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NIOSH HEALTH HAZARD EVALUATION REPORT

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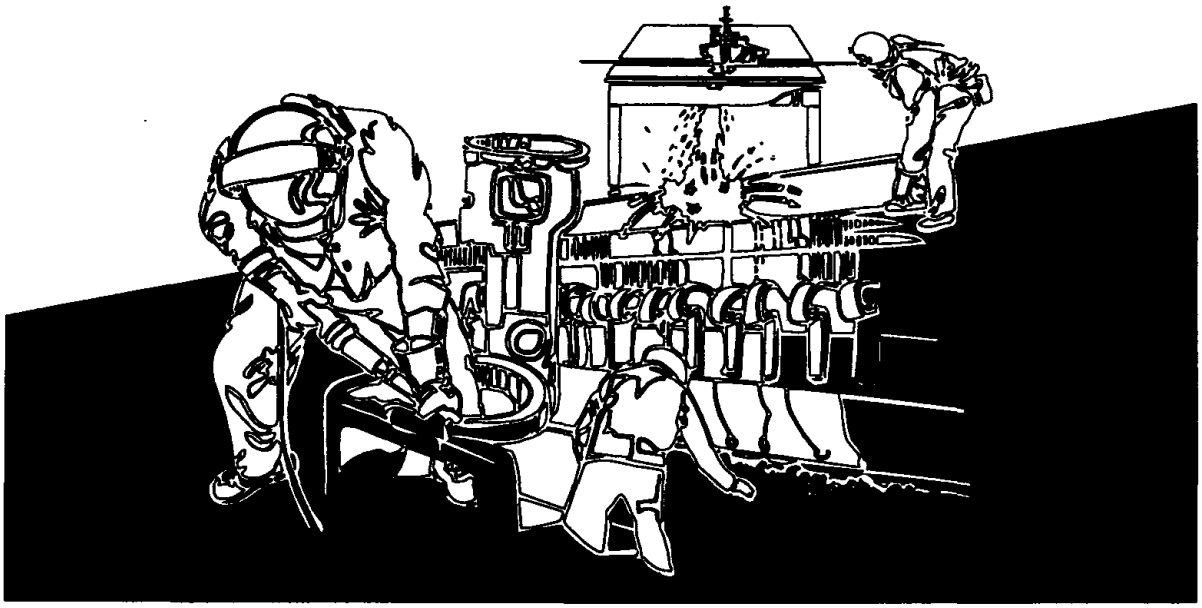
MD Anderson Cancer Center
Houston, Texas

Max Kiefer, MS, CIH



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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PREFACE

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 (OSHA) 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.

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ACKNOWLEDGMENTS AND AVAILABILITY OF REPORT

This report was prepared by Max Kiefer of HETAB, Division of Surveillance, Hazard Evaluations and Field Studies (DSHEFS). Analytical support was provided by Al Lunsford and Jim Arnold of the Division of Applied Research and Technology. Desktop publishing was performed by Nichole Herbert and Pat Lovell. Review and preparation for printing were performed by Penny Arthur.

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Highlights of the NIOSH Health Hazard Evaluation

Evaluation of Aerosolized 9-Nitrocamptothecin

NIOSH conducted a health hazard evaluation at the MD Anderson Cancer Center to evaluate exposure controls during the aerosol administration of an experimental anticancer drug, 9-nitrocamptothecin, in controlled trials.

What NIOSH Did

- We took air samples during the administration of the anticancer drug.
- We looked at work practices.
- We reviewed the ventilation system and the containment device used to control exposure to the anticancer drug.

What NIOSH Found

- The containment device worked well.
- Room ventilation and containment tent ventilation were good.
- Patient practices and habits affect the release of the anticancer drug.
- A home treatment setting will require special considerations to ensure safety.

What MD Anderson Cancer Center Managers Can Do

- Tell patients and health care workers about how they can affect contaminant release.
- Check for surface contamination.
- Make sure that when anticancer drugs are given in the home, that it is done safely.

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National Institute for Occupational Safety and Health
NIOSH

Health Hazard Evaluation Report 98-0052-2820

Health Hazard Evaluation Report 98-0052-2820
MD Anderson Cancer Center
Houston, Texas
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Max Kiefer, MS, CIH

SUMMARY

On November 25, 1997, the National Institute for Occupational Safety and Health (NIOSH) received a management request for a health hazard evaluation (HHE) at the MD Anderson Cancer Center in Houston, Texas. This request asked NIOSH to evaluate the efficacy of exposure controls during the administration of an experimental antineoplastic agent, 9-nitrocamptothecin (9-NC), to cancer patients, as an aerosol through breathing treatments. No worker health problems were reported in the request; the researchers were interested in evaluating the potential for exposure to health care workers during administration of the drug. During the NIOSH evaluation, experimental work was in the clinical trial stage, and the doses and administration method were agreed upon by the Food and Drug Administration (FDA) as part of their approval process.

