Rapport de veille n° 57

Surveillance biologique de l'exposition professionnelle aux médicaments cytotoxiques. Etude de terrain.

1er septembre 2022 – 31 octobre 2022

Objectifs : Disposer d'une connaissance actualisée du sujet en accompagnement des demandes d'assistance qui découlent de la valorisation de l'étude sur la surveillance biologique de l'exposition aux médicaments cytotoxiques en milieu hospitalier.

La validation des informations fournies (exactitude, fiabilité, pertinence par rapport aux principes de prévention, etc.) est du ressort des auteurs des articles signalés dans la veille. Les informations ne sont pas le reflet de la position de l'INRS.

Les liens mentionnés dans le bulletin donnent accès aux documents sous réserve d'un abonnement à la ressource.

- ***Articles de périodique (PREPRINT)***

Lema-Atán J.A., Lendoiro E., Paniagua-González L., Cruz A., López-Rivadulla M., de-Castro-Ríos A.
LC-MS-MS Determination of Cytostatic Drugs on Surfaces and in Urine to Assess Occupational Exposure.
Journal of Analytical Toxicology, 15 septembre 2022

Résumé : *The ever-increased usage of cytostatic drugs leads to high risk of exposure among healthcare workers. Moreover, workers are exposed to multiple compounds throughout their lives, leading to cumulative and chronic exposure. Therefore, multianalyte methods are the most suitable for exposure assessment, which minimizes the risks from handling cytostatic drugs and ensures adequate contamination containment. This study describes the development and full validation of two liquid chromatography-tandem mass spectrometry methods for the detection of gemcitabine, dacarbazine, methotrexate, irinotecan, cyclophosphamide, doxorubicinol, doxorubicin, epirubicin, etoposide, vinorelbine, docetaxel and paclitaxel in working surfaces and urine samples. The urine method is the first to measure vinorelbine and doxorubicinol. For surfaces, limits of detection (LOD) and limits of quantification (LOQ) were 5-100 pg/cm2, and linearity was achieved up to 500 pg/cm2. Inaccuracy was between -11.0 and 8.4%. Intra-day, inter-day and total imprecision were <20%, except for etoposide and irinotecan (<22.1%). In urine, LOD and LOQ were 5-250 pg/mL, with a linear range up to 1,000-5,000 pg/mL. Inaccuracy was between -3.8 and 14.9%. Imprecision was <12.4%. Matrix effect was from -58.3 to 1,268.9% and from -66.7 to 1,636% in surface and urine samples, respectively, and extraction efficiency from 10.8 to 75% and 47.1 to 130.4%, respectively. All the analytes showed autosampler (6°C/72 h), freezer (-22°C/2 months) and freeze/thaw (three cycles) stability. The feasibility of the methods was demonstrated by analyzing real working surfaces and patients' urine samples. Contamination with gemcitabine, irinotecan, cyclophosphamide, epirubicin and paclitaxel (5-4,641.9 pg/cm2) was found on biological safety cabinets and outpatients' bathrooms. Analysis of urine from patients under chemotherapy identified the infused drugs at concentrations higher than the upper LOQ. These validated methods will allow a comprehensive evaluation of both environmental and biological contamination in hospital settings and healthcare workers.*

https://doi.org/10.1093/jat/bkac073

Zhou H., Li Y., Xu F.
Comparison of permeabilities of eight different types of cytotoxic drugs to five gloves with different materials by LC-MS/MS methods to reduce occupational exposure of medical personnel.
Journal of Oncology Pharmacy Practice, 19 septembre 2022

Résumé : *Purpose: Occupational exposure is a long-standing public health concern, which has drawn more and more attention in recent years to the problem of how to carry out occupational protection effectively. Gloves are regarded as the most critical protective equipment for cytotoxic medications. However, there is still little research conducted on the protective performance of gloves made of different materials and the optimal glove combination for cytotoxic agents. Methods: In this research, a specific instrument intended for glove permeation experiment was designed, with various methods of liquid chromatography-tandem mass spectrometry (LC-MS/MS) developed and validated. By using the specific instrument and LC-MS/MS methods, a study was conducted on the permeation ability of eight selected cytotoxic drugs (fluorouracil, epirubicin (EPI), docetaxel (DCT), methotrexate (MTX), cyclophosphamide (CTX), etoposide (ETP), vincristine sulfate (VCR), and cisplatin derivatives Pt-(DDTC)$_3$) into five kinds of gloves (rubber (RB), nitrile (NT), chlorinated polyethylene (CPE), low-density polyethylene, and polyvinylchloride (PVC) resin) given different contact times. Then, the experimental data were analyzed*

