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Field evaluation of onsite near real-time monitors for surface contamination by 5-fluorouracil

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Abstract

Objectives: In order to produce near real-time onsite results to detect surface contamination by antineoplastic drugs, the National Institute for Occupational Safety and Health developed monitors for 5-fluorouracil, which use surface wiping and lateral flow immunoassay for measurement. The monitors were tested in the laboratory to assess the sensitivity of detection on laboratory-produced contaminated surfaces. A field evaluation to assess the capability of the monitors to make measurements in healthcare workplaces was carried out in collaboration with a medical device company and the results are presented in this report.

Methods: The 5-fluorouracil monitor was evaluated in areas where oncology drugs were prepared and administered to patients at five different hospitals. The levels of contamination measured with the monitors were compared to levels measured with liquid chromatography-tandem mass spectrometry.

Results: The 5-fluorouracil values measured with the liquid chromatography-tandem mass spectrometry ranged from 0 to over 200,000 ng/100 cm^2. Measurements by the 5-fluorouracil monitors in the range 10–100 ng/100 cm^2 correlated with the liquid chromatography-tandem mass spectrometry. Receiver operating characteristic curves developed for the data indicated that a positive limit of 22 ng/100 cm^2 would give an acceptable level of false-positives while retaining most true-positive samples. If the liquid chromatography-tandem mass spectrometry measured greater than 100 ng/100 cm^2, then the monitors also measured levels greater than 100 ng/100 cm^2 for the majority of samples.

Conclusion: The data indicate that there are many areas in hospitals that are contaminated with 5-fluorouracil and the monitors will be useful in identifying this contamination.

Keywords

5-fluorouracil, direct reading, surface contamination

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Introduction

Currently, an estimated eight million U.S. healthcare personnel are potentially exposed to antineoplastic drugs,[1] many of which have known carcinogenic, mutagenic, and adverse reproductive effects.[2,3] A number of past studies have documented workplace contamination by antineoplastic drugs.[4–8] This has resulted in the development of safe handling procedures,[9,10] and National Institute for Occupational Safety and Health (NIOSH) has published an Alert describing the effects of exposure, processes producing exposure, and procedures for lowering exposure.[1] However, recent studies have shown that despite following recommended safe handling practices, workplace contamination with antineoplastic drugs in pharmacy and patient care areas and other locations continues to occur.[11–19] The ability to monitor potential exposure in real time may reduce exposure.

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Typically, antineoplastic drug contamination on workplace surfaces is detected by wiping a specified surface area with a wetted swab or filter paper, extracting the swab or filter paper with sampling solution and analyzing the resulting solution with a laboratory-based analytical technique.[20,21] Analytical techniques for measurement of surface contamination by antineoplastic drugs, including liquid chromatography-tandem mass spectrometry (LC-MS/MS),[22–25] are sensitive and specific, but these techniques cannot provide near real-time assessments of contamination to help prevent exposure. Our group recently developed a direct reading monitor to evaluate 5-fluorouracil (5-FU) contamination based on surface wiping and lateral flow immunoassay.[26,27] Its primary purpose is to detect 5-FU contamination above a threshold value and provide a semi-quantitative estimate of the range of the level of contamination over its calibration range. This monitor detected contamination on 5-FU laboratory-spiked surfaces ranging from 10 to 100 ng/100 cm^2. As the lateral flow monitor was only laboratory-tested, the objective of the current study was to evaluate the performance of the monitor on various surfaces in healthcare facilities which prepare and administer 5-FU. Samples were collected in five different hospitals with oncology clinics where 5-FU was used. The measurements made by the monitors were compared to those determined by LC-MS/MS. In this evaluation, data concerning the efficacy of the monitors for detecting 5-FU as well as general data concerning the presence of 5-FU in the workplace were obtained.

Methods

Selection of field sites and areas for sampling

A number of field sites were contacted concerning participation in the field study. Five hospitals (numbered 1–5 in chronological order) that contained oncology pharmacies and areas where 5-FU was administered to patients were studied. Attempts were made at each site to sample all areas where 5-FU might be present, including areas where 5-FU came into the facilities, was stored, was prepared for use, and was administered to patients. The surfaces were selected by examining published studies of hospital contamination and by consulting with personnel in the pharmacies to determine which areas were of most interest to them. The surfaces of drug vials, storage bins, safety cabinets/isolators, floors in pharmacy areas, items in patient treatment areas such as chairs, IV poles, computers keyboards, floors, and waste disposal areas were sampled at all field sites. The surfaces included stainless steel (hoods and tables), vinyl (floors and countertop), and ceramic (tiles). These surfaces had similar recoveries in the previously completed laboratory study.