NIOSH investigators conducted a site visit to the MD Anderson Cancer Center on September 22, 1998, to review the process and determine an appropriate evaluation strategy. At this time, FDA approval to administer 9-NC to cancer patients had not been granted. On August 30, 1999, a return site visit was conducted to collect air samples during the use of 9-NC; low doses of 9-NC were being administered to one patient. Air sampling problems, however, invalidated the results and a return visit was conducted on August 15-16, 2000. During this site visit, area and personal breathing zone (PBZ) air samples for dilauroylphosphatidylcholine (DLPC), a surrogate indicator of 9-NC, were collected. The ventilation system was assessed, and particle monitoring was conducted. This report contains the findings of the August 15, 2000, site visit.

During the air monitoring, there were three ventilated patient containment tents in a separately ventilated treatment room operating under negative pressure. Each isolation tent contained the entire treatment ensemble and a chair for the patient. On both days sampled, there were two sets of treatments, with different patients for each set. Detectable concentrations of DLPC were found on area samples collected both inside (41 nanograms per liter [ng/l]) and outside (29.2 ng/l) the treatment tent during the second set of treatments on August 15, 2000. On both days sampled, detectable DLPC was measured inside the treatment tent from the same patient. DLPC was not detected in the treatment room outside the treatment tent during the first set of treatments on August 15, 2000, or during any treatments on August 16, 2000. No DLPC was detected in either of the PBZ samples collected from the treatment administrator or area samples outside the treatment room. Exposure criteria for 9-NC or DLPC has not been established and assessing the health consequences of exposure to the concentrations measured is not possible. Although only limited data was obtained, the particle monitoring conducted during the second set of treatments on both days also showed relatively higher numbers of particles $\geq$ 1.0 micrometers in diameter (µmd).

The detected DLPC and higher particle numbers can probably be attributed to patient activity; the patient undergoing treatment during the time period DLPC was detected, was active, frequently spoke, and occasionally lifted the treatment tent skirt. The ventilation controls and containment system appear to be adequate, but must be used properly to ensure proper function and that emissions are contained.

Surface contamination and the potential exposure of other personnel (e.g., hospital pharmacists) involved in the preparation of the 9-NC liposome were not evaluated during this project. Additionally, the MD Anderson researchers are developing a compassionate (home treatment) system for delivery of the anticancer treatment. Home treatment will present different issues that must be evaluated from a health and safety standpoint. The type of containment and ventilation device, adequacy of facilities, housekeeping, room ventilation, equipment maintenance, and agent storage will vary considerably. Training of personnel responsible for administering the drug to ensure it is handled and disposed of properly will be very important.

Under the conditions evaluated, the air monitoring results indicate the delivery and containment system used for the 9-NC treatments effectively control emissions to below detectable limits when patient activity during treatments is limited and the containment system is kept intact. Low airborne levels of DLPC were measured inside and outside the containment tent during treatments involving a patient who was active and talking. No measurable DLPC was detected outside the treatment room, indicating the ventilation system on the containment device, and the room ventilation were adequate to control emissions. Exposure criteria for DLPC or 9-NC has not been established. Surface contamination of 9-NC was not assessed during this project and the impact of increasing the 9-NC dose was not evaluated. A home treatment system will require additional evaluation to ensure all safety and health issues associated with this use are adequately addressed.

Keywords: SIC Code: 8069 (Specialty Hospitals, Except Psychiatric). 9-Nitrocamptothecin, Antineoplastic Agents, Aerosolized Drug Administration, Experimental Trials, Liposomal Aerosols.

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INTRODUCTION

In response to a management request from the MD Anderson Cancer Center, National Institute for Occupational Safety and Health (NIOSH) investigators conducted a health hazard evaluation (HHE) to assess the efficacy of exposure controls during the aerosol administration of an experimental antineoplastic agent, 9-nitrocamptothecin (9-NC). No health problems were reported, and NIOSH was asked to collect air samples and evaluate the containment system used to control health care worker exposure during the administration of the drug.

At the time of the request, the Food and Drug Administration (FDA) approval to use initial low doses of the drug (below the hypothesized therapeutic dose) for administration to cancer patients had not been granted. On September 22, 1998, NIOSH investigators conducted a site visit at the MD Anderson Cancer Center. The purpose of this site visit was to review the patient containment device, ventilation, and drug delivery system for the use of 9-NC. Analytical methodologies for measuring 9-NC and the liposome carrier, dilauroylphosphatidylcholine (DLPC) were discussed. Because the FDA required additional toxicological studies and other information, initial trials involving the administration of the 9-NC formulation (at low doses) to patients did not begin until the summer of 1999. On August 30, 1999, a NIOSH investigator conducted a site visit at the MD Anderson Cancer Center to collect air samples during the administration of 9-NC to a cancer patient. The ventilation system was evaluated and particle monitoring was also conducted. However, problems with the air sampling invalidated all samples and a return site visit was necessary. A followup site visit was conducted on August 15-16, 2000, to monitor airborne concentrations of DLPC, a surrogate indicator of the 9-NC. Prior to this visit, FDA had approved the use of higher doses and additional volunteers for the experimental cancer treatment were obtained; three treatment stations were operational during the NIOSH followup visit. This report describes the results of the August 15-16, 2000, site visit.

BACKGROUND

MD Anderson Cancer Center

The University of Texas MD Anderson Cancer Center was first established in 1944 and is one of the first three comprehensive cancer centers designated by the National Cancer Act of 1971. It is situated on 18 acres within the Texas Medical Center complex. Fundamental and applied cancer research is conducted, including clinical trials for every type of cancer. New drug and gene therapies are developed and evaluated to develop new cancer treatments.

