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CANCER CENTER PROFILE

Kimmel Cancer Center: Safety Procedures for Pharmacists and Patients

Safe Handling of Chemotherapy Agents

Donna deRemus, CPhT, decontaminates vials in the pharmacy at the Kimmel Cancer Center at Thomas Jefferson University Hospital.

Both oral and intravenous chemotherapy agents, and other drugs used to treat patients with cancer, can be hazardous to medical personnel who prepare, dispense, and administer these drugs, as well as to patients and their families. *The Oncology Pharmacist* spoke about safe-handling procedures and guidelines with Anne Marie Oberle, PharmD, BCOP, Advance Practice Clinical Oncology Pharmacist at the Kimmel Cancer Center at Thomas Jefferson University Hospital in Philadelphia, Pennsylvania.

Continued on page 22

CONFERENCE NEWS

Highlights From ASH and SABCS

Alice Goodman

The American Society of Hematology (ASH) and the San Antonio Breast Cancer Symposium (SABCS) held back-to-back meetings in December 2013. The ASH annual meeting hosted approximately 20,000 attendees in New Orleans, Louisiana, where more than 5300 abstracts were presented, orally or as posters. About 7500 participants from more than 90 countries attended the breast cancer symposium. Below are selected brief highlights from these meetings.

Continued on page 14

ONCOLOGY PHARMACY SAFETY

This is the third in a series of articles that will discuss issues related to hazardous materials in the workplace.

Chemotherapy: Biomarkers of Exposure, Effect, Reproductive Hazards, and Cancer

Christine Roussel, PharmD, BCOP
Clinical Pharmacy Manager, Doylestown Hospital Pharmacy

Thomas H. Connor, PhD
Research Biologist, National Institute for Occupational Safety and Health

In the May 2013 issue of *The Oncology Pharmacist*, Roussel and Connor described some of the hazards associated with handling chemotherapeutic drugs in the pharmacy and defined what constitutes a hazardous drug.[1] Next, in the October 2013 issue, the authors focused on sources of hazardous drug contamination and the evaluation of surface contamination as an indicator of environmental contamination.[2] The present article describes the use of biomarkers for the evaluation of occupational exposure to chemotherapeutic drugs, in an effort to better evaluate

Continued on page 10

LEUKEMIA

Raising the Bar: 4 Drugs for CLL

Alice Goodman

Several new drugs for the treatment of chronic lymphocytic leukemia (CLL) are considered major advances: 2 have been approved and 2 are under review by the US Food and Drug Administration (FDA). At the recent Chemotherapy Foundation Symposium, experts discussed ibrutinib, idelalisib, ofatumumab, and obinutuzumab.[1,2]

"Ibrutinib and idelalisib are 2 potent BCR [B-cell receptor] pathway inhibitors that are highly effective in both untreated and treated CLL," stated Morton

Continued on page 22

INSIDE

Chemotherapy: Biomarkers of Exposure… Continued from cover

and mitigate healthcare workers' risk of exposure during the care and treatment of patients. Current knowledge about adverse reproductive effects and cancer associated with occupational exposure to these highly toxic drugs is summarized.

This article discusses approaches that have been used to examine potentially adverse outcomes in healthcare professionals who work with or are exposed to chemotherapy drugs: (1) the use of biomarkers to evaluate genotoxic damage; (2) adverse reproductive outcomes; and (3) the association of cancer with exposure to chemotherapy drugs.

Biomarkers of exposure and effect have been used extensively to monitor both healthcare professionals who work with antineoplastic[3-5] and other hazardous drugs, and workers in other occupational settings who may be exposed to genotoxic chemicals. In general, biomarkers are based on mutagenic or other end points of genotoxicity of the drugs. As most of the first generation of antineoplastic drugs were genotoxic in one test system or another, they were ideal candidates for use in exposed worker populations. However, these end points are typically nonspecific in nature and can result from exposure to any genotoxic compound, certain types of radiation, and possibly viral infections. Therefore, studies of worker populations must be carefully designed to rule out extraneous factors such as smoking history, diet, age, and other variables that may compromise test results. Nevertheless, more than half of the 100-plus published studies in the literature have reported a statistically significant association between exposure to antineoplastic drugs and the end point being investigated. Most of these studies have originated outside the United States, and they often have been conducted in countries where safety precautions may not be as rigorous as in the United States.

