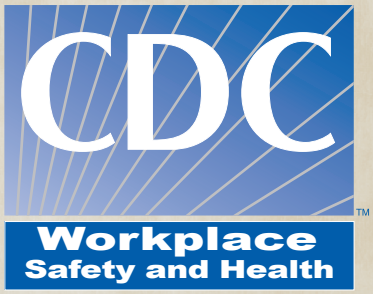

Multiple Sclerosis Cluster Evaluation in an Inpatient Oncology Ward – Wisconsin

Elena Page, MD, MPH

James Couch, CIH, MS, REHS/RS

Health Hazard Evaluation Report
HETA 2011-0047-3143
October 2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention

NIOSH *National Institute for Occupational Safety and Health*

The employer shall post a copy of this report for a period of 30 calendar days at or near the workplace(s) of affected employees. The employer shall take steps to insure that the posted determinations are not altered, defaced, or covered by other material during such period. [37 FR 23640, November 7, 1972, as amended at 45 FR 2653, January 14, 1980].

Contents

Abbreviations

ACGIH®	American Conference of Governmental Industrial Hygienists
CFR	Code of Federal Regulations
cm	Centimeter
cm^2	Centimeter squared
CO	Carbon monoxide
HHE	Health hazard evaluation
IARC	International Agency for Research on Cancer
LC/MS/MS	Liquid chromatography/mass spectrometry/mass spectrometry
LOD	Limit of detection
LOQ	Limit of quantification
mL	Milliliter
MS	Multiple sclerosis
NAICS	North American Industry Classification System
ND	Not detected
ng	Nanogram
ng/cm^2	Nanograms per square centimeter
NIOSH	National Institute for Occupational Safety and Health
OEL	Occupational exposure limit
OSHA	Occupational Safety and Health Administration
PEL	Permissible exposure limit
PPE	Personal protective equipment
ppm	Parts per million
REL	Recommended exposure limit
STEL	Short-term exposure limit
TLV®	Threshold limit value
TWA	Time-weighted average
WEEL™	Workplace environmental exposure level

Highlights of the NIOSH Health Hazard Evaluation

The National Institute for Occupational Safety and Health (NIOSH) received an employee request for a health hazard evaluation at the inpatient oncology unit of a university hospital in Wisconsin. Employees submitted the request because of concerns about exposure to chemotherapy drugs, the metabolites of these drugs (specifically acrolein), and helicopter exhaust. Three nurses had been recently diagnosed with multiple sclerosis, and several other staff reported symptoms possibly from exposure to the exhaust.

What NIOSH Did

- We visited the unit in May 2011.
- We interviewed employees about their work practices and health concerns.
- We sampled work surfaces in the unit for two chemotherapy drugs. We tested the samples for cyclophosphamide and ifosfamide.
- We measured carbon monoxide in the air in the unit.
- We looked at the helicopter landing area. We wanted to see if helicopter exhaust could enter the hospital ventilation system.

What NIOSH Found

- We found no association between the cases of multiple sclerosis and the work environment.
- Several employees reported symptoms when they smelled helicopter exhaust. Their symptoms included headache, dizziness, and nausea.
- Housekeepers reported symptoms when they used diluted bleach. Symptoms included headache, sore throat, and exacerbation of asthma.
- Most employees followed policies on the use of personal protective equipment (PPE).
- We found very small amounts of cyclophosphamide and ifosfamide on some surfaces.
- Levels of carbon monoxide were well below occupational exposure limits.
- We found the potential for hazardous drugs to contaminate the family areas of the hospital.
- Helicopter exhaust could enter the hospital ventilation system.

What Managers Can Do

- Continue to review and revise employee training on hazardous drugs and health effects. Make sure the training complies with the Occupational Safety and Health Administration's Hazard Communication Standard.
- Enforce use of PPE when handling hazardous drugs.
- Start a medical surveillance program for employees who handle hazardous drugs.
- Follow the NIOSH policy for handling hazardous drugs.
- Double bag hazardous drugs that will be transported from the central pharmacy to the unit.
- Relocate and expand the chemotherapy waste disposal system.
- Start a health and safety committee to look at hazardous drugs.
- Tell patient's families that hazardous drugs are used on the unit and how to reduce their exposure to these drugs.

What Employees Can Do

- Follow recommended work practices and PPE procedures.
- Continue to learn how to safely work with hazardous drugs.

Summary

NIOSH investigators evaluated workplace exposures to acrolein, CO, and chemotherapy drugs in an inpatient oncology unit. We also investigated a potential cluster of MS. We found no association between the MS cases and the work environment. The CO levels were well below OELs, but some employees could smell helicopter exhaust, which they associated with headache, dizziness, and nausea. We found small amounts of cyclophosphamide and ifosfamide on some surfaces, including the family areas of the hospital wing, which could indicate breaches in the handling of chemotherapeutic agents in this unit.

In January 2011 NIOSH received an employee HHE request concerning a potential cluster of MS cases among nurses employed in the inpatient oncology unit of a university hospital in Wisconsin. The request detailed concern about acrolein as a potential exposure from metabolized chemotherapy drugs used in the unit (cyclophosphamide and ifosfamide) and as a component of helicopter exhaust from the nearby hospital landing pad.