Aerosol Delivery of 9-nitrocamptothecin

Aerosol drug delivery systems are an effective mechanism for introducing therapeutic agents into patients with lung disease. The use of aerosol delivery systems is increasingly popular because it can provide localized topical therapy in the lungs and deposit high drug concentrations at sites of disease.[1,2] Complications, such as toxicity, can also be reduced by this technique as systemic exposure is minimized.

The development of liposome aerosols to deliver lipophilic drugs has greatly increased the potential for aerosol drug delivery systems.[3] Liposomes are microscopic spherical lipid vesicles that can be engineered to entrap drugs. Liposomes are commonly produced from phospholipids and cholesterol; the composition can be changed to affect solubility and other parameters. Liposomes are being widely used for aerosol drug treatments because of advantages such as enhanced efficacy, safety, or both. Liposome aerosols of appropriate particle size can increase lung deposition, decrease upper respiratory tract deposition, and prolong the residence time of deposited materials in the lower airways.[3,4] Liposomes as drug carriers can change the therapeutic

profiles of some antineoplastics in a favorable manner and allow them to be used in situations not previously considered.[5] Liposomes may reduce or prevent local irritation and toxic reactions; increased potency with reduced toxicity has also been reported for some formulations.[2] Liposome aerosols are typically administered from nebulizers where the liposome and drug are suspended in an aqueous medium in the reservoir of the nebulizer. During operation, the liquid and liposomes are aspirated up a tube to the nebulizer head where a stream of compressed air forces the material through a narrow aperture. A relatively monodisperse aerosol of a specific particle size (e.g., 1-3 micrometers in diameter [μmd]) is produced and delivered to the patient.

At the MD Anderson Cancer Center, the phospholipid DLPC was used to prepare liposomes of 9-NC for the experimental trials. A number of studies were initially conducted to assess the safety and tolerability of the liposome, efficacy against tumors, determine the particle size of the aerosol, and develop operational parameters for use in the trials.[3,6,7] The ratio of phospholipid to 9-NC is relatively constant and is approximately 50:1.

The aerosol delivery system used at MD Anderson for the 9-NC liposome treatments was an AeroTech II™ disposable nebulizer with a dual valve configuration that allows the patient to breathe normally while inhaling medication. This nebulizer is designed to generate particles in the size range of 1-2 microns in diameter. The nebulizer is connected to a breathing mask with flexible tubing and is worn by the patient for the duration of the treatment. A flexible exhalation tube from the breathing mask is fixed to the tent ventilation to assist with scavenging the exhaled aerosol. Dry compressed air is used as the air source for the nebulizer and breathing treatments.

Aerosol flow with compressed air was controlled to 10 liters per minute (L/min) to ensure consistent particle size and delivery. Particle size analysis conducted by the researchers using Anderson cascade impactors determined that the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the aerosol under these conditions ranged from 0.8-1.6 μmd and from 1.8-2.6 μmd, respectively.[6]

During the treatments, the patient is seated inside a ventilated containment tent and can read or watch television. The prepared drug is obtained from the pharmacy and injected by the health care worker (under the containment tent) into the nebulizer.

METHODS

Air Sampling

Integrated air samples were collected using 1 micron polytretrafluorethylene (PTFE) filters (SKC 223-1705) with a backup pad in 37 millimeter (mm) 2-piece cassettes as the collection medium. The samples were collected using constant-flow SKC model 224 Universal sampling pumps. Flow rates of 2.5 L/min were used to collect the samples. Sampling times varied from the duration of an individual treatment to the entire workshift. Personal breathing zone (PBZ) samples were collected on both days from the health care worker administering the 9-NC aerosol; monitoring was conducted for the duration of the treatments. Area samples were collected inside each treatment tent, in the treatment room, and a "control" area (Nurses Station) outside the treatment room. One high volume sample was collected on August 15, 2000, in the treatment room (outside the containment tents); this sample was collected to

maximize sensitivity. The pumps were calibrated with a BIOS dry-cell primary calibrator prior to and after collecting the samples and the flow rates averaged. The sample volume is the product of the flow rate and sampling duration. After collection, the sample cassettes were sealed and submitted with blanks to the NIOSH laboratory for analysis.

At the NIOSH laboratory the filters were analyzed for DLPC as a surrogate of potential exposure to 9-NC. Analysis was by high performance liquid chromatography (HPLC) with an evaporative light scattering detector (ELSD). Bulk samples of stock DLPC and camptothecin were provided to the NIOSH laboratory to develop standard solutions for calibration and quality control purposes. The instrument limit of detection (LOD) was 0.6 micrograms (µg) DLPC and the limit of quantification (LOQ) was 3.0 µg.

Particle monitoring was conducted with a factory calibrated Met One, Inc. Model 227B hand held laser particle counter. These units are capable of monitoring two particle size ranges simultaneously, and were set to monitor all particles ≥0.3 µmd and those ≥1.0 µmd. The unit was set to average three 1-minute count cycles with a 10 second interval between each cycle at a flow rate of 0.1 cubic feet per minute (cfm). Monitoring was conducted at various time intervals inside the treatment room and in a control area.

