Healthcare workers' exposure to hazardous drugs: A 15-year retrospective

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OHCOW's Occ|Tober & Beyond Webinar

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Speaker Biography

- 1998, MSc(A) in Occupational Health (McGill University)
- 2002, Canadian Registered Safety Profession (CRSP)
- 2003, Certified Industrial Hygienist (CIH)
- 2012, PhD in Occupational and Environmental Hygiene (UBC)
- 2012 - present, Toronto Metropolitan University (formerly Ryerson University)
- Google scholar

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Today's Agenda

- What are hazardous drugs
- Health effects due to occupational exposure
- Hazard assessment methods
- Scholarly activity overview: 2011 to 2026
- Controls to reduce the risk
- Q&A



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Hazardous Drugs

- Drugs designated as cytotoxic (cell-killing) and antineoplastic (anti-cancer) agents are some of the most hazardous chemicals ever developed
- Although primarily used in the treatment of cancer, some hazardous drugs are also used to treat non-cancerous diseases such as multiple sclerosis, psoriasis, among others.
- Nearly 200 hazardous drugs are currently in use, and up to thirty new drugs are identified every year
- Inherently toxic; however, to patients, benefits >> risks

Source: https://publications.aiha.org/hazardous-drugs

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Background

- Occupational exposure concerns initially surfaced in the 1970's
  - Non-selective mode of action – normal cells may also be affected
- Variety of reported health effects from exposed workers
  - Both acute effects as well as chronic



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Acute health effects

- Summarized in a review by Connor and McDiarmid (2006)

Connor and McDiarmid (2006). CA: A cancer journal for clinicians. 56(6):354–65.

- Reported primarily from nurses:
  - Hair loss
  - Headaches
  - Acute irritation
  - Hypersensitivity



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Chronic health effects – DNA damage

- The meta-analysis of micronuclei frequency from 24 studies confirmed an association between occupational exposure to antineoplastic drugs and **cytogenetic effects** with an overall meta-estimate of 1.67 [95% CI: 1.41–1.98]

Villarini et al. (2016) Mutation Research/Reviews in Mutation Research 770: 35-45

- A meta-analysis confirmed a significant association between occupational exposure to antineoplastic drugs during the course of a normal work day and **increases in chromosomal aberrations** in healthcare workers

Roussel et al. (2017) Mutation Research/Reviews in Mutation Research 781: 207-217



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Chronic Health Effects – Cancer and reproductive effects



1. Increased risk of cancer

a) Breast cancer:

- Ratner et al (2010): RR = 1.83; 95% CI = 1.03 - 3.23

b) Increase excess cases of cancer

- Sessink et al (1995): 1.4 to 10 per million



2. Reproductive toxicities

- Dranitsaris et al (2005): Spontaneous abortions (OR=1.46, 95% CI: 1.11-1.92)
- Fransman et al (2007): Longer to conceive (adjusted OR=0.8, 95% CI: 0.6–0.9)
- Connor et al (2016) : Systematic Review
  - Increased risk for congenital anomalies
  - Increased reports of miscarriages
  - Associated with an increased risk of subfertility

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Carcinogenic classification of common drugs

Cytotoxic chemotherapeutic agents	Groups	Group definition
CP and etoposide	Group 1	Carcinogenic to humans
Pt, Dox, and daunorubicine	Group 2A	Probably carcinogenic to humans
Bleomycin and dacarbazine	Group 2B	Possibly carcinogenic to humans
IF, 5FU, MTX, vincristine, and vinblastine	Group 3	Not classifiable as carcinogenic to humans
Pac, Doc, Top, Iri, Epi, Cyt, and Gem	–	Actually not classified in IARC monographs

CP cyclophosphamide, *Pt* cisplatin, *Dox* doxorubicin, *IF* ifosfamide, *5FU* 5-fluorouracil, *MTX* methotrexate, *Pac* paclitaxel, *Doc* docetaxel, *Top* topotecan, *Iri* irinotecan, *Epi* epirubicin, *Cyt* cytarabine, *Gem* gemcitabine

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Marie et al. (2017) Environ Monit Assess 189: 52-66

Occupational exposure

- Main route of occupational exposure is **dermal** or **skin contact**



Direct contact: touching drug themselves or drug vials/IV bags

Mainly during preparation and administration



Indirect contact**:** touching drug-contaminated surfaces

During any part of the hospital medication circuit

- **Inhalation** and **accidental ingestion** are also possible routes of exposure

