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Biological Monitoring via Urine Samples to Assess Healthcare Workers' Exposure to Hazardous Drugs: A Scoping Review

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Abstract: Although biological monitoring is beneficial as it assesses all possible routes of exposure, urine sampling of healthcare workers exposed to hazardous drugs is currently not routine. Therefore, a scoping review was performed on this subject matter to understand what is known about exposure and identify knowledge gaps. A literature search was performed on three databases: ProQuest, Web of Science, and PubMed. Articles published between 2005 and 2020 and written in English were included. Overall, this review consisted of 39 full-text articles. The studies varied with respect to design, sample sizes, sample collection times, and drugs examined. Many articles found at least one sample had detectable levels of a hazardous drug. Studies reported urinary drug contamination despite controls being employed. 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. Due to differences in sample collection and analysis, a comparison between studies was not possible. Nevertheless, it appears that biological monitoring via urine sampling is meaningful to aid in understanding healthcare workers' exposure to hazardous drugs. This is supported by the fact that most studies reported positive urine samples and that case-control studies had statistically significant findings.

Keywords: hazardous drugs; biological monitoring; urine samples; healthcare workers; occupational exposure

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1. Introduction

Hazardous drugs, also referred to as antineoplastic drugs and chemotherapy drugs, are commonly used in hospitals to treat cancer patients. These drugs are inherently toxic and healthcare workers may be inadvertently exposed to hazardous drugs while performing their usual duties. Studies have found that healthcare workers may be occupationally exposed to hazardous drugs through counting and breaking of tablets; during preparation, administration, and disposal of hazardous drugs; when cleaning spills of hazardous drugs; as well as from accidental spillage when transporting hazardous drugs [1–3]. It is estimated that approximately 8 million healthcare workers, primarily pharmacy and oncology nursing personnel, in the United States are exposed to hazardous drugs [4]. This number is likely an underestimate, as studies have found that any worker involved with a hospital's medication circuit (e.g., drug preparation, transport, and administration) may be at risk of exposure [5,6]. Regardless, the number of those occupationally exposed is likely on the rise as it is projected that more than 20 million people will be affected by cancer in 2025 [7]. A healthcare worker may be exposed to hazardous drugs on a daily basis, often for many years, which can lead to harmful effects such as genetic damage (which increases the risk of cancer) as well as adverse reproductive toxicities such as congenital malformations and infertility [7–9].

To assess healthcare workers' exposure to hazardous drugs, studies have analyzed surface wipe samples (environmental monitoring), dermal (hand) or glove samples, air samples, as well as biological specimens [10]. The latter, also known as biological monitoring

or biomonitoring, evaluates worker exposure by measuring the concentration of a chemical or its metabolite in biological specimens [11,12]. From an occupational health and safety perspective, biological exposure monitoring is beneficial as it assesses a worker's uptake through all possible routes of exposure, such as skin absorption, inhalation, and ingestion, resulting in a more accurate assessment of risk [11]. Urine is often used as a specimen for biological exposure monitoring because it is non-invasive, is readily available, and large volumes are possible [13]. In essence, by analyzing the concentration of hazardous drugs and/or their metabolites in urine from healthcare workers, it is possible to identify exposure risk factors as well as evaluate the effectiveness of control measures intended to reduce occupational exposure [14,15].

In their best practice document intended to prevent healthcare workers' exposure to hazardous drugs, the National Institute for Occupational Health and Safety (NIOSH) suggests that biological monitoring should be conducted "when exposure is suspected, or symptoms have been noted" [16]. This is especially important as dermal contamination has been reported despite gloves being worn by healthcare workers [17,18] and, therefore, uptake is likely. In addition, there is no known correlation between environmental contamination and urinary contamination levels. Despite the above, employing biological urinary monitoring to assess healthcare workers' exposure to hazardous drugs is currently not a common practice—most likely because there is little guidance surrounding the matter. This study sought to provide some clarity on the issue of biological monitoring of healthcare workers who may be exposed to hazardous drugs.

Therefore, the objective of this study was to conduct a scoping review of the current body of literature surrounding biological monitoring via urine samples for healthcare workers occupationally exposed to hazardous drugs. A scoping review is ideal to establish how urinary contamination studies were conducted, what the data to date indicate about exposure and, subsequently, identify knowledge gaps [19]. The goal was to understand what information is still required for biological monitoring via urine samples to become a more common or routine practice to protect the health and well-being of healthcare workers exposed to hazardous drugs.

2. Materials and Methods

We followed the PRISMA Scoping Review checklist [20] as well as the corresponding updated scoping review guidance by Peters et al. [21] and employed an iterative process to define the inclusion criteria as well as to collect, summarize, and report the findings. No appraisal of the studies included in this scoping review was performed as it was not part of the current study's objectives.

2.1. Search Databases and Inclusion Criteria

A literature search was performed on publications available in three databases: ProQuest Research Library, Web of Science, and PubMed (Medline). For inclusion in the current study, an article had to conduct exposure assessments of healthcare workers to hazardous drugs via biological exposure monitoring using urine samples, be written in English, and be published between the years 2005–2020. A decision was made to exclude articles published before 2005 as they would most likely be outdated since interventions were introduced in many facilities because of the 2004 NIOSH Alert [16], as well as the fact that there have been vast improvements in the laboratory analysis of biological samples, i.e., instrument sensitivity/detection limits have improved since 2005. Abstracts, editorials, case studies, review articles, study protocols, non-urine specimens, method development articles, and non-occupational and animal studies were excluded from this review.