5-FU monitor surface sampling

5-FU monitor sampling supplies and reagents. Cotton swabs were Puritan model 806-WC (Puritan, Guilford, ME). 5-FU (≥99%, product number F6627-1G) and Polyoxyethylenesorbitan monolaurate (Tween® 20, product number P-1379) were purchased from Sigma-Aldrich (St. Louis, MO). Ammonium acetate (product BP326-500) was purchased from Fisher Bioreagents (Fairlawn, NJ).

Surface sampling. The surface sampling procedure was developed to be convenient and rapid. A commercial paper template was used to define a 10 cm by 10 cm (100 cm^2) surface which was completely wiped with a cotton swab wetted in vial containing 1 ml of 10 mM ammonium acetate sampling buffer first in an up and down direction, then in a sideways direction, and finally repeating the up and down wiping direction. The swab was then returned to the vial containing sampling buffer, agitated vigorously for 2 min, and swab was removed. The sample was then divided into two aliquots, one for the lateral flow monitor and one for LC-MS/MS. The resulting aliquots were then frozen with dry ice, and one aliquot was shipped to the NIOSH laboratory for analysis using the 5-FU lateral flow monitors and the other aliquot was shipped to an analytical laboratory for LC-MS/MS analysis.

5-FU monitor

Principle of operation. The monitors employ competitive lateral flow immunoassay to detect the presence of 5-FU on surfaces.[20,21] The principle of the monitors is shown in Figure 1. The 5-FU monitors (Figure 2) are small cassettes 8 cm long by 2 cm wide by 0.4 cm thick and weigh about 4.5 g.[20] The monitors have an anti-5-FU antibody conjugated to gold particles in the conjugate pad and a 5-FU-bovine serum albumin (5-FU-BSA) conjugate at the test line. If there is 5-FU present in the sample applied to the sample pad, it will bind to the anti-5-FU antibodies on the gold particles, leaving fewer of the antibodies available to bind to the 5-FU-BSA conjugate on the test line. Thus, increasing concentrations of 5-FU in the applied sample will result in fewer gold particles binding to the test line. Since the gold particles impart a red color to the test line, the test line will become dimmer and eventually disappear with increasing concentrations of the drug in solution. A control line, employing a different antibody interaction should always be present and was used to indicate that the monitor was performing

