

The adverse health effects of occupational exposure to hazardous drugs

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For the past several decades, there has been growing concern regarding the safety and health of healthcare workers who are occupationally exposed to chemotherapy and other drugs. The activities that create greatest risk are preparing and administering antineoplastic agents, cleaning up chemotherapy spills, and handling patient excreta. This article will review the potential adverse health effects associated with handling these agents, including acute symptoms, reproductive health issues, and potential cancer development. Healthcare workers handling chemotherapeutic agents report an increased incidence of acute health symptoms such as nausea, vomiting, headaches, and hair loss. Additionally, many studies have identified an association between exposure to the drugs and adverse effects on reproductive health among female staff members, including infertility, preterm deliveries, spontaneous abortions, fetal abnormalities, and small-for-gestational-age births.

For the past decade, concern has been growing regarding the safety of healthcare workers who handle chemotherapy drugs. The handling of antineoplastic agents and other hazardous drugs has been an acknowledged occupational hazard to those healthcare personnel who work with these agents.¹ Knowledge gained from studies conducted in the early 1980s has provided a wealth of information regarding the routes of exposure from these agents.²⁻⁴ An investigation has concluded that the probable hazardous drug exposure routes include dermal absorption, primarily from handling contaminated material; ingestion; and inhalation.⁵ In addition, many of these agents or their metabolites are found in patients' excreta. This may expose personnel during the handling of the excreta.

Generally, the occupational activities that pose the greatest risk are preparing and administering antineoplastic agents, cleaning up chemotherapy spills, and handling patient excreta. During the course of patient treatment, healthcare professionals may inadvertently be exposed to these agents, thus placing themselves at risk.

Experimental evidence indicates that at least nine commonly used chemotherapeutic agents for which there is no known safe level of exposure may pose carcinogenic risks to humans.⁶ This evidence is based on epidemiological research that associates secondary tumors in cancer patients treated with these drugs.⁷ Experimental animal studies have also identified carcinogenic and teratogenic effects associated with exposure to several antineoplastic

agents, including the alkylating agents and antimetabolites.^{6,8-10}

Which anticancer drugs cause cancer?

The International Agency for Research on Cancer (IARC) in Lyon, France, has evaluated 900

KEY POINTS

Concern has been growing regarding the safety of healthcare workers who handle chemotherapy drugs.

Probable exposure routes include dermal absorption, ingestion, and inhalation.

Acute symptoms in nursing staff have been identified, including nausea, vomiting, headaches, dizziness, hair loss, and liver damage.

Exposure poses a significant risk to reproductive health among female staff members, including infertility, preterm deliveries, spontaneous abortions, fetal abnormalities, and small-for-gestational-age births.

A significant increase risk for leukemia has been noted among healthcare workers.

Implementing safety recommendations can prevent or reduce exposure and minimize potential adverse effects.

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agents for their potential to cause cancer in humans. Below is the list of drugs used to treat cancer patients that have made it onto the IARC's list of carcinogens, plus possible and probable carcinogens (Table 1).

Conceptually, an occupational exposure to hazardous chemotherapeutic agents is defined as the degree of internal exposure to hazardous antineoplastic agents after a healthcare worker's inadvertent occupational contact with chemotherapy drugs during the preparation, administration, and/or disposal process. The degree of internal antineoplastic chemotherapeutic exposure reflects the quantity of drug uptake, the metabolism of the drug in the body, and evidence of cellular manipulation after an accidental exposure with cytotoxic agents during the handling process.

The conceptual framework associated with occupational exposure is based on the epidemiological triad of host, agent, and environment. It is hypothesized that the adverse health effects identified in oncology healthcare workers are a product of an interaction between the person at risk (host), an exposure to antineoplastic chemotherapeutic (agent), and the environment (handling practices).¹¹ Each component of this theoretical triad may affect the validity and reliability of tools that attempt to quantify exposure to these agents. Individual variations in the host may affect

the absorption as well as the sensitivity and specificity of the measurement method. Such variations are associated with the subjects' genetic makeup; percentage of body fat; gender; social, religious, and cultural norms; and nutritional status and lifestyle habits. The metabolism of the chemotherapeutic agent, its pharmacokinetics, the temporal relationship between exposure and testing, and the agent's physiological toxicity may significantly affect the validity and reliability of the outcome data. Lastly, the handling practices of the subjects, such as the use of personal protective equipment and biological safety cabinets, may affect the quantity of internal absorption of these substances.^{12,13}