2.2. Search Strategy

The following search terms were used in this scoping review: "hazardous drugs" or "antineoplastic drugs" AND "occupational" or "healthcare workers" or "pharmacist" or "nurse" AND "urine" or "biomarkers". For example, in the "Documents" search field in the Web of Science database, one combination of terms included "hazardous drugs" AND "occupational" and "urine" with a custom publication date from 01 January 2005 to 31 December 2020.

2.3. Data Analysis and Reporting

The following parameters were extracted from each study: author, population, sample size, study type, sampling strategy, i.e., when samples were collected, drug(s) examined and the corresponding detection limit, and laboratory analytical method. In addition, we included a summary of findings and indicated whether collected samples were found to be above detectable limits for each article.

The data were analyzed in an iterative manner to establish what is known about hazardous drug contamination in healthcare workers' urine until a consensus was reached. Subsequently, a broad summary of the knowledge gaps was compiled.

3. Results

3.1. Literature Identified

The literature search of the three databases yielded a total of 3625 records: 506 articles from ProQuest, 2695 from Web of Science, and 424 from PubMed. After screening the titles and abstracts of these records, 3484 articles including 691 duplicates were excluded (2793 articles were excluded as they met the exclusion criteria, e.g., conference abstracts, case studies, etc.). An additional 102 articles were excluded because they were non-occupational in nature, collected non-urine specimens, or did not focus on biological exposure monitoring of healthcare workers, which fell outside the scope of this review. Overall, 39 full-text articles were included in this literature review. Of these, 30 employed biological exposure monitoring using strictly urine samples and 9 papers examined both urine samples as well as non-urine specimens (Figure 1).

3.2. How Studies Were Conducted

Of the 39 papers included in this review, 18 of the studies were cross-sectional in nature. Another 18 were case-control studies, whereas the remaining 3 were longitudinal (n = 2) or single-subject studies (n = 1) (Table 1). Healthcare workers that participated primarily consisted of nurses, pharmacists, and pharmacy technicians. Overall, there was quite a range of sample sizes—from 1 sample by Hama et al. [22] to 385 samples in the study conducted by Sottani et al. [11].

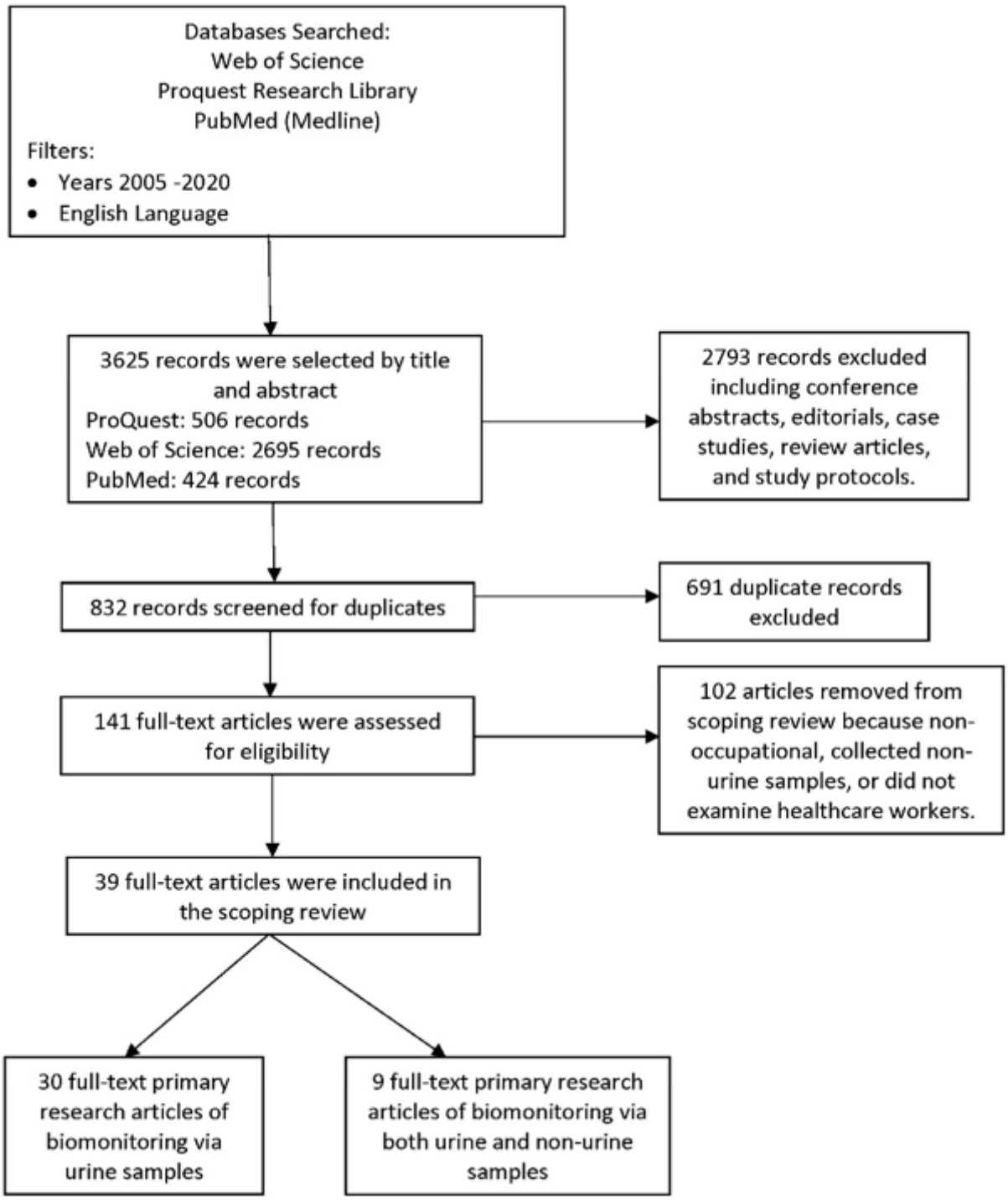


Figure 1. Flow diagram outlining the stepwise selection of studies included in the review.