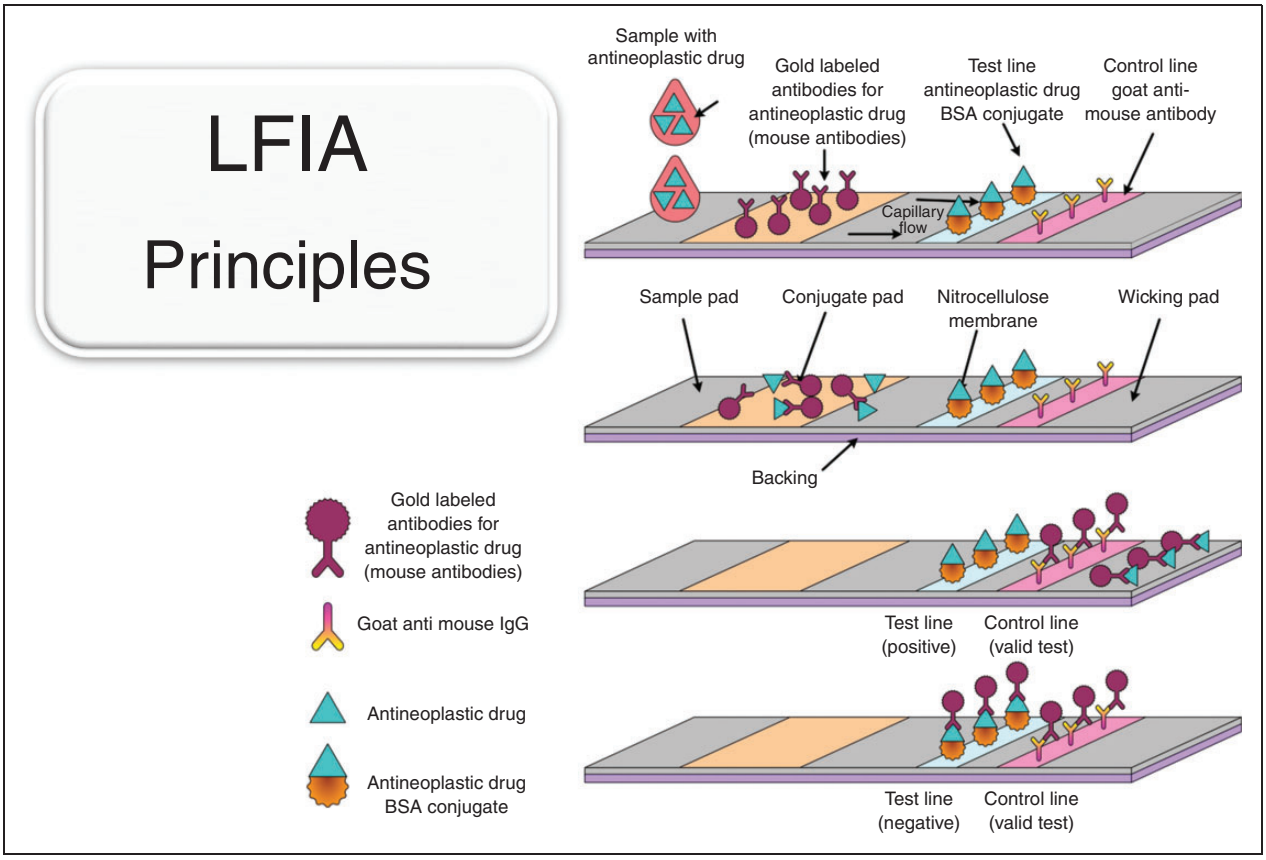

Figure 1. Schematic of lateral flow immunoassay operating principle: competitive assay-drug in solution binds to gold-labeled antibodies resulting in less antibody binding to drug–BSA conjugate at test line. Test line becomes less intense with increasing drug concentration while control line is relatively constant.

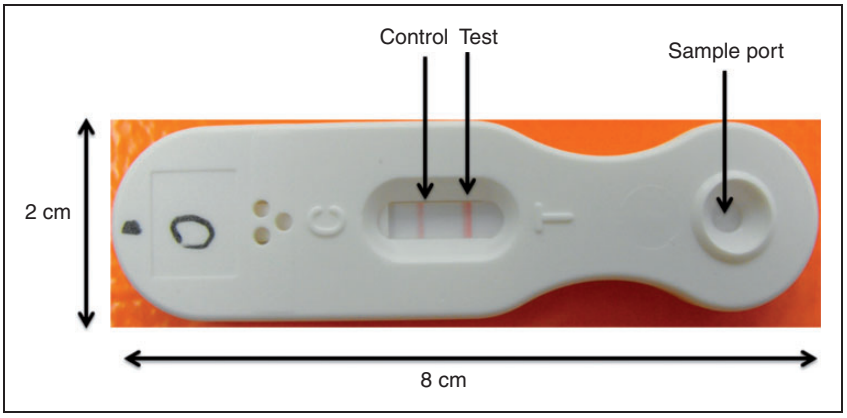

Figure 2. Developed lateral flow monitor for 5-fluorouracil where the test line is more intense than control line (ratio of control line intensity/test line intensity (C/T) = 0.56). The figure shows the test line, control line, and the sample port where the sample is added.

properly. The control line is examined visually and also read with the electronic reader and as will be explained later. The monitor shown in Figure 2 shows an example of a negative sample, where the test line is more intense than the control line.