It has been hypothesized that many antineoplastic drugs actually target developing fetuses in the same way they target the rapidly proliferating cells and active DNA metabolism of cancer cells.[6] Reproductive health is one of the most vulnerable end points because many hazardous drugs used for cancer treatment target rapidly dividing cells in the same way teratogens target rapidly dividing embryonic cells. Some of the same genotoxic properties that make chemotherapy drugs good candidates for biomarker testing confer adverse reproductive properties to them. Laboratory studies have demonstrated that many chemotherapeutic drugs are teratogenic, often in more than one animal species. Some classes of drugs are more hazardous than others and, as a group, chemotherapeutic drugs have been shown in animal studies to be some of the most potent teratogenic agents known, at doses typically used in cancer treatment.

Chemotherapeutic agents have demonstrated the ability to induce multiple types of genetic damage in mammalian cells in both in vitro and in vivo models. DNA-damaging effects on healthy nontarget tissues have been documented in patients with cancer treated with chemotherapy drugs, and the risk of secondary malignancies from these treatments is factored into the treatment decisions made for each potentially curable patient. It was through identification of the risk of secondary malignancies in patients that concern shifted to occupational exposure from antineoplastics and the potential genotoxic effects in healthcare workers. While their systemic exposure does not approach the peak concentrations achieved through therapeutic administration, chronic low-level occupational exposure to chemotherapy drugs is a realistic concern, as workplace contamination is well documented in almost 100 studies worldwide, and worker absorption of chemotherapy has been detected in more than 50 studies.[2,7-9] Although worker exposure has been well documented, relatively few studies of their risk of developing cancer have been published.

> *As a group, chemotherapeutic drugs have been shown in animal studies to be some of the most potent teratogenic agents known, at doses typically used in cancer treatment.*

Understanding genotoxicity and therapy-related secondary cancers in chemotherapy-treated patients can provide insight into the increased risks of cancer in occupationally exposed healthcare workers. Leukemias are the most common secondary malignancy following chemotherapy, with acute myelogenous leukemia (AML) being the predominant pathology. About 10% to 20% of myeloid neoplasms are therapy related, prompting the World Health Organization to classify "hematopoietic stem cell disorders related to previous exposure to chemotherapy and or radiation" separately in 2008.[10,11] Only a small percentage of exposed patients develop therapy-related disorders (2%-20% of long-term survivors), and positive associations exist between the types of agents, cumulative doses, and dose intensity.[12] In patients with cancer, alkylating agent–induced leukemia and myelodysplastic syndromes generally have a latency period of 4 to 10 years and are associated with partial loss or deletions of chromosomes 5 and 7.[10,13] A clear example of dose-response relationships was shown in pediatric patients with cancer, in whom a 5-fold increase in risk of secondary leukemia rose to greater than a 23-fold increase with high-dose alkylator therapy.[14] Topoisomerase II inhibitors (etoposide and doxorubicin) are associated with translocations on chromosome 11 (11q23), loss or deletion of chromosome 7, and many other balanced translocations, and have a latency period of 1 to 3 years.[13] One cohort and case control analysis reported that 3% of pediatric patients with germ cell tumors developed treatment-related AML (t-AML) after receiving etoposide <2 g/m^2, compared with more than 11% of patients developing t-AML after receiving >2 g/m^2.[15] Cumulative dosing and treatment regimens in both children and adults have evolved based on this information.

Though the risk of secondary malignancies in patients treated with chemotherapy is its own topic, the dose-response relationship with chemotherapy highlights the need for genotoxic risk assessment of chronic subtherapeutic chemotherapy exposure in healthcare workers. Biomarkers of exposure and effect are tools employed by occupational toxicologists to help define risk. The same mechanisms that induce genetic damage in patients also affect healthcare workers—hematopoietic progenitor cells can incur DNA damage, resulting in acquired mutations that go unrepaired, which can lead to malignant transformation. Evaluation of damage in healthcare workers has evolved but is limited to clinical research, which is currently beyond the reach of employees and employers.

Biomarkers of Exposure

A *biomarker of exposure* is defined as an exogenous substance or its metabolite or the product of an interaction between an exogenous agent and a target molecule or cell that is measured in a compartment within an organism. For most antineoplastic drugs, the intact drug and/or a metabolite of the drug is usually measured in urine samples.