Ventilation

The ventilation assessment consisted of measuring the air velocity of the containment tent exhaust at the exhaust hood opening (face velocity) and determining the hood dimensions. The exhaust volume, in cfm, is the product of the average face velocity and the area of the hood opening. The dimensions of the containment tent were approximated, and an estimate of air exchanges was determined.

Air velocity measurements were obtained with a TSI Velocicalc® model 8600 anemometer. This instrument measures air velocity in feet per minute (fpm). For each system evaluated, 12 measurements were obtained and the results averaged to obtain the mean velocity.

Ventilation information for the room containing the treatment tents was obtained from Baylor/MD Anderson safety and health representatives.

EVALUATION CRITERIA

As a guide to the evaluation of the hazards posed by workplace exposures, NIOSH field staff employ environmental evaluation criteria for the assessment of a number of chemical and physical agents. These criteria are intended to suggest levels of exposure to which most workers may be exposed up to 10 hours per day, 40 hours per week for a working lifetime without experiencing adverse health effects. It is, however, important to note that not all workers will be protected from adverse health effects even though their exposures are maintained below these levels. A small percentage may experience adverse health effects because of individual susceptibility, a pre-existing 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 worker to produce health effects even if the occupational exposures are controlled at the level set by the criterion. These combined effects are often not considered in the evaluation criteria. Also, some substances are absorbed by direct contact with the skin and mucous membranes, and thus potentially increases the overall exposure. Finally, evaluation criteria may change over the years as new information on the toxic effects of an agent become available.

The primary sources of environmental evaluation criteria for the workplace are: (1) NIOSH Recommended Exposure Limits (RELs),[8] (2) the American Conference of Governmental Industrial Hygienists' (ACGIH®) Threshold Limit Values (TLVs®),[9] and (3) the U.S. Department of Labor, Occupational Safety and Health Administration

(OSHA) Permissible Exposure Limits (PELs).[10] Employers are encouraged to follow the OSHA limits, the NIOSH RELs, the ACGIH TLVs, or whichever are the more protective criterion.

OSHA requires an employer to furnish employees a place of employment that is free from recognized hazards that are causing or are likely to cause death or serious physical harm [Occupational Safety and Health Act of 1970, Public Law 95-596, sec. 5.(a)(1)]. Thus, employers should understand that not all hazardous chemicals have specific OSHA exposure limits such as PELs and short-term exposure limits (STELs). An employer is still required by OSHA to protect their employees from hazards, even in the absence of a specific OSHA PEL.

A time-weighted average (TWA) exposure refers to the average airborne concentration of a substance during a normal 8- to 10-hour workday. Some substances have recommended STEL or ceiling values which are intended to supplement the TWA where there are recognized toxic effects from higher exposures over the short-term.

Antineoplastic agents

Effective antineoplastic drugs are difficult to design because they must selectively kill or impair the growth of malignant cells with minimal affect on only subtly different host cells. There are many agents that are highly toxic to tumor cells, but are also toxic to normal cells, primarily those that are rapidly dividing.[11] Because of the toxicity of antineoplastic and other hazardous drugs, occupational exposure risks to health care workers handling these agents must be addressed. The health risk to personnel will depend on the inherent toxicity of the drug and the extent of exposure. Exposure pathways could include inhalation, inadvertent ingestion, and skin contact. Administration of drugs via aerosolization is of particular concern and evaluations of these activities (e.g., ribavirin, pentamidine) have found measurable air concentrations in the breathing zone of workers providing the treatment.[13] Depending on the drug, potential adverse health effects from overexposure could include carcinogenicity, teratogenicity, or serious organ or other toxicity.[4] Because of these concerns, guidelines for the safe handling of hazardous drugs have been developed by both regulatory agencies and professional associations.[12,13,14]

Exposure to potentially significant workplace levels can occur during the preparation, administration, or disposal of hazardous drugs both in the health care and home treatment settings. Pharmacists, nurses, physicians, and other health care workers may be at risk of exposure. The degree of exposure and absorption, and the significance of the exposure, are difficult to assess and vary depending on the drug.[13] Establishing exposure criteria for many of these drugs is difficult and there are few established exposure limits for hazardous drugs. Good safety and health programs should focus on minimizing exposure to all potentially hazardous drugs.

Camptothecin

The anticancer drug camptothecin is a water insoluble natural plant alkaloid that has the ability to halt the growth of a wide range of human tumors. The compound was first isolated in 1966 from the Chinese plant *Camptotheca accuminata*, and was shown to have major antitumor activity in animal models.[15,16] The camptothecin family appears to have unique antitumor properties by inhibiting topoisomerase I, an enzyme involved in the maintenance of DNA topology.[16,17] Unfortunately, these drugs have significant toxic effects and rapidly lose antitumor activity, and their use has been limited. Toxic effects include myelosuppression, severe diarrhea, and chemical cystitis.[18,19] Various derivatives of camptothecin have been formulated and used in animal and human trials in an attempt to overcome these shortcomings. These efforts have generally involved altering the solubility of the parent camptothecin compound to increase the specific activity of the drug. One derivative, 9-NC, has been shown to have increased specific activity, higher potency than camptothecin, and one of the best activity/toxicity ratios.[16,20] Adverse effects from

exposure to 9-NC can include bladder irritation, anemia, hair loss, myelosuppression, nausea, and vomiting. Regulatory criteria or guidelines describing recommended exposure limits for camptothecin or 9-NC have not been established.