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Outlook

- It is projected that the number of new cancer cases in Canada is expected to steadily increase as population ages => increased use of hazardous drugs

Ruan et al. (2023) Prev Med. 168:107425

- Also, these drugs are being used outside of acute care settings

Is currently a concern and will continue to be of concern in the foreseeable future

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Healthcare workers at risk

- Healthcare workers who prepare or administer hazardous drugs or who work in areas where these drugs are found are at risk of exposure
- According to NIOSH, approximately 8 million U.S. healthcare workers are potentially exposed to hazardous drugs (https://www.cdc.gov/niosh/topics/hazdrug/default.html)
- According to CAREX Canada, approximately 79,000 Canadians are occupationally exposed (https://www.carexcanada.ca/profile/antineoplastic_agents-occupational-exposures/)
- Essentially, anyone working in the hospital medication circuit is at risk *(see next slide)*

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Hospital medication circuit

Typical stages where drugs travel and/or are handled within a hospital

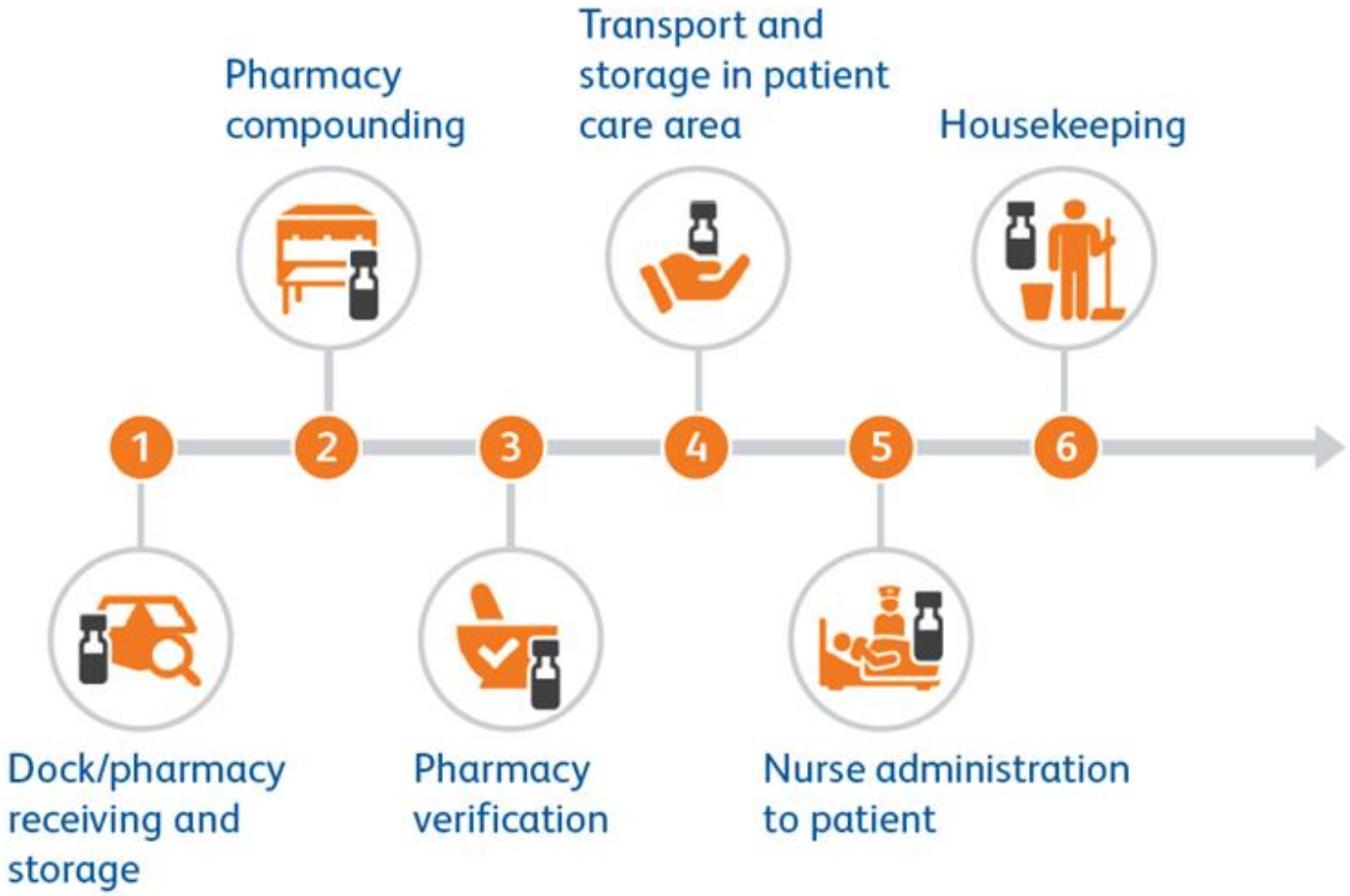


Image provided by BD

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Occupational exposure limits?

