and confounding have been ruled out with reasonable confidence.

Limited evidence of carcinogenicity implies that a positive association has

been observed between exposure to the agent, mixture, or exposure circumstance and cancer for which a causal interpretation is considered to be credible, but chance, bias, or confounding cannot be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity means that the available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association or that no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity means that there are several adequate studies covering the full range of exposure levels that human beings are known to encounter that are mutually consistent in not showing a positive association between exposure to the agent and the studied cancer at any observed level of exposure.

Criteria for Evaluating Carcinogenicity Based on Total Evidence

A set of criteria analogous to those for assessing risk in human studies is used to classify cancer risk even when definitive human data are not available. This process takes into account information from carcinogenesis bioassays and other experimental studies of animals along with toxicity and other biologic data. The expert committee deliberations take into account epidemiologic, animal, and other types of data, including in vitro and metabolic studies where appropriate, from which an overall assessment of carcinogenicity to humans is synthesized within a scheme that consists of four broad groups. To date, 61 volumes of IARC Monographs have been published, and 782 agents or exposure circumstances have been classified.

The distribution of these 782 agents or exposure circumstances within the carcinogenicity groupings is shown in Table 1. Group 2, likely carcinogens, is subdivided into Group 2A, probably carcinogenic to humans, and Group 2B, possibly carcinogenic to humans. These categorizations take explicit note of the relevance of animal studies to human cancer risk and are most often used to classify substances for which human data may be limited or inadequate but where animal data are deemed sufficient and mechanistically relevant to humans (Group 2A) or less than sufficient but strongly supportive of existing human data (Group 2B).

The seemingly large number of agents denoted as carcinogenic or probably carcinogenic (Groups 1 and 2A, N=117) is a reflection of the selection process for inclusion in the monographs. Agents are generally evaluated only when substantial data bases already exist. These data bases, in turn, have usually evolved over a period of years in response to concerns of industry, workers, or the public. Tables 2 and 3 present the IARC Monograph groupings of known and probable human carcinogens (Groups 1 and 2A) and typical uses or occurrences.[7] Table 4 summarizes occupational exposure situations that have been classified as falling into Groups 1, 2A, and 2B.

Some Examples of Exposures and Controls in Health Care

The history of occupational cancer identification and control has been recounted by many authors.[8] The potential for work-related cancers has been recognized at least since the work of Ramazzini in the sixteenth century, and in fact our modern understanding of the influence of environmental factors on human cancer is due in large measure to occupational studies, ironically many of them drawn from the exposures of people in the health care professions. Examination of the known and probable occupational carcinogens and exposure situations, given in Tables 2 to 4, reveals a number that are found in health care situations and for which work practices are still inadequate

Table 1
International Agency for Research on Cancer Assessments of Chemical Carcinogenicity

Category	Carcinogenicity	Number of Agents or Exposure Situations (1972-1995)
Group 1:	Carcinogenic to humans	66
Group 2A:	Probably carcinogenic to humans	51
Group 2B:	Possibly carcinogenic to humans	210
Group 3:	Data insufficient to decide carcinogenicity	454
Group 4:	Probably not carcinogenic to humans	1
Total Evaluated		782

to protect health care personnel with potential exposures.

X-rays provide a good case study. Much of the knowledge about the dangers of the industrial use of x-rays is based on the "lamentable history" of the pioneers in the medical field, according to occupational medicine pioneer Donald Hunter.[9] The first death recognized to be the result of the action of x-rays occurred in 1914 to the Italian radiologist, Emilio Tiraboschi. By 1922 at least one hundred radiologists had died from malignant diseases arising from their occupation. Much of the natural course of radiation poisoning was elucidated by following the progression of disease among these early victims. It is estimated that many hundreds of people have died as a result of occupational exposures to medical x-rays.

The recognition of the potential deadliness of exposure to x-rays led to the relatively early establishment of national and international regulatory bodies, such as the International Commission on Radiological Protection, which was formed in 1928. Important safety concepts, such as maximum permissible dose, appropriate design and control of x-ray equipment, and basic principles for the elimination of unnecessary exposures, were developed over the years, along with systems of administrative control for registration and surveillance of people occupationally exposed to radiation.

In many ways the control of exposure to x-rays is a paradigm for the basic principles for prevention of occupational cancer. The primary means of prevention is to reduce exposure to x-rays. This is facilitated by providing equipment designed to be as safe as possible and by testing and maintaining the equipment on a specified schedule. Exposure is also minimized through the use of appropriate shielding. Other preventive measures include administrative procedures to control potential exposures and rigorous programs of registration and surveillance (medical record keeping and exposure monitoring by radiation badges). All personnel who work with x-rays must receive training, and some job categories require

Table 2
Known Human Carcinogens:
IARC Group 1 Ratings in Monographs 1-61

Group 1 Definition. The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans.