Urinary Mutagenicity

Urinary mutagenicity was first used as a marker of exposure to antineoplastic drugs in 1979 by Falck and colleagues using bacterial mutagenicity assays.[16] The test is nonspecific and may be influenced by several extraneous factors, including dietary intake and smoking. For these reasons, this test is used sparingly. Nevertheless, the urinary mutagenicity test was instrumental in changing the use of horizontal flow cabinets for the preparation of antineoplastic drugs, which exposed the workers to high levels of drugs, to vertical flow biological safety cabinets (BSCs). This change greatly affected how these drugs were handled and helped reduce worker exposure to them.[17]

Urinary Excretion of Drugs/Metabolites

Biomarkers of exposure to chemotherapy drugs most commonly include urinary cyclophosphamide and ifosfamide, urinary platinum (for all platinum-containing drugs), methotrexate, and the urinary metabolite of 5-fluorouracil, α-fluoro-β-alanine.[7,18,19] A small number of other drugs have been measured in the urine, but less commonly. Measurement of these drugs directly in the urine is an indication that exposure levels may be high and uptake of the drugs is taking place either dermally or by inhalation.[9] When assessing the validity of urinary excretion studies, it is important to consider the pharmacokinetics of the drug being evaluated. For example, searching for mitomycin exposure through urinary excretion may provide a false-negative, as mitomycin is primarily hepatically metabolized, and only 10% of the dose is excreted unchanged in the urine.[20] Identification of exposure is the first step, but quantifying the damage is considerably more difficult. The application of such testing to the general population and the commercial availability of assays for surface sampling but not for biologic monitoring remain an issue.

Biomarkers of Effect

A *biomarker of effect* is defined as a measurable biochemical, physiological, behavioral, or other alteration within an organism that can be associated with a specific exposure. Biomarkers of effect have been utilized as biomarkers of exposure when comparing potentially exposed to nonexposed (control) populations.

Chromosomal Aberrations

A chromosomal aberration is a missing, extra, or irregular portion of chromosomal DNA. Numeric and structural abnormalities are evaluated in cultured peripheral blood lymphocytes or other cell types that are arrested at metaphase and stained in order to visualize individual chromosomes. Chromosomal aberrations can result from exposure to many genotoxic agents, including chemicals and radiation, and are further divided by type of damage. Chromosome-type aberrations involve the same locus on both sister chromatids on one or multiple chromosomes, such as double-strand breaks like those caused by ionizing radiation. Chromatid-type aberrations affect only one of the sister chromatids on one or more chromosomes. Examples include several insults: DNA cross-linking, base substitutions, and single-strand breaks such as the damage mediated by a variety of cytotoxic agents. Significant differences in various types of chromosomal damage have been reported in a large number of studies in potentially exposed healthcare workers, most with an increase 1.5 to 3.5 times that of appropriately matched controls. Selected references include Nikula and colleagues (1984), Burgaz and colleagues (2002), Tompa and colleagues (2006), Musák and colleagues (2006), Testa and colleagues (2007), Kopjar and colleagues (2009), McDiarmid and colleagues (2010), and El-Ebiary and colleagues (2013).[21-28]

Evaluation of chromosomal aberrations is a validated method to assess exposure to genotoxic agents, and their association with cancer risk has been demonstrated in prospective studies in which cohorts were followed for up to 25 years. Several studies have shown a significant association between increased frequency of chromosomal aberrations in peripheral blood lymphocytes and increased incidence of multiple cancer types in the healthy individuals tested. The cancer types documented were similar to the distribution of cancer in the general population, a finding that supports the assumption that genetic damage in the cells examined is reflective of similar genetic damage occurring in the tissues where carcinogenesis is occurring.[29-32] Smerhovsky and colleagues were able to validate this relationship through cytogenetic assessment of mine workers exposed to radon beginning in 1975 in the Czech Republic.[33] Their data showed a strong and significant relationship, such that a "1% increase in chromosomal aberrations was followed by a 64% increase in risk of cancer (P <.000)." While decades-long follow-up in antineoplastic-exposed healthcare workers would be ideal, 5 studies published since 2002 have shown a statistically significant increase in chromosomal aberrations in exposed healthcare workers, with an average of 1.5 to 3.5 times the controls, supporting the sensitivity of this biomarker for detecting low-level DNA damage.[22-26]

More recently, McDiarmid and colleagues targeted chromosomes 5, 7, and 11[27] because specific nonrandom chromosome damage to these genetic targets is known to be mediated by alkylating agents and topoisomerase II inhibitors, resulting in associated treatment-induced malignancies. Compared with looking at aberrations in all chromosomes, this study allowed for increased sensitivity such that it detected a 7-fold increase in abnormalities on chromosome 5 in exposed healthcare workers versus nonexposed healthcare workers. Evaluation of chromosomal abnormalities is a validated biomarker for cancer risk, sensitive to low-level DNA damage induced by chemotherapeutic drugs; however, the large biological sample required, coupled with a labor-intensive analysis, does not lend itself to mass-scale biologic monitoring for occupational exposure.