We visited the hospital on May 23–24, 2011. We observed work processes, practices, and conditions in the oncology unit. We interviewed employees in the unit about their concerns related to chemotherapy drugs. We collected surface wipe samples for two chemotherapy drugs used in the unit, cyclophosphamide and ifosfamide. Additionally, we examined the helicopter landing pad and its proximity to the outdoor air intake for the ventilation system for the oncology unit and sampled for CO (a constituent of the helicopter exhaust).

We interviewed all 29 employees working first or second shift in the unit, and one employee by phone. Of the interviewed employees, 17 reported no work-related symptoms. The remaining employees reported symptoms, including headache, dizziness, nausea, and light sensitivity, when they smelled helicopter exhaust. None of the unusual patterns of reproductive health problems that can occur with exposure to many chemotherapeutics were seen. The three employees with MS were all women within the average age range for diagnosis of MS; none had a family history of MS. On the basis of what we currently know about the epidemiology, characteristics, and treatment of MS, it is unlikely that these cases are associated with workplace exposures, including acrolein.

Most of the surface wipe samples we collected for cyclophosphamide and ifosfamide were below the LOQ; only one sample was above the LOQ. CO concentrations were well below OELs. We found that under certain meteorological conditions helicopter exhaust could enter the ventilation system of the unit.

We recommended that the unit continue to control exposures to chemotherapy drugs to levels as low as are reasonably achievable because some of these drugs are considered hazardous [NIOSH 2010a]. Control of exposures can be validated by routine surface sampling for chemotherapy drugs used in the unit.

Keywords: NAICS 622110 (General Medical and Surgical Hospitals), acrolein, multiple sclerosis, hazardous drugs, chemotherapy drugs

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Introduction

NIOSH received a request from three employees in the inpatient oncology unit ("unit") of a university hospital in Wisconsin about exposures to chemotherapy drugs and helicopter exhaust. Three nurses in the unit were diagnosed with MS, and several other staff reported symptoms from exposure to the exhaust. The employees were also concerned that exposure to acrolein, a metabolite from exposure to some chemotherapy drugs that is also present in helicopter engine exhaust, may be associated with MS.

The 39-bed unit housed hematology/oncology, bone marrow transplant, and palliative care patients. At the time of this evaluation, the average occupancy was 68%, and 17% of the patients received chemotherapy daily. A pharmacy in the unit was staffed by two pharmacists daily. Chemotherapy drugs were delivered to the unit by tube or by cart. These drugs left the pharmacy enclosed in resealable plastic bags that reportedly were cleaned before being delivered to the unit. Hazardous drugs were mixed, and lines were primed in the main pharmacy, but up until 1 week before our visit pills were crushed on the unit. Registered nurses were the only hospital personnel allowed to clean up chemotherapy spills. They used commercially available spill kits.

The unit had family lounges and no age restrictions on visitors; however, visitors were not supposed to use patient bathrooms. In the evenings patients and family members were allowed to use a washer and dryer behind the nurse's station to do their personal laundry.

Assessment

We visited the unit from May 24–26, 2011. During the visit we met with employer and employee representatives to discuss the HHE request. We observed work processes, practices, and workplace conditions and spoke with employees. We reviewed new chemotherapy PPE requirements, chemotherapy certification training, and the university policy for preventing occupational exposure to hazardous drugs. We held confidential interviews with all employees present on the day and evening shifts during our visit to discuss health and workplace concerns.

Details of the sample collection and analysis for cyclophosphamide and ifosfamide, two chemotherapy drugs used in the unit, are provided in Appendix A. We collected surface wipe samples throughout the unit and in other locations in the hospital for

Assessment (continued)

comparison. These samples were analyzed for cyclophosphamide and ifosfamide by LC/MS/MS.

We checked for CO by placing five GasAlert Extreme monitors (BW Technology America, Arlington, Texas) in the unit to measure CO concentrations from Tuesday afternoon until Wednesday evening. The CO concentrations were compared to the helicopter event log and the air quality log kept by the unit employees. Using a Q-Trak™ monitor (TSI, Shoreview, Minnesota), we also measured CO concentrations in the building housing the unit.

We chose to measure CO instead of acrolein as an indicator for helicopter exhaust entering into the unit's ventilation system for several reasons. One reason was that previous air sampling for acrolein by a consulting group hired by the hospital did not detect acrolein in the ventilation system that services the unit. Another reason was that we could continuously monitor CO levels in and around the unit over a 2-day period with direct-reading monitors. We checked the hospital's helicopter landing area and its proximity to the outdoor air intake for the unit's ventilation system and visually examined the plenum (the space above the suspended ceiling) in the unit.

During the opening conference, a problem with chemotherapy gloves breaking was raised. The gloves, Esteem® Stretchy Nitrile (Cardinal Health, Dublin, Ohio), were approved for use with chemotherapy drugs. The staff provided us with a box of gloves that was perceived to have a high breakage rate. We visually inspected the gloves and contacted the manufacturer.

Results

We interviewed 29 employees in person and one by phone. This included 13 registered nurses, 9 certified nurse assistants, 2 health unit clerks, 3 housekeepers, and 3 pharmacists. Three were men. They had worked on the unit from 3 months to 17 years.

Of the interviewed employees, 17 reported no symptoms that they related to work. One employee reported coughing at work for several weeks when on the palliative wing near an area being renovated. Several reported symptoms when they smelled helicopter exhaust: four reported headache, two reported dizziness, two reported nausea, and one reported light sensitivity. In addition, one employee reported headaches and lightheadedness

at work unrelated to helicopter exhaust, and one reported having a carboxyhemoglobin level of 1.9 (laboratory upper limit of normal 1.5) after fainting at work. A repeat measurement on another day was normal. All housekeepers reported that using household bleach diluted 1:10 caused symptoms, including asthma exacerbation in one. None of the unusual patterns of reproductive health problems that can occur with exposure to many chemotherapeutics were seen.

