Application and Assessment of a Regular Environmental Monitoring of the Antineoplastic Drug Contamination Level in Pharmacies - The MEWIP Project

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A large-scale study was carried out in order to determine the contamination level of antineoplastic drugs in pharmacies and to investigate the suitability and effects of wipe sample monitoring at regular intervals. A specific study design was developed. The 130 participating pharmacies were divided into a study and a control group, carrying out five and two wipe sampling cycles, respectively. The work practice was analyzed using questionnaires to identify factors that influence the contamination level. From 1269 wipe samples, 774 (61%) were contaminated with at least one of the analyzed cytotoxic drugs: cyclophosphamide, docetaxel, etoposide, 5-fluorouracil, gemcitabine, ifosfamide, methotrexate, and paclitaxel. A significant decrease of the contamination with cyclophosphamide and 5-fluorouracil was observed in the study group. The Monitoring-Effect Study of Wipe Sampling in Pharmacies method has proven to be a reliable and affordable tool for contamination control. Based on the 90th percentile of the contamination values, a substance-independent performance-based guidance value of 0.1 ng cm\(^{-2}\) has been derived.

Keywords: cleaning; cytotoxic drugs; pharmaceuticals; wipe samples

INTRODUCTION

Many pharmaceuticals pose a health risk to employees occupationally exposed (NIOSH, 2004). Most antineoplastics, immunosuppressants, antiviral, and other agents have been identified as hazardous because of their carcinogenic, mutagenic, and/or reproductive toxicity properties (cmr). Although these drugs are still indispensable to fight life-threatening diseases, exposure of personnel handling these substances needs to be minimized. Besides pharmacists, nurses, physicians, and other healthcare workers, staffs involved in cleaning, transport, and disposal of hazardous drugs or contaminated material are concerned. This generally applies to all areas where these substances are handled (veterinary practices, pharmaceutical companies, medical laboratories, specialized laundries or research centers etc.). Since the first studies of environmental monitoring of antineoplastic drugs in hospitals and pharmacies...
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(Sorsa et al., 1988; Sessink et al., 1992a), various surveys have been published. As a result, comprehensive guidelines and safety precautions especially for handling of hazardous drugs have been elaborated and adopted during the last three decades. Despite these efforts, recent studies have revealed that contamination of the workplace (safety cabinets and isolators, work tops, floors, vials, equipment etc.) with antineoplastic drugs still frequently occurs (Turci et al., 2003; Hedmer et al., 2008; Connor et al., 2010; Yoshida et al., 2010; Davis et al., 2011; Chu et al., 2012). Monitoring via wipe samples can be applied to investigate mechanisms of release and spread and thus help identify possible sources and routes of exposure. Furthermore, environmental monitoring can be useful to control and improve the effectiveness of protective measures and equipment.

European and national regulations, in the case of cmr substances, stipulate the identification of the exposure of workers and the regular check of the effectiveness of the technical protective measures taken by the employer (Council Directive 98/24/EC, 1998; Council Directive 2004/37/EC, 2004; German Ordinance on Hazardous Substances, 2010). For both tasks, either workplace measurements or other methods to identify the exposure of workers are mentioned. In addition, Council Directive 2004/37/EC, 2004 stipulates the measurement of carcinogenic substances for early detection of abnormal exposures resulting from unforeseeable events or accidents. However, there are no official occupational exposure levels for cmr drugs. Instead, monitoring results may be classified in comparison with trigger or guidance values based on benchmarking studies. For the individual facility, its ranking position within a large collective and the change of the contamination level over the course of time can be more helpful than the single measured values. Some suggestions for trigger values for antineoplastic drugs have been presented recently by Schierl et al. (2009).