Analysis of monitor samples. At the NIOSH laboratory, the field samples were thawed and analyzed using the 5-FU lateral flow monitors. Twenty-five microliters of 10% Tween® 20 solution in 10 mM ammonium acetate sampling buffer were added to 225 µl of the sample to

produce a 1% Tween® 20 solution. This was necessary because the monitors were designed to use 1% Tween® 20 solution to operate properly. However, the Tween® 20 interfered with the LC-MS/MS analysis, so wiping was done with 10 mM ammonium acetate buffer only and the Tween® 20 was added afterward. The laboratory calibration curve for the 5-FU monitors was developed using this procedure. Three lateral monitors were used for each sample, 75 µl was added to each monitor and the average of the response of the three monitors was used as the response from the sample. The monitors were allowed to develop for 15 min and the intensity of the test and control lines was determined at 5, 10, and 15 min using an electronic lateral flow reader (Hamamatsu model 10066). The 5 and 10 min readings were made to determine how the monitor responded at shorter time intervals and only the 15 min readings were used for comparison to the LC-MS/MS data. To obtain line intensities for the test and control lines with the reader, the monitor is placed into a small drawer, which is pushed into the reader where the measurement is made. A visual reading method was also used, where the intensity of the test line was compared to the control line. The visual comparison of the test and control lines is a useful check on the operation of the lateral flow reader. The visual comparison is illustrated in Figure 2 for a situation where the test line is more intense than the control line.

LC-MS/MS analysis. The LC-MS/MS analysis was done using gradient elution and a 5-FU-$^{15}N_2$ internal standard. The quantification of test samples was performed using a calibration plot from standard solutions prepared in sampling buffer at the contract laboratory Bureau Veritas North America as described previously.[26]

Data interpretation. The ratio of the control line intensity to the test line intensity (C/T ratio) was calculated and compared to calibration curves that were produced in the NIOSH laboratory using ceramic surfaces spiked with various masses of 5-FU. If the C/T value for a sample is less than the zero mass value on the calibration curve, a negative value will be calculated for the sample since a linear fit was applied to the C/T ratio versus concentration calibration curve produced in the laboratory. For 5-FU monitor data where the LC-MS/MS measurement was 0–100 ng/100 cm^2, the 5-FU monitor data were plotted directly against the LC-MS/MS data for semi-quantitative comparison. 5-FU monitor data where the LC/MS/MS data was >100 ng/100 cm^2 were treated separately, since the upper limit of calibration for the monitors is 100 ng/100 cm^2, and there is no expected relationship of the 5-FU monitor and LC-MS/MS response except that both would be greater than 100 ng/100 cm^2. An important parameter to determine is the threshold for detection of the positive result with the test method. Receiver operator characteristic (ROC) analysis is often used in a number of fields such as medicine to determine the optimal threshold value of a diagnostic test and was used in this study to determine the optimal cut-off for a positive result.[28] The sample data for test method and reference method are divided into four classes: (1) True-positives (TPs) where both the test method and reference method detect contamination, (2) true-negatives (TNs) where both the test method and reference method detect no contamination, (3) false-positives (FPs) where the test method detects contamination but the reference method detects no contamination, (4) false-negative (FN) where the reference method detects contamination but the test method detects no contamination. For ROC analysis, the sensitivity which is (TP/(TP + FN)) is plotted on the y axis against (1−specificity) on the x axis where specificity = (TN/(TN + FP)) at various threshold values. A diagonal line divides the plot with points above the diagonal representing good classification results (better than random), points below the line representing poor results (worse than random). The laboratory evaluation of the monitors established that 10 ng/100 cm^2 could be reliably detected. Therefore, ROC analysis was performed on the data and an LC-MS/MS value greater than 10 ng/100 cm^2 was rated as a positive reference sample. The ROC analysis of the data was done using SAS® (Release 9.4, SAS Institute, Inc., Cary, North Carolina).

Results

A total of 204 samples were collected (14 from hospital 1, 10 from hospital 2, 43 from hospital 3, 39 from hospital 4, and 98 from hospital 5). The 5-FU monitors were calibrated in the NIOSH laboratory from 0 to 100 ng/100 cm^2 where semi-quantitative results can be obtained,[26] and for values above this range, the response of the monitors is flat. Therefore, the field data were divided into two ranges: (1) Less than or equal to 100 ng/100 cm^2 and (2) greater than 100 ng/100 cm^2, where only qualitative interpretation is possible from the 5-FU monitors. Figure 3 is a plot of the LC-MS/MS data from 0 to 100 ng/100 cm^2 comparing the 5-FU monitor response with LC-MS/MS. There is correlation of the 5-FU monitor and LC-MS/MS values with $r^2 = 0.7$ and the 5-FU monitor generally gave higher values. There are also a wide range of 5-FU monitor values ranging from −20 to 40 at LC-MS/MS = 0 ng/100 cm^2 and LC-MS/MS = 4 ng/100 cm^2. For this plot, LC-MS/MS values below the limit of detection were assigned zero and LC-MS/MS