The three employees with MS were all women, and none had a family history of MS. One reported having mononucleosis as a child (a risk factor for MS). All were within the average age range for diagnosis of MS (usually between the ages of 20 and 50). One was born in May, one in November, and one in August (Cases of MS are more common in persons born in May, suggesting that seasonality and the gestational environment may influence the risk of MS.) Two reported menarche at age 11, one at 13 (There is some evidence that early menarche may increase risk of MS).

Hospital policy dictates that nurses are to don two pairs of chemotherapy protective gloves and a chemotherapy protective gown when handling chemotherapy drugs. Eleven nurses reported always wearing double gloves when handling chemotherapy drugs, one reported sometimes wearing double gloves, and one reported never wearing double gloves. The latter two reported wearing single gloves. Twelve nurses reported always wearing a gown when handling chemotherapy drugs, and one reported wearing a gown sometimes. Nursing assistants are supposed to wear double gloves, a gown, and a face shield when handling excreta from patients on cytotoxic precautions and single gloves for others. Seven nursing assistants reported always wearing double gloves when disposing of excreta from patients on cytotoxic precautions, one reported sometimes using double gloves, and one reported using single gloves for handling all excreta. Three reported wearing a gown always, four sometimes, and two reported never wearing a gown. Two reported always wearing a face shield, two reported sometimes wearing a face shield, and five reported never wearing a face shield.

All registered nurses were required to take a 3-day chemotherapy certification course and a 1-day practicum and pass a test before administering these drugs. The course included a module on safe handling of cytotoxic agents but lacked hazard communication training for other personnel who handled or came into contact with these drugs. Nurses who handled chemotherapy drugs had a

computer-based annual review, but that did not include the safe handling module. Employees who handled hazardous drugs were not part of a medical surveillance program.

The university policy for preventing occupational exposure to hazardous drugs was based upon the University Health Consortium Guidelines that categorizes hazardous drugs into high risk hazardous drugs, low risk hazardous drugs, and reproductive risk hazardous drugs. Employees who are trying to conceive or who are pregnant or nursing are considered at risk from reproductive risk hazardous drugs.

The results of the surface samples for cyclophosphamide and ifosfamide are reported in Table 1. Most samples collected (29 of 39) were below the LOD. Surface concentrations in nine samples were between the LOD and the LOQ for either cyclophosphamide or ifosfamide. The highest result, 6.7 ng/100cm^2 for cyclophosphamide, was collected in Room B6-674 on the floor in front of the sink.

All three samples collected in patient rooms on the floor in front of the sink were positive for cyclophosphamide, while one of the three was also positive for ifosfamide. The maximum concentration (6.7 ng/100 cm^2) of cyclophosphamide was found in front of the sink in Room B6-674.

The maximum CO concentration measured by the direct reading monitors was 3 ppm. This occurred on May 24, 2011, around 4:00 p.m. in the nurses' charting area. According to a helicopter event log obtained from the university, no helicopter events were conducted around this time. All other CO monitors measured less than 1 ppm, the reporting limit for this device.

The helicopter landing area was on the roof of a building next to the building housing the oncology unit. A large open green space separated the helicopter landing area from the unit's outdoor air intakes. Additionally, the unit's outdoor air intakes were on the side opposite from the helicopter pad, further decreasing the likelihood of helicopter exhaust entering the unit. These two factors suggest that helicopter exhaust would not routinely enter the unit's outdoor air intakes. We spoke with the helicopter pilot who informed us that wind patterns normally would take the exhaust away from the unit's outdoor air intakes but at times the wind would carry the exhaust towards the unit's outdoor air intakes.

RESULTS (CONTINUED)

Table 1. Surface wipe sample results: May 25, 2011

Room or Area	Location	Cyclophosphamide (ng/100 cm^2)	Ifosfamide (ng/100 cm^2)
	Countertop near pill crusher	ND	ND
B6-666	Countertop beneath suspended IV bags	ND	ND
Pharmacy	Floor in front of medicine station	ND	ND
	Top of chemotherapy waste receptacle	ND	ND
	Countertop near first computer	ND	ND
B6-663	Countertop between two computers	ND	ND
Nurse	Floor between two computers	ND	ND
Station	Hallway directly outside nurse station	ND	ND
	Computer keyboard near printer	ND	ND
B6-622	Hallway floor outside patient room	ND	ND
B6-670	Hallway floor outside patient room near keyboard	(1.4)*	ND
B6-616	Hallway floor outside patient room near keyboard	ND	ND
	Coffee table surface	ND	ND
B6-604 Family	Cyclophosphamide sampled on the right arm of chair Ifosfamide sampled on the left arm of chair	(2.1)†	(3.7)†
Lounge	Exercise bike. Cyclophosphamide sampled on right handle bar and ifosfamide sampled on left handlebar	(3.0)†	ND†
	Table surface	ND	ND
	Cyclophosphamide sampled on inside door handle and ifosfamide sampled on exterior handle	ND†	ND†
B6-652	Floor in front of sink	(3.0)	(2.9)
	Top of bedside table	ND	ND
B6-BMT	Top of coffee table	ND	ND
Family Room	Top of table	(1.7)	ND
	Food rollaway table	ND	ND
B6-672	Bathroom door handle	ND†	ND†
	Floor in front of sink	(2.1)	ND
	Bathroom door handle	ND†	ND†
B6-674	Floor in front of sink	6.7	ND
	Food rollaway table	ND	ND
B6-687	Floor near coffee table	ND	ND
Family	Entrance door	ND	ND
Room	Top of coffee table	ND	ND
B6-665	Floor near computer	(1.9)	ND
Break Room	Floor near doorway	(2.6)	ND
Chart Area	Table top	ND	ND
B6-699	Staff bathroom door handle	ND†	ND†
	Staff bathroom floor	(1.7)	ND
	Door handle	ND†	ND†
	Floor near doors	ND	ND
HSLC	Floor near stairs	ND	ND
Atrium	Table top in lounge	ND	ND
	Stair hand rail near middle of stairs	ND†	ND†

