Rapport de veille n° 56

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

1er juillet 2022 – 31 août 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)***

Yildirim F. D., Ekmekci I.
Design of analytical method validation protocol evaluating environmental monitoring of and contamination on surfaces based on cleaning validation procedures: a multi component RP-UHPLC method.
Journal of Chromatographic Science, 18 août 2022

Résumé : *Environmental monitoring of anti-neoplastic drug (AND) residues in workplaces is crucial to limit exposure to workers who handle with them. Although wipe sampling is the most appropriate methodology to evaluate the risk, conflicting results are also reported due to the lack of standardized and validated procedures. In this study, procedures for surface contamination of ANDs in workplaces are presented, with a focus on sampling, sample preparation and instrumentation. The analytical method validation parameters are designed to comply with requirements of The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q7 Good Manufacturing Practice (GMP) for active pharmaceutical ingredients. Additionally, the study provides a simple, specific, rapid and multi-component analytical method to evaluate seven ANDs that are Gefitinib, Imatinib, Dasatinib, Axitinib, Erlotinib, Nilotinib and Sorafenib at very low concentration levels, simultaneously. Quantitative, precise and reproducible results obtained from the study show that environmental monitoring procedure and analytical method validation protocol presented in the study can be used to reduce and monitor occupational exposure risk to ANDs in wokplaces.*

https://doi.org/10.1093/chromsci/bmac071

Arnold S., Jeronimo M., Astrakianakis G., Kunz M., Petersen A., Chambers C., Johnson D.M., Zimdars E., Davies H.W.
Developing wipe sampling strategy guidance for assessing environmental contamination of antineoplastic drugs.
Journal of Oncology Pharmacy Practice, 4 août 2022

Résumé : *Surveillance for environmental contamination of antineoplastic drugs has been recommended by authoritative bodies such as the United States Pharmacopeia and the National Association of Pharmacy Regulatory Authorities. Clear guidance is needed on how to develop sampling strategies that align with surveillance objectives efficiently and effectively. We conducted a series of simulations using previously collected surveillance data from nine cancer treatment centers to evaluate different sampling strategies. We evaluated the impact of sampling 2, 5, 10, or 20 surfaces, at monthly, quarterly, semi-annual, and annual frequencies, while employing either a random or sentinel surface selection strategy to assess contamination by a single antineoplastic drug (AD) or by a panel of three ADs. We applied two different benchmarks: a binary benchmark of above or below the limit of detection and AD-specific hygienic guidance values, based on 90th percentile values as quantitative benchmarks. The use of sentinel surfaces to evaluate a three-drug panel relative to 90th percentile hygienic guidance values (HGVs) resulted in the most efficient and effective surveillance strategy.*

https://doi.org/10.1177/10781552221118535

- ***Articles de périodique***

Benoist H., Eveno C., Wilson S., Vigneron N., Guilloit J.M., Morello R., Simon N., Odou P., Saint-Lorant G.
Perception, knowledge and protective practices for surgical staff handling antineoplastic drugs during HIPEC and PIPAC.
Pleura Peritoneum, Volume 7, Numéro 2, 13 avril 2022, Page 77-86

Résumé: *OBJECTIVES: Two surgical techniques used for peritoneal metastasis involve a risk of exposure to antineoplastic drugs (ADs): hyperthermic intraperitoneal chemotherapy (HIPEC) and pressurized intraperitoneal aerosol chemotherapy (PIPAC). The objective of this study was to assess the differences in perception, training, and knowledge of the risks as well as in the protection practices and occupational exposures of all worker categories. METHODS: This descriptive study, led in two hospitals from two distant French regions, was performed through a face-to-face interview and assessed the perception, knowledge and handling practices of ADs by a questionnaire consisting of 52 questions. RESULTS: Fifty-one professionals participated in this survey. A total of 29.4% (n=15) professionals were afraid to handle ADs. Very few workers have been trained on handling ADs during initial training dedicated to all caregiver (5.9%; n=3). HIPEC is considered to involve a higher risk of exposure to ADs than PIPAC (81.6% (n=31) vs. 57.9% (n=22), respectively, p=0.022, agreement 65.8%). Protective equipment is considered to be less suitable for HIPEC than for PIPAC (29% (n=11) vs. 10.5% (n=4), respectively, p=0.016, agreement 81.6%). Concerning the potential AD contamination location, the participants identified a significant difference between these two practices. During HIPEC, 15.7% (n=6) of caregivers indicated that they had negative symptoms perceived in their practice vs. 2.6% (n=1) during PIPAC. CONCLUSIONS: This study shows that perception, knowledge and protection practices are different between HIPEC and PIPAC. It also shows a difference between the worker categories. In view of the difficulties in making operating room staff available, the related training programmes must have an adapted format.*

https://doi.org/10.1515/pp-2021-0151

Sottani C., Grignani E., Cornacchia M., Negri S., Saverio Robustelli Della Cuna F., Cottica D., Bruzzese D., Severi P., Strocchi D., Verna G., Leso V., Iavicoli I.
Occupational Exposure Assessment to Antineoplastic Drugs in Nine Italian Hospital Centers over a 5-Year Survey Program.
International Journal Environmental Research Public Health, Volume 19, Numéro 14, Juillet 2022, Page 8601