Occupational health issues related to handling hazardous drugs

Acute symptoms

Valanis et al¹⁴ identified an association between the degree of cytotoxic drug skin contact or exposure and the presence of acute symptoms reported by nursing staff. The investigators concluded that unprotected handling is a factor most associated with positive symptomatology. A number of studies^{15,16} documented adverse health effects that are connected with occupational exposure to antineoplastic chemotherapeutic agents. The most frequent acute toxicities noted

include nausea, vomiting, headaches, dizziness, hair loss, and liver damage. These acute symptoms were positively correlated with the number of doses handled and the use of protective equipment. Additionally, body mass was significantly associated with the development of acute symptoms.¹⁴ Hepatocellular damage was noted in nurses employed on an oncology unit. This symptom was associated with the employee's duration of work exposure and the volume of handling.¹⁷

Reproductive and developmental effects

In addition to acute adverse effects, several studies have indicated an association of hazardous drug exposure with long-term adverse effects. Exposure to chemotherapeutic agents poses a significant risk to female reproductive health. The literature reports the incidence of such reproductive deficits as infertility, spontaneous abortions, fetal abnormalities, and menstrual-cycle abnormalities.¹⁸⁻²¹

Among nurses and pharmacists who reported occupational chemotherapy exposure, a cross-sectional self-reported survey found an increased prevalence of infertility.¹⁸ Among women, there was a significant increase in reported cases of infertility among nurses handling chemotherapy (odds ratio [OR] = 1.5; 95% confidence interval [CI] = 1.1-2.0), regardless of a history of skin contamination with chemotherapeutic drugs.

Results of studies evaluating the association between spontaneous abortions among nurses and occupational exposures to anesthetic agents and chemotherapeutic agents^{19,22-25} are contradictory. In 1993, Saurel-Cubizolles noted a relationship between ectopic pregnancies and occupational exposure to chemotherapeutic agents. A significant relationship was noted between the length of chemotherapeutic drug exposure, the women's age, and adverse pregnancy outcomes.²⁶ Another study investigated the incidence of fetal loss and the degree of occupational

TABLE 1

Potentially carcinogenic chemotherapeutic agents

Carcinogenic to humans	Probable carcinogens	Possible carcinogens
Azathioprine	Azacitidine	Bleomycin
Busulfan (Busulfex, Myleran)	Carmustine (BiCNU)	Dacarbazine
Chlorambucil (Leukeran)	Cisplatin	Daurubicin
Cyclophosphamide	Doxorubicin	Mitomycin
Melphalan	Etoposide	Mitoxantrone
Semustine*	Lomustine (CCNU, CeeNU)	Streptozocin (Zanosar)
Tamoxifen	Mechlorethamine	
Thiotepa	(nitrogen mustard)	
Treosulfan*	Procarbazine (Matulane)	
MOPP† and other regimens containing alkylating agents	Teniposide (Vumon)	

* Not approved in the US † MOPP = mechlorethamine, vincristine, procarbazine, and prednisone
For details, visit the IARC Web site: www.cie.iarc.fr/monoeval/grlist.html

exposure to cytotoxic agents.²⁰ The researchers found that women exposed to antineoplastic drugs during the first trimester of pregnancy were more than twice as likely to experience fetal loss as women who were not exposed and carried their pregnancies to full term. Stucker et al²⁴ showed a relative risk of 1.7 (95% CI = 1.0–2.8) among nurses who, on average, prepared and administered 18 chemotherapy infusions per week without personal protective equipment. Valanis and colleagues²⁵ reported that spontaneous abortions were associated with chemotherapy handling during pregnancy (OR = 1.5; 95% CI = 1.2–1.8).