Christine Roussel, PharmD, BCOP

Thomas H. Connor, PhD

Micronuclei

Micronuclei are small collections of enveloped nuclear material present in the cytoplasm that separate from the main nucleus during cellular division. The formation of micronuclei in dividing cells results either from chromosome breakage (clastogenesis) or from chromosome mis-segregation due to mitotic malfunction. Micronuclei content may correspond to whole chromosomes with a centromere or to acentric chromosomal fragments. Similar to chromosomal aberrations, micronuclei result from exposure to genotoxic chemicals and radiation, and significant differences in increases in micronuclei frequencies in either peripheral blood lymphocytes or buccal epithelial cells have been reported in a large number of studies comparing potentially exposed healthcare workers with appropriately matched controls. Selected references include Thiringer and colleagues (1991), Maluf and Erdtmann (2000), Pilger and colleagues (2000), Hessel and colleagues (2001), Cavallo and colleagues (2007), Rekhadevi and colleagues (2007), Cornetta and colleagues (2008), and Cavallo and colleagues (2009).[34-41]

Preliminary evidence supports increased frequency of micronuclei formation in peripheral blood lymphocytes as being predictive of cancer risk.[42-44] While most of the positive micronucleus studies show doubling in the frequency of micronuclei in exposed healthcare workers compared with controls, the study by Rekhadevi and colleagues showed a 4.7-fold increase.[39] This study, evaluating oncology nurses in southern India, also showed an increase in micronuclei associated with years of exposure, age, duration of exposure within the average workday, and detection of urinary cyclophosphamide, which was also recorded. At the time of the study, there were fewer safety precautions for these test subjects than were commonly found in pharmacies in the United States that compounded hazardous drugs. Though not related to micronuclei, it is worth mentioning that the data did show an association between increased cyclophosphamide in the urine of the staff and increased age, years of exposure, and exposure per day.

Sister Chromatid Exchanges

Sister chromatid exchanges (SCEs) result from symmetric exchange of DNA replication products between 2 identical sister chromatids at a given locus and do not result in any alteration in chromosomal number or structure. The biological purpose of SCEs is not known, but they are hypothesized to be related to DNA repair and believed to be involved very early in the process of neogenesis. Their frequency is increased as a result of chromosomal fragility due to genetic or environmental factors such as ultraviolet or ionizing radiation and other mutagenic agents. To further increase the sensitivity of detection, some studies limit quantification to only high-frequency cells (HFCs), often defined as an increase in SCEs above the 95th percentile. SCE analysis has been applied in many earlier studies of occupational exposure to antineoplastic drugs, and 6 studies have reported increases in SCEs compared with control populations. Selected references include Norppa and colleagues (1980), Thiringer and colleagues (1991), Pilger and colleagues (2000), Jakab and colleagues (2001), Tompa and colleagues (2006), and Kopjar and colleagues (2009).[23,26,34,36,45,46] However, the large population-based cohorts that validated chromosomal aberration analysis and risk for cancer did not validate the association between increased SCEs or HFCs and cancer.[47] That, coupled with the unknown biological mechanism of SCE, has led to the decline in use of this biomarker despite the positive associations with exposure to genotoxic agents.

DNA Damage and Mutations

Hypoxanthine-guanine phosphoribosyltransferase (HPRT)

The *HPRT* gene controls the enzyme hypoxanthine-guanine phosphoribosyltransferase that plays a role in purine salvage. In addition to its normal substrates, *HPRT* catalyzes the transformation of purine analogues such as 6-thioguanine (6-TG), rendering them cytotoxic to normal cells. Cells with mutations in the *HPRT* gene cannot phosphoribosylate the analogue and survive treatment with 6-TG. HPRT-deficient T lymphocytes determined by the cloning assay are mutant cells resulting from in vivo mutations at the *HPRT* locus.[48,49] A limited number of occupational studies of healthcare workers exposed to chemotherapy drugs have utilized this assay. Selected studies include Dubeau and colleagues (1994) and Thulin and colleagues (1995).[50,51]