RESULTS

During the NIOSH evaluation the liposome was prepared daily by the pharmacy team by lypholizing 2 milligrams (mg) of 9-NC in 10 milliliters (ml) of water into a 20 ml vial with 100 mg of DLPC. This was combined by the attending nurse with 10 ml of water in the nebulizer by injection. Each individual treatment lasts approximately 30 minutes and is repeated after a short patient break to provide a total treatment time of 60 minutes per patient per day. This results in a delivered patient dose of 4 mg of 9-NC per day. The nebulizer output is 10 L/min, and a 15 L/min breathing rate is assumed. Based on a 70 kilograms (kg) person, this translates to approximately 6.7 µg 9-NC/kg/day and a theoretical delivery concentration of 4.1µg/liter of air. The treatment course for each patient during the NIOSH evaluation was 8 weeks, 5 days per week. According to the MD Anderson researchers, plans call for eventually increasing the dose by a factor of four (hypothesized therapeutic dose) pending the outcome of the current trials. MD Anderson researchers have developed a written protocol describing the preparation and administration methodology for the 9-NC liposome aerosol.

Workplace Observations

There were three patient containment tents (Demistifier™ Isolation and Source Control System, Peace Medical) in the treatment room (Figure 1). Each isolation tent contained the entire treatment ensemble (nebulizer, hose, mask) and a chair for the patient. The containment system consisted of a metal frame and a clear vinyl enclosure which surrounds the patient. The system was ventilated at the back of the tent through a powered exhaust fan. The exhaust air passes through a pre-filter, charcoal filter, and final high efficiency particulate air (HEPA) filter prior to discharging into the room. The treatment room has both a supply air and return air vent, and the bathroom exhaust is operational during the treatments. Administratively, the door to the treatment room is closed during treatments and for 15 minutes after cessation of the last treatment.

The treatment administrator wore disposable gloves while handling the drug and injecting it into the nebulizer. After initiating the treatments, the administrator spent most of the time outside the treatment room.

Following each treatment, the tubes and masks are soaked in a cleaning solution with disinfectant by the treatment administrator. Gloves are worn during this activity. The nebulizers are discarded and the tubes and masks are air dried in preparation for subsequent treatments.

Air Sampling Results

DLPC

The results of the air sampling for DLPC are shown in Table 1. These results show the concentration of DLPC detected in air in nanograms of DLPC per liter of air (ng/l). On both days sampled, there were two sets of treatments, with different patients for each set. On August 15, 2000, all three treatment tents in the treatment room were utilized for the first set of treatments. However, only one patient was treated (treatment tent #2) during the second set of treatments. There was some overlap as one patient during the first set of treatments started later than the other two and did not complete the treatment until the second set of treatments had begun. On August 16, 2000, two treatment tents were used during the first set of treatments and one patient was treated (treatment tent #2) during the second set. During the monitoring, ambient conditions in the treatment room were 72° F and 54% relative humidity.

As shown in Table 1, detectable concentrations of DLPC were found on area samples collected both

inside (41 ng/l) and outside (29.2 ng/l) the treatment tent during the second set of treatments on August 15, 2000. On August 16, 2000, a concentration of DLPC between the LOD and LOQ was measured inside treatment tent #2 during the second set of treatments. On both days sampled, detectable DLPC was measured inside the treatment tent from the same patient. DLPC was not detected in the treatment room outside the treatment tent during the first set of treatments on August 15, 2000, or during any treatments on August 16, 2000.

It was observed that patient practices during treatments vary. Most patients sat quietly and read or watched television during administration of the treatment aerosol. All patients were ambulatory and each took a break between treatments and left the treatment tent. Other patients engaged in some conversation or adjusted their surroundings to improve comfort. One patient was being trained for home administration and her husband was assisting with preparing and administering the treatments. The patient who was treated in treatment tent #2 during the second set of treatments on both August 15 and 16, 2000, was somewhat active during the treatments, used a portable laptop computer, and it was observed that he lifted the tent flap occasionally and engaged in some conversation. On one occasion the patient got up and then returned to the treatment tent.

Except for one sample (treatment tent #1, concentration of DLPC between the LOD and LOQ) during the first set of treatments on August 15, 2000, DLPC was not detected in any other samples collected inside the treatment tents. No DLPC was detected in either of the PBZ samples collected from the treatment administrator.

Particle Monitoring

The results of the particle monitoring are shown in Table 2. Inside the treatment room, the monitor was positioned on a table between treatment tents #2 and #3. These results only provide information on the relative number of particles present during the sampling period. The specific chemical constituents of these particles is not determined by this technique. As depicted in the table, a much greater number of particles ≥ 0.3 μmd were detected than those ≥ 1.0 μmd. This was not an unexpected finding and is typical of most environments. There was also a fairly large difference in the number of particles detected in the control area on August 15 and August 16, 2000. It is likely that the primary source of the particles is from recent activities in the area (filing, paperwork, other activities). The short time period of the sampling, the sensitivity of the monitor, and the non-specific nature of the detection technique, could explain this type of variability. Furthermore, sampling conducted during the second set of treatments on both days showed relatively higher numbers of particles ≥ 1.0 μmd.