Explanation. This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

Agents or Groups of Agents [CAS #]	Human Cancer Site for Which Reasonable Evidence Is Available	Typical Use or Occurrence
Aflatoxins [1402-68-2]	Liver	Toxins produced by *Aspergillus flavus* and *Aspergillus parasiticus*. No commercial use
4-Aminobiphenyl [92-67-1]	Bladder	Former color additive and rubber antioxidant. No longer manufactured in most countries because of carcinogenic potential
Arsenic and arsenic compounds* [7740-38-2]	Lung, skin, hemangiosarcoma	By-product of metal smelting. Component of alloys, electrical and semiconductor devices, medications and herbicides, fungicides and animal dips
Asbestos [1332-21-4]	Lung, mesothelioma, gastrointestinal tract (esophagus, stomach, large intestine)	Formerly used for many applications because of fire, heat, and friction resistance; will still be found in existing construction, as well as fire-resistant textiles, friction materials (i.e., brake linings), underlayment and roofing papers, and floor tiles
Benzene [71-43-2]	Leukemia, Hodgkin's disease	Principal component of light oil. Although use as solvent is discouraged, many applications in printing and lithography, paint, rubber, dry cleaning, adhesives and coatings and detergents. Formerly widely used as solvent and fumigant
Benzidine [92-87-5]	Bladder	Formerly widely used in dye manufacture. Relatively small amounts now used in diagnostic testing (clinical laboratories)
Beryllium & beryllium compounds* [7440-41-7]	Lung	Missile fuel and space vehicles. Hardener for lightweight metal alloys, particularly in aerospace applications and nuclear reactors

*Evaluated as a group.
†This evaluation applies to the group of chemicals and not necessarily to all individual chemicals within the group.
‡There is also evidence that these agents have a protective effect against cancers of the ovary and endometrium.
IARC = International Agency for Research on Cancer; CAS # = Chemical Abstracts Service Registry Number.
CAS Registry Numbers are widely used unique identifiers for specific substances assigned by the
Chemical Abstracts Service, a Division of the American Chemical Society.
Adapted with permission from Boffetta et al.[7]

Table 2 (Continued)

Agents or Groups of Agents [CAS #]	Human Cancer Site for Which Reasonable Evidence Is Available	Typical Use or Occurrence
Bis (chloromethyl) ether (BCME) [542-88-1]	Lung	Experimental chemical. Formerly alkylating agent in production of some polymers. Can be contaminant of processes containing chloride and formaldehyde
Chloromethyl methyl ether (CMME technical-grade) [107-30-2]	Lung	Commonly contaminated with BCME. Alkylating agent and solvent in manufacture of ion-exchange resins, industrial polymers, and water repellents
Cadmium & cadmium compounds* [7440-43-9]	Prostate	Uses include yellow pigments and phosphors. Found in solders. Used in batteries and as alloy, metal platings and coatings
Chromium[VI] compounds*	Lung	Component of metal alloys, paints, pigments, and preservatives
Diethylstilbestrol [56-53-1]	Testis, vagina	Veterinary drug and growth promoter in cattle and sheep. Formerly used in human drug therapies
Erionite [66733-21-9]	See asbestos	Natural product related to asbestos
Ethylene oxide [75-21-8]	Leukemia	Ripening agent for fruits and nuts. Used in rocket propellant and chemical syntheses; fumigant for foodstuffs and textiles; sterilant for hospital equipment
Helicobacter pylori (infection with)	Stomach	
Hepatitis B or C virus (chronic infection with)	Liver	Can be occupational hazard where blood-borne pathogens are an exposure risk
Melphalan (Nitrogen mustard gas) [148-82-3]	Lung	Antineoplastic and alkylating agent.
Mustard gas (Sulfur mustard) [505-60-2]	Lung	Poison war gas
2-Naphthylamine [91-59-8]	Bladder	Formerly used in rubber manufacture. No longer produced commercially

*Evaluated as a group.

†This evaluation applies to the group of chemicals and not necessarily to all individual chemicals within the group.

‡There is also evidence that these agents have a protective effect against cancers of the ovary and endometrium.

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Table 2 (Continued)

Agents or Groups of Agents [CAS #]	Human Cancer Site for Which Reasonable Evidence Is Available	Typical Use or Occurrence
Nickel compounds*	Nasal, lung	Nickel plating. Component of ferrous alloys, ceramics, batteries. By-product of stainless-steel arc welding
Radon and its decay products [10043-92-2]	Lung	From decay of minerals containing uranium. Can be serious hazard in quarries and underground mines
Schistosoma haematobium (infection with)	Bladder	Outdoor work in areas of endemic infestation
Solar radiation	Skin	Outdoor work
Talc containing asbestiform fibers	See asbestos	
Vinyl chloride [75-01-4]	Angiosarcoma, liver	Refrigerant. Monomer for vinyl polymers. Adhesive for plastics. Formerly "inert" aerosol propellant in pressurized containers

Mixtures

Alcoholic beverages	Salted fish (Chinese style)
Betel quid with tobacco	Shale oils [63808-34-9]
Coal-tar pitches [65996-93-2]	Tobacco products, smokeless
Coal-tars [8007-45-2]	Tobacco smoke
Mineral oils, untreated and mildly treated	

Drugs and medicinals

Analgesic mixtures containing phenacetin	MOPP and other combined chemotherapy including alkylating agents
Azathioprine [446-86-6]	Methyl-CCNU [13909-09-6]
Busulfan (Myleran) [55-98-1]	Estrogen replacement therapy†
Chlorambucil [305-03-3]	Estrogens, nonsteroidal†
Chlornaphazine [494-03-1]	Oral contraceptives, combined‡
Ciclosporin [79217-60-0]	Oral contraceptives, sequential
Cyclophosphamide [50-18-0] [6055-19-2]	Thiotepa [52-24-4]
8-Methoxypsoralen (Methoxsalen) plus ultraviolet A radiation [298-81-7]	Treosulfan [299-75-2]

*Evaluated as a group.
†This evaluation applies to the group of chemicals and not necessarily to all individual chemicals within the group.
‡There is also evidence that these agents have a protective effect against cancers of the ovary and endometrium.
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specific licensure. A regulatory structure provides guidance and specifies the minimum legal requirements.

