Bulletin de veille n° 69

1er novembre 2024 – 31 décembre 2024

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

Objectif : *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 éléments issus de cette veille sont founis sans garantie d'exhaustivité.

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

Portilha-Cunha M.F., Alves A., Ribeiro A.R.L., Silva A.M.T., Norton P. and Santos M.S.F.
Development and validation of a multicompound LLE-LC-MS/MS method for biomonitoring of hazardous medicinal products in urine of exposed workers.
Toxicology Letters, 28 novembre 2024

Résumé: *Antineoplastic drugs are carcinogens, mutagens, or teratogenic substances, which can pose serious risks to professionals. Concerns about chronic exposure to these hazardous medicinal products (HMPs) have led to their prominence in the EU strategic framework on health and safety at work 2021-2027. To estimate and mitigate human exposure to HMPs, regular monitoring programs and, consequently, reliable, sensitive, multicomponent methods are crucial. In this study, an unconventional liquid-liquid extraction coupled with liquid chromatography-tandem mass spectrometry analysis is proposed to simultaneously identify and quantify seven HMPs of high concern in urine: cyclophosphamide, etoposide, ifosfamide, paclitaxel, megestrol, mycophenolate mofetil, and tamoxifen, the last three for the first time. Recoveries of all drugs from urine samples were close to 100 %, and method detection limits (0.6-4.1 ng/L) were noticeably lower than most previously reported. This novel, non-invasive method for biomonitoring is thus suitable to unequivocally identify the target drugs at the expected trace levels in urine and to infer about workers' exposure. The method contributes to the conception of regular monitoring programs for antineoplastic drugs, in line with recommendations under EU Directive 2004/37/EC. This is especially relevant in Portugal, where neither analytical methods nor exposure data exist due to lack of formal surveillance.*

https://doi.org/10.1016/j.toxlet.2024.11.012

Iwasaki Y., Hiraide M., Taguchi H., Iehisa R., Akiyama H., Suzuki K., Shimizu H. and Yamaguchi M.
Removal efficiency of antineoplastic drug cyclophosphamide by hypochlorous acid.
Journal of Occupational Environmental Hygiene, 10 décembre 2024.

Résumé: *Hypochlorous acid (HClO), one of the major reactive oxygen species, is obtained by electrolyzing a sodium chloride solution. HClO is a safe and effective disinfectant and decomposing agent widely used as an alternative to sodium hypochlorite (NaClO). In this study, the authors aimed to evaluate the safety and efficiency of HClO generated by electrolyzing sodium chloride as a decontaminant. Cyclophosphamide (CPA), an antineoplastic drug, was selected as the model drug, and various solvents (HClO, NaClO, etc.) were compared to identify the solvents that could react with and efficiently decompose CPA. To identify a solvent that efficiently decomposes CPA, the CPA concentration was measured using liquid chromatography with photodiode array detection. When either NaClO or HClO was used, the CPA concentration decreased, and a peak corresponding to 3-chloro CPA, identified by mass spectrometry, was detected. Furthermore, to investigate the reversibility of the reaction between CPA and ClO(-), ClO(-) was removed from the reaction solution using solid-phase extraction, resulting in the previously decreased CPA concentration returning to nearly its original level. Occupational exposure to antineoplastic drugs poses a significant risk to worker health. This study's results suggest that CPA can be replaced by 3-chloro CPA when HClO is used as the wiping solvent like NaClO, thereby reducing occupational exposure from wiping. Future studies should investigate the wiping and degradation efficiencies of other anti-cancer agents. Occupational exposure to anti-cancer drugs can be significantly reduced by integrating various mitigation measures, thereby contributing to a safer work environment for healthcare professionals.*

https://doi.org/10.1080/15459624.2024.2423752

Sessink P.J.M., Barry B., Dunbar L., Cameron L.T., Kirkness T. and Campbell K.
Workflow evaluation of environmental contamination with hazardous drugs during compounding and administration in an UK hospital.
Journal of Oncology Pharmacy Practice, 13 décembre 2024