Ventilation

Containment Tents

Each portable containment tent was approximately 32" X 32" X 64" (estimated volume = 40 cubic feet) when fully extended and with the bottom of the vinyl containment skirt about 1 foot off of the floor. The filtered exhaust was located at the back of the unit by the steel support stand, behind the patient chair. Air draws upward from the area around the bottom of the skirt and flows through the HEPA exhaust system prior to discharge into the room. The exhaust hose

from the breathing mask was fixed to the ventilation filter to aid in scavenging any exhaled or bypassed aerosol. An average of 12 measurements across the face of the filter found a mean velocity of 82 fpm on tent #1, 80 fpm on tent #2, and 85 fpm on tent #3. The overall average for the three systems was 82 fpm. The dimensions of the filter (22.5 inches X 10.5 inches) provided a filtered surface area of 1.64 square feet. The product of the area of the exhaust face and the average velocity in fpm provides an average exhaust volume of 135 cfp. Given an estimated tent volume (empty) at full extension of 40 cubic feet, this equates to approximately 200 air changes per hour inside the tent. A yellowish discoloration was observed at the point where the breathing mask exhaust hose connects to the filter.

Room Ventilation

Negative pressure in the treatment room was verified only qualitatively during the NIOSH site visit. Light tissue paper was held adjacent the treatment room door when it was open approximately one inch and the direction of air flow was observed. MD Anderson safety and health personnel subsequently provided information about the ventilation in the treatment room. The treatment room ventilation has its own air handling unit and is separately exhausted and not connected to the main ventilation system. The room and bathroom combined are approximately 1340 cubic feet in volume. Recently measured exhaust and supply rates found the exhaust air to be 212 cfm in the main room and 29 cfm in the bathroom. The return air volume was measured to be 183 cfm. This equates to approximately 9.5 air changes per hour.

DISCUSSION

Patient behavior and activity will affect the potential for release outside the immediate containment area. Airborne DLPC was detected when the patient undergoing treatment was active and this possibly affected the integrity of the containment system. The particle monitoring was limited and should not be over-interpreted. However, higher numbers of particles $\geq$ 1.0 µmd were measured during the second set of treatments on both days monitored. This is consistent with the DLPC monitoring and observations of patient practices increasing the likelihood of agent release from the containment tent. These results suggest that particle monitoring may have some utility in assessing the efficacy of containment systems and the effect of work practices on releases during administration of aerosolized drugs.

The levels of DLPC detected were very low, and these were a surrogate indicator of the antineoplastic 9-NC. Actual concentrations of 9-NC are estimated at approximately 50X less than the measured DLPC. However, MD Anderson researchers anticipate increasing the delivered patient dose of 9-NC by a factor of four, which may affect potential exposures. Exposure criteria has not been established for 9-NC and assessing the health consequences of exposure to the concentrations measured is not possible. However, the toxicity of 9-NC is well described and, as with other antineoplastic agents overexposure can result in adverse health effects. As such, precautions should be taken to minimize exposure. In the absence of specific exposure criteria, prudence suggests that exposure should be controlled to as low a level as feasible. This can be accomplished by using existing, available engineering controls (containment, filtered ventilation), good work practices, health care and patient training, and good housekeeping between treatments.

The delivery ensemble and containment system appeared to work well, and in most trials effectively contained the administered drug. The exhaust capacity appears to be sufficient to maintain the containment area under negative pressure and provided a considerable turnover of filtered air. The treatment room was separately ventilated and is maintained under negative pressure with respect to the main nurses' station.

Surface contamination was not evaluated during this project. Although associating surface contamination with exposure is very difficult, surface contamination

is an important consideration with antineoplastic agents and should be addressed.[21,22] Exposure standards, guidelines, or recommendations by NIOSH or regulatory agencies have not been established for antineoplastic agents on surfaces, skin, or work clothes. However, skin exposures are often considered to be an important portion of total exposure and there is little data regarding the potential for and extent of low-level dermal exposure to antineoplastic agents from contaminated work surfaces. Additionally, the potential exposure of other personnel (e.g., hospital pharmacists) involved in the preparation of the 9-NC liposome were not evaluated during this project.

As part of the FDA approval process, the MD Anderson researchers have been developing a compassionate (home treatment) system for delivery of the anticancer treatment. Home treatment, where a family member is trained to administer the drug, can be beneficial from the standpoint of patient comfort and cost. Home treatment will present different issues that must be evaluated from a health and safety standpoint. - a new type of containment and ventilation device, adequacy of facilities, housekeeping, room ventilation, equipment maintenance, and agent storage will vary considerably. Training of personnel responsible for administering the drug to ensure it is handled and disposed of properly will be very important.