Monitoring procedures and strategies applied in scientific studies have been adjusted to specific questions and differ significantly in study size and design, e.g. time of sampling, investigated spots and compounds as well as in the methods for sampling and analysis. This makes the comparison of the results and the subsequent derivation of trigger or guidance values difficult. Furthermore, not all sampling procedures have been optimized to be carried out by the personnel of the respective unit themselves, which is a prerequisite to make the monitoring affordable for a large number of establishments without sacrificing reliability. So far, only a few research teams (Sessink et al., 1997; Fransman et al., 2007; Schierl et al., 2009; Sottani et al., 2010; Turci et al., 2011) have investigated the indirect impact of monitoring on the contamination level through targeted improvements, e.g. working procedures or cleaning protocols. These studies showed a positive influence of participation in an environmental monitoring program based on the analysis of results from previous monitoring programs. However, no study has been presented, which was especially designed to investigate the influence of a regular monitoring on the contamination level that was large enough to detect statistical significant effects.

Monitoring-Effect Study of Wipe Sampling in Pharmacies (MEWIP) has a special position among the monitoring studies published till date, not only because of its size but especially because of its special objectives and the corresponding study design. The primary aim of MEWIP was (i) to determine the level of workplace contamination with antineoplastic agents using environmental monitoring. Among the other targets was (ii) the further development of the existing monitoring procedures for routine application in occupational hygiene. For this purpose, a thorough validation and extensive standardization of all procedures such as sampling, transportation, sample pretreatment analysis and the reporting of the results was necessary. Furthermore, (iii) the impact of a regular monitoring program on the contamination level in the course of the study was investigated. Another important objective of MEWIP was (iv) to obtain a comprehensive overview of the current work practice and conditions of antineoplastic drug preparation in German pharmacies focusing on factors possibly influencing the contamination level. Correlation analysis between measured values and details of the working procedures has been applied to identify critical work steps and conditions. Finally, the project served (v) to create an extensive database of ambient contamination levels for the assessment of future individual measurement values and the derivation of a guidance value for antineoplastic drugs at the workplace.

METHODS

The objectives of the study required a sufficiently large number of participants (minimum 50 based on statistical calculations) in order to obtain statistically significant results. Therefore, and in order to be affordable as a regular safety measure beyond the runtime of this project, all steps of the monitoring procedures have been optimized with respect to time and cost-effectiveness. Environmental monitoring has been preferred instead of biological monitoring to obtain information on reasons, mechanisms, and pathways of drug release and spread. Pharmacies have been chosen
because their way of working is largely standardized, and monitoring results, therefore, are well comparable between the individual establishments.

**Selection and distribution of the participants**

In Germany, antineoplastic drugs are prepared in an estimated number of 800 hospital and public pharmacies. A first questionnaire recording the number and amount of preparations of the eight drugs selected for MEWIP was sent to those of which the addresses were available. A total of 254 establishments showed interest in participating in this study. After elimination of 10 pharmacies with a too small number of annual preparations (<500), isolators instead of safety cabinets, planned (re)constructions, and/or secluded locations, 201 pharmacies were registered for MEWIP. Because of the limited resources, only 130 randomly selected participants could participate in this study.

To investigate the effect of the monitoring, participants were randomly divided into two study groups, a study group (Group A) and a control group (Group B). Members of Group A (33 hospital and 22 public pharmacies) carried out monitoring approximately every 3 months (five monitoring cycles) and received their results in comparison with the other participants. The participants of the study group were informed about the drug amounts on the respective surfaces in their pharmacy, and their ranking number for each compound and spot within the study group shortly after the respective monitoring cycle. (An exception was that we did not circulate results until after the second cycle so that we could observe the normal degree of variation without participant corrective action.) After notification, these pharmacies were able to take targeted actions to reduce the contamination level within the run of the study.

To compensate for an expected higher dropout rate in the control group, a higher number of participants were included in the Group B. The Group B (45 hospital and 30 public pharmacies) acted as a control group, where wipe samples were taken only at the beginning and the end of the project. The results were not submitted before the end of the study. Pharmacies that already carried out regular environmental monitoring were set in Group B because in these cases, the effect of a regular environmental monitoring could have taken place before MEWIP. At this stage, it was decided not to exclude these applicants but to place them into the Group B to minimize any distorting effect.