ND = Not detected. The LOD was 1 ng/sample for cyclophosphamide and 2 ng/sample for ifosfamide.
*Parentheses indicate that more uncertainty is associated with these sample concentrations because they were between the LOD and the LOQ. The LOQ was 3.5 ng/sample for cyclophosphamide and 6.7 ng/sample for ifosfamide.
†Estimated 100 cm^2

The outdoor air dampers on the ventilation intake system for the building containing the helicopter pad could be electronically opened or closed depending on helicopter arrivals and departures. However, the outdoor air damper for the unit's ventilation system was not connected to this electronic control system. During departures, the dispatcher remotely closed the outdoor air dampers prior to the helicopter engine starting. The outdoor air dampers were reopened approximately 15 minutes after a departure. For arrivals, the dampers were closed and not reopened until approximately 15 minutes after the helicopter engines had been shut down.

The maximum CO concentration we measured in spot checks with the Q-Trak handheld instrument was 1.0 ppm, well below the NIOSH REL of 35 ppm for a full-shift TWA and a ceiling limit of 200 ppm [NIOSH 2010b]. The ventilation system in the plenum of the unit appeared clean and well maintained.

Our visual inspection of the gloves from the high breakage box revealed no abnormalities. We also asked several volunteers to put on two pairs of the gloves (simulating double-gloving) and observed no breakage problems. The manufacturer had received no reports of problems with the gloves or the specific lot number of the gloves that was provided to us.

DISCUSSION

Multiple Sclerosis

MS is the most common inflammatory disease of the central nervous system. The incidence of MS varies depending on the population and geographic area, but ranges from less than 5 to 200 per 100,000 persons [Milo and Kahana 2010]. MS is more common in women and usually is diagnosed between the ages of 20 and 50, with a peak at about 30 years of age [Milo and Kahana 2010]. MS is significantly more common in persons born in May and significantly less common in persons born in November, suggesting that the gestational environment and seasonality may influence the risk of MS later in life [Pugliatti et al. 2008]. This disease is uncommon in Asia and in tropical and subtropical parts of all continents. In temperate climates, MS incidence and prevalence are generally higher with increasing latitude (for example, in colder climates); however, this latitude gradient is

disappearing [Ascherio and Munger 2007]. The incidence of MS in migrants usually lies between the incidence of their birthplace and the incidence of their final residence. MS risk declines for persons migrating from high to low risk areas, but does not always increase if migration is in the opposite direction [Ascherio and Munger 2007]. Thus, migration data imply that exposures early in life determine if a person gets MS, although Australian migration studies indicate that the risk may extend into early adulthood [Hammond et al. 2000].

Although we know some of the risk factors associated with MS, we do not know what causes this disease. Some studies suggest an interaction between genes and the environment [Giovannoni and Ebers 2007; Asherio and Munger 2008; Pugliatti et al. 2008]. The incidence of MS is about 30 times higher in siblings of MS patients than in the general population [Asherio and Munger 2008]. In addition, this appears to be related to the mother, with maternal half-siblings having much higher risk than paternal half-siblings [Ebers et al. 2004; Handel et al. 2010; Ramagopalan et al. 2010]. HLA-DRB1 and HLA-DBQ1 are genetic loci currently linked to MS [Giovannoni and Ebers 2007; Asherio and Munger 2008].

The three main theories about environmental risk factors for MS, sunlight and vitamin D, infection (especially with Epstein-Barr virus), and smoking are discussed in Appendix C. Employees in this evaluation were concerned that exposure to acrolein (an aldehyde) caused an increased risk of MS. Increased levels of reactive aldehydes, including acrolein, in the brain and cerebrospinal fluid have been noted in a number of neurodegenerative diseases [Wood et al. 2007]. A recent study induced experimental autoimmune encephalomyelitis (the animal model of MS) in mice and determined acrolein levels in these and mice without the disease [Leung et al. 2011]. This particular study led the nurses on the unit to suspect acrolein as the cause of their MS because cyclophosphamide and ifosfamide, two commonly used chemotherapeutic agents, are metabolized to acrolein. In addition, acrolein exposure from the helicopter exhaust was a concern because exhaust can contain acrolein.

Acrolein is difficult to study because it is ubiquitous in food and the environment and can be produced within the body [Stevens and Maier 2008]. While the role of acrolein in MS is unclear, refractory MS (MS that resists treatment) can be successfully treated with high doses of cyclophosphamide [Krishnan et al.

2008]. No published studies demonstrating a higher risk of MS in persons treated with cyclophosphamide or ifosfamide for cancer or other medical conditions could be found.