Comet Assay

The single cell gel electrophoresis assay (also known as the comet assay) is a sensitive technique for the detection of DNA damage at the level of the individual eukaryotic cell. Recently, it has increased in popularity as a stan-

Continued on page 12

Chemotherapy: Biomarkers of Exposure… Continued from page 11

dard technique for evaluation of DNA damage/repair, biomonitoring, and genotoxicity testing. It involves the encapsulation of cells in a low-melting-point agarose suspension, lysis of the cells in neutral or alkaline (pH >13) conditions, and electrophoresis of the suspended lysed cells. The term *comet* refers to the pattern of DNA migration through the electrophoresis gel, which often resembles a comet. Undamaged cells have an intact nucleus without a tail, whereas damaged cells have a comet appearance in which the greater tail length is proportional to increased DNA damage.

A growing number of studies have employed the comet assay in comparing potentially exposed populations with controls, and most have shown significant differences between the 2 groups. Selected studies include Ündeger and colleagues (1999), Maluf and Erdtmann (2000), Kopjar and Garaj-Vrhovac (2001), Yoshida and colleagues (2006), Sasaki and colleagues (2008), Rekhadevi and colleagues (2007), and Connor and colleagues (2010).[35,39,52-56]

One comet assay study found equivalent results when comparing patients with therapeutic high-dose limited-duration exposure to healthcare workers with low-dose chronic exposure.[8] Although the significance of this method as a biomarker remains unclear because of the lack of prospective data correlating it with an increased risk of cancer, the comet assay may be better suited as a biomarker of exposure.[57]

Cancer in Healthcare Workers

Relatively few reports have addressed the relationship of cancer occurrence to healthcare workers' exposures to antineoplastic drugs. A significantly increased risk of leukemia has been reported among oncology nurses identified in the Danish cancer registry for the period 1943–1987.[58] The same investigators found an increased, but not significant, risk of leukemia in physicians employed for at least 6 months in a department where patients were treated with antineoplastic drugs.[59]

Hansen and Olsen reported elevated risks for nonmelanoma skin cancer (standardized incidence ratio [SIR] 1.5; 95% confidence interval [CI], 1.1-2.1) and non-Hodgkin lymphoma (SIR 3.7; 95% CI, 1.2-8.9) in 8500 Danish female pharmacy technicians.[60] In addition, a Canadian study reported an increased risk for breast cancer (relative risk [RR] 1.83; 95% CI, 1.03-3.23) and cancer of the rectum (RR 1.87; 95% CI, 1.07-3.29) among nurses potentially exposed to antineoplastic drugs.[61]

Biomarkers of Susceptibility

A biomarker of susceptibility is an indicator of an organism's inherent or acquired ability to respond to the challenge of exposure to a specific substance. Genetic polymorphisms have the ability to alter the body's response to an assault from chemotherapeutic drugs and account for an individual's increased susceptibility to damage. Genetic polymorphisms that alter drug metabolism and detoxification are increasingly being identified, and their use in clinical practice is emerging. Furthermore, genetic polymorphisms that relate to DNA repair mechanisms are also emerging, with one study identifying at least a 10% incidence in decreased DNA repair capacity in lymphocytes exposed to genotoxic chemicals.[62] Considering that only a small percentage of chemotherapy-treated patients develop a therapy-related malignancy, it is hypothesized that genetic predispositions may be involved related to either or both the ability to detoxify the toxicant and/or the ability to repair the damage caused by the toxicant. Differences in chromosomal aberrations and micronuclei tests in patients with cancer before and after receiving the same type of chemotherapy showed wide interpatient variability, even in those of the same sex and with the same type of cancer.[63] The effects of genetic polymorphisms related to DNA repair are not fully understood, but there is enough evidence to warrant further evaluation of individual susceptibility to damage from chemotherapeutic drugs and potentially evaluate this association with occupational risk.

