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Environmental, Health & Safety Symposium for Healthcare

October 25, 2018
Stanford University Medical Center
Palo Alto, CA

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Results of Class II A2 vs. Class II B2 Bio-Safety Cabinet Sampling Study

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Study Overview

- Background
- The Dilemma, Purpose, Objectives
- Methods
- Results
- Conclusions
- Questions/Answers

Background

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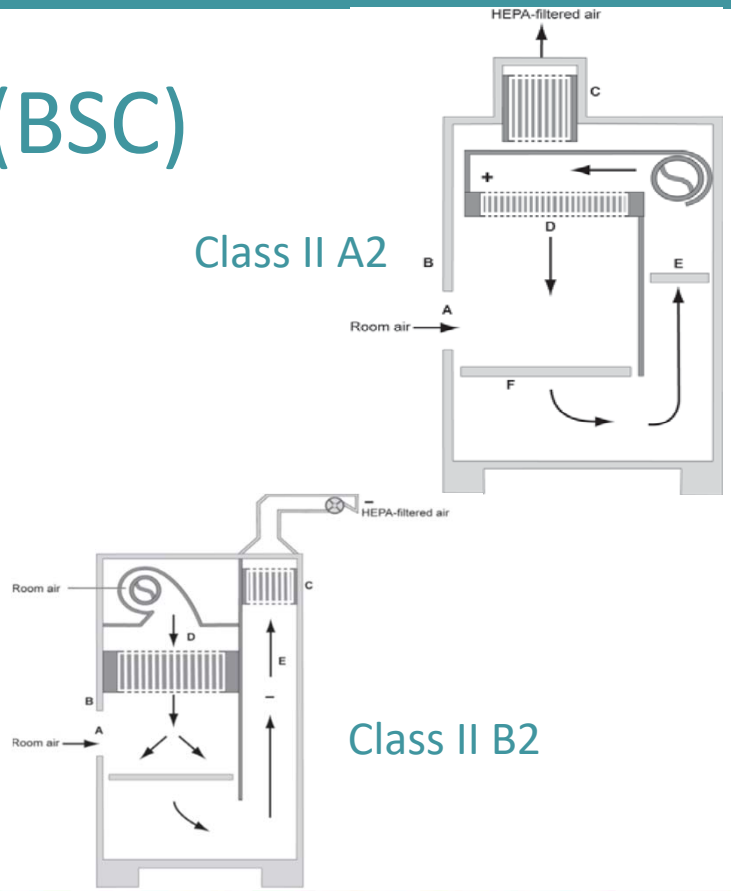
Compounding of Hazardous Drugs

- Hazardous Drugs: antineoplastic agents or cancer treatment drugs
- Compounding: process of combining components or active ingredients of haz drugs
- USP 800 and Title 16, Div 17, Article 4.5 Compounding, Section 1735.6: Compounding Facilities/Rooms
  - 30 ACH
  - Negative Pressure of 0.01 – 0.03 inches of water
  - Exhaust air externally vented (Room and BSC)
- USP 800 and Title 24 of CA Building Code, Part 4, Section 505: all compounding shall be done in laminar flow BSC either:
  - Class II Type A2 BSC (recirculating)
  - Class II Type B2 BSC

Biological Safety Cabinets (BSC)

Many healthcare facilities use Class II BSC for compounding of chemotherapy (antineoplastic) drugs prior to administration to cancer patients

- Recirculating Class II Type A2 ventilated cabinets exhaust ~30% airflow to the exterior and recirculate 70% back into the BSC
- Class II Type B2 ventilated cabinets exhaust 100% of all air to the exterior of the building



The Dilemma

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The Question and Dilemma

Do recirculating Class II A2 ventilated cabinets offer the same, or similar worker protection as Class II B2 ventilated cabinets during chemo drug compounding activities, or a spill (particularly for volatile fractions)?