Table 1. Summary of articles in which urine samples were collected for biomonitoring of hazardous drugs, arranged in chronological order.

Author	Population	Sample Size	Study Type	Urine Sampling Strategy	Drugs Tested and Corresponding Detection Limit (LOD Unless Otherwise Indicated)	Laboratory Analytical Method	Summary of Results	Detectable Levels?
Cavallo D. et al. (2005) * [23]	Healthcare workers (nurses, pharmacy technicians)	60	Case-Control 30 exposed and 30 controls	Collected at the beginning of the work shift after 3 working days.	AFBA: 18 ng/mL	GC-MS	Both exposed and control subjects showed detectable levels of AFBA only in the urine of nurses administering drugs. AFBA values of 30 and 1140 μg/L were found in 2 day-care hospital nurses and a value of 20 μg/L in a ward nurse.	Yes
Mason H. et al. (2005) [24]	Pharmacy technicians	46	Case-Control 6 exposed and 40 controls	Collected daily pre-shift and post-shift samples.	CP: 1 ng/mL IF: 1 ng/mL MTX: 10 ng/mL (LLOQ) Pt: 0.022 ng/mL	GC-MS (CP and IF), ICP-MS (Pt), ELISA (MTX)	All urinary CP, IF, and MTX results were less than the detection limits of the assays. However, the urinary creatinine-corrected, post-shift Pt results from cases were significantly higher ($p < 0.01$) than control group.	No
Ursini C. et al. (2006) * [25]	Nurses and pharmacy technicians	60	Case-Control 30 exposed and 30 controls	Collected in the morning at the beginning of the work shift on the third working day.	AFBA: 18 ng/mL	GC-MS	Both exposed and control subjects showed detectable levels of AFBA only in the urine of nurses administering drugs. Authors found 30 and 1140 μg/L AFBA in 2 day-hospital nurses and 20 μg/L AFBA in a ward nurse.	Yes
Fransman W. et al. (2007) [26]	Nurses	26 in 1997 13 in 2000	Longitudinal 1997–2000	1997-Starting at the beginning of a work shift, urine samples were collected for 24 h. 2000-Collected urine samples during three workdays in separate fractions for 24 h.	CP: 0.1 ng/mL	GC-MS/MS	The percentage of positive urine fractions had decreased by a factor of 4 between 1997 and 2000 (factor difference = 0.24; 95% CI = 0.10–0.57). The CP levels in the nurses' positive urine samples decreased 3-fold between 1997 and 2000. The percentage of detectable urine samples did not differ statistically significantly between nurses who reported having performed one of the CP-related tasks and nurses who reported not having performed one of the CP-related tasks.	Yes

Table 1. *Cont.*

Author	Population	Sample Size	Study Type	Urine Sampling Strategy	Drugs Tested and Corresponding Detection Limit (LOD Unless Otherwise Indicated)	Laboratory Analytical Method	Summary of Results	Detectable Levels?
Rekhadevi P. et al. (2007) * [27]	Nurses	120	Case-Control 60 exposed and 60 controls	Samples were collected from all the exposed personnel on the last day of their 6-day work shift in the morning hours before the beginning of their work shift. Six controls and six exposed samples were taken every 7 days.	CP: 0.04 ng/mL; 0.13 ng/mL (LOQ)	GC-MS	Varying concentrations of CP in the range of 0.08–0.9 µg/mL of urine were found in 42 subjects only. The mean CP concentration in 42 subjects was 0.44 +/− 0.26 µg/mL. The rest of the samples had CP below the limit of detection.	Yes
Hedmer M. et al. (2008) [28]	Pharmacy workers, nurses, cleaners	22	Cross-Sectional	Spot samples of urine were collected before and after work.	CP: 0.01 ng/mL IF 0.03 ng/L	LC-MS/MS	No CP or IF was detected in any of the pre- and post-shift urine samples from workers.	No
Tanimura M et al. (2009) [29]	Pharmacists	4	Cross-Sectional	24-h urine samples.	CP: N/A	GC-MS/MS	The urinary concentration of CP decreased for 3 pharmacists and increased for 1 pharmacist after the revision of the compounding standard operating procedure. The mean urinary CP before the revision was 165.3 ng/24 h and decreased to 47.4 ng/24 h after the revision, although this difference was not statistically significant ($p = 0.15$).	Yes
Yoshida J. et al. (2009) [30]	Pharmacists	6	Cross-Sectional	24-h urine samples.	CP: 0.01 ng/mL	HPLC-MS	The mean and median values among the six pharmacists during the conventional method were 39 and 12 ng/day, respectively. The mean and median values during the closed-system method were 4.9 and 2.0 ng/day, respectively. The mean CP of urine samples when using closed-system method was reduced to 13% of the conventional method.	Yes
Connor T et al. (2010) * [10]	Nurses, pharmacists, pharmacy technicians, nurse assistants	121	Case-Control 68 exposed and 53 controls	Collected every void for the last 4 h of the work shift and the first 4 h after the end of the shift.	CP: 0.015 ng/mL PTX: 0.015 ng/mL	HPLC-MS/MS	Two of the urine samples from exposed pharmacists demonstrated concentrations of CP above LOD of 0.015 ng/mL and one pharmacy technician had a concentration of PTX at the LOD of 0.015 ng/mL. None of the urine samples from non-exposed demonstrated concentrations of either drug greater than LOD.	Yes