CONCLUSIONS

Under the conditions evaluated (9-NC doses approximately 4X below the hypothesized therapeutic dose), the air monitoring results indicate the delivery and containment system used for the 9-NC treatments effectively control emissions to below detectable limits when patient activity during treatments is limited and the containment system is kept intact. DLPC was used as a surrogate indicator of 9-NC; actual 9-NC concentrations would be expected to be lower. Low airborne levels of DLPC were measured inside and outside the containment tent during treatments involving a patient who was active, frequently spoke, and on occasion moved or raised the containment skirt. No measurable DLPC was detected outside the treatment room, indicating the ventilation system on the containment device, and the room ventilation were adequate to control emissions. Exposure criteria for DLPC or 9-NC has not been established and the emphasis should be on controlling potential exposures to as low as possible. The particle monitoring results were somewhat consistent with the DLPC air monitoring results; higher concentrations of particles $\geq$ 1 µmd were detected during administration of treatments to the active patient. Particle monitoring with direct-reading instrumentation appears to be a useful screening method for assessing the efficacy of a containment system. Surface contamination of 9-NC was not assessed during this project and the impact of increasing the 9-NC dose was not evaluated. Although criteria for surface contamination of antineoplastic agents has not been developed, surface monitoring can provide useful information regarding the spread of contamination and housekeeping practices. A home treatment system will require additional evaluation to ensure all safety and health issues associated with this use are adequately addressed. Adequate procedures, proper equipment, and training of personnel conducting the home treatments, as well as family members will be necessary for home treatment applications.

RECOMMENDATIONS

1. The potential for surface contamination of 9-NC should be evaluated. This could entail collection of wipe samples to determine the level and extent of contamination. Although standards defining "acceptable" levels of surface contamination have not been established, surface wipe samples can provide information regarding the effectiveness of housekeeping practices, the potential for exposure to contaminants from other exposure routes (e.g., surface contamination on a table that is also used for food consumption), the potential for contamination of worker clothing and subsequent transport of the contaminant, and the potential for non-process related

activities to generate airborne contaminants (e.g., custodial sweeping).

2. The potential for exposure to other personnel (e.g., hospital pharmacists) involved in preparing the 9-NC should be evaluated to ensure appropriate procedures and safeguards are in place.

3. Ensure that safety considerations for the administration of the 9-NC in the home setting are fully addressed. Evaluation of a number of factors, including equipment, training, storage, maintenance, etc. is necessary.

4. Patients receiving treatment, and the treatment administrator, should be informed of the effect of patient activities on the potential for releasing the administered drug outside the containment system. Procedures to ensure that patients remain within the containment tent for the entire treatment and do not affect the integrity of the containment should be implemented.

5. After determining the final therapeutic dose that will be used, additional assessments should be conducted to determine if the increased concentration of 9-NC affects the potential for health care worker exposure.

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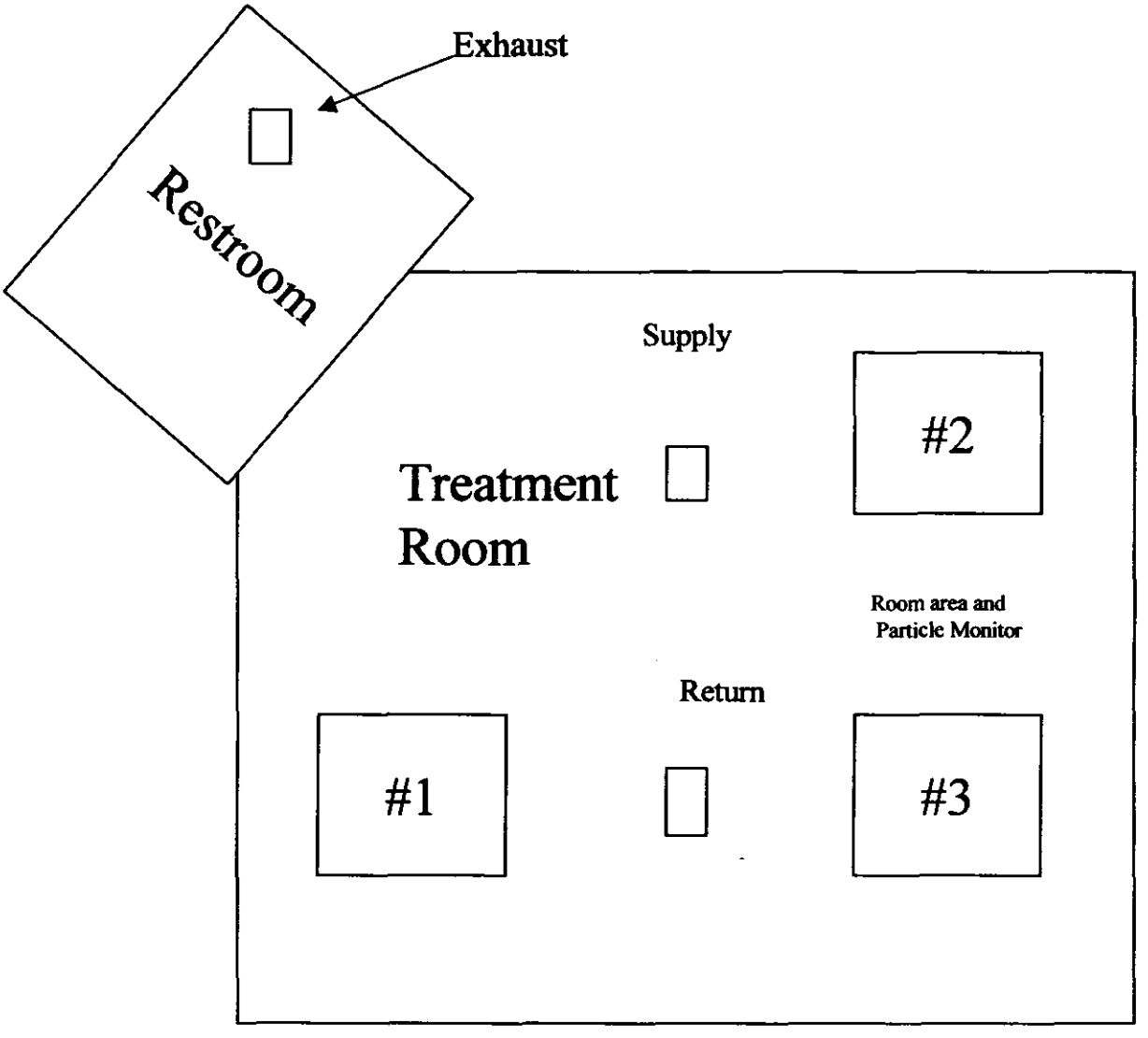