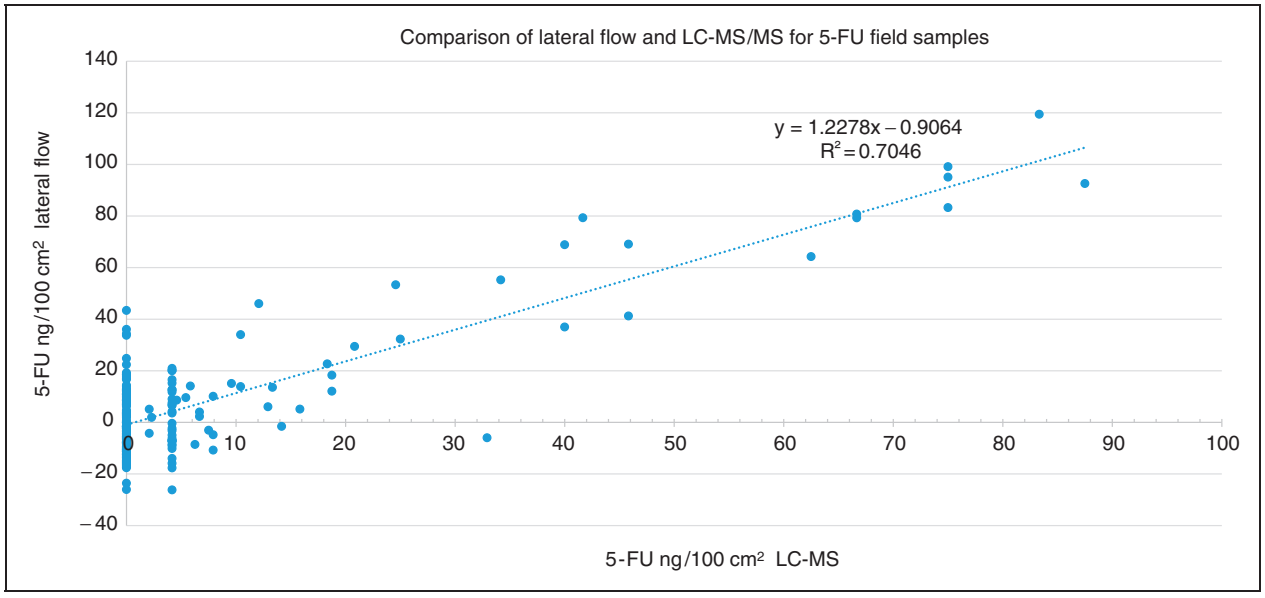

Figure 3. Comparison of 5-FU Lateral flow monitors with LC-MS for values less than 100 ng/100 cm^2. The fit of the lateral flow data with the LC-MS/MS data is a least square regression (N = 187 samples).

Table 1. LC-MS/MS and lateral flow monitor response for 5-FU.

Hospital	Sample #	LC-MS/MS (ng/100 cm^2)	Lateral flow (ng/100 cm^2)	Location
1	23	81,250	>100	Base of IV pole
2	25	204	279	Outpatient infusion biological safety cabinet (BSC)
3	22	35,833	>100	5-FU bin on carousel 50 ml vials
4	16	413	291	Yellow bin
4	27	6250	899	Tray and counter where 5-FU store in blue tray
4	36	1333	1487	Shelf where used IV pumps are placed
4	48	383	403	5-FU storage bin
4	58	237,500	>100	Pharmacy clean room 5-FU storage bin
4	63	396	212	IV pole and IV pump
5	7	2083	336	5-FU bin 50 ml bottles
5	9	8333	>100	5-FU bin #3
5	31	750	308	5-FU CADD™ pump
5	51	500	228	Pump face and keyboard
5	67	167	10	Cart right side extension
5	85	1042	495	Counter outside pass thru
5	88	296	43	IV pump face and keyboard
5	91	16,667	2325	5-FU bin

Note: LC-MS/MS values greater than 100 ng/100 cm^2. The hospital where the sample was taken as well as the location within the hospital are given. If a value for the lateral flow monitor is indicated as >100, the test line was completely absent and a value could not be calculated.
LC-MS/MS: liquid chromatography-tandem mass spectrometry; 5-FU: 5-fluorouracil.

detected values that were below limit of quantification were assigned four, so any of these 5-FU monitor data that are greater than 10 would be possible FP if 10 is used as lower threshold of the 5-FU monitor. This will be discussed more in the ROC analysis section.