Several additional negative reproductive outcomes have been noted following cytotoxic drug exposure. Savitz et al²⁷ found that women who were occupationally exposed to antineoplastic agents reported an increased risk of preterm deliveries and small-for-gestational-age births. This study did not delineate, however, whether the noxious drug exposure was preconception or during pregnancy. The effects of potential chromosomal aberrations are reflected in increased incidences of miscarriages and malformations in offspring. Two studies of nurses occupationally exposed to cytotoxic drugs showed relative risks for miscarriages of 2.30 and 1.70, respectively.^{28,29} Hemminki et al²⁰ found an OR of 4.70 for malformations in the offspring of nurses handling cytotoxic agents.

Genetic effects

The genetic effects associated with exposure to a broad spectrum of antineoplastic agents have been studied extensively.^{10,30} Genotoxic activity of some antineoplastic agents in humans has been noted in both patients treated with the agents as well as those healthcare personnel administering the agents.^{31,32} The incidence of DNA single-strand breaks in peripheral mononuclear blood cells was 50% higher in nurses not utilizing

recommended safety precautions.³² This finding is significant since other major carcinogens, such as exposure to smoke, present with the identical DNA strand breaks. Chromosomal aberrations were also noted in nurses and physicians handling antineoplastic drugs. The length of handling exposure was the predominant factor that correlated with the degree of chromosomal damage.³³

Cancer development

An increased risk of malignancy, predominately leukemia, among healthcare workers in general has been previously reported.^{34–36} Blair and colleagues³⁴ reported that hospital workers were 2.9 times (95% CI = 1.4–6.9) more likely to develop acute myelogenous leukemia than non-hospital workers in the Iowa area.

The literature regarding the risk of cancer among healthcare personnel who handle antineoplastic drugs is limited and has focused predominantly on leukemia. Skov et al³⁷ reported a nonsignificant increased risk of developing leukemia among physicians who handled chemotherapy (relative risk [RR] = 2.85; 95% CI = 0.51–16.02). A significant increased risk for leukemia was noted among oncology nurses who handled chemotherapy agents (RR = 10.65; 95% CI = 1.29–38.5).²³ Nevertheless, there is a wealth of information in the literature regarding occupational chemotherapy exposure and elevated levels of nonspecific markers for carcinogen exposure, such as sister chromatid exchanges and chromosomal aberrations.^{5,38–43} Sister chromatid exchanges are symmetrical rearrangements of DNA within chromosomal structures in T lymphocytes; they were noted after exposure to a known carcinogen.⁴⁴

Conclusion

Occupational exposure from hazardous drugs may pose a significant risk to healthcare workers. Since the mid 1980s, several organizations have

published recommended hazardous drug handling guidelines.^{45–48} Most recently, the National Institute of Safety and Health (NIOSH)¹ published an alert that presents the most updated recommendations for hazardous drug handling. Implementing these recommendations may prevent or reduce the inadvertent exposure to these drugs, thus minimizing the potential adverse health effects associated with their handling.

For more on implementing the NIOSH guidelines, see the following article, "Developing a hazardous drug safe-handling program," by Martha Polovich, MN, RN, AOCN®.

References

1. National Institute of Occupational Safety and Health: 2004. NIOSH alert: preventing occupational exposures to antineoplastic and other hazardous drugs in the health care setting. Washington, DC: US Department of Health and Human Services. Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
2. Falck K, Grohn P, Sorsa M, Vaino H, Heinonen E, Holsti LR. Mutagenicity in urine of nurses handling cytotoxic drugs. *Lancet* 1979;8128:1250–1251.
3. Crudi C, Stephen B, Maier P. Possible occupational hazards associated with the preparation, administration of antineoplastic agents. *NITA* 1982;5:264–266.
4. Valanis B, Browne M. Use of protection by nurses during occupational handling of antineoplastic drugs. *NITA* 1985;8:218–222.
5. Sessik P, Bos R. Drugs hazardous to healthcare workers. *Drug Safety* 1999;20:347–359.
6. International Agency for Research on Cancer. Pharmaceutical drugs. IARC Monograph on the Evaluation of Carcinogenic Risks to Humans, vol 50. Lyon, France: International Agency for Research on Cancer; 1990.
7. Green D, Hyland A, Barcos M, et al. Second malignant neoplasms after treatment for Hodgkin's disease in childhood or adolescence. *Am J Clin Oncol* 2000;18:1492–1499.
8. Erlichman C, Moore M. Carcinogenesis: a late complication of cancer chemotherapy. In: Chabner BA, Longo DL, eds. *Cancer Chemotherapy and Biotherapy: Principles and Practice*. 2nd ed. New York, NY: Lippincott-Raven Publishers; 1996.
9. Anderson D, Bishop JB, Garner RC, Ostroskywegman P, Selby PB. Cyclophosphamide: review of its mutagenicity for an assess-