Disease Clusters

It may be helpful to discuss disease clusters because of the three cases of MS in this small work group. Diseases often appear to occur in clusters, which scientists define as an unusual concentration of cases in a defined area or time [CDC 1990]. The cases may have a common cause or may be the coincidental occurrence of unrelated causes. The number of cases may seem high, particularly among the small group of people who have something in common with the cases, such as working in the same building. Although the occurrence of a disease may be random, diseases often are not distributed randomly in the population, and clusters of disease may arise by chance alone [Metz and McGuinness 1997].

In many workplaces the number of cases is small. This makes detecting whether the cases have a common cause difficult, especially when there are no apparent causative exposures. It is common for the borders of the perceived cluster to be drawn around where the cases are located (in this case, the unit), instead of defining the population and geographic area first. This often leads to the inaccurate belief that the rate of disease is high. This is referred to as the "Texas sharpshooter effect" because the Texas sharpshooter shoots at the barn and then draws his bull's eye around the bullet hole. This may well be the case on this unit. It is possible, even likely, that the population is a much larger population, possibly the entire hospital, including past and present employees, and even visitors and patients. It may be larger than the hospital. In addition, no clusters of MS among employees handling chemotherapy drugs were identified in our search of the medical literature. One cluster of MS was reported among nurses in Key West, Florida, in the 1980s, with 7 of 307 nurses diagnosed with MS [Dean and Gray 1990]. This led to a study of MS death rates among nurses and qualified medical practitioners in the United Kingdom, which found no increase compared to the general population [Dean and Gray 1990].

Discussion (continued)

Environmental Exposures

We found small amounts of cyclophosphamide and ifosfamide on surfaces in the unit, including the family areas. This suggests breaches in hospital controls when handling these drugs. This is important because even small amounts of these drugs can cause serious adverse effects, including cancer and adverse reproductive outcomes. We believe that when dealing with hazardous drugs, programmatic efforts towards continuous improvement are paramount in controlling potential exposures to as low as reasonably achievable. Control of these exposures should be confirmed by routine sampling for chemotherapy drugs that are used on the unit.

Although CO exposures were low, employees occasionally reported odors and symptoms when the helicopter took off or landed. Activated charcoal filters were recently installed on the unit ventilation system to address the odor and potential helicopter exhaust issues. While the activated charcoal filters will not effectively remove CO, they would be effective in removing acrolein and helping reduce nuisance odors from the air.

Conclusions

On the basis of what we currently know about MS, its epidemiology, characteristics, and treatment, it is unlikely that the MS cases are associated with workplace exposures. Small amounts of cyclophosphamide or ifosfamide were detected on some surface wipe samples, including samples collected from family areas. The measured CO levels were well below OELs, suggesting that helicopter exhaust was not routinely entering the ventilation system servicing the unit.

Recommendations

On the basis of our findings, we recommend the actions listed below to create a more healthful workplace. We encourage the hospital to use a labor-management health and safety committee or working group to discuss the recommendations in this report and develop an action plan. Those involved in the work can best set priorities and assess the feasibility of our recommendations for the specific situation at the hospital. Our recommendations are based on the hierarchy of controls approach (refer to Appendix B: Occupational Exposure Limits and Health Effects). This approach

groups actions by their likely effectiveness in reducing or removing hazards. In most cases, the preferred approach is to eliminate hazardous materials or processes and install engineering controls to reduce exposure or shield employees. Until such controls are in place, or if they are not effective or feasible, administrative measures and/or personal protective equipment may be needed.

Engineering Controls

Engineering controls reduce exposures to employees by removing the hazard from the process or placing a barrier between the hazard and the employee. Engineering controls are very effective at protecting employees without placing primary responsibility of implementation on the employee.

1. Investigate the feasibility of incorporating the ventilation system for the unit into the existing electronic system for opening and closing outdoor air ventilation intakes during takeoff and landing helicopter events. Ensure that closing the intakes will not negatively affect any special ventilation requirements in the unit, i.e., positive and negative air pressure rooms.

Administrative Controls

Administrative controls are management-dictated work practices and policies to reduce or prevent exposures to workplace hazards. The effectiveness of administrative changes in work practices for controlling workplace hazards is dependent on management commitment and employee acceptance. Regular monitoring and reinforcement are necessary to ensure that control policies and procedures are not circumvented in the name of convenience or production.

1. Ensure compliance with the OSHA Hazard Communications Standard, 29 CFR 1910.1200. The Safe Handling and Disposal of Chemotherapy training module that is part of the initial chemotherapy certification course may be modified to fulfill the initial training requirement. All employees who may be exposed to chemotherapy drugs, not only registered nurses who will be administering chemotherapy, should participate in this training before beginning work.