through a generalized estimation equation and Pearson correlation analysis. Results: The results show that within a short period of time (less than five minutes), ETP, CTX, fluorouracil, DCT, and cisplatin passed through five types of gloves but the level of MTX, VCR, and EPI permeation was minimal, despite the duration of contact between the three drugs and the gloves reaching as long as three hours. Furthermore, the permeation of DCT and ETP was found to be positively correlated with time. Conclusions: Chlorinated polyethylene and PVC resin perform well in protecting against most cytotoxic drugs and are recommendable for clinical practice. Due to the poor protective ability, RB gloves are not recommended for this purpose. Based on the performance of various gloves in offering protection, the protection grade of two gloves can be deduced. Chlorinated polyethylene + PVC resin, CPE + NT glove combination shows good protective performance against most target drugs and can be recommended for clinical practice.

https://doi.org/10.1177/10781552221127698

Crul M., Breukels O.
Safe handling of cytostatic drugs: recommendations from independent science.
European Journal of Hospital Pharmacy, 16 septembre 2022

Résumé : *Objectives: Due to their mechanism of action, most classical cytostatic drugs have carcinogenic, mutagenic and/or reprotoxic properties. Therefore, occupational exposure of healthcare staff to these drugs should be prevented. Our objective was to lay out European legislation on this topic and reflect on the process of revising the European CM-directive. We summarise independent European and Dutch studies, and give a concise set of basic recommendations for safe working with cytotoxic drugs in healthcare facilities. Methods: We were directly involved in the process of revising the CM-directive: first, through an EU commissioned workshop in the Netherlands, and after that by contributing to the pan-European stakeholder symposium. For this aim, we had to gather the relevant study data from the Netherlands and from Europe. We analysed all relevant industry-independent studies and collated a set of basic recommendations. Results: Independent studies show that the development of measures in recent years can lead to a safe work environment. Standardising the cleaning process leads to a significant improvement in environmental contamination in the majority of hospitals. In the Netherlands, exposure of workers was shown to be well beneath the limit value of 0.74 µg cyclophosphamide per week, therefore showing that the measures taken in recent years are adequate. Conclusions: The safety of healthcare workers is of the utmost importance. Current practice in the Netherlands show that measures taken in recent years are adequate. European legislation should be based on independent scientific research and practice. The first goal should be to bring countries with less safe working levels to a higher level instead of introducing measures that only increase healthcare budgets but not healthcare safety.*

http://dx.doi.org/10.1136/ejhpharm-2022-003469

- ***Articles de périodique***

Kadlcikova D., Musilova P., Hradska H., Vozdova M., Petrovova M., Svoboda M., Rubes J.
Chromosomal damage in occupationally exposed health professionals assessed by two cytogenetic methods.
Archives of Environmental and Occupational Health, 8 septembre 2022

Résumé: *The study assessed occupationally induced chromosomal damage in hospital personnel at risk of exposure to antineoplastic drugs and/or low doses of ionizing radiation by two cytogenetic methods. Cultured peripheral blood lymphocytes of eighty-five hospital workers were examined twice over 2 to 3 years by classical chromosomal aberration analysis and fluorescence in situ hybridization. The comparison of the 1(st) and the 2(nd) sampling of hospital workers showed a significant increase in chromatid and chromosomal aberrations (all p < .05) examined by classical chromosomal aberration analysis, and in unstable aberrations (all p < .05) detected by fluorescence in situ hybridization. Both cytogenetic methods were able to detect an increase of unstable aberrations in the 2(nd) sampling. The raised frequency of unstable cytogenetic parameters suggested higher recent exposure to genotoxic agents.*

https://doi.org/10.1080/19338244.2022.2118213

Valero García S., Centelles-Oria M., Palanques-Pastor T., Vila Clérigues N., López-Briz E., Poveda Andrés J.L.
Analysis of chemical contamination by hazardous drugs with BD HD Check(®) system in a tertiary hospital.
Journal of Oncology Pharmacy Practice, Volume 28, Numéro 7, Octobre 2022, Page 1583-1593

Résumé : *The presence of contamination in the healthcare work environment by one of the types of hazardous drugs, cytostatics, has been found in multiple international studies. Recent studies and guidelines recommend surface monitoring for risk assessment of healthcare professionals' exposure. The availability of detection techniques is critical to successfully carry out this type of monitoring. The use of new semi-quantitative techniques allows quicker results. The main objective of this study was to determine the existence of hazardous drugs on the working surfaces in different locations of a tertiary hospital using the BD HD Check(®) semi-quantitative device. The presence of methotrexate, doxorubicin and cyclophosphamide was analysed at 80, 89 and 82 locations in 10, 13 and 11 clinical units, respectively. A total of 251 samples were analysed. The monitoring results were positive for 13.1% of the analysed samples, with 36.3% of the methotrexate samples, 0% of the doxorubicin samples and 4.9% of the cyclophosphamide samples. Mapping the presence of HD in our hospital has allowed us to evaluate the effectiveness of controls established in the hospital to minimise the exposure of healthcare professionals to hazardous drugs. The speed in obtaining results has enabled immediate corrective actions in cases where contaminated surfaces were detected.*

https://doi.org/10.1177/10781552211038518

Levin G., Sessink P.J.
Validation of chemotherapy drug vapor containment of an air cleaning closed-system drug transfer device.
Journal of Oncology Pharmacy Practice, Volume 28, Numéro 7, Octobre 2022, Page 1508-1515