- ment of potential germ cell risks. *Mutat Res* 1995;330:115–181.
10. International Agency for Research on Cancer. Some antiviral and antineoplastic drugs, and other pharmaceutical agents. IARC Monograph on the Evaluation of Carcinogenic Risks to Humans, vol 76. Lyon, France: International Agency for Research on Cancer; 1999.
11. Gordis L. *Epidemiology*. Philadelphia, Pa: WB Saunders Co, 1996.
12. Ong C. Reference values and action levels of biological monitoring in occupational exposure. *Toxicol Lett* 1999;108:127–135.
13. Schulte P, Talaska G. Validity criteria for the use of biological markers of exposure to agents in environmental epidemiology. *Toxicology* 1995;101:73–88.
14. Valanis B, Vollmer W, Labuhn K, Glass A. Acute symptoms associated with antineoplastic drug handling among nurses. *Cancer Nurs* 1993;16:288–295.
15. McDiarmid M, Egan T. Acute occupational exposure to antineoplastic agents. *J Occup Med* 1988;30:984–987.
16. Ladik C, Stroehr G, Mauer M. Precautionary methods in the preparation of antineoplastics. *Am J Hosp Pharm* 1980;37:1184–1186.
17. Sotaniemi EA, Sutinen S, Arranto AJ, et al. Liver damage in nurses handling cytostatic agents. *Acta Med Scand* 1983;214:181–189.
18. Valanis B, Vollmer W, Labuhn K, Glass A. Occupational exposure to antineoplastic agents and self-reported infertility among nurses and pharmacists. *J Occup Environ Med* 1997;39:574–580.
19. Hemminki K, Axelson O, Niemi ML, Ahlborg G. Assessment of methods and results of reproductive occupational epidemiology: spontaneous abortions and malformations in the offspring of working women. *Am J Ind Med* 1983;4:293–307.
20. Hemminki E, Kyyronen P, Lindblom M. Spontaneous abortions and malformations in the offspring of nurses exposed to anesthetic gases, cytostatic drugs and other hazards in hospitals, based on registered information of outcome. *J Epidemiol Community Health* 1985;39:141–147.
21. Harris P, Conner T, Stevens K, Thesis J. Cytogenetic assessment of occupational exposure of nurses to antineoplastic agents. *J Occup Med Toxicol* 1992;1:243–254.
22. McGregor D. Occupational exposure to trace concentrations of waste anesthetic gases. *Mayo Clin Proc* 2000;75:273–277.
23. Skov T, Maarup B, Olsen J, Rorth M, Winthereik H, Lynge E. Leukaemia and reproductive outcome among nurses handling drugs. *Br J Ind Med* 1992;49:855–861.
24. Stucker I, Caillard J, Collin R, Poyen D, Hemon D. Risk of spontaneous abortion among nurses handling antineoplastic drugs. *Scand J Work Environ Health* 1990;17:133–138.
25. Valanis B, Vollmer W, Steele P. Occupational exposure to antineoplastic agents: self reported miscarriage and stillbirths among nurses and pharmacists. *J Occup Environ Med* 1999;41:632–638.
26. Saurel-Cubizolles M. Ectopic pregnancy and occupational exposure to antineoplastic drugs. *Lancet* 1993;34:1169–1171.
27. Savitz D, Whelan E, Kleckner R. Effects of parents' occupational exposures on risk of stillbirth, pre-term delivery and small-for-gestational-age infants. *Am J Epidemiol* 1989;129:1201–1217.
28. Selevan S, Lindbohm M, Hornung R, Hemminki K. A study of occupational exposure to antineoplastic drugs and fetal loss in nurses. *N Engl J Med* 1985;313:1173–1178.
29. Stucker I, Hirsch A, Doloy T, Bastie-Sigec I, Hemon D. Urine mutagenicity, chromosomal abnormalities and sister chromatid exchanges in lymphocytes of nurses handling cytostatic drugs. *Int Arch Occup Environ Health* 1986;57:195–205.