Cancer Chemotherapeutic Agents: An Apposite Example

Unlike the medical use of x-rays, which represents a paradigm for proper engineering and administrative controls in the use of dangerous substances, the mixing and administration of cancer chemotherapeutic agents provide an example of working conditions that have in many cases remained poorly conceived and controlled. The toxicity of drugs used as antineoplastics is well documented, yet until 1979, when a serendipitous experiment revealed elevated levels of mutagens in the urine of nurses who administer the drugs,[10] no routine precautions were taken to prevent potential exposure, particularly to pharmacy and nursing staff.

The major route for possible exposure arises from the aerosolization of drugs during mixing and administration. The presence of a vacuum in the syringe in which drugs are dissolved and from which they are administered leads to an imperceptible spraying of droplets unless a special "blow-back" device is used. Other preventive methods for avoiding contamination include the use of chemical hoods to provide exhaust ventilation during mixing and the use of personal protective equipment—such as disposable gloves, masks, and clothing—during drug administration. Such precautions are straightforward, yet they are not routinely followed in all health care settings. Indeed, as the number of patients requiring treatment with cancer chemotherapeutic agents grows and as the availability of in-hospital facilities decreases, one can envision that the possibilities of occupational exposures will increase rather than decrease.

Despite the extreme biologic potency of antineoplastic drugs, including carcinogenicity, and the large number of antineoplastic agents that appear on the IARC lists of known and probable human carcinogens, no regulations requiring safe handling procedures have been promulgated, although the Occupational Safety and Health Administration (OSHA) published guidelines a few years after the exposure became widely recognized.[11] This is in sharp contrast to the rapid growth of information, training, and regulation to control unnecessary exposure to medical x-rays. Thus, the extent of current exposure among health care personnel to these drugs is not known. While most major academic medical centers have, in fact, incorporated the recommended OSHA guidelines into their routine practices, many situations still exist in physician offices and among professionals who provide treatment at patient homes, for example, in which staff may be unnecessarily exposed to these drugs.

Epidemiology and Occupational Cancer Hazard Identification

Identification of human carcinogens in an occupational setting is a laborious and time-consuming process. Accumulation of enough evidence to classify a chemical or exposure as Group 1 can take years or decades. The process is an ongoing one, and lists such as those in Tables 2 to 4 are always incomplete because (1) established exposures are periodically reevaluated as more data become available and as industrial practices and hence exposure situations shift and (2) new chemicals and exposures are constantly being introduced into the workplace.

Thus, health professionals, and clinicians in particular, must be alert to the changing spectrum of workplace exposures and the possibility that new exposure situations will lead to shifts in existing patterns of disease and perhaps to new occupational cancer hazards. The process of identifying or confirming sus-

Table 3
Probable Human Carcinogens:
IARC Ratings Group 2A in Monographs 1-61

Group 2A Definition. The agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans.

Explanation. This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent, mixture or exposure circumstance may be classified in this category solely on the basis of limited evidence of carcinogenicity in humans.

Agents and Groups of Agents [CAS #]	Typical Use or Occurrence
Acrylamide [79-06-1]	Starting product for polyacrylamides. Used in many syntheses, particularly water treatment processes
Acrylonitrile [107-13-1]	Monomer for polyacrylonitrile plastics, resins, and fibers
Adriamycin [23214-92-8]	(Doxorubicin) - antineoplastic agent
Androgenic (anabolic) steroids	
Azacitidine [320-67-2]	
Benz[a]anthracene [56-55-3]	Combustion by-product. No commercial uses
Benzidine-based dyes	Textile industry
Benzo[a]pyrene [50-32-8]	Laboratory experiments
Bischloroethyl nitrosourea (BCNU) [154-93-8]	
1,3-Butadiene [106-99-0]	Widely used monomer for butadiene polymers and latexes
Captafol [2425-06-1]	(Difolatan) Fungicide, particularly for seeds, field crops, grapes, and to prevent wood rot
Chloramphenicol [56-75-7]	Antibiotic and antifungal agent
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) [13010-47-4]	(Lomustine) Antineoplastic agent
para-Chloro-ortho-toluidine and its strong acid salts [95-69-2]	Chemical intermediate for diazo dyes (cottons, silks, acetate, and nylon)
3 Chlorozotocin [54749-90-5]	
Cisplatin [15663-27-1]	Antineoplastic agent
Clonorchis sinensis (infection with)	
Dibenz[a, h]anthracene [53-70-3]	Research chemical
Diethyl sulfate [64-67-5]	Chemical intermediate and alkylating agent
Dimethylcarbamoyl chloride [79-44-7]	Chemical intermediate (formerly for pesticides)
Dimethyl sulfate [77-78-1]	Former war gas. Methylating and sulfating agent for agrichemicals, synthetic drugs, and various intermediates

IARC = International Agency for Research on Cancer; CAS # = Chemical Abstract Registry Number
Adapted with permission from Boffeta et al.[7]

Table 3 (Continued)