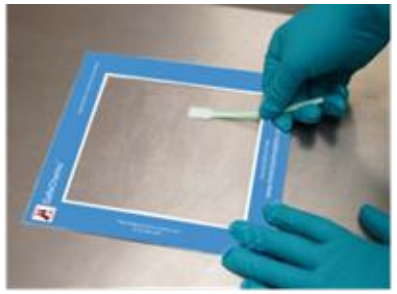
- No ACGIH threshold limit values (TLVs®)
- No OSHA permissible exposure limits (PELs)
- Hygienic guidance values (HGVs) have been suggested in other countries e.g. Germany, Italy, Sweden
  - However, not necessarily enforceable and applies to surface contamination only

The Precautionary Principle of ALARP applies (As Low As Reasonably Practicable)

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Exposure assessment

- No standard exposure assessment method available
- Studies have employed the following four methods:



1. Surface contamination



2. Dermal contamination



3. Urinary contamination



4. Genotoxicity assays

- Good summaries by Turci et al. (2003), Nussbaumer et al. (2011), Portilha-Cunha et al. (2021) and Vermette et al. (2024)

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Surface contamination

- Also known as **environmental monitoring**
- Surface wipe sampling is a suitable means to: i) evaluate work practices, ii) evaluate the effectiveness of applied control measures and iii) to identify the potential risk for health care workers

Bohlandt and Schierl (2016) Pharma Tech Hosp Pharm 1(3): 139-150

- Studies have found contamination on various surfaces and objects
- Detectable levels reported in patient areas – now a possible public health issue

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2011 - Dermal exposure (pilot study)

- Three workers from six hospital pharmacies participated
- Hands wiped with premoistened tissue
- Analyzed for cyclophosphamide and methotrexate
- At 50% of the sites, at least one sample was above the limit of detection
- From the participating sites, five samples had measurable levels:
  - 3 for cyclophosphamide
  - 2 for methotrexate
  - No sample had both drugs that were detectable
- **Canadian healthcare workers are at risk of exposure to hazardous drugs**

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Hon et al. (2011) Canadian Journal of Hospital Pharmacy. 64:(5): 327–332.

2011 – Healthcare job categories at risk of exposure

- Surface contamination was found in all stages of the hospital medication circuit at participating facilities *(could not sample waste disposal and retrieval)*

Stage	Mean contamination level
Delivery	3.2 ng/wipe
Preparation	51.18 ng/wipe
Transport	9.68 ng/wipe
Administration	7.40 ng/wipe

- Job categories consistently found to be at risk of exposure were nurses, pharmacists, pharmacy technicians, and pharmacy receivers
- **Up to 11 job categories per site may be at risk of exposure at some point during the hospital medication circuit**

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Hon et al. (2011) Safety and Health at Work. 2(3): 273–28

2012 – Contamination levels pre- vs post-cleaning

- High-touch surfaces in hospital pharmacies were wiped after drug preparation pre- and post-clean
- 14/23 (61%) surfaces sampled pre-clean were contaminated with either methotrexate or cyclophosphamide (CP)
- Post-clean contamination levels were generally lower than its pre-clean equivalent; difference was statistically significant for CP only
- Some samples appeared to have *higher* post-clean contamination levels
- **Drug contamination on surfaces is common, and cleaning protocols may <u>not</u> be effective in completely removing residual**

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Chu et al. (2012). Journal of Oncology Pharmacy Practice. 18(1): 46–51

2013 – Surface contamination levels

- 438 surfaces high-touch surfaces throughout the hospital medical circuit were sampled
- Mean concentration of cyclophosphamide (CP) was 0.201 ng/cm^2, the GM was 0.019 ng/cm^2, and the GSD was 2.54, with a range of less than detection to 26.1 ng/cm^2
- **Every stage of the hospital medication circuit had measurable levels of drug contamination; highest in drug preparation**
- Neither the reported handling of CP prior to wipe sampling nor the cleaning of surfaces appeared to be associated with contamination levels