30. Rieche K. Carcinogenicity of antineoplastic agents in man. *Cancer Treat Rev* 1984;11:39–67.
31. Hengstler JG, Fuchs J, Oesch F. DNA strand breaks and DNA cross links in peripheral mononuclear blood cells of ovarian cancer patients during chemotherapy with cyclophosphamide/carboplatin. *Cancer Res* 1992;52:5622–5626.
32. Fuchs J, Hengstler D, Jung D, Hiltl G, Konietzko J, Oesch F. DNA damage in nurses handling antineoplastic agents. *Mutat Res* 1995;342:17–23.
33. Grummt T, Grummt H, School G. Chromosomal aberrations in peripheral lymphocytes of nurses and physicians handling antineoplastic drugs. *Mutat Res* 1993;302:19–24.
34. Blair A, Zheng T, Linos A, Stewart P, Zhang Y, Cantor K. Occupation and leukemia: a population-based case-control study in Iowa and Minnesota. *Am J Ind Med* 2002;40:3–14.
35. Rix B, Lynge E. Cancer incidence in Danish health care workers. *Scand J Soc Med* 1996;24:114–120.
36. Petralia S, Dosemeci M, Adams E, Zahm S. Cancer mortality among women employed in health care occupations in 24 US states, 1984–1993. *Am J Ind Med* 1999;36:59–165.
37. Skov T, Maarup B, Olsen J, Rorth M, Lynge E, Winthereik H. Risk for physicians handling antineoplastic drugs. *Lancet* 1990;336:1446.
38. Lanza A, Robustelli della Cuna FS, Zibera C, Pedrazzoli P, Robustelli della Cuna G. Somatic mutations at the T-cell antigen receptor in antineoplastic drug-exposed populations: comparison with sister chromatid exchange frequency. *Int Arch Occup Environ Health* 1999;72:315–322.
39. Jakab M, Major J, Tompa A. Follow-up genotoxicological monitoring of nurses handling antineoplastic drugs. *J Toxicol Environ Health* 2001;62:307–318.
40. McDiarmid M, Kolodner K, Humprey F, Putman D, Jacobson-Fram D. Baseline and phosphoramidate mustard-induced sister-chromatid exchanges in pharmacists handling anticancer drugs. *Mutat Res* 1992;279:199–204.
41. Mucci M, Ianni A, Ursini C, Orsini M, Arzani D, Ramano-Spica V. Cytostatic drugs and health risks for exposed personnel: search for new biomarkers. *Cancer Res* 2000;20:2995–3000.
42. Pilger A, Kohler I, Stettner H, et al. Long-term monitoring of sister chromatid exchanges and micronucleus frequencies in pharmacy personnel occupationally exposed to cytostatic drugs. *Int Arch Occup Environ Health* 2000;73:442–448.
43. Turci R, Sottani C, Rochi A, Minoia C. Biological monitoring of hospital personnel occupationally exposed to antineoplastic agents. *Toxicol Lett* 2002;134:57–64.
44. Baker E, Connor T. Monitoring occupational exposure to cancer chemotherapy drugs. *Am J Hosp Pharm* 1996;53:2713–2723.
45. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990;47:1033–1049.
46. OSHA (1986). Guidelines for cytotoxic (antineoplastic) drugs. Washington, DC: Department of Labor, Occupational Safety and Health Administration, Office of Occupational Medicine Publication No. 8–1.1.
47. OSHA (1999). OSHA technical manual, TED 1–0.15A, Sec VI, Chapter II: Categorization of drugs as hazardous. Available at: www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html#2. Accessed: July 21, 2005.
48. Polovich M, ed. *Safe Handling of Hazardous Drugs*. Pittsburgh, PA: Oncology Nursing Society; 2003.

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