Table 1. *Cont.*

Author	Population	Sample Size	Study Type	Urine Sampling Strategy	Drugs Tested and Corresponding Detection Limit (LOD Unless Otherwise Indicated)	Laboratory Analytical Method	Summary of Results	Detectable Levels?
Maeda S. et al. (2010) [31]	Pharmacists and nurses	8	Cross-Sectional	(1) 24-h sampling (1 pharmacist). (2) Spot sampling (6 pharmacists): 6–10 h or 20–24 h after preparing CP. (3) Spot sampling (2 nurses): collected from each voiding when on duty after treating patients with CP.	CP: 0.4 ng/mL IF: 0.4 ng/mL	LC-MS/MS	CP and IF were not detected in any urine samples.	No
Ndaw S. et sl. (2010) [32]	Pharmacy technicians, nurses, and auxiliary nurses	19	Cross-Sectional	Urine samples were collected before and after work shifts. Five consecutive days were considered in this study.	AFBA: 1 ng/mL	HPLC-MS/MS	AFBA was found at least once in 74% of subjects, mainly in the post-shift samples. In the hospital pharmacy, AFBA was detected in 83% of the pharmacy technicians, the concentrations ranging from 1.17 to 6.06 µg/L. In the oncology ward, AFBA was found in the urine of 69% of the nurses and auxiliary nurses with concentrations ranging from 1.00 to 22.7 µg/L. The pharmacy technicians had 15 positive results, the nurses 4, and the auxiliary nurses 16 positive urine samples.	Yes
Sottani C. et al. (2010) [11]	Pharmacy technicians	385 (1998–2007) 263 (2002–2007)	Longitudinal 1998–2007 2002–2007	Pre- and post-work shift samples were collected from workers after 6 h of their work shift.	CP: 0.02 ng/mL (LLOQ) DOXO: 0.10 ng/mL EPI: 0.10 ng/mL	HPLC–ESI–MS/MS	The percentage of positive urine samples was found to be around 30% in the 1990s and 2% in the 2000s. Moreover, no positive samples were detected in 2006 or 2007.	Yes
Yoshida J. et al. (2010) [33]	Pharmacists	17	Cross-Sectional	24-h urine samples.	CP: 0.1 ng/mL Pt: 2.0 ng/mL	GC-MS (CP), ICP-MS (Pt)	CP was detected from one pharmacist each in Hospital B, Hospital D, and Hospital E. Pt was not detected in any samples.	Yes (CP) No (Pt)
Hama K. et al. (2011) [22]	Pharmacist	1	Single-Subject Study	29-h urine samples.	CP: 0.05 ng/mL	GC-MS/MS	Over the 29-h period, seven separate urine samples were collected from the pharmacist. The total amount of CP excreted was 13.5 ng/24 h, but CP was detected in only the 7th urine sample, 13.5 ng (0.05 ng/mL).	Yes

Table 1. *Cont.*

Author	Population	Sample Size	Study Type	Urine Sampling Strategy	Drugs Tested and Corresponding Detection Limit (LOD Unless Otherwise Indicated)	Laboratory Analytical Method	Summary of Results	Detectable Levels?
Konate A. et al. (2011) [34]	Surgeons, anesthesiologist, surgical nurse, anesthesiologist's nurse, and cleaner	17	Case-Control 11 exposed and 6 controls	A sample was obtained from each of the control subjects in the morning. Two samples were obtained from each member of the exposed group: the first was taken in the morning before surgery and the second in the evening after the HIPEC procedure.	Pt: 0.0015 ng/mL	ICP-MS	For the 11 exposed cases, Pt concentrations were above LOD (1.5 ng/L) but below LOQ (5 ng/L). In the control group, the Pt concentration was below the LOD In five instances and was 5.8 ng/L in one subject.	Yes
Sugiura S. et al. (2011) [35]	Physicians, pharmacists, nurses	41	Cross-Sectional	24-h urine samples.	CP: N/A	GC-MS/MS	Overall, 276 samples were collected. CP was detected in 90 samples obtained from 23 subjects. The excretion of CP per staff member was between 2.7 and 462.8 ng/24 h.	Yes
Sugiura S. et al. (2011) [36]	Doctors, pharmacists, nurses	10	Cross-Sectional	24-h urine samples.	CP: 0.01 ng/mL	GC-MS/MS	A total of 62 urine samples were collected from the ten hospital workers. CP was detected in 11 urine samples from two nurses from Department A and a medical doctor from Department B. The mean amount of CP excreted on a group basis was 29.3 ng/24 h.	Yes
Turci R. et al. (2011) [37]	Nurses and pharmacists	102	Cross-Sectional	Samples were collected at the beginning and at the end of the work shifts.	CP: 20 ng/mL (LOQ) 5-FU: 0.1 ng/mL (LOQ) AFBA: 2 ng/mL (LOQ) DOXO: 0.1 ng/mL (LOQ) EPI: 0.1 ng/mL (LOQ) Pt-compounds: 0.4 ng/mL (LOQ)	HPLC-MS/MS (CP, TAX, DOXO, and EPI), Q-DRC (Pt), HPLC-UV (5-FU), GC-MS (AFBA)	No analytes (drug or metabolite) were detected above the LOQ in any of the collected urine samples.	No
Villarini M. et al. (2011) * [38]	Pharmacy technicians, day hospital nurses, ward nurses, attendants	104	Case-Control 52 exposed and 52 controls	Samples were collected at the end of the work shifts.	CP: 0.1 ng/mL	GC-MS	Exposed subjects showed detectable levels of CP in the post-shift urine samples in 17.5% of participants, with CP concentrations in the range of 0.1–0.2 µg/L. One subject had a urinary CP concentration of 1.2 ug/L.	Yes