RECOMMENDATIONS (CONTINUED)

2. Follow the NIOSH policy for handling hazardous drugs instead of the University Health Consortium guidelines. The NIOSH policy is to use standard precautions or a universal precautions approach to hazardous drugs. This means that all hazardous drugs should be handled in the same manner as outlined in the NIOSH Alert titled "NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings 2010," which is available at http://www.cdc.gov/niosh/docs/2010-167/.
3. Clarify the central pharmacy procedures to determine if the pharmacy is cleaning the outside of bags containing hazardous drugs before they are transported outside the pharmacy.
4. Use double bags to transport hazardous drugs from the central pharmacy to the unit to reduce the potential for bag contamination and to contain accidental spills.
5. Relocate and expand the chemotherapy waste disposal system. The central disposal unit currently in the pharmacy is relatively small and may require removal during the day when the pharmacy has high occupancy and foot traffic.
6. Implement a medical surveillance program for employees potentially exposed to hazardous drugs as recommended in the NIOSH document titled "Medical Surveillance for Health Care Workers Exposed to Hazardous Drugs," which is available at http://www.cdc.gov/niosh/docs/wp-solutions/2007-117/pdfs/2007-117.pdf.
7. Form a hazardous drug health and safety committee to discuss topics specific to the use and disposal of hazardous drugs. This committee should include at least one employee representative who can voice the concerns of his or her peers. The committee should also include a safety and health professional to provide insight into controlling occupational exposures to these drugs.
8. Inform family members of patients who visit the unit that hazardous drugs are used on the unit and how to minimize exposure to them, i.e., washing hands upon leaving the unit. This includes family members of patients not receiving hazardous drugs themselves because the family lounge areas and bathrooms are shared by all visitors. This information could be conveyed to the patient and family at the time of admission, and reinforced by placement of posters or placards throughout the unit.

9. Review the cleaning procedures for the family areas to determine how chemotherapy drug contamination occurs and revise to ensure the surfaces are cleaned appropriately.
10. Alert housekeeping staff of the potential for chemotherapy drug contamination in the family areas and remind them to wear chemotherapy protective gloves when cleaning these areas.
11. Continue to log air quality events in the unit including time, location, duration, and associated health effects. The logs should be reported to or reviewed weekly by the nurse manager. Report concerns about air quality to plant engineering for investigation and potential corrective action.

Personal Protective Equipment

PPE is the least effective means for controlling employee exposures. Proper use of PPE requires a comprehensive program, and calls for a high level of employee involvement and commitment to be effective. The use of PPE requires the choice of the appropriate equipment to reduce the hazard and the development of supporting programs such as training, change-out schedules, and medical assessment if needed. PPE should not be relied upon as the sole method for limiting employee exposures. Rather, PPE should be used until engineering and administrative controls can be demonstrated to be effective in limiting exposures to acceptable levels.

Educate employees on the proper techniques for donning and doffing chemotherapy protective gloves. This education should include the potential for tears of the gloves by fingernails, rings, etc.

1. Consider changing to a different chemotherapy protective glove or offer an alternative glove for employees who are experiencing breakage if the perceived high breakage rates continue.

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Appendix A: Chemotherapy Methods

The cyclophosphamide samples were collected on Alpha® Texwipe swabs moistened with an extraction solvent comprised of 50% acetonitrile and 50% deionized water. A 10 cm x 10 cm disposable square template was used to outline a 100 cm^2 sampling area. Wipe samples were analyzed for cyclophosphamide by LC/MS/MS with an LOD of 1 ng of cyclophosphamide/sample and an LOQ of 3.5 ng of cyclophosphamide per sample. All media and field blanks were below the LOD. The sampling method is an internal procedure developed by Bureau Veritas North America, the NIOSH contract laboratory.

The ifosfamide samples were collected on 70-mL glass fiber filters moistened with deionized water. A 10 cm x 10 cm disposable square template was used to outline a 100 cm^2 sampling area. Wipe samples were analyzed for ifosfamide by LC/MS/MS with an LOD of 2 ng of ifosfamide/sample and an LOQ of 6.7 ng of ifosfamide/sample. All media and field blank results were below the LOD. The sampling method is an internal procedure developed by Bureau Veritas North America.

Appendix B: Occupational Exposure Limits and Health Effects

In evaluating the hazards posed by workplace exposures, NIOSH investigators use both mandatory (legally enforceable) and recommended OELs for chemical, physical, and biological agents as a guide for making recommendations. OELs have been developed by federal agencies and safety and health organizations to prevent the occurrence of adverse health effects from workplace exposures. Generally, OELs suggest levels of exposure that most employees may be exposed to for up to 10 hours per day, 40 hours per week, for a working lifetime, without experiencing adverse health effects. However, not all employees will be protected from adverse health effects even if their exposures are maintained below these levels. A small percentage may experience adverse health effects because of individual susceptibility, a preexisting medical condition, and/or a hypersensitivity (allergy). In addition, some hazardous substances may act in combination with other workplace exposures, the general environment, or with medications or personal habits of the employee to produce adverse health effects even if the occupational exposures are controlled at the level set by the exposure limit. Also, some substances can be absorbed by direct contact with the skin and mucous membranes in addition to being inhaled, which contributes to the individual's overall exposure.

Most OELs are expressed as a TWA exposure. A TWA refers to the average exposure during a normal 8- to 10-hour workday. Some chemical substances and physical agents have recommended STEL or ceiling values where adverse health effects are caused by exposures over a short period. Unless otherwise noted, the STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday, and the ceiling limit is an exposure that should not be exceeded at any time.