Adverse Reproductive Effects

Studies of healthcare workers occupationally exposed to antineoplastic drugs have examined the occurrence of adverse reproductive outcomes, including infertility, spontaneous abortions, stillbirths, pregnancy outcomes, and congenital malformations. Seven studies and 1 meta-analysis of congenital malformations and occupational exposure to antineoplastic drugs were identified. Many studies of congenital malformations had small sample sizes (fewer than 20 exposed cases, resulting in several limitations, such as limited ability to adjust for confounding factors; grouping of anomalies that may have different etiologies; and wide confidence intervals, indicating poor power). However, of the studies that had more than 5 exposed cases, 3 studies showed significantly increased risks associated with exposure,[64-66] and 2 showed increased risks that were not statistically significant.[58,61] The odds ratios (ORs) of adjusted models ranged from 1.36 (95% CI, 0.59-3.14)[58] to 5.1 (95% CI, 1.1-23.6)[66]. A meta-analysis of 4 studies[67] with exposure periods ranging from 1966 to 2004[58,64,66,68] reported a crude OR of 1.64 (95% CI, 0.91-2.94) for all congenital anomalies combined. Although in general these studies suggest an increased risk for congenital anomalies with maternal occupational exposure, the limitations and wide confidence intervals make interpretation of the results inconclusive.

Previous studies of spontaneous abortion and maternal occupational exposure to antineoplastic drugs had mixed results, and several of these studies were limited by small sample sizes. The 4 largest studies[69-72] showed increased occurrence of spontaneous abortions with self-reported exposure during the first trimester through handling or compounding of antineoplastic drugs. Most exposures were among oncology nurses and pharmacists (ORs ranged from 1.5 to 2.3 in samples that included 18 to 223 exposed cases). Other studies that did not find statistically significant associations had ORs ranging from 0.7 to 2.8 and limited sample sizes (3 to 34 exposed cases). A meta-analysis that pooled the results of 5 studies[58,66,69-71] found an overall adjusted increased risk of 46% among exposed workers (95% CI, 11%-92%).[67]

A number of biomarkers for genotoxicity have proved useful when evaluating occupational exposures of healthcare workers to antineoplastic drugs.

More research is needed to examine the effects of occupational exposure to antineoplastic drugs on stillbirth. One study showed a statistically significant 3-fold increased risk of menstrual cycle irregularities from occupational exposure to antineoplastic drugs.[73] Another study showed an increased risk of learning disabilities among offspring of workers exposed to antineoplastic drugs.[74]

Summary

Chemotherapy contamination in the workplace has been extensively documented, as has worker uptake of these hazardous drugs through their daily workflow. The magnitude of the contamination has changed little over the past decade and, even with maximum compliance in optimally designed facilities (which may not always be the case), exposure has not been eliminated. It should be stressed that most of the biomarker studies reported herein were undertaken in countries outside of the United States. Therefore, the potential for exposure may have been greater in countries where exposure controls may not be as widely used as they are here. Quantification of genotoxic damage incurred in the workplace has the potential to offer invaluable information about the effectiveness or lack of it in current procedures and safety controls. Ultimately, this problem will not go away, as growing numbers of patients are receiving chemotherapy and other hazardous drugs prepared and/or administered by dedicated pharmacists, pharmacy technicians, and nurses.

A number of biomarkers for genotoxicity have proved useful when evaluating occupational exposures of healthcare workers to antineoplastic drugs. Early studies utilized urinary mutagenicity testing, but this assay is rarely used today. Many studies have used chromosomal aberrations, SCEs, and, more recently, the micronucleus assay to monitor workers who handle these drugs. Lately, the comet assay has proven to be a helpful tool for assessing damage to DNA. Because more than half of the published studies have demonstrated a significant association between occupational exposure to antineoplastic drugs and one of these biomarkers, it must be assumed that workers are being exposed to a degree sufficient enough to elicit a response in the biomarkers being studied.

Although the majority of the adverse reproductive effects observed in healthcare workers are related to exposures in the past decade or more, and most study results suffer from small sample size, there is evidence to support the theory that these exposures can have an adverse effect on a developing fetus. Increased rates of spontaneous abortion, malformations, and other outcomes have been documented in these studies, indicating that these outcomes are possible if sufficient exposures occur.

Certainly, studies of cancer outcomes in healthcare workers are lacking. Because it has not been possible to link cancer registry data to occupation in the United States, we will have to look to other countries for these types of data. The association between certain biomarkers (eg, chromosomal aberrations and micronuclei) and cancer outcome in unexposed populations raises the question of whether exposed workers with increased levels of genotoxic damage are also at an elevated risk for cancer later in life. Currently, these types of studies are only employed on a population basis and do not translate to use in individual subjects. Many risk factors are involved in the complexity of the cancer process, and chromosomal damage may be one more potential risk factor.

Disclaimers

The findings and conclusions of this report have not been formally disseminated by NIOSH and should not be construed to represent any agency determination or policy.

Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health.

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Continued on page 18

Continued from page 13

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