Résumé : *PURPOSE: The purpose of this study was to test the efficacy of ChemfortTM, an air filtration closed-system drug transfer device to prevent release of chemotherapy drug vapors and aerosols under extreme conditions. The air cleaning system is based on the adsorption of drug vapors by an activated carbon filter in the Vial Adaptor before the air is released out of the drug vial. The functionality of the carbon filter was also tested at the end of device's shelf life, and after a contact period with drug vapors for 7 days. Cyclophosphamide and 5-fluorouracil were the chemotherapy drugs tested. METHODS: The Vial Adaptor was attached to a drug vial and both were placed in a glass vessel. A needle was punctured through the vessel stopper and the Vial Adaptor septum to allow nitrogen gas to flow into the vial and to*

exit the vial via the air filter into the glass vessel which was connected to a cold trap. Potential contaminated surfaces in the trap system were wiped or rinsed to collect the escaped drug. Samples were analyzed using liquid chromatography tandem mass spectrometry. RESULTS: Cyclophosphamide and 5-fluorouracil were detected on most surfaces inside the trap system for all Vial Adaptors without an activated carbon filter. Contamination did not differ between the Vial Adaptors with and without membrane filter indicating no effect of the membrane filter. The results show no release of either drug for the Vial Adaptors with an activated carbon filter even after 3 years of simulated aging and 7 days of exposure to drug vapors. CONCLUSIONS: Validation of air cleaning CSTDs is important to secure vapor and aerosol containment of chemotherapy and other hazardous drugs. The presented test method has proven to be appropriate for the validation of ChemfortTM Vial Adaptors. No release of cyclophosphamide and 5- fluorouracil was found even for Vial Adaptors after 3 years of simulated aging and 7 days of exposure to drug vapors.

https://doi.org/10.1177/10781552211030682

Ml H., T W., Jq Z., Yj S., Tj G., Lk Z., J L., Jf Y.
Evaluation of external contamination on the vial surfaces of some hazardous drugs that commonly used in Chinese hospitals and comparison between environmental contamination generated during robotic compounding by IV: Dispensing robot vs. manual compounding in biological safety cabinet
Journal of Oncology Pharmacy Practice, Volume 28, Numéro 7, Octobre 2022, Page 1487-1498

Résumé : *OBJECTIVES: The aims of the study were to evaluate the external contamination of hazardous drug vials used in Chinese hospitals and to compare environmental contamination generated by a robotic intelligent dispensing system (WEINAS) and a manual compounding procedure using a biological safety cabinet (BSC). METHODS: Cyclophosphamide, fluorouracil, and gemcitabine were selected as the representative hazardous drugs to monitor surface contamination of vials. In the comparative analysis of environmental contamination from manual and robotic compounding, wipe samples were taken from infusion bags, gloves, and the different locations of the BSC and the WEINAS robotic system. In this study, high-performance liquid chromatography coupled with double mass spectrometer (HPLC-MS/MS) was employed for sample analysis. RESULTS: (1) External contamination was measured on vials of all three hazardous drugs. The contamination detected on fluorouracil vials was the highest with an average amount up to 904.33 ng/vial, followed by cyclophosphamide (43.51 ng/vial), and gemcitabine (unprotected vials of 5.92 ng/vial, protected vials of 0.66 ng/vial); (2) overall, the environmental contamination induced by WEINAS robotic compounding was significantly reduced compared to that by manual compounding inside the BSC. Particularly, compared with manual compounding, the surface contamination on the infusion bags during robotic compounding was nearly nine times lower for cyclophosphamide (10.62 ng/cm(2) vs 90.43 ng/cm(2)), two times lower for fluorouracil (3.47 vs 7.52 ng/cm(2)), and more than 23 times lower for gemcitabine (2.61 ng/cm(2) vs 62.28 ng/cm(2)). CONCLUSIONS: The external contamination occurred extensively on some hazardous drug vials that commonly used in Chinese hospitals. Comparison analysis for both compounding* procedures revealed that robotic compounding can remarkably reduce environmental contamination.

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