In the United States, OELs have been established by federal agencies, professional organizations, state and local governments, and other entities. Some OELs are legally enforceable limits, while others are recommendations. The U.S. Department of Labor OSHA PELs (29 CFR 1910 [general industry]; 29 CFR 1926 [construction industry]; and 29 CFR 1917 [maritime industry]) are legal limits enforceable in workplaces covered under the Occupational Safety and Health Act of 1970. NIOSH recommended exposure limits are recommendations based on a critical review of the scientific and technical information available on a given hazard and the adequacy of methods to identify and control the hazard. NIOSH RELs can be found in the *NIOSH Pocket Guide to Chemical Hazards* [NIOSH 2010]. NIOSH also recommends different types of risk management practices (e.g., engineering controls, safe work practices, employee education/training, personal protective equipment, and exposure and medical monitoring) to minimize the risk of exposure and adverse health effects from these hazards. Other OELs that are commonly used and cited in the United States include the TLVs recommended by ACGIH, a professional organization, and the WEELs recommended by the American Industrial Hygiene Association, another professional organization. The TLVs and WEELs are developed by committee members of these associations from a review of the published, peer-reviewed literature. They are not consensus standards. ACGIH TLVs are considered voluntary exposure guidelines for use by industrial hygienists and others trained in this discipline "to assist in the control of health hazards" [ACGIH 2011]. WEELs have been established for some chemicals "when no other legal or authoritative limits exist" [AIHA 2011].

Outside the United States, OELs have been established by various agencies and organizations and include both legal and recommended limits. The Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA, Institute for Occupational Safety and Health of the German Social Accident

Insurance) maintains a database of international OELs from European Union member states, Canada (Québec), Japan, Switzerland, and the United States. The database, available at http://www.dguv.de/ifa/en/gestis/limit_values/index.jsp, contains international limits for over 1,500 hazardous substances and is updated periodically.

Employers should understand that not all hazardous chemicals have specific OSHA PELs, and for some agents the legally enforceable and recommended limits may not reflect current health-based information. However, an employer is still required by OSHA to protect its employees from hazards even in the absence of a specific OSHA PEL. OSHA requires an employer to furnish employees a place of employment free from recognized hazards that cause or are likely to cause death or serious physical harm [Occupational Safety and Health Act of 1970 (Public Law 91–596, sec. 5(a)(1))]. Thus, NIOSH investigators encourage employers to make use of other OELs when making risk assessments and risk management decisions to best protect the health of their employees. NIOSH investigators also encourage the use of the traditional hierarchy of controls approach to eliminate or minimize identified workplace hazards. This includes, in order of preference, the use of (1) substitution or elimination of the hazardous agent, (2) engineering controls (e.g., local exhaust ventilation, process enclosure, dilution ventilation), (3) administrative controls (e.g., limiting time of exposure, employee training, work practice changes, medical surveillance), and (4) personal protective equipment (e.g., respiratory protection, gloves, eye protection, hearing protection). Control banding, a qualitative risk assessment and risk management tool, is a complementary approach to protecting employee health that focuses resources on exposure controls by describing how a risk needs to be managed. Information on control banding is available at http://www.cdc.gov/niosh/topics/ctrlbanding/. This approach can be applied in situations where OELs have not been established or can be used to supplement the OELs, when available.

Below we provide the OELs and surface contamination limits for the compounds we measured, as well as a discussion of the potential health effects from exposure to these compounds.

Cyclophosphamide

Cyclophosphamide is categorized as a Group 1 Carcinogen (carcinogenic to humans) [IARC 1998]. This designation means that there is sufficient evidence that cyclophosphamide can cause cancer in humans. Cyclophosphamide metabolizes in the body to acrolein, which can cause adverse effects in the bladder.

Cyclophosphamide is a cytotoxic drug used for a wide range of neoplastic diseases including breast and lung cancer, pediatric malignancies, leukemia, lymphomas, etc. It can be prescribed as a single agent or in combination with other chemotherapy drugs and can be administered via oral tablets or intravenously.

Cyclophosphamide is normally found in a white powder form for chemical stability and is usually brought into liquid solution by the addition of water and infused with sodium chloride, glucose, or glucose/saline solutions. Once in solution, it is recommended that cyclophosphamide be administered to the patient within 8 hours to prevent degradation or stored at cold temperatures but never frozen.

No OELs for cyclophosphamide exist. However, because of the carcinogenic nature of the drug, NIOSH investigators believe that exposures to cyclophosphamide should be kept as low as reasonably achievable.

Ifosfamide

Ifosfamide is a cytotoxic drug used for a wide range of neoplastic diseases including ovary, testis, lung, and breast cancers, and soft-tissue sarcomas. It can be prescribed as a single agent or in combination with other chemotherapy drugs and can be administered via oral tablets or intravenously. Ifosfamide is normally found in a white powder form for chemical stability and is usually brought into solution by the addition of water and infused with sodium chloride, glucose, or glucose/saline solutions.

Ifosfamide is not designated as carcinogenic to humans by IARC, OSHA, or NIOSH. It has been reported to be mutagenic in bacterial cells through the Ames test. Ifosfamide metabolizes in the body to acrolein, which can cause adverse effects in the bladder. No OELs for ifosfamide exist. However, because of its highly reactive nature within the human body, NIOSH investigators believe that exposures to ifosfamide should be kept as low as reasonably achievable.

Hazardous Drugs in Healthcare Settings

Exposures to hazardous drugs including chemotherapy drugs may occur through inhalation, skin contact, skin absorption, ingestion, or injection. Inhalation and skin contact/absorption are the most likely routes of exposure, but unintentional ingestion from hand to mouth contact and unintentional injection through a needlestick or sharps injury are also possible [Duvall and Baumann 1980; Black and Presson 1997; Schreiber et al. 2003].