- Few peer-reviewed studies evaluating this topic and no comprehensive data, particularly for volatile fractions of chemotherapy drugs
- No known validated air-sampling test protocols for volatile fractions of chemotherapy drugs

Study Purpose and Objective

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Study Purpose and Objective

- **Study Purpose**: to evaluate whether Class II A2 BSC, together with administrative controls used by many healthcare facilities for compounding, are effective at controlling workplace exposures or require change or modification
- **Study Objective**: obtain representative air sampling data to evaluate the relative effectiveness of Class II A2 BSC as compared with Class II B2 BSC at controlling workplace exposures to select chemotherapy agents and/or a suitable surrogate compound
- **Study Impact**: Provide regulators with preliminary baseline data for review for future decision-making regarding compliance with applicable regulations
- **Study Impact**: Assist healthcare organizations with future decision-making on use/effectiveness of Class II A2 BSC vs. Class II B2 BSC for their own facilities

Study Phases

- **Phase 1**: Assess the airborne levels of two chemo drugs (particulate and aerosol fractions) in the breathing zones of personnel and the ambient air in rooms and/or areas of compounding during typical compounding activities and during a simulated spill condition in Class II A2 BSC vs. Class II B2 BSC
- **Phase 2**: Assess the airborne levels of a suitable surrogate chemical compound (vapor fraction) to evaluate simulated incidental and worst-case spill conditions involving chemotherapy drugs in Class II A2 BSC vs. Class II B2 BSC

Study Team

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Key Study Personnel and Primary Responsibilities

- Jeff Rochon (WSPA): Study advocate, recruitment of healthcare partner facilities
- Alex Truchot (KP): Study advocate, study design and planning, review/comment of methods, final report
- Xavier Alcaraz (BSI): Principal investigator, study design, data analysis, reporting
- Michael Peterson (BSI): Onsite assessments, data management, reporting
- Russell Snyders (BSI): Study coordination, study oversight and management, reporting quality review
- Nick Filipp (BSI): Reporting quality review, technical resource
- WA L&I Subject Matter Expert: Review of study design and final report

Participating Healthcare Facilities

The facilities evaluated were located in larger hospitals or medical centers in the greater Seattle-Tacoma area

- CHI Franciscan Health, Highline Cancer Center Pharmacy, Burien, WA
- CHI Franciscan Health, St. Joseph Medical Center, Tacoma, WA
- Group Health (Kaiser), Bellevue Medical Center, Bellevue, WA
- Group Health (Kaiser), Capitol Hill Campus, Seattle, WA
- MultiCare Health System, Tacoma General Hospital, Tacoma, WA

Phase 1 Methods

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Selection of Chemotherapy Drugs and BSC

Several common chemotherapy drugs were considered for incorporation into the study including the following:

- 5-Fluorouracil (5-FU) - selected
- Cyclophosphamide (CP) - selected
- Ifosfamide
- Methotrexate

6 BSC were selected for inclusion in Phases 1 and 2

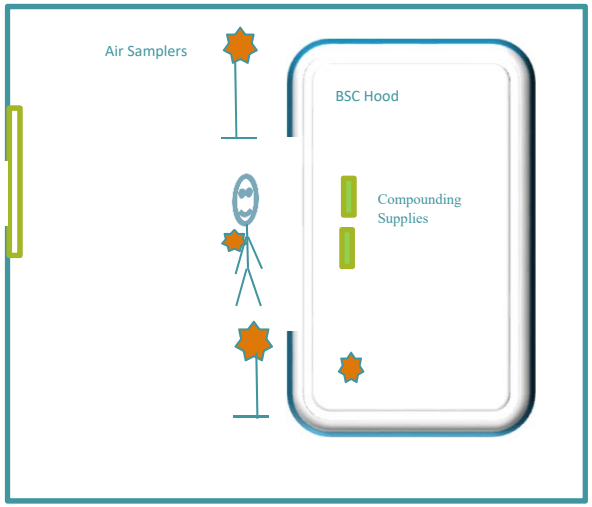
- 3 Class II A2 BSC
- 3 Class II B2 BSC

Study Conditions – Compounding

- Cyclophosphamide and 5-Fluorouracil chemotherapy solutions were individually prepared/compounded in each cabinet, in series
- Duration of compounding tasks for both agents ranged from 75 - 92 minutes including preparation and clean-up time
- Air sampling was conducted during the entire duration of compounding and continued at least 30 minutes after the completion of compounding