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Hon et al. (2013) Journal of Occupational and Environmental Hygiene. 10(7): 374–383

2014 – Contamination on workers' hands

- 225 wipe samples from workers' hands were collected
- 20% (N = 44) of samples were above the LOD for cyclophosphamide (CP). The mean concentration was 0.36 ng per wipe, the GM < LOD, the GSD was 1.98, and the range was < LOD to 22.8 ng per wipe
- **All job categories evaluated had contamination levels > LOD**
  - Those workers in the drug administration unit who were not responsible for drug administration (volunteer, oncologist, ward aide, dietician) had the highest proportion of samples > LOD
  - The highest recorded concentration was from a worker who had no known contact with CP on their work shift!

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Hon et al. (2014) The Annals of Occupational Hygiene. 58(6): 761–770

2015 – Urinary contamination in workers

- 24-hr urine samples were collected from 201 healthcare workers
- 55% (n = 111) had levels > LOD of 0.05 ng/mL
- Mean urinary cyclophosphamide (CP) concentration was 0.156 ng/mL, the GM was 0.067 ng/mL, the GSD was 3.18, and the range was <LOD to 2.37 ng/mL
- **All eight job categories evaluated had some urinary concentrations in > LOD with unit clerks having the highest average level**
- Workers who worked in the drug administration unit, but were not responsible for administering, had the largest proportion of samples > LOD
- No correlation between the urinary concentration levels and known contact with CP during the work shift

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Hon et al. (2015) International Archives of Occupational and Environmental Health. 88(7): 933–41

2015 – Analytical Method #1

- Developed a wipe sampling method that could simultaneously analyze six drugs (methotrexate, paclitaxel, cyclophosphamide, 5-fluorouracil, vincristine, and oxaliplatin)
- Analyzed using High Performance Liquid Chromatography – Tandem Mass Spectrometry (HPLC-MS/MS) ***gold standard***
- **The LODs achieved were significantly lower than similar previous studies for OXP, CP, VNC, and PTX and comparable to previous studies for 5-FU and MTX**
- Wipe sampling procedure: https://www.youtube.com/watch?v=6Wv-sLMyOkA

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Jeronimo et al. (2015) Analytical and Bioanalytical Chemistry. 407(23): 7083–92

2017 – Analytical Method #2

- Building on the previous analytical method development project; this time the updated method can simultaneously analyze 10 drugs (5-fluorouracil, oxaliplatin, methotrexate, vindesine, ifosfamide, cyclophosphamide, vincristine, vinblastine, docetaxel, and paclitaxel)
- Good overall recoveries and sensitivity values
- Relatively short run time (8 min)
- **Able to evaluate trace surface contamination levels down to the single picogram per square centimeter (pg/cm^2)**

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Colombo et al. (2017) Annals of Work Exposures and Health. 61(8): 1003–14.

2022 – Biological monitoring (scoping review)

- Biological monitoring assesses all routes of exposure
- Currently, not routinely done for healthcare workers' exposed to hazardous drugs
  - Wanted to know if routine urine sampling is worth pursuing
- Scoping review included 39 full text articles between 2005 and 2020
- Most studies reported urine samples with detectable levels of hazardous drugs and case-control studies had statistically significant findings
- Knowledge gaps included a lack of an exposure limit, lack of a standardized sampling method, and lack of correlation between health effects and urinary contamination levels; also, cost considerations
- **Based on our findings, we do not recommend biological monitoring**

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Hon and Motiwala. (2022).Applied Sciences, 12(21):11170.

2023 – Testing of a novel qualitative surface wipe method

- Wipe sampling and subsequent analysis via HPLC-MS/MS is resource intensive and results are not available for at least several days
- Tested a new device which allows for near real-time qualitative assessment of surface contamination (single drug at a time, +/- only)
- Five sets of wipe samples with known drug concentrations were collected – one set using traditional wipe, the other set using the new device
- New device worked well for methotrexate (MTX) at all concentrations but, for cyclophosphamide (CP), the device did not detect all samples at 50% and 75% concentration of the LOD
- **Novel device might be suitable as a screening tool for higher levels of drug contamination with MTX and CP**

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Hon (2023) Can J Hosp Pharm. 76(2):87-93