Protection from hazardous drug exposures depends on safety programs established by employers and followed by workers. Factors that affect worker exposures include drug handling circumstances (preparation, administration, or disposal), amount of drug prepared, frequency and duration of drug handling, potential for absorption, use of ventilated cabinets, PPE, and work practices. More information on this topic is available in the NIOSH Alert titled "Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings" [NIOSH 2004].

Carbon Monoxide

CO is a colorless, odorless, tasteless gas produced by incomplete burning of carbon-containing materials. The initial symptoms of CO poisoning may include headache, dizziness, drowsiness, or nausea. Symptoms may advance to vomiting, loss of consciousness, and collapse if exposures to much higher concentrations than those measured in this evaluation are encountered. The NIOSH REL for CO is 35 ppm for full-shift TWA exposure [NIOSH 1972]. NIOSH has established a CO ceiling limit of 200 ppm that should never be exceeded and an immediately dangerous to life or health value of 1200 ppm [NIOSH 1992, 2000]. The

ACGIH recommends an 8-hour TWA TLV of 25 ppm [ACGIH 2011], and the OSHA PEL for CO is 50 ppm for an 8-hour TWA exposure [29 CFR 1910.1000].

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Appendix C: Risk Factors for Multiple Sclerosis

MS is the most common inflammatory disease of the central nervous system and is characterized by demyelination, loss of axons, gliosis, and perivascular infiltration of monocytes primarily in the white matter [Milo and Kahana 2010]. MS patients usually present with a clinically isolated syndrome, which is a first neurological event with documented demyelination in the optic nerve or central nervous system [Ramagopalan et al. 2010]. More than half of individuals with a clinically isolated syndrome go on to develop MS. Radiological abnormalities consistent with MS can be identified in persons without symptoms; this is called a radiologically isolated syndrome, and these individuals also have a high risk of developing MS [Ramagopalan et al. 2010]. MS manifests in a variety of ways, including numbness and or tingling in the extremities, tremors, visual disturbances, and muscle weakness.

The three main theories about environmental risk factors for MS involve sunlight and vitamin D, infection (especially with Epstein-Barr virus), and smoking. Latitude is related to numerous physical, chemical, biological, and social factors, but one of its strongest correlates is the intensity and the duration of sunlight, the primary source of vitamin D. Numerous studies support a role of sunlight exposure and vitamin D in development of MS. For example, outdoor workers are significantly less likely to die from MS than indoor workers, and actinic damage to the skin is inversely related to MS incidence [Asherio and Munger 2007]. Other studies have shown an inverse relationship between vitamin D intake and MS risk, and between serum 25(OH)D levels prior to diagnosis of MS and the risk of MS [Asherio and Munger 2007]. Having higher serum levels of 25(OH)D exerts a much stronger protective effect before age 20 than after [Asherio and Munger 2007]. In addition, exposure to ultraviolet radiation has an immunosuppressive effect.

Numerous studies support a role of infection in risk for MS. Evidence for Epstein-Barr virus infection as a risk factor is the strongest [Giovannoni and Ebers 2007; Pugliatti et al. 2008]. Epstein-Barr virus is a lifelong dormant infection in B cells. More than 99% of MS patients are infected with Epstein-Barr virus compared to about 90% of controls [Ebers et al. 2004; Giovannoni and Ebers 2007]. Individuals negative for Epstein-Barr virus have a 10-fold lower risk of developing MS than those with evidence of asymptomatic childhood infection [Pugliatti et al. 2008]. In addition, infectious mononucleosis, which is symptomatic Epstein-Barr virus infection, places people who have had this condition at more than twice the risk of developing MS than those who have not [Ebers et al. 2004; Giovannoni and Ebers 2007; Pugliatti et al. 2008; Ramagopalan et al. 2010]. Higher titers of anti-Epstein-Barr virus are associated with increased risk of developing MS than lower titers [Ramagopalan et al. 2010].

Several studies documented a positive association between cigarette smoking and MS [Ebers et al. 2004; Asherio and Munger 2007; Giovannoni and Ebers 2007; Pugliatti et al. 2008]. Smoking has also been linked to aggravation of MS [Asherio and Munger 2007].

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Acknowledgments and Availability of Report

The Hazard Evaluations and Technical Assistance Branch (HETAB) of the National Institute for Occupational Safety and Health (NIOSH) conducts field investigations of possible health hazards in the workplace. These investigations are conducted under the authority of Section 20(a)(6) of the Occupational Safety and Health Act of 1970, 29 U.S.C. 669(a)(6) which authorizes the Secretary of Health and Human Services, following a written request from any employer or authorized representative of employees, to determine whether any substance normally found in the place of employment has potentially toxic effects in such concentrations as used or found. HETAB also provides, upon request, technical and consultative assistance to federal, state, and local agencies; labor; industry; and other groups or individuals to control occupational health hazards and to prevent related trauma and disease.

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This report was prepared by Elena Page and James Couch of HETAB, Division of Surveillance, Hazard Evaluations and Field Studies. Industrial hygiene field assistance was provided by Kemka Hekerem. Industrial hygiene equipment and logistical support was provided by Donnie Booher and Karl Feldmann. Analytical support was provided by Bureau Veritas North America. Health communication assistance was provided by Stefanie Evans. Editorial assistance was provided by Ellen Galloway. Desktop publishing was performed by Robin Smith.

Below is a recommended citation for this report:
NIOSH [2011]. Health hazard evaluation report: multiple sclerosis cluster evaluation in an inpatient oncology ward – Wisconsin. By Page E, Couch J. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, NIOSH HETA No. 2011-0047-3143.

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