Figure 1: Treatment Room, MD Anderson Cancer Center

Table 1 MD Anderson Cancer Center Air Sampling Results - DLPC HETA 98-0052-2820 August 15, 2000		
Location	**Time (minutes)**	**Concentration (ng/l)**
Area - Treatment Room	07:40-9:04 (84)	<0.59
Area - Treatment Tent #2 (1st treatment)	07:40-09:00 (80)	<3.0
Area - Treatment Tent #1	08:27-09:57 (90)	(6.2)
Area - Treatment Tent #3	07:39-09:17 (98)	<2.5
Area - Nurses Station outside Treatment Room	07:36-11:03 (207)	<1.2
Area - Treatment Room	09:06-11:02 (114)	29.2
Area - Treatment Tent #2 (2nd treatment)	09:20-10:56 (96)	41
Personal - Treatment Administrator	07:38-11:06 (206)	<1.2
August 16, 2000		
Area - Treatment Room	07:30-11:16 (226)	<1.1
Area - Treatment Tent #2 (1st treatment)	07:39-9:05 (86)	<2.8
Area - Treatment Tent #3	07:39-9:37 (118)	<2.0
Area - Nurses Station outside Treatment Room	07:31-11:22 (231)	<1.0
Area - Treatment Tent #2 (2nd treatment)	09:21-11:16 (115)	(9.6)
Personal - Treatment Administrator	07:30-11:23 (233)	<1.0

DLPC = dilauorylphosphatidyl choline
ng/l = nanograms of DLPC per liter of air sampled
( ) = values in parentheses indicate a value between the analytical limit of detection and the limit of quantification
< = less than

Table 2
MD Anderson Cancer Center
Particle Monitoring Results
HETA 98-0052-2820
August 15-16, 2000

Location	Time	Criteria	Particles Counted by Size Range	
			>0.3 µmd	>1.0 µmd
August 15, 2000				
Treatment Room, Background - Prior to Administration	7:30 a.m.	Average	8921	565
		Minimum	8519	526
		Maximum	9197	596
Treatment Room during 1st set of treatments. Ventilation on	7:45 a.m.	Average	8204	684
		Minimum	8045	622
		Maximum	8311	755
Treatment Room during 1st set of treatments. Ventilation on	7:55 a.m.	Average	8084	577
		Minimum	7987	538
		Maximum	8140	629
Nurses Station outside treatment room (control area)	8:02 a.m.	Average	10052	336
		Minimum	9995	303
		Maximum	11007	372
Treatment Room during 1st set of treatments (2nd course)	8:15 a.m.	Average	8739	644
		Minimum	8695	610
		Maximum	8775	667
Treatment Room during 1st set of treatments (2nd course)	8:30 a.m.	Average	10692	820
		Minimum	9732	727
		Maximum	12022	980
Treatment Room during 2nd set of treatments. Two tents operational	9:55 a.m.	Average	16656	1106
		Minimum	15562	1048
		Maximum	17947	1143

Location	Time	Criteria	Particles Counted by Size Range	
			>0.3 µmd	>1.0 µmd
Treatment Room, Background - Prior to Administration	7:33 a.m.	Average	12212	607
		Minimum	11562	545
		Maximum	13064	646
Treatment Room during 1st set of treatments. Ventilation on	7:50 a.m.	Average	10553	784
		Minimum	10031	713
		Maximum	11343	869
Treatment Room during 2nd set of treatments. 1 person in Tent 2	8:40 a.m.	Average	11087	994
		Minimum	10929	942
		Maximum	11305	1090
Nurses Station outside treatment room (control area)	8:50 a.m.	Average	14327	778
		Minimum	13815	712
		Maximum	15019	868

Note:
Particles were counted over 3 - one-minute sampling cycles, with a 10-second interval between cycles.
µmd = diameter of particle in microns (10^{-6} meters)

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