Table 1 shows the values of 5-FU monitor response for LC-MS/MS greater than 100 ng/100 cm^2. Note that the data for LC-MS/MS less than 100 ng/100 cm^2 shown in Figure 3 are not included in these data. If a value for the 5-FU monitor is indicated as >100,

the test line was completely absent and a value could not be calculated since calculation of C/T would involve division by 0. This would involve a mass concentration much greater than the 100 ng/100 cm^2 upper calibration value. For the other values in Table 1, the test line was measurable by the lateral flow reader but was very small compared to the control line and C/T was much larger than the upper calibration value obtained at the upper calibration point 100 ng/100 cm^2. This allowed calculation of a loading in ng/100 cm^2 for the sample, but this value is only qualitative and cannot be semi-quantitatively compared to the value for LC-MS/MS as was done for the data in Figure 3. Samples 67 and 88 from hospital 5 were different from the other samples in the table and will discussed more later.

To determine the appropriate lower limit for a positive result from the 5-FU monitor, a ROC analysis was performed on the data. The lower limit is important because it must be low enough to protect workers but not so low that clean areas are deemed contaminated and require additional cleaning due to possible FP values. There are no workplace standards to provide guidance in determining the lower limit. ROC analysis was performed on the data in which an LC-MS/MS value greater than 10 ng/100 cm^2 was rated as a positive reference sample, since 10 ng/100 cm^2 was the lowest level that could be detected by the monitors in the laboratory study.[26] The ROC curve for the data is shown in Figure 4 with the area under the curve indicated. The area is close to one and that indicates good fit of the model to the data. The efficiency which is defined as (TP + TN)/(TP + TN + FP + FN) was a maximum at a threshold of about 22 ng/100 cm^2.

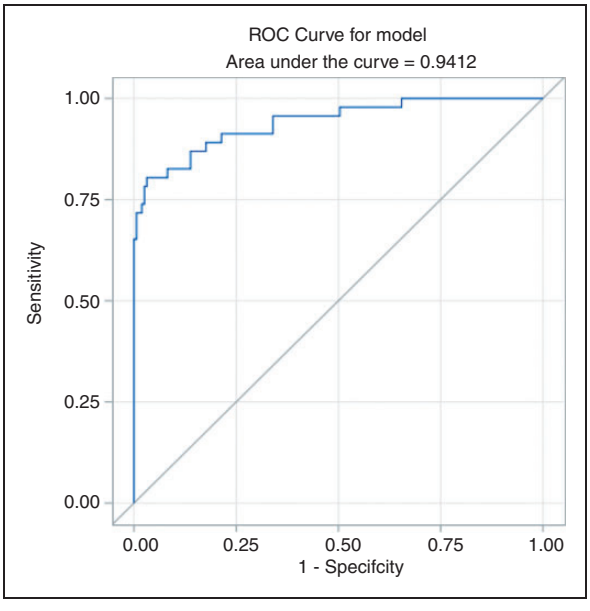

Figure 4. ROC curve for 5-FU lateral flow monitor data for the five hospitals using an LC-MS/MS value of 10 or greater as a positive reference value (N = 204 samples).

Discussion

The 5-FU monitors were able to detect contamination in many areas which was confirmed by LC-MS/MS. About 20% of the 5-FU samples showed measureable contamination with 17 (8%) having values exceeding 100 ng/100 cm^2. The 5-FU monitors showed some FPs. For values of LC-MS/MS greater than 100 ng/100 cm^2, the values of LC-MS/MS were often considerably larger than those of the 5-FU monitor, which would be expected because 5-FU monitor response was above the standard curve. Samples 67 and 88 from hospital 5 were different since LC-MS/MS was above 100 ng/100 cm^2, but lateral flow was less than 100 ng/100 cm^2. It is suspected that something in the workplace environment may have compromised these samples giving an artificially low value for the 5-FU monitor for these samples. Even though both samples showed some response with the 5-FU monitor, a threshold above 10 is used for a positive lateral flow result, which would result in an FN for sample 67 and this will be discussed more in the ROC analysis section.