Résumé: *Introduction Exposure of healthcare workers to hazardous drugs may result in adverse health effects underscoring the importance of validating working procedures and safety precautions to minimise the risk. The objective was to monitor environmental contamination caused by the hazardous drug workflow: from drug vials, compounding process, to patient administration.Methods Surface wipe samples were collected from potentially contaminated surfaces in the compounding department and in the administration department. The outside of drug vials, compounded syringes, bags, elastomeric pumps, and gloves used by the nurses for administration were also monitored. Stationary air samples were collected near the isolators and above the bench top. Personal air samples were collected from pharmacy technicians, pharmacists, and nurses. Monitoring was performed in three trials during two-months. Samples were analysed for cyclophosphamide, 5-fluorouracil, docetaxel, and paclitaxel using liquid chromatography tandem mass spectrometry.Results Contamination was mainly found for 5-fluorouracil and cyclophosphamide on isolator surfaces, bench top, trays, and compounded products. Lower levels of contamination were measured in the administration department on trays, trolley arms and gloves of the nurses. Paclitaxel and docetaxel were incidentally detected. Air contamination was found for paclitaxel in the compounding department in one trial, and 5-fluorouracil was detected once in front of an isolator. Docetaxel was found in one air sample of a nurse.Conclusions Contamination was mainly found for 5-fluorouracil and cyclophosphamide on the products compounded in the isolators. Contamination was further spread along the workflow towards the administration department causing surfaces in between being contaminated too.*

https://doi.org/10.1177/10781552241285138

Favier B., Simonin C., Tokatian S., Guitton J., Darnis S., Basset M., Chabaud S. and Gilles L.
Cytotoxic surface contamination in hospitals: Current practices, challenges and perspectives.
Journal of Oncology Pharmacy Practice, 19 décembre 2024.

Résumé: *OBJECTIVE: Despite significant advances in cancer treatment with targeted therapies and immunotherapies, cytotoxic chemotherapies are still extensively used. Potential cytotoxic contamination in preparing and administrating cytotoxics is still a major source of concern. Besides advanced protections including biological safety cabinets, work surface contamination needs to be continuously controlled to ensure that handling procedures and cleaning were appropriate. Contamination monitoring needs to be standardized. DATA SOURCES: The study searched Pubmed/Medline and Embase with"hazardous drug", "cytotoxic drug", "surface contamination", "environmental contamination", "wipe sample", "pharmacy", "care unit", and selected studies reporting contamination results in work environment for pharmacy technicians and nurses, from 1 January 2017 to 31 December 2022. DATA SUMMARY: The 29 studies totalized 16,196 samples and 189,571 assays. Contamination results showed 39.8% sample positivity, and 8.2% assay positivity. Multicentric studies gathering at least 500 samples or up to 800 samples would limit heterogeneity in sample positivity. In addition, monitoring of an appropriate tracer selection including at least the 7 tracers with the highest contamination frequencies (cyclophosphamide, gemcitabine, fluorouracile, ifosfamide, platinum derivatives, paclitaxel and methotrexate) would facilitate contamination comparisons amongst studies and local results. Most recent*

studies reported thresholds for cyclophosphamide close to 0.1 ng/cm² at the 90(th) percentile. CONCLUSIONS: The overall risk of exposure for healthcare professionals is a major concern. Sample size in multicentric studies would require at least 500 samples; quantification of all tracers with the highest contamination frequencies need to be quantified. This approach would provide a basis to develop guidelines to appropriately monitor contamination in pharmacies and patient care area managers.

https://doi.org/10.1177/10781552241307905

- ***Articles de périodique***

Sessink P.J., Tans B., Spriet I., Devolder D. (Préprint dans Bulletin n° 65)
Longitudinal evaluation of environmental contamination with hazardous drugs by surface wipe sampling.
Journal of Oncology Pharmacy Practice, Volume 30, Numéro 7, octobre 2024, Page 1181-1185

Résumé : *Introduction: Exposure of healthcare workers to hazardous drugs can lead to adverse health effects supporting the importance of a continuous monitoring program, for example, by taking surface wipe samples. The objective was to describe the results of repeated monitoring of contamination with hazardous drugs on multiple surfaces in a hospital pharmacy and at two wards using standardized preparation techniques and cleaning procedures. Methods: Twelve surfaces in the hospital pharmacy and at two wards were sampled and analyzed for contamination with the hazardous drugs cyclophosphamide, doxorubicin, 5-fluorouracil, gemcitabine, methotrexate, and paclitaxel. The drugs were prepared with a closed-system drug transfer device (CSTD). Sampling of the drugs was performed in four trials during eight months. Liquid chromatography tandem mass spectrometry was used for the analysis of the drugs. Results: During the four trials, contamination with five of the six hazardous drugs was found on half of the surfaces in the pharmacy and in a ward. Seventeen out of 288 possible outcomes were positive (6%), with the biological safety cabinet grate (n= 6) and scanner (n= 5) most frequently contaminated. The highest level of contamination was observed on the pass-thru window (cyclophosphamide: 2.90 ng/cm(2)) and the touch screen of the Diana device (5-fluorouracil: 2.38 ng/cm(2)). Both levels were below the action level of 10 ng/cm(2). Conclusions: The long-term use of a CSTD in combination with appropriate cleaning has proven effective in achieving low levels of surface contamination with hazardous drugs.*