Agents and Groups of Agents [CAS #]	Typical Use or Occurrence
Epichlorohydrin [106-89-8]	Solvent and widely used intermediate. Monomer for acrylates; cross-linking agent; sporocide
Ethylene dibromide [106-93-4]	Anti-knock agent, gasolines; fumigant; widely used solvent
N-Ethyl-N-nitrosourea [759-73-9]	Laboratory chemical
Formaldehyde [50-00-0]	Monomer, preservative and disinfecting agent. Solvent for textile finishes
IQ (2-Amino-3-methylimidazo[4, 5-f]quinoline) [76180-96-6]	Mutagen produced during cooking of foods
5-Methoxypsoralen [484-20-8]	Used to promote tanning in suntan preparations
4,4′-Methylene bis(2-chloroaniline) (MOCA) [101-14-4]	Curing agent for urethane foams
N-Methyl-N′-nitro-N-nitrosoguanidine (MNNG) [70-25-7]	Experimental mutagen and carcinogen for laboratory experiments
N-Methyl-N-nitrosourea [684-93-5]	Laboratory studies of mutagens and possible antineoplastic agent
Nitrogen mustard [51-75-2]	(Mechlorethamine) - Antineoplastic agent
N-Nitrosodiethylamine [55-18-5]	Not produced commercially in US. Has been gasoline and lubricant additive
N-Nitrosodimethylamine [62-75-9]	Research uses currently. Formerly rubber accelerator and inhibition of nitrification in soil
Phenacetin [62-44-2]	Analgesic
Procarbazine hydrochloride [366-70-1]	Antineoplastic agent
Silica, crystalline [14808-60-7]	Hard rock mining and sandblasting
Styrene-7, 8-oxide [96-09-3]	Used in production of epoxy resins and as fragrance in perfumes and other chemical products
Tris(2, 3- dibromopropyl)phosphate [126-72-7]	Flame retardant in textiles. May be additive to polystyrene foams
Ultraviolet radiation A,B,C	Outdoor work and welding
Vinyl bromide [593-60-2]	Monomer in vinyl polymers and flame retardant in some acrylic fibers
Mixtures	
Creosotes [8001-58-9]	Hot mate (South American beverage)
Diesel engine exhaust	Polychlorinated biphenyls [1336-36-3] - formerly in transformers; currently in heat transfer systems and as mounting medium in microscopy; formerly in carbonless copy papers, cutting oils

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Adapted with permission from Boffeta et al.[7]

Table 4
Occupational Exposure Circumstances With Cancer Risks as Rated by the International Agency for Research on Cancer

Known Human Carcinogens - Group 1 Ratings

Aluminum production	Iron and steel founding
Auramine, manufacture of	Isopropanol manufacture (strong-acid process)
Boot and shoe manufacture and repair	Magenta, manufacture of
Coal gasification	Painter (occupational exposure as)
Coke production	Rubber industry
Furniture and cabinet making	Strong-inorganic-acid mists containing sulfuric acid (occupational exposure to)
Hematite mining (underground) with exposure to radon	

Probable Human Carcinogens - Group 2A Ratings

Art glass, glass containers and pressed ware (manufacture of)	Nonarsenical insecticides (occupational exposures in spraying and application of)
Hairdresser or barber (occupational exposure as a)	Petroleum refining (occupational exposures in)

Possible Human Carcinogens - Group 2B Ratings

Carpentry and joinery	Textile manufacturing industry (work in)

pected hazards is often carried out through epidemiologic studies, and cancer risk is usually expressed in epidemiologic terms. Controversies over published studies often involve sharp differences in interpretation of data or criticism of methodology. Therefore, to provide a sound basis for interpreting such studies, it is useful to review the basic epidemiologic strategies that have been and continue to be used to study and to quantify the impact of cancer in the workplace.

This brief overview is intended to improve understanding of some of the concepts and tables in this article. It is not meant to replace the many existing treatises on epidemiology and occupational studies that are available.[12-14]

The goal of a workplace epidemiologic study is to relate an occupational exposure to a health outcome, such as a specific type of cancer. Direct measurement of exposure, though a desirable goal, is rarely achieved. Few workplaces systematically monitor the work environment for hazardous chemicals. In those that do, it is unusual to have records that cover the entire time period during which exposure may have affected development of cancer. It is far more common for exposure to be defined qualitatively, through classification of workers according to job

title, work location, or industry of employment. For studies based solely on death certificates, the recorded occupation and/or industry serves as an exposure surrogate.

In recent years occupational studies have frequently used industrial hygienists to help reconstruct likely exposure scenarios. In addition, a technique that uses a "job exposure matrix" has been developed to assign probable exposures to various combinations of occupations and industries of employment.[15] Finally, exposure to toxic chemicals is sometimes estimated from human-derived measurement of the chemicals themselves, their metabolites, or other effects of their interaction with biologic materials, such as adducts with DNA. These methods are collectively known as biomarker methods.[16] While biomarker methods are becoming increasingly popular, their reliability still remains to be fully established, chiefly because they usually require extrapolation from current or relatively recent measurements to exposures that may have taken place in the distant past when carcinogenic effects may have, in fact, been more relevant.

Types of Epidemiologic Studies

Case Reports and Sentinel Events

The appearance of a highly unusual cancer, such as angiosarcoma of the liver in chemical workers or scrotal cancer in chimneysweeps,[17] or the appearance of an otherwise common cancer among a group ordinarily at low risk, such as lung cancer in very young workers exposed to bis (chloromethyl) ether, is termed a signal cancer. The first identified chemical carcinogen, β-naphthylamine, was discovered in 1895 after an astute clinician reported a large excess of bladder cancer in chemical dye industry workers.[18,19]

Vinyl chloride was first identified as a human carcinogen following reports of angiosarcoma of the liver in chemical

workers. Animal studies showing carcinogenicity of vinyl chloride appeared at about the same time as the case reports.[20] Angiosarcoma of the liver is so rare that few physicians ever see such a patient in a lifetime of practice, yet three workers were diagnosed in a brief period in a tire plant in Kentucky in 1974.[21]

Bis (chloromethyl) ether, an unwanted by-product in the production of polymeric resins, was initially reported in 1971 as a lung carcinogen by a pulmonary physician at a local hospital serving the area of residence of many Rohm & Haas workers in Philadelphia,[22] but only after the workers themselves identified a number of their colleagues who had contracted the disease.[23]

A signal cancer is a special case of a sentinel health event, which was defined by Rutstein et al[24] as a preventable disease, disability, or untimely death whose occurrence serves as a warning signal of a potentially hazardous situation that may require investigation and correction. The discovery of a signal or sentinel cancer, if promptly and properly followed up, can result in identification and elimination of an unsuspected hazard. However, sentinel health events rarely occur, and workplace cancer hazards are more often discovered through clinical observations and traditional epidemiologic methods. It should be noted that unlike many current epidemiologic investigations, which focus on "weak associations" (i.e., those characterized by a risk increase smaller than twofold), many of the occupational carcinogens in Tables 2 and 3 were originally recognized because their effects were sufficiently large to be noticeable at the clinical level.