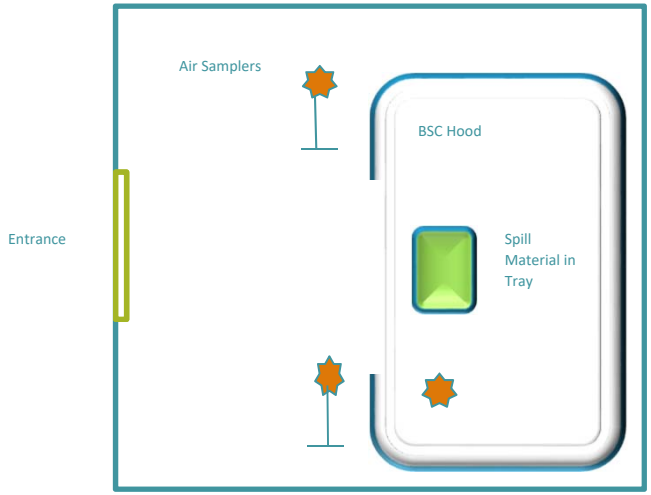
Study Conditions – Compounding

- Typical compounding room and the personnel and air sample locations (orange) during compounding



Study Conditions – Simulated Spill Condition

- Typical compounding room and the area air sample locations (orange) during a simulated spill scenario



Phase 2 Methods

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Surrogate Sampling Chemical

Selected use of propylene glycol (PG) as the surrogate chemical for several reasons:

- Low vapor pressure
  - VP of PG at room temp is approximately 1,000x higher than CP, 5-FU, and several other chemo agents = greater safety factor for use of PG as a surrogate
- Miscible in water
- Low toxicity
- Validated air sampling method for the volatile fraction
- Readily available
- NIOSH considered PG as one of several potential surrogate compounds for evaluating the effectiveness of CSTD

Study Conditions – Simulated Minor Spill Condition

PG used to simulate minor (incidental) spill or leakage of a chemo agent in solution that could occur during compounding in a BSC using a closed system transfer device (CSTD)

- Small quantity of propylene glycol (5 ml) was dispensed onto an absorbent wipe using a 5–10 ml syringe and placed inside a single containment tray (18”x18”x4”) inside BSC with sash position maintained at working height
- Air sampling for PG was conducted for at least 30 minutes under this condition

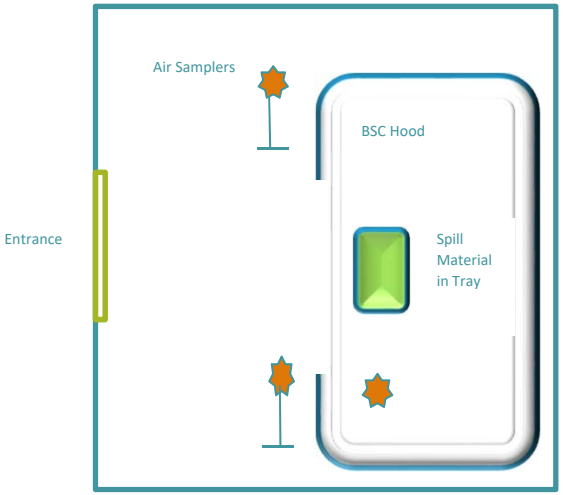
Study Conditions – Simulated Large Spill Condition

Propylene glycol was used to simulate a worst-case spill condition in each BSC

- The max volume used for compounding (~250 ml) was poured into a single containment tray (18”x18”x4”) inside of the cabinet with the cabinet sash position maintained at working height
- Air sampling was conducted for at least 30 minutes under this condition
- The spilled materials were cleaned using DSS ChemoSorb pads
- Air sampling continued for an additional 30 minutes following spill clean-up activities

Study Conditions – Simulated Spill Conditions

- Typical compounding room and the area air sample locations (orange) during a simulated spill scenario: minor and large



Phase 1 Results

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General Observations

- The compounding areas were generally small rooms (<100 ft^2) to medium sized rooms (100 ft^2 – 500 ft^2)
- The compounding rooms generally had 1–2 BSC within the room
  - One site (St. Joseph Medical Center) had 3 BSC in the room
- Compounding was performed by one individual, and technicians follow strict methods for preparation of chemotherapy solutions which were very similar across all sites
- All facilities used CSTD for compounding during sampling events which minimizes the risk of spillage or release of chemotherapy compounds
- Duration of compounding activities ranged from 20-30 minutes for each of the two solutions

General Observations – Continued

- Total task time, including preparation, compounding, and cleanup, ranged from 75-92 minutes per compounding event
- Compounding at each facility reportedly varies from <1 hr/day to >8 hrs/day
- Compounding technicians generally wore disposable coveralls or lab coat, sterile nitrile gloves, hairnet, and patient mask
- CP is in dry-powder form prior to compounding, whereas 5-FU is in liquid solution
- 50ml of sodium chloride solution is added to 1 gram of dry-form CP, mixed by hand; an aliquot of the solution is extracted and mixed into 250ml saline solution (IV bag); the process was similarly repeated, but using 5 grams of 5-FU pre-prepared in solution
- No spillage or release was observed during compounding activities at any of the sites