https://doi.org/10.1177/10781552231205481

Creta M., Verscheure E., Tans B., Devriese H., Devriendt A., Devolder D., Lebegge R., Poels K., Godderis L., Duca R.C. and Vanoirbeek J.A.J.
An Assessment of Surface Contamination and Dermal Exposure to 5-Fluorouracil in Healthcare Settings by UPLC-MS/MS Using a New Atmospheric Pressure Ionization Source.
Toxics, Volume 12, Numéro 11, novembre 2024, Article 766

Résumé: *5-Fluorouracil (5-FU) is a well-known cytostatic drug, which is often used in cancer treatments. Yet, it is also a very dangerous compound for people who are occupationally exposed to it for a long time, such as pharmacy employees, nurses and cleaning staff. We aimed to improve and implement a LC-MS/MS method for 5-FU quantification on surface contamination samples collected with swabs in a pharmacy department and outpatient nursing station of a university hospital. To improve the existing methods to*

quantify 5-FU, we compared a LC-MS/MS method using the frequently applied electrospray ionization source (ESI) with a UniSpray ionization source (USI). To determine the contamination of 5-FU in a pharmacy department preparing 5-FU infusion bags, which are then given to patients in the outpatient nursing stations, we collected multiple surface swabs of the laminar flow cabinets and frequently touched objects, before the preparation and administration of 5-FU and afterwards. Furthermore, we sampled the protective gloves and the bare hands of employees of the pharmacy department, involved in the preparation of the infusion bags. Using the USI source, we were able to reach the lowest limit of quantification (LOQ). With this technique, we were able to detect 5-FU contamination on the laminar flow cabinets and frequently used objects in the pharmacy department and the outpatient nursing station in the very low ng/cm(2) range. This contamination was mostly higher after preparation or administration than before. While we also found 5-FU on the protective gloves, we almost found no 5-FU on the skin of the pharmacy technicians preparing the 5-FU infusion bags. In conclusion, our method was able to detect very low concentrations of 5-FU contamination, but the contamination we found is very unlikely to result in any issues for the personnel working in these areas.

https://doi.org/10.3390/toxics12110766

van Huizen P., Wembridge P., Russo P. L., Manias E., Connell C. J.
The handling of hazardous medications by nurses and midwives: A retrospective cohort study.
International Journal of Nursing Studies, Volume 160, décembre 2024, Article 104889

Résumé *: Background: Occupational exposure of healthcare workers to hazardous medications can be potentially harmful. Hazardous medications can be carcinogenic, developmentally toxic, reproductively toxic, genotoxic and/or toxic to organs at low doses. These hazardous medications can be used in many healthcare settings, but published research of occupational exposure has focused almost exclusively on cancer services. Aim: To identify the healthcare settings where nurses and midwives are responsible for the administration of hazardous medications. Method: A retrospective cohort study was undertaken of all medication administration events occurring during a two-week period at a public metropolitan health service in 2023. All medication administration events from six hospital sites were identified using the electronic (Oracle Health-Cerner-Millennium®) and paper (Chemotherapy Chart) medication administration records. From all of the medications administered, the subset of medications classified as hazardous were identified based on the Victorian Therapeutics Advisory Group Framework for Handling of Hazardous Medicines (2021) and other guidelines. Poisson regression modelling was used to explore associations between the number of hazardous medications and the healthcare area where they were administered ($p < 0.001$). Results: Of the 121,567 administration events, 6054 (5.0 %) involved hazardous medications. The healthcare areas with the highest rate of hazardous medication administration events, as a proportion of all medication administration events, were outpatient cancer service (301/695, 43.3 %), birth suite (13/86, 15.1 %) and mental health (404/4011, 10.1 %) areas. During the two-week period, 6054 hazardous medication administration events occurred, involving 117 different medications. The greatest number of these events took place in the medical (1729/6054, 28.6 %) and geriatric (1579/6054, 26.1 %) inpatient healthcare areas. A total of 1258 nurses and midwives were directly involved in either administering, or checking and witnessing the administration of hazardous medications to 996 patients (25.2 % of the total 3958 patients). Most hazardous medications administered to patients were in an oral dosage form (5426/6054, 89.6 %). Conclusion: Hazardous medications were administered in all healthcare areas, with the exception of endoscopy services. Nurses and midwives were at risk of occupational exposure from hazardous medications.*

https://doi.org/10.1016/j.ijnurstu.2024.104889

van Huizen P., Russo P. L., Manias E., Kuhn L., Connell C. J.
Knowledge and safe handling practices affecting the occupational exposure of nurses and midwives to hazardous drugs: A mixed methods systematic review.
International Journal of Nursing Studies, Volume 160, décembre 2024, Article 104907