Ecologic Studies

All modern countries systematically collect data on cause of death in their population. Ecologic studies are built on the hypothesis that workers in specific industries may have higher rates of cancer than

the general population. By comparing cancer death rates in those industries with population rates of the same cancers, conclusions as to whether workers are at increased risk can be drawn. The advantage of this type of analysis is that it makes use of existing death records and, therefore, requires no new data acquisition—provided occupational information is available. The drawback is that such data normally do not contain any information about exposures of individuals to specific substances. The primary contribution of this descriptive epidemiology is to uncover new associations between particular occupations or industries and disease. The drawback of ecologic methods is that they are very weak tools that are inadequate to establish cause-effect relationships.[25] Stronger methods require comparison of cancer risks between groups of people with and without established exposures. These are often provided by analytic methods such as cohort and case-control studies.

In Great Britain, the Registrar-General (equivalent to the National Center for Health Statistics in the United States) has published "Decennial Supplements" to the vital statistics reports that specifically compare age-adjusted death rates of workers in various occupations and industries with each other and with the general population.[26] These valuable reports have identified, for instance, the high rate of lung cancer in woodworkers, which has been confirmed in other studies.[27]

In the Nordic countries, where citizens are assigned identification numbers that are used in a variety of governmental data systems, census data can be linked electronically with occupational data and with cancer registration data to permit direct calculation of cancer rates in workers in specific industries. A number of studies of occupational cancer have been published on workers in Denmark,[28] Norway,[29] and Sweden.[30] By linking census data with national cancer registries, a collaborative group found increased risks for bladder and lung cancer in hairdressers in Denmark, Norway, and Sweden.[31]

ANALYTIC EPIDEMIOLOGY

The most common types of epidemiologic studies are those in which exposures and health outcomes are determined for individuals. Many treatises now exist that explain the application of analytic epidemiology to occupational cancer.[32-36] The two study methodologies most commonly encountered are cohort studies and case-control studies. In ideal circumstances, they ought to yield equivalent results, but in practice the availability of workers and the quality of work-related records and/or measurements usually dictate choice of study design.

In a typical cohort or follow-up study, a group of workers with some common characteristic, such as employment in a target industry or well-characterized exposure to a known hazardous substance, is identified as of a specific time and their vital status (in a mortality study) or cancer occurrence (in an incidence study) is ascertained as of a later time. Subjects may be identified through records and followed into the present or future (a design sometimes called retrospective), or they may be identified currently and followed up prospectively. The classic studies of Selikoff et al[37] on asbestos insulation workers that linked asbestos exposure to cancer of the lung and other sites were of this design. Occupational cohorts have been used to investigate the etiology of cancer in workers exposed to sulfuric acid mists,[38] in rubber workers,[39] and in workers occupationally exposed to formaldehyde.[40]

Cancer risk as determined by a cohort study is commonly expressed as a standard incidence ratio (SIR) or standard mortality ratio (SMR), depending on whether the outcome is a newly diagnosed cancer or cancer death. The simplest SIR (or SMR) is calculated as the number of

Table 5
Standardized Mortality Ratios for Lung Cancer Among South Carolina Textile Workers*

Estimated Exposure (days)	White Males			White Females		
	Observed	Expected	SMR[†]	Observed	Expected	SMR[†]
<500	7	7.6	0.92	7	5.1	1.37
500 - 1,000	4	5.5	0.73	3	2.7	1.11
1,000 - 2,500	15	6.2	**2.42**	4	3.9	1.03
2,500 - 10,000	10	5.1	1.96	8	3.2	2.50
10,000 - 40,000	16	5.2	**3.08**	13	2.8	**4.64**
40,000 - 100,000	18	2.2	**8.18**	3	0.7	**4.29**
>100,000	2	0.2	**10.00**	0	0.01	–
Total	72	32.0	**2.25**	38	18.4	**2.06**

*Exposure primarily to chrysotile asbestos with at least 15 years' latency.

[†]Boldface indicates p<0.01.

SMR = standardized mortality ratio

Data from Brown et al.[41]

observed cases (or deaths) in a population exposed to a suspected carcinogen divided by the number expected based on rates in an unexposed population (the reference or control group). SIRs and SMRs are usually adjusted statistically for possible confounding factors, most commonly age.

Table 5 shows the lung cancer SMRs calculated for white male workers and white female workers in a South Carolina textile plant where chrysotile asbestos was the primary exposure.[41] The analysis was restricted to workers at least 15 years since first exposure to allow for the fact that cancers may develop many years after first exposure. The gradual increase in the SMR associated with an increase in the estimated fiber concentration is typical of a dose-response relationship and is a key piece of evidence in favor of a causal relationship.

A similar dose-response relationship was observed for mortality from pneumoconiosis, a noncancer outcome, which increases confidence that the lung cancer observation is real and not a reporting artifact.