**Selection of sampling spots, time, and substances**

In order to obtain comparable results from all pharmacies, three sampling spots have been identified, which are used and exposed in a largely similar way in all establishments:

1. the floor in front of the (most intensively used) safety cabinet,
2. the most frequently used work top close to the safety cabinet, and
3. the refrigerator door including the door handle.

The exact location of the 900-cm² sampling spots were identified, documented, and photographed during the preceding visits by Institute of Energy and Environmental Technology (IUTA) personnel in each pharmacy. As far as possible, square areas (30 × 30 cm) were defined. During the whole study, wipe sampling was carried out after the daily shift but before cleaning of the respective surfaces, if possible by the same person. The sampling area was marked with red measuring tape, which was removed after each sampling.

Based on the results of the previous questionnaire in the run-up of the study and the analytical possibilities, eight frequently handled compounds were selected, which can be sampled and analyzed simultaneously (cyclophosphamide, etoposide, 5-fluorouracil, ifosfamide, gemcitabine, methotrexate, paclitaxel, and docetaxel). Limits of quantification (LOQ) ranged from 3.7 to 92 pg cm⁻² for these eight compounds (see Table 1).

**Table 1. LOD (signal-to-noise ratio = 3:1) and LOQ (lowest calibration level) of the HPLC-MS/MS analysis (Tuerk et al., 2011).**

<table>
<thead>
<tr>
<th>Compound</th>
<th>LOD (ng ml⁻¹)</th>
<th>LOQ (ng ml⁻¹)</th>
<th>LOQ (ng/sample)</th>
<th>LOQ (pg cm⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluorouracil</td>
<td>0.17</td>
<td>0.3</td>
<td>9.9</td>
<td>11</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>0.10</td>
<td>0.2</td>
<td>6.6</td>
<td>7.3</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0.08</td>
<td>0.1</td>
<td>3.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>0.07</td>
<td>0.1</td>
<td>3.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>0.08</td>
<td>0.1</td>
<td>3.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Etoposide</td>
<td>0.10</td>
<td>0.1</td>
<td>3.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>0.21</td>
<td>0.5</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>0.35</td>
<td>1.0</td>
<td>33</td>
<td>37</td>
</tr>
</tbody>
</table>
Sampling kit and procedure

All steps of the monitoring procedure [sample collection, storage, transport, sample pretreatment, high-performance liquid chromatography using mass selective detection (HPLC-MS/MS) analysis] have been optimized in order to increase sensitivity and reliability as well as throughput. Due to the large number of participants and measurements, it has been necessary to develop a specially designed kit (Fig. 1) as well as standard operation procedures to allow reproducible and comparable wipe sampling performed by the individual pharmacy personnel.

All pharmacies were visited by personnel of IUTA to jointly fill in the main questionnaire, locate the sampling spots, and explain and train the wiping procedure. Samples were taken using three sampling tissues (Kimtech Science 7120) for wiping in three directions, each moistened with 1 ml of a pH 3 phosphate buffer. Tissues were wetted with 1 ml of sterilized phosphate buffer at pH 3 each. Surfaces were thoroughly swept clean in vertical and horizontal strokes, changing the direction with every new tissue. The three tissues were combined to one sample, stored, and transported in a 100-ml urine beaker (Uritop S; B. Braun Petzold GmbH, Melsungen, Germany). The five monitoring cycles were carried out between February 2006 and September 2007.

Analytical methods

All steps of the monitoring procedure, i.e. sampling, storage, transport, sample pretreatment and HPLC-MS/MS analysis have been developed and optimized according to the needs of MEWIP. Details of the analytical methods and the thorough validation are presented elsewhere by Tuerk et al. (2011).