Table 1. *Cont.*

Author	Population	Sample Size	Study Type	Urine Sampling Strategy	Drugs Tested and Corresponding Detection Limit (LOD Unless Otherwise Indicated)	Laboratory Analytical Method	Summary of Results	Detectable Levels?
Huang Y. et al. (2012) [9]	Pharmacy technicians	80	Case-Control 40 exposed and 40 controls	A spot urine sample was obtained from each subject before lunch on the last working day.	Urinary 8-OHdG: N/A	ELISA	The urinary 8-OHdG concentration in exposed group I was significantly higher than that in control group I and exposed group II ($p < 0.01$). Moreover, there was a significant correlation between urinary 8-OHdG concentrations and spill frequencies per person ($p < 0.01$).	Yes
Sottani C. et al. (2012) [39]	Pharmacy technicians and nursing personnel	36	Cross-Sectional	Pre- and post-work shift samples were collected from workers after 6 h of their work shift.	GEM: 0.2 ng/mL (LLOQ) CP: 0.2 ng/mL (LLOQ) IF: 0.2 ng/mL (LLOQ)	HPLC-MS/MS	Pre- and post-shift urine samples did not show significant concentrations of CP, IF, and GEM for any of the healthcare workers involved in manipulating hazardous drugs.	No
Kopp B. et al. (2013) [40]	Pharmacy personnel	17	Case-Control 12 exposed and 5 controls	Collected on Mondays and Fridays before starting work, as well as an additional sample on Fridays after work.	Pt: 0.002 ng/mL	Voltammetry	None of the urine samples contained an increased amount of platinum. There was no statistical difference between the platinum concentrations in the urine taken from exposed or non-exposed pharmacy personnel.	Yes
Miyake T. et al. (2013) [41]	Pharmacists	4	Cross-Sectional	24-h urine samples.	CP: 0.01 ng/mL	GC-MS/MS	Before PhaSeal, CP was detected in 76% of samples. The mean value of CP excreted was 47.4 ng/24 h. After PhaSeal, CP was detected in 6% of samples. The mean value for these samples was 3.6 ng/24 h.	Yes
Yoshida J. et al. (2013) [42]	Pharmacists	11	Cross-Sectional	24-h urine samples.	CP: 0.003 ng/mL; 0.02 ng/mL (LOQ) AFBA: 0.016 ng/mL; 0.04 ng/mL (LOQ)	GC-MS	During the non-attainment period (<80%), urinary CP and AFBA were detected in 45% and 55% of the pharmacists, respectively. During the attainment period, urinary CP and AFBA were detected in 0% and 17% of the pharmacists, respectively. The median urinary CP and AFBA concentrations of the pharmacists tended to be lower in the attainment versus non-attainment period; however, they were not statistically significant ($p = 0.061$ and 0.061, respectively).	Yes

Table 1. *Cont.*

Author	Population	Sample Size	Study Type	Urine Sampling Strategy	Drugs Tested and Corresponding Detection Limit (LOD Unless Otherwise Indicated)	Laboratory Analytical Method	Summary of Results	Detectable Levels?
Ramphal R. et al. (2014) [43]	Nurses	90	Case-Control 41 exposed and 49 controls	24-h urine samples.	CP: 0.01 ng/mL	GC-MS	CP was detected in at least one urine sample in 34% of oncology nurses and 33% of control nurses (p = 1.0). No CP was detected in any of the urine samples from the 10 community controls. There was a statistically significant difference in the proportion of participants who tested positive between the nurses (combined oncology and control nurses) and the community controls (p = 0.03), between the oncology nurses and the community controls (p = 0.05), control nurses and the community controls (p = 0.04), and between the oncology nurses and the community controls (p = 0.05).	Yes
Sessink P. et al. (2014) [44]	Pharmacy technician	2	Cross-Sectional	24-h urine samples.	CP: 0.10 ng/mL	GC-MS	CP was not detected in any of the 14 urine samples.	No
Friese C. et al. (2015) [2]	Nurses, medical assistants, pharmacists, and pharmacy technicians	40	Cross-Sectional	Participants saved all urine voids for a total of 8 h. They began their urine collection 4 h after drug exposure occurred.	ETOP: 0.02 ng/mL (LLOQ) PTR: 0.10 ng/mL (LLOQ) DOCE: 0.025 ng/mL (LLOQ)	LC-MS/MS	Of the 6 urine samples from workers who reported ETOP exposure, 1 sample exceeded the LOD but not the LLOQ. The samples from workers without a reported drug spill did not yield detectable levels of ETOP. Of the 3 samples analyzed from workers with exposure to DOCE, PTR, and CIS, all were above the LOD for DOCE and no samples were above the LOD for PTR. All 3 of these samples exceeded the LLOQ and were expressed as drug levels: 0.58, 0.10, and 0.03 ng/mL, respectively. Four samples from workers who did not report a drug spill were above the LOD for DOCE, but not above the LLOQ. Urine samples from cancer center employees who did not report a drug spill had detectable but no quantifiable levels of docetaxel.	Yes