There are many studies where numbers of cancer deaths are available from death certificates, but SMRs cannot be computed because of lack of other essential data on the population at risk. In such studies a proportional mortality ratio (PMR) is computed by comparing the ratio each type of cancer makes to the total number of deaths in the exposed population with similar ratios in a reference population, adjusted for age. This method, which gives a surprisingly good idea of excesses or deficits in various types of cancer, has the drawback that because all proportions must add to 100 percent, a

Table 6
Proportional Mortality Ratios for Lung Cancer*

Occupation	Proportional Mortality Ratio	95-Percent Confidence Interval
Sheet metal workers	226	(117–394)
Machinists	204	(108–348)
Bartenders	163	(127–206)
Material-moving-equipment operators	161	(108–231)
Science technicians	160	(112–223)
Crossing guards	157	(112–214)
Construction	147	(106–200)
Engineering technicians	142	(115–173)
Waitresses	142	(133–151)
Food preparation, supervisors	140	(114–171)

*White women dying at age 65 years or younger in 28 states, 1979-1990, in selected occupations with significantly elevated proportional mortality ratios.

Data from Rubin et al.[42]

PMR for one particular cause may artificially appear to be very high or very low if some other common cause of death, such as heart disease, is unusually high or low in the study population. Nevertheless, the PMR method is well accepted as an inexpensive and valid way to obtain a first look at a possible cancer problem.

In the United States, the ready availability of death certificates, many of which list the industry and occupation of the decedent, makes PMR analysis a useful screen for unexpected cancer risks. The US National Institute for Occupational Safety and Health supports an occupationally coded data base of death certificates containing nearly five million entries. This data base has been used to evaluate age-adjusted and race-specific PMRs for women in eleven broad occupational groupings and over 400 specific occupations.[42,43] For both white and black women, significantly elevated lung cancer PMRs were noted for the categories of executive-managerial, technician, sales, administrative support (clerical), precision production, and operator-laborer.

This large-scale methodology makes it possible to detect increases in risk within occupational groups for which other types of analytic studies are impractical or impossible because women are typically employed in many small workplaces that would be difficult to identify individually. Table 6 shows the occupations listed on death certificates for white women younger than 65 years and for which the PMR was significantly above 140. These included, for instance, sheet metal and construction workers, many of whom have documented exposure to asbestos,[44] and waitresses and bartenders,

among whom the prevalence of cigarette smoking is higher than for many other occupations.[45]

A case-control study is conducted by identifying subjects who already have contracted or died of a specific disease and comparing their exposures with exposures of subjects diagnosed with some other disease or with no disease at all. A case-control study has the advantage of being highly efficient for study of rare diseases such as cancer. It has two major weaknesses. First, by definition it can be used to investigate only one disease outcome, whereas cohort studies provide information about practically all observable health outcomes. Second, case-controls studies are limited by the frequency with which subjects with specific occupations present at hospitals or die within the geographic area where the study is carried out. The people who make up the cases may be identified through hospital canvass or by examining local or regional tumor registries and subsequently interviewed. Cases may also be constructed by selecting decedents from death certificate registries, in which case exposure information is ordinarily restricted to information recorded on the death certificate, although interviews with family members are sometimes conducted.

The case-control design has been used to study bladder cancer, for which occupational risks arise in chemical and other industries,[46-48] and lung cancer in shipyard workers, many of whom have been exposed to high levels of asbestos.[49]

Cancer risks ascertained in case-control studies are commonly expressed by means of an odds ratio, which is a statistical estimate of the relative risk. Blot and Fraumeni[50] combined data from four case-control studies of lung cancer in relation to cigarette smoking and shipyard work and reported a relative risk of 21.7 for men employed as shipyard workers who smoked at least two packs of cigarettes per day and a relative risk of 10.3 for men who were not shipyard workers but smoked two packs a day. The reference group (relative risk, 1.0) was nonsmoking, nonshipyard workers.

Case-control studies are less frequently used to screen occupations and industries for increased risk, but the availability of large data files has improved the feasibility of this approach. Cantor et al[51] examined death certificates covering over 59,000 female breast cancer deaths in 24 states from 1984 through 1989 that were coded for occupation and industry. They used noncancer deaths from the same data base as a comparison group. After adjusting for age and socioeconomic status, they reported suggestive associations for probability and level of exposure for styrene, several organic solvents (methylene chloride, carbon tetrachloride, and formaldehyde), several metals/metal oxides, and acid mists. Such associations would have to be investigated in specific workplaces before causal inferences could be made.

Methodological Issues in Epidemiology Studies

Because epidemiologic studies are observational and thus are rarely subject to the types of controls that operate in experimental laboratory science, to be credible they must deal rigorously with methodological issues. Some of the more important ones are described in this section.

Exposure assessment is obviously an essential element of any occupational study. Exposures may be ascertained through company records, which under favorable circumstances might include actual industrial hygiene measurements of ambient levels of hazardous materials, or exposures may be inferred indirectly through job titles or even more crudely as employment in a specific plant or industry. Obviously, the more information available regarding exposures incurred by individuals, the more precisely cancer risks can be related to such exposures. However, reconstruction of historical ex-

Exposure History Form

Part 1. Exposure Survey   Name: Date:

Please circle the appropriate answer.   Birthdate: Sex: M   F

1. Are you currently exposed to any of the following?

   metals   ❑ no   ❑ yes
   dust or fibers   ❑ no   ❑ yes
   chemicals   ❑ no   ❑ yes
   fumes   ❑ no   ❑ yes
   radiation   ❑ no   ❑ yes
   loud noise, vibration, extreme heat or cold   ❑ no   ❑ yes
   biologic agents   ❑ no   ❑ yes

2. Have you been exposed to any of the above in the past?   ❑ no   ❑ yes

3. Do any household members have contact with metals, dust, fibers,
   chemicals, fumes, radiation, or biologic agents?   ❑ no   ❑ yes

   If you answered yes to any of the items above, describe your exposure in detail–how you were exposed; to what you were exposed. If you need more space, please use a separate sheet of paper.