Assessment of working conditions

The study has been utilized to collect data on work procedures, working environment, safety measures, and equipment, possibly influencing the frequency and level of contamination. Therefore, a 16-page questionnaire (basic questionnaire) has been developed. In addition, the amounts of drugs handled during the day and the week before wiping as well as information on cleaning measures and accidental spillage were requested for each monitoring cycle (study accompanying questionnaire). Experiences and satisfaction with the monitoring process were recorded with a final questionnaire at the end of the study (feedback questionnaire). Special attention was paid to modifications established as consequences of the monitoring results. The challenge in this context was to record the often very different answers in defined categories to allow systematic assessment of correlation with results of the monitoring. Because of the large amount of data acquired and in order to obtain statistically confirmed conclusions, all information (from monitoring and questionnaire) was inserted in a database.

Applied statistical methods

The measured values on the three sampling spots have been regarded as independent for statistical analysis, although they might be dependent because of a common source of several detected contamination. Because the measured values showed a very skewed distribution, the 90th percentile has been used to describe the data instead of normal statistical coefficients such as mean and standard deviation. Apart from the measured values themselves, the rate of positive wipe samples (contaminated with at least one compound) and rate of positive analytical

Fig. 1. The MEWIP wipe sampling kit. Key: 1, isolated transport box; 2, sample documentation sheet; 3, four urine beakers with three sampling tissues each (Kimtech Science 7120); 4, standard operation procedure sheet; 5, two 50-ml tubes with 5 ml of sampling solution (phosphate buffer pH 3); 6, three 2-ml pipettes for measuring 1 ml of sampling solution; 7, measuring tape; 8, adhesive tape; 9, two freeze packs.
findings have been used for the statistical analysis. Depending on the question of interest, the results of the wipe samples in one pharmacy at one wipe cycle were summarized in one value, e.g. sum of positive wipe samples, or were used independently from their origin in one specific pharmacy. The non-parametric Mann–Whitney U-test and Kruskal–Wallis test have been used to compare two and more groups, e.g. study and control group, concerning their contamination level. Spearman’s correlation coefficient has been calculated to assess the strength of statistical associations between details of the working procedures of the pharmacies and their contamination level.

RESULTS

Monitoring results

From the 1269 usable wipe samples, 774 (61%) were positive. A sample was regarded as positive, when at least one of the eight substances was detected. Referring to the single compounds, 16% of the 10 152 measured values was positive, i.e. the sought substance was detected in the sample. The detected contamination values extend over two orders of magnitude. A large part of the total contamination of 2892 ng/cm² has been caused by a single value of 1888 ng/cm² gemcitabine on a refrigerator door. Table 2 lists the 10 highest measured values, revealing that the nine highest values were detected in three different pharmacies only.

Substance-specific results

The following results are presented as percentage of positive samples and the 90th percentile of the area contamination values (see Table 3). The 90th percentile has been chosen because lower values such as the 75th percentile or the median would fall below the analytical detection limit and give no relevant information.

Concerning the eight investigated antineoplastics, frequency and extent of contamination do correlate overall. The four most frequently detected substances cyclophosphamide (37%), gemcitabine (32%), 5-fluorouracil (31%) and ifosfamide (21%) also account for 95% of the quantitative area contamination. The other four compounds were found in no more than 5% of the samples, and their 90th percentiles fall below the LOQ.

Results of the three sampling spots

Regarding the three sampling spots, the floor in front of the safety cabinet had the highest percentage of positive samples (73%) and was most contaminated, followed by the work top (61%) and the refrigerator door (49%) (see Table 4). On the floor and the refrigerator door, cyclophosphamide was found most frequently (45% and 33%), whereas on the work top, 5-fluorouracil, gemcitabine, and cyclophosphamide were present in 32–34% of the samples. Looking at the 90th percentiles, 5-fluorouracil was found in the highest concentrations on all three areas. Especially on the work tops, this compound accounts for the largest part of the total contamination.