Ventilation Assessment

- All BSC were of stainless steel construction with an adjustable sash
- The BSC were equipped with airflow monitoring devices which alarm when they fall below a minimum performance level
- The compounding rooms were designed to maintain a negative air pressure in relation to the adjacent rooms
- All BSC had average face velocity measurements above 100 fpm when the sash was at working height
- Particle testing data indicated that the Class II A2 supply HEPA filters which recirculate air back into the BSC were operating effectively on the dates of our sampling events
- All BSC cabinets were performance-tested and certified by an independent ventilation test contractor within six months prior to our sampling events

Air Sampling Results for 5-FU and CP during Representative Compounding Activities

- All air sampling results for CP and 5-FU during compounding in both Class II A2 BSC and Class II B2 BSC were non-detect
- Limits of detection ranged from <0.00319 µg/m^3 to <0.00549 µg/m^3

Air Sampling Results for 5-FU and CP during Simulated Large Spill Conditions

- All air sampling results for CP and 5-FU during simulated large spill conditions in both Class II A2 BSC and Class II B2 BSC were non-detect
- Limits of detection ranged from <0.00629 µg/m^3 to <0.00712 µg/m^3

Summary of Recommended Occupational Exposure Limits for Study Compounds

Compound Name	Recommended Occupational Exposure Limit 8-hour TWA	Source
5-Fluorouracil	Occupational Exposure Band 5 = <1 µg/m^3	Pfizer Safety Data Sheet: Fluorouracil Injection Revision date: 19-Jul-2012
Cyclophosphamide	0.1 µg/m^3	Edward V. Sargent, et. al. (2002

Phase 2 Results

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Sampling Results for PG During Simulated Minor-Spill Conditions

- The majority of air sampling results for PG during simulated incidental (minor) spill conditions outside of both Class II A2 BSC and Class II B2 BSC were non-detect
- One of the integrated air samples collected outside of a Class II A2 BSC resulted in a detection of PG at 0.10 ppm
- Two air samples collected inside of two separate Class II A2 BSC resulted in detections of PG ranging from 0.014 ppm to 0.017 ppm.
- Similarly, one integrated air sample collected inside of a Class II B2 BSC resulted in detection of PG at 0.051 ppm

Results for Propylene Glycol During Simulated Incidental Spillage in Class II A2 BSC vs. Class II B2 BSC Across All Study Sites

Cabinet Type	Sample Type: Task, Location	Sampling Duration (min)	Integrated Air Sampling Results - Range (ppm)	Direct-Read Sampling Results - Range (ppm)
Class II A2	**Inside cabinet** (right)	30	ND, <0.0052 **0.014** **0.017**	ND
Class II A2	Outside cabinet (left)	30	ND, <0.0052 ND, <0.0052 ND, <0.0053	ND
Class II A2	**Outside cabinet (right)**	30	ND, <0.0053 ND, <0.0054 **0.10**	ND
Class II B2	**Inside cabinet** (right)	30	ND, <0.0054 ND, <0.0056 **0.051**	ND
Class II B2	Outside cabinet (left)	30	ND, <0.0051 ND, <0.0054 ND, <0.0056	ND
Class II B2	Outside cabinet (right)	30	ND, <0.0052 ND, <0.0054 ND, <0.0055	ND

Sampling Results for PG during Simulated Large-Spill Conditions

- The majority of the integrated air sampling results for PG during large spill scenario on outside of both Class II A2 BSC and Class II B2 BSC were non-detect
- Two integrated air samples collected inside of two separate Class II A2 BSC during the simulated large spill condition resulted in detections of PG
- One integrated air sample collected inside of a Class II B2 BSC during the large spill condition resulted in detection of PG

Sampling Results for PG during Simulated Large Spill Conditions (continued)

- Direct-read PID air sampling measurements outside of a Class II B2 BSC at one facility detected values from non-detect to 3,850 ppb
  - Likely due to cleaning activities in an adjacent room concurrently with our air sampling
- All other direct-read PID air sampling results for PG during simulated incidental (minor) and large spill conditions inside and outside of both Class II A2 BSC and Class II B2 BSC were non-detect (<1 ppb)