   ....
   ....
   ....
   ....

4. Do you know the names of the metals, dusts, fibers, chemicals, fumes,
   or radiation that you are/were exposed to? *(If yes, list them below)*   ❑ no   ❑ yes

   ....
   ....
   ....
   ....

5. Do you get the material on your skin or clothing?   ❑ no   ❑ yes

6. Are your work clothes laundered at home?   ❑ no   ❑ yes

7. Do you shower at work?   ❑ no   ❑ yes

8. Can you smell the chemical or material you are working with?   ❑ no   ❑ yes

9. Do you use protective equipment such as gloves, masks
   respirator, hearing protectors? *(If yes, list them below)*   ❑ no   ❑ yes

   ....
   ....
   ....
   ....

10. Have you been advised to use protective equipment?   ❑ no   ❑ yes

11. Have you been instructed in the use of protective equipment?   ❑ no   ❑ yes

12. Do you wash your hands with solvents?   ❑ no   ❑ yes

13. Do you smoke at the workplace?   ❑ no   ❑ yes   At home?   ❑ no   ❑ yes

14. Do you eat at the workplace?   ❑ no   ❑ yes

Developed by ATSDR in cooperation with NIOSH, 1992

Form for taking a patient's exposure history to carcinogens developed by the Agency for Toxic Substances and Disease Registry.

Appendix
For Further Information

The American College of Occupational and Environmental Medicine: 55 West Seegers Road, Arlington Heights, IL 60005. Tel: 847-228-6850. Official publication: Journal of Occupational and Environmental Medicine.

The Association of Occupational and Environmental Clinics: 1010 Vermont Avenue, NW Suite 513, Washington, DC 20005. Tel: 202-347-4976.

The National Institute for Occupational Safety and Health can provide a list of the Education Resource Centers established throughout the United States. Contact the NIOSH Division of Training and Manpower Development. Tel: 1-800-536-4674.

The American Association of Poison Control Centers is a clearinghouse for Regional Poison Control Centers. Regional centers can be found in the blue pages of the telephone directory. Most operate under the aegis of the local department of health.

The Agency for Toxic Substances and Disease Registries, a branch of the Centers for Disease Control and Prevention: 1600 Clifton Road, NE, Room 3726 - Mail Stop E28, Atlanta, GA 30333. Tel: 404-639-0700.

The National Library of Medicine is connected to a vast network of on-line data resources, including Medline, PDQ, and Toxnet. The library can be contacted directly by telephone at 301-496-6095. Many physicians and researchers may already have access to these resources through their institutional libraries, which should be consulted first.

posures over a long period of time is challenging and has been done accurately only in a few industries.

In recent years exposure records have been supplemented by "biologic dosages," exemplified by levels of certain chemicals in serum or other body fluids.[52] As these biomarker methods become more refined, they will increasingly be incorporated into future studies.

Outcome assessment is also important, particularly for cohort studies where failure to obtain complete follow-up data on a proportion of the cohort might lead to biased results. Some occupational mortality studies rely solely on death certificates as a source of outcome data. This source may be less accurate for some types of cancer than for others.[53]

A basic concept of carcinogenesis is latency, the time from an initial exposure to a carcinogen to the clinical appearance of disease. Latency of occupational cancers is generally measured in decades. This greatly complicates the epidemiologic study of these illnesses because of the difficulty of reconstructing past levels of exposure. The latency for occupational skin cancer can be as brief as one year. In contrast, the latency for lung cancer attributed to exposure to bis (chloromethyl) ether was reported to range from eight to

26 years,[54] while the latency for bladder cancer can be more than 40 years.[55]

A second fundamental idea is that exposure to certain combinations of carcinogens can result in cancer risk that not only exceeds the risk from exposure to either alone, but exceeds the risk from both exposures combined. This phenomenon is known as synergism. The best known synergistic risk is that of lung cancer in asbestos workers who also smoke cigarettes, which is at least fifty times the risk in nonsmoking asbestos workers.[56]

BIAS

Because epidemiologic studies are largely observational, their interpretation relies strongly on comparison of risks between persons with and without disease or with and without exposure (depending on the study design). In either case, the information from the comparison group is as important as that from the study group, and information from both groups is potentially subject to bias.[57] Problems may arise if controls are selected in a manner that is not comparable to the way in which cases are selected. For instance, if cases are selected from a regional tumor registry and controls are selected through a population sampling method, such as random-digit telephone dialing, a low response rate among those called may result in a biased risk estimate based on those who are actually contacted and interviewed.

