



Highly sensitive LC–MS/MS methods for urinary biological monitoring of occupational exposure to cyclophosphamide, ifosfamide, and methotrexate antineoplastic drugs and routine application



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ABSTRACT

Highly sensitive ESI–LC–MS/MS methods were developed for urinary biological monitoring of occupational exposure to cyclophosphamide (CP), ifosfamide (IF), and methotrexate (MTX), which are hazardous antineoplastic drugs frequently handled by healthcare professionals. Extraction methods consisted of liquid/liquid extraction for simultaneous urinary CP and IF assays, and of solid phase extraction for the urinary MTX assay. A good linearity ($r^2 > 0.997$), precision ($CV < 14.6\%$), and accuracy (bias $< 9.9\%$) were achieved for all compounds. The limit of detection (LOD) was 10 pg/ml and the lower limit of quantification (LOQ) was 20 pg/ml for all three drugs. Applying these methods in routine, more than 116 healthcare professionals occupationally exposed to antineoplastic drugs were monitored and 635 urines were analysed. Eleven healthcare professionals (9.5%) were found to be contaminated to at least one of the three antineoplastic drugs. Among analysed urines, 22 samples were found positives. The measured concentrations ranged from 20.1 to 1850 pg/ml and, for six samples, concentrations were at CP trace level, between the LOD and LOQ values (10–20 pg/ml). Such efficient analytical tools combining high specificity with high sensitivity are essential for reliable detection and routine biological monitoring of healthcare professionals occupationally exposed to these widely used antineoplastic drugs. These methods allow to monitor the healthcare professionals exposure to antineoplastic drugs in the aim to assess the effectiveness of collective and individual protective measures.

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1. Introduction

The increased incidence of cancer over the last three decades in France [1] has led to an increase in the use of antineoplastic drugs [2]. For instance, in 2010 chemotherapies in France were administered to 260 000 patients [3] and more than 49 400 healthcare professionals handling these drugs are exposed occupationally and could be contaminated [4].

Antineoplastic drugs, also called cytotoxic drugs, is a class of drugs that includes numerous compounds with various mecha-

nisms of action that are used to prevent or disrupt cell division of neoplastic cells. However, their action on neoplastic cells is only partially selective and normal cells may also be affected as a result of exposure, leading to significant toxic side effects such as DNA changes for example. On the basis of in vitro studies, animal carcinogenicity data, and epidemiological findings, the International Agency for Research on Cancer has classified several antineoplastic drugs as carcinogenic for humans (group 1) such as cyclophosphamide (CP) [5]. Some are also mutagenic and/or toxic for reproduction, as is the case for methotrexate (MTX) [6,7]. Antineoplastic drugs have also been listed as hazardous drugs for handling in healthcare settings [8] due to their potential risk of carcinogenic and/or mutagenic effect and/or toxicity for reproduction. On healthcare professionals, it is reported that occupational exposure to these drugs can lead to acute effects such as skin rashes

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