2025 – Adoption of Engineering Control

- Wanted to confirm the effectiveness of closed-system drug transfer devices (CSTDs) in reducing surface contamination as well as the perceptions of workers with their adoption into practice
- Contamination levels were assessed at 3 time points: 1 month before (T_0); 1 month after (T_1); and 5 months after implementation (T_2)
  - **Statistically significant reduction** in the sum of the mass of drug contaminants from T_0 to T_1 (25.82 vs 4.01 ng/cm^2) and from T_1 to T_2 (4.01 vs 0.068 ng/cm^2)
- Surveyed healthcare workers
  - **Mainly positive comments regarding the transition process**; suggestions for improvement included offering various forms of training and ensuring ongoing communication

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Hon et al. (2025). Canadian Journal of Hospital Pharmacy. 78(3):e3676,

2026 – Applying exposure judgement tools

- Exposure judgement tools are meant to assist with interpreting the results – less subjective
- These tools can be used even if the sample size is not large
- Evaluate the utility of Expostats to estimate the risk of contamination exceeding the hygienic guidance value of different drugs published by Quartucci et al. (2023)
- 255 wipe samples were collected and ~90% were not detectable
  - Median values were quite low and maximum detected level was 3,280 pg/cm^2 for cyclophosphamide from an IV pump in an oncology ward
- **Unfortunately, due to the large proportion of non-detects, Expostats is not suitable**

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Challenges regarding occupational exposure

- Mechanism of spread is unknown
- No known “safe” threshold
- Healthcare workers are exposed to multiple drugs on a shift
- Unclear how surface contamination levels relate to uptake
- Training and PPE usage may not be consistent
- Associated cost of control measures and environmental monitoring
- No standardized cleaning protocols

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Administrative controls

- Train workers about when and how exposure can occur
- Ensure proper labelling of drugs and associated containers
- Ensure appropriate PPE is worn which may vary depending on task
- Encourage all workers to report exposure incidents
- Ensure workforce follows proper hand hygiene protocols



Nurse wearing gloves, a gown, an N95 respirator and face protection

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Surface cleaning

- Not standardized
- Four elements:
  1. deactivation,
  2. decontamination,
  3. cleaning, and
  4. disinfection
- Multi-wipe process has been found be more effective

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Routine environmental monitoring

- Long-term repeated monitoring seems beneficial to:
  a) characterize the actual exposure, and
  b) to assess surface contamination over time

Böhlandt and Schierl (2016). Pharmaceutical Technology in Hospital Pharmacy. 1(3):139-50

- Regular environmental monitoring is a good practice to maintain contamination as low as reasonably achievable

Roland et al. (2017) Journal of occupational and environmental hygiene. 4(8):650-8.

- Repeated environmental monitoring has a stronger effect on the contamination level than a single measurement

Kiffmeyer et al. (2012). Annals of occupational hygiene. 57(4):444-55.

- Routine testing is useful in identifying areas of contamination and implementing changes to prevent future contamination

Salch et al. (2019) Am J Health Syst Pharm. 76(9):591–8

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“Take home” messages

- Surface contamination is prevalent
- Potential for occupational exposure for all healthcare workers that are part of hospital medication circuit
  - Not just nurses and pharmacy personnel
- Although surface contamination levels have reduced over time, some maximum levels > suggested threshold
  - Cannot use exposure judgment tools to assist with data interpretation
- Assessing exposure via dermal and urinary samples has limited benefits
- To reduce contamination levels, adhere to safe work practices and exposure control programs
  - However, cannot completely eliminate the risk

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Additional References *(articles listed in sequential presentation order)*

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- Sessink et al. (1995) Cancer risk assessment for health care workers occupationally exposed to cyclophosphamide. Int Arch Occup Environ Health. 67(5):317-23
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- Portilha-Cunha et al. (2021) Cytostatics in indoor environment: an update of analytical methods. Pharmaceuticals. 14(6):574.
- Vermette ML et al. (2024) Wipe sampling of antineoplastic drugs from workplace surfaces: A review of analytical methods and recommendations. Hygiene and Environmental Health Advances. 9:100089.
- AIHA Hazardous Drug Surface Contamination
- NIOSH Hazardous Drug Exposure in Healthcare
- Best practices to prevent healthcare workers' exposure to antineoplastic (hazardous) drugs
- NAPRA Guidance Document (Non-Sterile)
- NAPRA Guidance Document (Sterile)

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Thank you and contact information



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Questions?



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