Confounding is the introduction of artifacts into risk estimates when critical variables, such as age, are distributed differently in a study group relative to controls. Confounding can be controlled through statistical methods, but only when it is initially identified and relevant information on confounding variables collected.[58]

Choice of an appropriate comparison group is sometimes complicated by lack of acceptable alternatives. Comparison of death rates between a specific occupational group and the general population is likely to be biased against reporting an association due to the well-known healthy worker effect. This arises because workers are recruited, possibly via medical screening, from a pool of people healthy enough to work in industry where continuation of employment is conditional on continued good health. By contrast, the general population, which furnishes the comparison rates, contains people who are very sick. Therefore, death rates in an employed group are expected to be lower than those of the general population even before considering possible work-related hazards.[59]

SAMPLE SIZE AND STATISTICAL POWER

A fundamental requirement of an epidemiologic study is that there be enough exposed workers or cases of the disease of interest to permit meaningful statistical testing. Where the relative risk is very high, as with asbestos and lung cancer, this is less of a concern, but for cancers that are very rare or where few people are exposed, even a well-designed study might not uncover a provable effect due to small numbers. A study by the Centers for Disease Control that was originally designed to look for a possible relationship between exposure to phenoxy herbicides in Vietnam and nasal cancer in Vietnam veterans had to be given up as inconclusive after only two of 48 veterans interviewed were found to have actually seen Vietnam service.[60]

OTHER EXPOSURES

While studies of occupational cancers focus by definition on potential carcinogenic exposures in the workplace, workers can be exposed to cancer-causing or cancer-preventing substances or conditions outside of the workplace. Cigarette smoking is the most-recognized nonoccupational carcinogenic exposure, and it is well recognized that information on smoking habits should be collected when

feasible. Unfortunately, this is sometimes impossible, especially in studies where exposure data are reconstructed from past employment and medical records or from death certificates.

Less well understood is the possible influence of diet and nutrition on occupational cancer. Fruits and vegetables have been associated with reduced lung cancer risk in many studies, even after adjustment for smoking. In a large-scale, prospective study in Japan, Hirayama[61] found independent (additive) effects for employment as a "material metal worker" and cigarette smoking on the risk of death from lung cancer. The study also found an independent protective effect for regular consumption of green-yellow vegetables. Nevertheless, few occupational studies have actually taken nutrition into account as a possible etiologic factor, and the negative association between consumption of fruits and vegetables with cigarette smoking[62] makes it difficult to generalize such findings to occupational settings.

REPLICABILITY

The foregoing discussion has highlighted most of the methodological factors that must be considered in interpreting epidemiologic studies of occupational cancer. However, even the most meticulous studies have limitations, often because of imperfect estimation of exposure to specific substances over the long time period during which cancer develops. Acceptance by the scientific community that a specific occupational exposure causes cancer nearly always requires replication by different investigators in a variety of populations or occupational settings.

Evaluating Occupational Exposures in a Clinical Setting

In this era of increased public awareness and concern about occupational and environmental health hazards, clinicians should be alert to the possibility that cancers may have occupational origins. This concern is appropriate if only because it may lead to reduction of the harmful exposure for the patient and his or her coworkers. As we have noted previously, it is especially important to keep the patient fully informed of any findings relating his or her illness to the workplace, as there may be many other workers who can benefit from this knowledge.[63] Also, while physicians should take every opportunity to counsel their patients who smoke to give up the habit, the possibility that smoking may exacerbate cancer risk simply increases the importance of this step.

While there has been dramatic growth in the number of professionals with formal training in occupational and environmental health and parallel growth in the resources available to clinicians for diagnosing occupational diseases, most clinicians require assistance when faced with determining whether a particular cancer can be linked to an occupational or environmental origin.

A work or exposure history is an essential component for diagnosis of an occupational cancer. The Agency for Toxic Substances and Disease Registry has developed a form for taking a patient's exposure history.[64] The form (Figure) is designed for quick scanning of important details. The form comprises three components: a survey of possible exposures to physical and chemical agents, a work history of every job held over the working lifetime, and an environmental history of hobbies and conditions in the home environment that could be associated with the cancer.

In general, it is not necessary to understand the jargon of a particular trade to take an adequate exposure history. According to the Agency for Toxic Substances and Disease Registry, persistent questioning by the clinician can clarify the tasks involved in most jobs and can

reveal possible exposures.

It may be, however, that further technical information is required. This can usually be obtained from the employer or a local government or university resource. The American College of Occupational and Environmental Medicine can provide a list of board-certified occupational physicians, and the Association of Occupational and Environmental Clinics is a network of clinics affiliated with medical schools throughout the United States. The National Institute for Occupational Safety and Health has established Education Resource Centers that can also provide information as well as formal training opportunities. Often the local Poison Control Center can provide specific information about the toxicity and health effects of hazardous exposures involved in poisonings. This may be of use in attempting to evaluate the more chronic effects generally associated with long-term environmental exposures. Finally, systematic and extensive information is now available in electronic format on the toxicology of thousands of chemicals used in the occupational environment. Many are available on CD-ROM. The National Library of Medicine in Bethesda, MD, and the Agency for Toxic Substances and Disease Registry in Atlanta, Ga, are two important resources for obtaining such information. The Appendix lists addresses and telephone numbers for these resources. CA

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American Cancer Society and International Union Against Cancer On-Line Information Resources

The American Cancer Society and the International Union Against Cancer both have sites on the World Wide Web offering information resources for patients and health care professionals.

The American Cancer Society's site provides general information about programs and events, meetings, publications, and grants and awards and also includes educational information about cancer, including fact sheets and data on various topics. The site also features information on breast cancer through the Society's Breast Cancer Network. The Internet address is http://www.cancer.org. For further information, call Derrick Wheeler at 404-329-7931.

The International Union Against Cancer's site includes information about programs and publications, a calendar of events, and a membership directory. The site also allows membership access to GLOBALink, an electronic network designed to serve those active in tobacco control, cancer control, and public health. Sponsored by the Europe Against Cancer Programme and the American Cancer Society, GLOBALink provides members of the network with electronic services including news bulletins, electronic conferences, interactive forums, electronic mail, and full text data bases. The Internet address is http://www.uicc.ch/. For further information, contact International Union Against Cancer GLOBALink Department, 3, rue du Conseil-General, 1205 Geneva-Switzerland, telephone +41 22 809 18 50; fax +41 22 809 18 10; e-mail: globalink@uicc.ch.