Air Sampling Results for Propylene Glycol During Simulated Large Spill Conditions in Class II A2 BSC vs. Class II B2 BSC Across All Study Sites

Cabinet Type	Sample Type: Task, Location	Sampling Duration (min)	Integrated Air Sampling Results - Range (ppm)	Direct-Read Sampling Results - Range (ppm)
Class II A2	**Inside cabinet** (right)	30	ND, <0.0026 x3 (repeat sampling) **0.04** **0.044**	ND
Class II A2	Outside cabinet (left)	60	ND, <0.0026 x3 (repeat sampling) ND, <0.0026 ND, <0.0027	ND
Class II A2	Outside cabinet (right)	60	ND, <0.0026 x3 (repeat sampling) ND, <0.0027 ND, <0.0027	ND
Class II B2	**Inside cabinet** (right)	60	ND, <0.0026 ND, <0.0028 **0.0070**	ND
Class II B2	Outside cabinet (left)	60	ND, <0.0026 ND, <0.0027 ND, <0.0027	ND
Class II B2	Outside cabinet (right)	60	ND, <0.0026 ND, <0.0027 ND, <0.0028	**ND – 0.70 /3.85***

Conclusions – Phase 1

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Phase 1 Conclusions

Air sampling results assessing CP and 5-FU during compounding activities and large spill events in Class II A2 BSC vs. Class II B2 BSC:

- Air sampling results across all study sites were below the occupational exposure limits
- Current exposure control methods (e.g., strict compounding protocols and use of certified BSC) appear to be similarly effective for particulates forms of chemo agents
- Strict compounding protocols established at each facility using CSTD for both the liquid form of 5-FU and the powder form of CP also serve to minimize exposure to particulate fractions of the chemo agents
- Risk of exposure to particulate fractions of chemotherapy agents could be higher if powders were incidentally released as a spill inside the hood and/or if the spill extended beyond the confines of the BSC
  - However, these spill conditions reportedly have a low probability and, thus were not assessed as part of study scope

Conclusions – Phase 2

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Phase 2 Conclusions

Air sampling results assessing the vapor fraction of surrogate compound during simulated minor and large spill events in Class II A2 BSC vs. Class II B2 BSC:

- Almost all air sampling results for PG outside of both BSC types across all sites were non-detect
- No notable difference in effectiveness of control of volatile fractions of PG outside of Class II A2 BSC as compared to Class II B2 BSC
  - This is relevant to healthcare workers such as compounding technicians who work in the compounding rooms
- During minor and/or large spills, there is potential for airborne exposure to volatile fractions of chemotherapy drugs inside BOTH BSC types
  - BSC sash would need to be lifted and EE insert their face/breathing zone into BSC
  - Possible scenario: spill requiring extensive cleaning of interior surfaces of BSC

Considerations for Further Study

- Perform additional sampling to include additional sites and repeat sampling
- Perform sampling at small metro facilities and small rural facilities to document potential variations in procedures, equipment, and/or facilities
- Use a semi-volatile surrogate chemical during typical chemotherapy compounding activities to evaluate the effectiveness of exposure control during use of CSTD and other compounding protocols not involving use of a CSTD
- Perform qualitative ventilation assessments to evaluate capture efficiency and/or potential air turbulence conditions at the face of each cabinet; excess air turbulence and poor capture efficiency at the face of the cabinet can affect exposure potential even when cabinets meet minimum face-velocity performance requirements
- Further evaluate the relative volatile chemical properties of antineoplastic agents and how they are handled in Class II A2 BSC to screen their potential exposure risk
- Develop a sampling and analytical method to simultaneously monitor the volatile and non-volatile fractions of antineoplastic agents in workplace air

Acknowledgements

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The authors wish to thank……

- Washington State Department of Labor & Industries Safety and Health Investment Programs (SHIP) for funding this study
- Washington State Pharmacy Association (WSPA)
- Partner healthcare facilities for volunteering access to their facilities for this study. Without their cooperation, this study would not have been possible.
  - CHI Franciscan Health - Highline Cancer Center Pharmacy
  - CHI Franciscan Health - St. Joseph Medical Center
  - Group Health - Bellevue Medical Center (now known as Kaiser Permanente)
  - Group Health - Capitol Hill Campus (now known as Kaiser Permanente)
  - MultiCare Health System - Tacoma General Hospital
- Additional funding was provided by BSI EHS Services and Solutions and Group Health

Thank You!

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Questions?

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