Table 1. *Cont.*

Author	Population	Sample Size	Study Type	Urine Sampling Strategy	Drugs Tested and Corresponding Detection Limit (LOD Unless Otherwise Indicated)	Laboratory Analytical Method	Summary of Results	Detectable Levels?
Hon C. et al. (2015) [45]	Pharmacists, pharmacy receiver, pharmacy technician, nurse, transport staff, unit clerks, and others working in drug administration units (volunteers, ward aides, oncologists, and dieticians)	103	Cross-Sectional	24-h urine samples. A total of 103 provided the 1st sample and 98 participants provided a 2nd sample.	CP: 0.05 ng/mL	HPLC-MS/MS	A total of 55% of samples had CP levels greater than the LOD with a maximum reported concentration of 2.37 ng/mL. The mean urinary CP concentration was 0.156 ng/mL, the GM was 0.067 ng/mL, the GSD was 3.18, and the 75th percentile was 0.129 ng/mL. All eight job categories examined had a maximum urinary concentration level above the LOD of 0.05 ng/mL.	Yes
Moretti M, et al. (2015) * [46]	Nurses	148	Case-Control 71 exposed and 77 controls	Samples collected at the end of the work shift.	CP: 0.05 ng/mL	LC–ESI–MS/MS	Samples from two exposed nurses had CP levels which exceeded LOD of 0.05 µg/L (0.08 and 0.12 µg/L).	Yes
Villa A, et al. (2015) [47]	Surgeons, anesthesiologist, operating room nurse, and nurse anesthetist, room cleaner)	51	Case-Control 44 exposed and 7 controls	Sample collected from the first void in the morning after the procedure.	Pt: 0.005 ng/mL; 0.016 ng/mL (LOQ)	ICP-MS	Pt was undetectable (<5 ng/L) in all workers. The Pt concentration was situated between the LOD and the LOQ (16 ng/L). In 1 of the 42 samples (2.38%) obtained before hyperthermic intraperitoneal chemotherapy (HIPEC), the worker concerned had participated in another HIPEC procedure one month previously.	No
Zhang J. et al. (2016) * [48]	Pharmacists and nurses	301	Case-Control 158 exposed and 143 controls	A 5 mL urine sample was collected from each subject before lunch.	8-OHdG: N/A	ELISA	The urinary 8-OHdG mean concentration in 158 workers occupationally exposed to antineoplastic drugs was 22.05 ± 17.89 ng/mg creatinine, which was significantly higher than the levels observed in a control population (17.36 ± 13.50 ng/mg creatinine (p = 0.014)).	Yes
Poupeau C et al. (2017) [49]	Doctors, nurses, pharmacists, or pharmacy technicians	102	Case-Control 92 exposed and 9 controls	One sample collected per participant at the end of the work shift.	CP: 0.1 ng/mL Pt: 2.0 ng/mL	UPLC-MS/MS	None of the samples analyzed (0/101) had detectable concentrations of any of the four drugs evaluated.	No

Table 1. *Cont.*

Author	Population	Sample Size	Study Type	Urine Sampling Strategy	Drugs Tested and Corresponding Detection Limit (LOD Unless Otherwise Indicated)	Laboratory Analytical Method	Summary of Results	Detectable Levels?
Baniasadi S. et al. (2018) [50]	Nurses, nurse assistants, cleaners, and secretary	30	Case-Control 15 exposed and 15 controls	Urine samples were collected before the start and at the end of the work shift.	CP: 0.04 ng/mL (LLOQ) IF: 0.05 ng/mL (LLOQ)	GC-MS	The results indicated 46.66% and 16.66% of the subjects' urine samples were positive for CP and IF, respectively. CP and IF were found in 33.32% and 6.66% of the pre-shift samples, respectively. Large amounts of CP (0.57 ng/mL (0.22–1.04)) and IF (0.26 ng/mL (0.12–0.35)) were found in post-shift urine samples.	Yes
Koller M. et al. (2018) [51]	Nurses and physicians	15	Cross-Sectional	Collected before and after their daily shift.	CP: 0.05 ng/mL 5-FU: 0.2 ng/mL Pt: 0.001 ng/mL	GC-MS/MS (CP, 5-FU) Inverse voltammetry (Pt)	No AFBA or CP residues were detected in any urine sample. Regarding Pt analysis, most urinary Pt concentrations (96 out of 98 samples) were below the reference value of 10 ng/L. Two nurses had pre-shift urine Pt concentrations of 10.3 and 16.2 ng/L.	No (AFBA or CP) Yes (Pt)
Ndaw S. et al. (2018) [52]	Anesthetist, surgeon, an operating room cleaner, an anesthetist nurse, and auxiliary nurse	15	Case-Control 10 exposed and 5 controls	24-h urine samples from those exposed. Pre-shift and post-shift urine samples were obtained from controls.	Pt: 0.01 ng/mL (LOQ)	ICP-MS	Control group: Pt concentrations were above the LOQ (10 ng/L) in 72% of samples. The concentrations ranged from below the LOQ to 91 ng/L. HIPEC treatment: Pt concentrations were above the LOQ in 44% of samples. The concentrations varied from below the LOQ to 87 ng/L. PIPAC treatment: Pt concentrations were above the LOQ in 48% of the samples. The concentrations varied from below the LOQ up to 136 ng/L.	Yes
Azari M. et al. (2019) [53]	Pharmacy technicians, nurses, and auxiliary workers	32	Cross-Sectional	Specimens were obtained at the end of the work shift.	CP: 0.2 ng/mL (LLOD); 0.5 ng/mL (LLOQ)	GC-ECD which was subsequently confirmed by GC-MS	A total of 10 out of 32 urine samples had CP concentrations higher than LLOD. Most positive samples were from oncology nurses. The highest recorded CP concentration (21.4 µg/L) was from a nurse working in Hospital B.	Yes