The laboratory evaluation of the monitors established that 10 ng/100 cm^2 could be reliably detected; however, for field samples from hospitals 3, 4, and 5, this would result in FP values. Raising the positive limit for the lateral flow monitor from 10 ng/100 cm^2 to 22 ng/100 cm^2 resulted in reduction of FP fraction from 18% to about 3%. However, the FN values would increase from 2% to 4%, so it would be an individual decision whether missing these values between 10 and 22 ng/100 cm^2 were important. Note that sample 67 from hospital 5 in Table 1 would become an FN at the 22 ng/100 cm^2 limit, but sample 88 would still be a TP sample even though it is lower than the LC-MS/MS value. The 32 ng/100 cm^2 LC-MS/MS value where the 5-FU monitor gave no response would be an FN at both 10 ng/100 cm^2 and 22 ng/100 cm^2 positive cut-off values.

The 5-FU monitors were the initial prototypes and were designed to give qualitative/semi-quantitative results.[26] The 5-FU monitors show good stability over the long term, since they were about five years old when the samples from hospitals 3–5 were analyzed. The 5-FU monitors were two to three years old when they were used to evaluate samples from hospitals 1 and 2. Production of a second generation 5-FU monitor would most likely produce a more reliable and reproducible monitor based on improvements made in lateral flow technology made in the years since the monitors

were produced. The use of the lateral flow technology for assessment of workplace contamination by antineoplastic drugs has recently been licensed to a medical device company making further development of devices such as the 5-FU monitor highly likely. Reduction of FP and FN values as well as improved reproducibility would be the goals in the design of the second generation 5-FU monitor. Also, the development of a second-generation 5-FU monitor would make it compatible with a portable reader system such as those for point-of-care clinical measurements.

In addition to routine detection of contamination, the monitors will also be useful in the development and evaluation of controls and work practices. Workers will be able to determine rapidly if a control or change in work practice has a significant effect on the level of contamination. This would be difficult to do with a laboratory-based technique which would provide results long after the control or work practice is used in the workplace and would make it difficult to directly observe any change in contamination levels.

Disclaimer

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. Mention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC).

Declaration of Conflicting Interests

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References

1. Bureau of Labor Statistics. May 2011 employment and wage estimates. Occupational employment statistics homepage, www.bls.gov/oes/home.htm (accessed 6 June 2018).
2. NIOSH. *NIOSH alert: preventing occupational exposure to antineoplastic and other hazardous drugs in healthcare settings*. Cincinnati, OH: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, 2004. [DHHS (NIOSH) Publication No. 2004–165.].
3. IARC. *Overall evaluations of carcinogenicity: an updating of IARC monographs* (Vols. 1–42). IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Lyons, France: World Health Organization, International Agency for Research on Cancer, 1987, p. 210.
4. Connor TH, Anderson RW, Sessink PJ, et al. Surface contamination with antineoplastic agents in six cancer treatment centers in Canada and the United States. *Am J Health Syst Pharm* 1999; 56: 1427–1432.
5. Fransman W, Vermeulen R and Kromhout H. Occupational dermal exposure to cyclophosphamide in Dutch hospitals: a pilot study. *Ann Occup Hyg* 2004; 48: 237–244.
6. Touzin K, Bussières JF and Langlois É. Evaluation of surface contamination in a hospital hematology-oncology pharmacy. *J Oncol Pharm Pract* 2009; 15: 53–61.
7. Bigelow S, Schulz H, Dobish R, et al. Antineoplastic agent workplace contamination study: the Alberta Cancer Board Pharmacy perspective phase III. *J Oncol Pharm Pract* 2009; 15: 157–160.
8. Connor TH, DeBord G, Pretty JR, et al. Evaluation of antineoplastic drug exposure of health care workers at three university-based US cancer centers. *J Occup Environ Med* 2010; 52: 1019–1027.
9. Sessink PJM, Connor TH, Jorgenson JA, et al. Reduction in surface contamination with antineoplastic drugs in 22 hospital pharmacies in the US following implementation of a closed-system drug transfer device. *J Oncol Pharm Pract* 2011; 17: 39–48.
10. Turci R, Minola C, Sottani C, et al. Occupational exposure to antineoplastic drugs in seven Italian hospitals: the effect of quality assurance and adherence to guidelines. *J Oncol Pharm Pract* 2011; 17: 320–332.
11. Bussières JF, Tanguay C, Touzin K, et al. Environmental contamination with hazardous drugs in Quebec hospitals. *Can J Hosp Pharm* 2012; 65: 428–435.
12. Kiffmeyer T, Tuerk J, Hahn M, et al. Application and assessment of a regular environmental monitoring of the antineoplastic drug contamination level in pharmacies – the MEWIP project. *Ann Occup Hyg* 2013; 57: 444–455.
13. Hon C-Y, Teschke K, Chu W, et al. Antineoplastic drug contamination of surfaces throughout the hospital medication system in Canadian hospitals. *J Occup Environ Hyg* 2013; 10: 374–383.
14. Fleury-Souverain S, Nussbaumer S, Mattiuzzo M, et al. Determination of the external contamination and cross-contamination by cytotoxic drugs on the surfaces of vials available on the Swiss market. *J Oncol Pharm Pract* 2014; 20: 100–111.
15. Viegas S, Padua M, Veiga AC, et al. Antineoplastic drugs contamination of workplace surfaces in two Portuguese hospitals. *Environ Monit Assess* 2014; 186: 7807–7818.
16. Fleury-Souverain S, Mattiuzzo M, Mehl F, et al. Evaluation of chemical contamination of surfaces during the preparation of chemotherapies in 24 hospital pharmacies. *Eur J Hosp Pharm* 2015; 22: 333–341.
17. Berruyer M, Tanguay C, Caron NJ, et al. Multicenter study of environmental contamination with antineoplastic drugs in 36 Canadian hospitals: a 2013 follow-up study. *J Occup Environ Hyg* 2015; 12: 87–94.