Résumé : *In the present study, surface contamination where antineoplastic drugs (ADs) are present was investigated, as occupational exposure risk is still an open debate. Despite recommendations and safety standard procedures being in place in health care settings, quantifiable levels of ADs are being reported in the recent literature. Thus, a survey monitoring program was conducted over five years (2016-2021) in nine Italian hospitals. The repeated surveys produced 8288 data points that have been grouped according to the main hospital settings, such as pharmacy areas and patient care units. Based on the most often prepared ADs, the investigated drugs were cyclophosphamide (CP), gemcitabine (GEM), 5-fluorouracil (5-FU), and platinum compounds (Pt). Patient care units had a frequency of positive wipe samples (59%) higher than pharmacies (44%). Conversely, pharmacies had a frequency of positive pad samples higher (24%) than patient care units (10%). Moreover, by statistical analysis, pad samples had a significantly higher risk of contamination in pharmacy areas than in patient care units. In this study,*

the 75th and the 90th percentiles of the contamination levels were obtained. The 90th percentile was chosen to describe a suitable benchmark that compares results obtained by the present research with those previously reported in the literature. Based upon surface contamination loads, our data showed that 5-FU had the highest concentration values, but the lowest frequency of positive samples. In pharmacy areas, the 90th percentile of 5-FU data distribution was less than 0.346 ng/cm(2) and less than 0.443 ng/cm(2) in patient care units. AD levels are higher than those reported for health care settings in other European countries yet trends of contamination in Italy have shown to decrease over time.

https://doi.org/10.3390/ijerph19148601

Yu B., Wang Y., Geng Z., Qu Y., Pan J., Zhai Q.
Establishment and validation of analytical methods for 15 hazardous drugs by UPLC-Q/Orbitrap-HRMS.
Annals of translational medicine, Volume 10, Numéro 12, Juin 2022, Page 686

Résumé : *Background: Cytotoxic drug residues in pharmacy intravenous admixture services (PIVAS) have always been a major problem for pharmaceutical workers and the PIVAS environment,which is not only pollutes the PIVAS environment, but also causes serious harm to the life and health of the staff. This study aimed to establish an ultra-high performance liquid chromatography quadrupole orbitrap high resolution mass spectrometry (UPLC-Q/Orbitrap-HRMS) method for the rapid detection and monitor of 15 cytotoxic drugs**.** Methods: UPLC-Q/Orbitrap-HRMS method was used to establish a rapid detection method for 15 cytotoxic drugs such as cytarabine, gemcitabine and so on. The daily precision and accuracy of this method were verified by injecting four concentrations of standard solution on the same day, and the same four concentrations of standard solution were injected within three days respectively to verify the daily precision of this method. The signal-to-noise ratio (SNR) of 10:1 was calculated as the limit of quantity. The mixed standard solution of 15 cytotoxic drugs with concentrations of 0.5, 1, 3, 10, 30, 100, 300, and 1,000 ng/mL was configured and detected by this method for linearity and range.The stability of this method was investigated using a mixture of 15 drugs (15MIX) standard solutions at high concentration (300 ng/mL) and low concentration (10 ng/mL) at room temperature for 12 and 24 hours, respectively. A standard solution of each drug, 15MIX and blank solution were taken to verify the exclusivity of the method. Results: The results showed that the method had good specificity, and the intraday precision of all drugs was less than 10% and the intraday precision was less than 15%. At the same time, the standard curve had good linearity, R^2 was greater than 0.99, and the limit of quantification of most drugs was about 1 ng/mL. Conclusions: In this study, an UPLC-Q/Orbitrap-HRMS method was established for the rapid detection of 15 cytotoxic drugs, providing technical support for the monitoring of cytotoxic drug residues in PIVAS, which is of great significance for environmental contamination mornitoring as well as occupational exposure alert.*

https://doi.org/10.21037/atm-22-2330

Villa A., Tremolet K., Martinez B., Petit M., Dascon X., Stanek J., Ducint D., Titier-Debeaupuis K., Verdun-Esquer C., Molimard M., Canal-Raffin M.
Urine biomonitoring of occupational exposure to methotrexate using a highly sensitive UHPLC-MS/MS method in MRM3 mode.
Journal of Chromatography B, Volume 1209, 15 octobre 2022, Article 123411

Résumé : *Methotrexate (MTX) is widely used as antineoplastic drug (AD) and as an immunosuppressive. As a result, many healthcare professionals are exposed to this drug which is classified as dangerous to handle due to its reproductive toxicity in humans. Since the 1990 s, cases of internal contamination of professionals handling this molecule have been reported in the literature and even recently MTX was detected in the urine of professionals. To date, there is no toxicological reference value for occupational exposure to MTX. Given the toxicity of this molecule, the internal contamination of professionals must be reduced and kept as low as possible according to the ALARA principle (as low as reasonably achievable). The aim of this work was to develop an UHPLC-MS/MS method in MRM (Multiple Reaction Monitoring) and MRM3 modes for routine application in MTX occupational biomonitoring. Good linearity (r greater than 0.997), precision (CV < 15 %), and accuracy (94.97-97.80% of the nominal value in MRM mode; 105.90-112.25% in MRM3 mode) were achieved. This method is reliable with high specificity and high sensitivity especially in MRM(3)mode and has better LOD and LLOQ (1 ng/L and 2.5 ng/L) than published methods to date. The MRM3 mode increases the signal-to-noise ratio compared to the MRM mode. It was then applied routinely for the biological monitoring of healthcare professionals exposed to methotrexate. One hundred and seventeen urine samples from 93 healthcare professionals occupationally exposed to methotrexate were analyzed. Fifteen healthcare professionals (16.1 %) were found to be contaminated with methotrexate. Urine concentration levels ranged from 2.5 to 380 ng/L with a median value of 8.9 ng/L. Such efficient analytical tool is essential for the routine biological monitoring of healthcare professionals exposed to methotrexate. It also enables the traceability of occupational exposure to this molecule and the evaluation of the effectiveness of preventive measures such as individual and collective protective equipment.*

https://doi.org/10.1016/j.jchromb.2022.123411