Table 1. *Cont.*

Author	Population	Sample Size	Study Type	Urine Sampling Strategy	Drugs Tested and Corresponding Detection Limit (LOD Unless Otherwise Indicated)	Laboratory Analytical Method	Summary of Results	Detectable Levels?
Santos A. et al. (2019) * [7]	Non-exposed professionals, pharmacist, nurses	59	Case-Control 49 exposed and 10 controls	Samples were collected on Friday afternoon at the end of the week's work shift.	N-trifluoroacetylated CP: 0.03 ng/mL; 0.11 ng/mL (LOQ)	GC	The presence of CP and/or its metabolites were evaluated in the urine samples of exposed and non-exposed individuals ($p < 0.05$), and 6- and 6.5-fold increases were observed for pharmacists and nurses, respectively, compared with the controls.	Yes
Ursini C. et al. (2019) * [54]	Pharmacy technicians and nurses	95	Case-Control 42 exposed and 53 controls	24-h urine samples.	AFBA: 20 ng/mL	LC–MS/MS	No sample with AFBA above its detection limit of 0.02 µg/mL was found.	No
Palamini M. et al. (2020) [55]	Nurses and pharmacy technicians	18	Cross-Sectional	24-h urine samples.	CP: 0.09 ng/mL IF: 0.0097 ng/mL MTX: 0.0075 ng/mL AFBA: 0.12 ng/mL	UPLC-MS/MS	A total of 128 urine samples were analyzed for the 18 workers. All urine samples were negative for the 4 antineoplastics drugs tested.	No

* Denotes publication that also examined non-urine samples (n = 9).

When stratified by study type, the median sample size for the cross-sectional studies was 18 (range from 2 to 103), whereas the median for the case-control studies was 70 (range from 15 to 301). The majority of the case-control studies strived for an equal number of cases and controls, but there was an imbalance in several studies, typically with more case subjects than controls [7,24,47,49].

Collection of urine samples differed between studies, with some research teams electing for spot samples (sampling at some point before, during and/or after work shifts (n = 23)), whereas others collected 24-h urine voids (n = 16). In fact, one study by Maeda et al. employed three different sample collection times for their subjects [31].

Most of the articles examined only one drug and it was primarily the parent compound that was analyzed. Of the various hazardous drugs, cyclophosphamide (CP) was the most common analyte (69%), with a detection limit ranging from 9.0 pg/mL [49,55] to 20 ng/mL [37] with an average close to 0.1 ng/mL (not including one study with an outlier detection limit [37]). Other common analytes were alpha-fluoro-beta-alanine (AFBA), which is a metabolite of 5-fluorouracil, ifosfamide, and platinum-containing compounds. The most common laboratory analytical method (82%) was chromatography (either liquid or gas) coupled with a mass spectrometer or a tandem mass spectrometer.

3.3. Exposure Findings

Overall, most of the articles (71%) reported at least one sample had detectable levels of a hazardous drug. When stratified by study type, 78% of case-control studies reported detectable levels, whereas 61% of cross-sectional studies reported detecting a hazardous drug in at least one sample. For those case-control studies which reported positive urinary contamination results, three concluded that their findings were statistically significant [9,43,48]. Several others found detectable levels in some case subjects, whereas all of the controls in the study had non-detectable levels of urinary contamination [10,23,25,27,46,50].

There was no apparent correlation between sample size and whether detectable drug levels were reported. However, it bears mentioning that the majority (11/15 or 73%) of those studies which collected 24-h urine voids had at least one urine sample with detectable levels of a hazardous drug. Of note, the two longitudinal studies included in this review reported decreases in the percentage of positive urine samples over time [11,26].

It was not possible to compare exposure results between studies, even if they were of the same design, because of different sample collection methods, differences in the analytical limit of detection, and/or different analytes examined. In fact, in their methodologies, Maeda et al. [31] and Konate et al. [34] utilized various urine sampling methods *within* the study itself.

Urinary contamination was often detected even though control measures were reportedly implemented. For instance, several studies found detectable urinary drug levels despite gloves being worn by workers as personal protection, including Baniasadi et al. [50], Villarini et al. [38], Ursini et al. [25], and Sugiura et al. [35] among others. In fact, in the study by Tanimura et al., a revised standard operating procedure (SOP) was introduced which included the use of gloves, but detectable levels of urinary contamination were found in healthcare workers both before and after the SOP implementation [29]. Furthermore, although the use of a closed-system transfer device reduced healthcare workers' urinary contamination levels, detectable results were still found in two studies [30,41].

3.4. Knowledge Gaps

Despite 39 articles being included in this review, there was no mention of an occupational exposure limit. According to OSHWiki, "occupational exposure limit values are set to prevent occupational diseases or other adverse effects in workers exposed to hazardous chemicals in the workplace".

Most of the studies included in this review collected urine samples from three main occupations: nurses, pharmacists, and pharmacy technicians. However, as previously stated, it has been demonstrated that other healthcare workers who are part of the hospital

medication circuit may also be at risk of exposure to hazardous drugs. At present, there is a paucity of literature with respect to the biological exposure monitoring results of these other healthcare workers.