18. Poupeau C, Roland C and Bussières JF. J Surveillance urinaire des professionnels de la santé exposés aux antinéoplasiques dans le cadre de leur travail: revue de la littérature de 2010 à 2015. *J Can Pharm Hosp* 2016; 69: 376–387.
19. Müller-Ramírez C, Squibb K and McDiarmid M. Measuring extent of surface contamination produced by the handling of antineoplastic drugs in low to middle-income country oncology health care settings. *Arch Environ Occup Health* 2017; 72: 289–298.
20. Connor TH, Zock MD and Snow AH. Surface wipe sampling for antineoplastic (chemotherapy) and other hazardous drug residue in healthcare settings: methodology and recommendations. *J Occup Environ Hyg* 2016; 13: 658–667.
21. Kibby T. A review of surface wipe sampling compared to biologic monitoring for occupational exposure to antineoplastic drugs. *J Occup Environ Hyg* 2017; 14: 159–174.
22. Pretty JR, Connor TH, Spasojevic I, et al. Sampling and mass spectrometric analytical methods for five antineoplastic drugs in the healthcare environment. *J Oncol Pharm Pract* 2012; 18: 23–36.
23. Jeronimo M, Colombo M, Astrakianakis G, et al. A surface wipe sampling and LC-MS/MS method for the simultaneous detection of six antineoplastic drugs commonly handled by healthcare workers. *Anal Bioanal Chem* 2015; 407: 7083–7092.
24. Bobin-Dubigeon C, Amiand M, Percheron C, et al. A new, validated wipe-sampling procedure coupled to LC–MS analysis for the simultaneous determination of 5-fluorouracil, doxorubicin and cyclophosphamide in surface contamination. *J Anal Toxicol* 2013; 37: 433–439.
25. B'Hymer C, Connor T, Stinson D, et al. Validation of an HPLC-MS/MS and wipe procedure for mitomycin C contamination. *J Chromatogr Sci* 2015; 53: 619–624.
26. Smith JP, Sammons DL, Pretty JR, et al. Detection of 5–fluorouracil surface contamination in near real time. *J Oncol Pharm Pract* 2016; 22: 396–408.
27. Connor TH and Smith JP. New approaches to wipe sampling methods for antineoplastic and other hazardous drugs in healthcare settings. *Pharm Technol Hosp Pharm* 2016; 1: 107–114.
28. Pandey M and Jain A. *ROC curve: making way for correct diagnosis SP-11*. Denver, Colorado, USA: PharmaSUG, 2016.