Résumé : *Background: Hazardous drugs are inherently toxic and present a potential occupational exposure risk to nurses and midwives. Hazardous drugs require special handling to minimise the risk of exposure and adverse health effects. Although the use of hazardous drugs in oncology services is well recognised, they are also used in other healthcare areas where nurses and midwives may be unaware there is a risk. Objective: To investigate what nurses and midwives know and do about their occupational exposure to hazardous drugs, and what factors affect their knowledge and practice. Design: Mixed methods systematic review. Methods: A systematic review was conducted, and studies were included if the authors described what nurses or midwives knew about hazardous drugs, or what they did in their clinical practice to reduce their risk of occupational exposure (PROSPERO registration CRD42024437493). The databases were searched for any year until the 26th of January 2024.Two independent reviewers extracted data using Covidence and assessed the risk of bias. The data were extracted into the categories of knowledge of risk and safe handling practices, attitude and factors affecting these, and activities that posed the greatest risk of exposure (preparation, administration, and disposal of hazardous drugs, cleaning hazardous drug spills, and handling excreta from patients who had recently been treated with hazardous drugs). Results: Of the 2702 articles that were identified, 59 quantitative and 3 qualitative studies were included in this review. No studies reported on midwives handling hazardous drugs. Most studies investigated nurses working in oncology services. Nurses reported a lack of education about the risk and safe handling. They were often responsible for preparing hazardous drugs and there was inconsistency in their compliance when using personal protective equipment. Nurses did not always perceive that there was a real risk of exposure, were concerned about the effect of wearing personal protective equipment on their relationship with patients and perceived they lacked the time to don equipment. Conclusions: The risk of occupational exposure to hazardous drugs outside of oncology services was rarely investigated. There were no studies reporting what midwives knew and did about their risk of occupational exposure to hazardous drugs. When nurses were aware of the risks, this did not necessarily translate into the implementation of safe handling practices or the consistent use of personal protective equipment because of a perceived low risk, lack of personal protective equipment availability, and prioritising personal or patient comfort over safety measures.*

https://doi.org/10.1016/j.ijnurstu.2024.104907

Campbell K., Afseth J., Dunham M., King M. and Dicksit D.
Global Cancer Nurse's Experiences and Perceptions of Potential Occupational Exposure to Cytotoxic Drugs: Mixed Method Systematic Review With Framework Synthesis.
Journal of Clinical Nursing, Volume 33, Numéro 12, décembre 2024, Page 4585-4601

Résumé: *AimTo conceptualise experiences and perceptions of cancer nurses' potential for occupational exposure when dealing with cytotoxic drugs (CDs).DesignA mixed methods systematic review with framework synthesis.Methods and Data SourcesA literature search was conducted in February 2022 in CINAHL PubMed, Web of Science, Ovid Nursing, and PsycINFO, and it was reported using the PRISMA guidance.ResultsA synthesis of 38 studies revealed new categories of perceived solutions, side effects, and risky behaviour as well as three levels of experience and perception: individual, shared, and cultural, rather than the a priori theory.ConclusionsThe review conclude that individuals espouse safe handling and administration of CDs. Synthesis highlights a complex interplay between self-reported perception and the observed experience of potential occupational exposure to cytotoxic drugs.Implications for Professional PracticeThe framework synthesis highlights the difference between the perception of*

espoused practice and the experience of practice. Observation and risk assessment must be used to enhance safe practice. Organisations must take seriously the perception and experience of the adverse effects of administering cytotoxic drugs to support cancer nurses.Reporting MethodJoanna Briggs Institute's (JBI) methodology for systematic reviews and framework synthesis indexed studies deductively and inductively. No patient or public contribution.Reporting MethodJoanna Briggs Institute's (JBI) methodology for systematic reviews and framework synthesis indexed studies deductively and inductively. No patient or public contribution.

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