It is unclear if those workers who had detectable levels of drugs in their urine were experiencing health effects associated with exposure to hazardous drugs. As noted earlier, displaying symptoms is one of the reasons for conducting biological monitoring.

The various determinants of exposure which result in positive urinary contamination levels are unclear. Some studies indicated that the amount of drug handling was related, some stated the duration of handling was a determinant, while many other studies included in this review did not even document the different factors which could contribute to exposure.

Lastly, the cost of sampling and analysis for biological exposure monitoring was not addressed in any of the studies. Although not germane to exposure per se, this is a critical element from an administrative and resource perspective, as the associated costs must be taken into consideration if biological exposure monitoring will be adopted as a routine practice by an organization.

4. Discussion

This scoping review consisted of 39 articles related to the biological exposure monitoring of healthcare workers, mainly nurses, pharmacists, and pharmacy technicians, via urine sampling. Based on the review, it appears that biological exposure monitoring has some value as most of the studies, regardless of study design, reported at least one sample with detectable levels of hazardous drugs. In addition, several studies found that uptake was still possible despite the existence of control measures such as gloves and closed-system transfer devices. This is noteworthy as studies have concluded that such exposure has led to statistically significant increases in genotoxic health effects in healthcare workers who are in contact with hazardous drugs [6,56].

Regarding how the studies were conducted, there was a lack of standardization with respect to several important sample collection criteria, including when urine samples were collected during the shift and how samples were collected. This bears mentioning as there is a great deal of variability between individuals with respect to absorption, distribution, metabolism, and excretion of the exposed chemical agent [57]. Furthermore, there are already existing differences in the chemical and physical properties of various drugs, the quantity of drugs handled, as well as compliance with personal protective equipment usage—all of which can influence individual exposure [56]. Given that: (a) 24-h urine samples are more reflective of daily exposure [58], (b) the majority of studies which collected 24-h urine samples had at least one positive result, and (c) CP, the most commonly evaluated hazardous drug, is essentially eliminated in 24 h [59], it might be most prudent that 24-h urine voids be collected for biological exposure monitoring purposes. Unfortunately, there are very few details as to how 24-h urine samples are to be collected, with the exception of Hon et al. [45], who collected each void over a 24-h period. The voided samples were refrigerated in between, and, subsequently, all of the individuals' voids were collated after sample collection was completed.

The differences in results within and between studies are also likely associated with the inconsistency of the analytical methods, the number of drugs examined, and the analytical limit of detection. CP, IF, AFBA, and platinum compounds were commonly examined in the studies included in this review; however, because the limit of detection varied between studies, some of the study participants may have actually had drug contamination, but the analytical method employed was not sensitive enough to detect the drug in the urine. This is especially true for those studies which did not employ LC-MS/MS—which is currently accepted as the gold standard for the analysis of urine samples [15,60]. Furthermore, some studies only examined one drug, whereas others were able to simultaneously detect multiple drugs from one sample. The latter is noteworthy as simultaneous analysis allows for a more thorough and representative assessment of the uptake of an individual occupationally

exposed to hazardous drugs [60]. In addition, examining both the parent compound as well as urinary metabolites might provide a more accurate understanding of uptake [43,44].

Although it was not possible to compare exposure results between studies, the longitudinal studies included in this review did suggest that the proportion of positive urinary samples decreased over time. This may be correlated with the fact that hazardous drug contamination on hospital surfaces is also showing a downward trend over time [11,61]. This is reassuring from a health and safety perspective; however, without an established occupational exposure limit, it is best to adhere to the precautionary principle of as low as reasonably practicable or ALARP [62].

In addition to the lack of an occupational exposure limit, other knowledge gaps include limited studies on the urinary contamination levels of other healthcare workers besides nurses, pharmacists, and pharmacy technicians, as well as an understanding of the determinants of exposure. Biological exposure monitoring of these other workers, such as those in shipping/receiving, transport, and housekeeping, would be beneficial to demonstrate that the uptake of hazardous drugs is likely in these jobs rather than just simply a risk potential [5]. To better understand how drug uptake is possible, identifying the determinants of urinary contamination is suggested. This has been performed for surfaces, and knowledge of determinants can lead to the development of specific strategies to minimize exposure to hazardous drugs [63].

Whether those individuals who had positive urinary contamination experienced health effects is unclear. If there was a definitive association between adverse health effects and detectable levels of a biomarker, such as the case for lead or mercury [12], there would likely be an increased need to conduct biological exposure monitoring for those healthcare workers who come into contact with hazardous drugs. Further studies on whether such an association exists are suggested.

5. Conclusions

We have attempted to highlight some of the findings associated with biological monitoring to assess healthcare workers' exposure to hazardous drugs via urine sampling. Overall, from the 39 articles included in this scoping review, there appears to be benefits associated with biological exposure monitoring as many studies (71%) reported positive urine samples and, in some instances, the findings were statistically significant between exposed and non-exposed populations. However, there remain challenges with biological exposure monitoring due to the lack of standardization with respect to both sample collection and analysis and, in turn, the ability to benchmark biological monitoring results. In addition, because there are currently no established exposure limits for hazardous drugs [64], it is difficult to ascertain if reported biological exposure monitoring results are considered acceptable.

Additional studies are therefore warranted to address some of the listed shortcomings, as biological exposure monitoring via urine sampling offers plenty of promise as a tool to better understand the risk of healthcare workers' uptake of hazardous drugs.

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