Comparison of the two study groups

Table 5 shows the frequency and extent of contamination of the two study groups (A and B) during the five and two monitoring cycles, respectively. The decrease of the part of contaminated samples in Group A when compared with Group B

<table>
<thead>
<tr>
<th>Pharmacy</th>
<th>Sampling spot</th>
<th>Sampling cycle</th>
<th>Type of pharmacy</th>
<th>Study group</th>
<th>Substance</th>
<th>Contamination level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ng cm⁻²     mg m⁻²</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>Refrigerator door</td>
<td>1</td>
<td>Hospital A</td>
<td>Gemcitabine</td>
<td>1888       18.88</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>Work top</td>
<td>4</td>
<td>Hospital A</td>
<td>Gemcitabine</td>
<td>190        1.90</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>Refrigerator door</td>
<td>2</td>
<td>Hospital A</td>
<td>Gemcitabine</td>
<td>109        1.09</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>Floor</td>
<td>2</td>
<td>Hospital A</td>
<td>Gemcitabine</td>
<td>105        1.05</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>Floor</td>
<td>3</td>
<td>Hospital A</td>
<td>Ifosfamide</td>
<td>89         0.89</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>Work top</td>
<td>1</td>
<td>Hospital A</td>
<td>Methotrexate</td>
<td>35         0.35</td>
</tr>
<tr>
<td>7</td>
<td>C</td>
<td>Work top</td>
<td>1</td>
<td>Hospital A</td>
<td>Ifosfamide</td>
<td>31         0.31</td>
</tr>
<tr>
<td>8</td>
<td>D</td>
<td>Floor</td>
<td>1</td>
<td>Hospital A</td>
<td>Ifosfamide</td>
<td>26         0.26</td>
</tr>
<tr>
<td>9</td>
<td>C</td>
<td>Work top</td>
<td>1</td>
<td>Hospital A</td>
<td>5-Fluorouracil</td>
<td>24    0.24</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>Work top</td>
<td>1</td>
<td>Public B</td>
<td>5-Fluorouracil</td>
<td>18    0.18</td>
</tr>
</tbody>
</table>
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from the first to the fifth monitoring cycle (cycle 1 versus cycle 5) is significant regarding the total of the investigated substances \((P = 0.050)\). Overall, as shown in Fig. 2a, b, the percentage of positive samples remained largely constant during the five cycles. In contrast, the level of contamination decreased constantly in the Group A pharmacies after they had received the first report of results. Fig. 2a, b depict the development of the part of positive samples and the contamination level (90th percentile of all substances) in both groups during the study.

In Fig. 3a, b, the results of each monitoring cycle are depicted for the four substances for which the 90th percentiles were above the LOQ. The decrease of the contamination level in Group

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**Table 3.** Results for the eight different substances, summed over all sampling spots, cycles, and pharmacies.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Number of positive samples</th>
<th>Percentage of positive samples (%)</th>
<th>Area contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>90th percentile (ng cm(^{-2}))</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>468</td>
<td>37</td>
<td>0.048</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>396</td>
<td>31</td>
<td>0.117</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>402</td>
<td>32</td>
<td>0.034</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>270</td>
<td>21</td>
<td>0.014</td>
</tr>
<tr>
<td>Etoposide</td>
<td>67</td>
<td>5</td>
<td>&lt;LOQ(^a)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>42</td>
<td>3</td>
<td>&lt;LOQ(^a)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>15</td>
<td>2</td>
<td>&lt;LOQ(^a)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>7</td>
<td>1</td>
<td>&lt;LOQ(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Below LOQ.

**Table 4.** Results of the three sampling spots, summed up for all substances, cycles, and pharmacies.

<table>
<thead>
<tr>
<th>Sampling spot</th>
<th>Total samples</th>
<th>Number of positive samples</th>
<th>Percentage of positive samples (%)</th>
<th>Area contamination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>90th percentile (ng cm(^{-2}))</td>
</tr>
<tr>
<td>Floor</td>
<td>424</td>
<td>309</td>
<td>73</td>
<td>0.020</td>
</tr>
<tr>
<td>Work top</td>
<td>421(^b)</td>
<td>256</td>
<td>61</td>
<td>0.011</td>
</tr>
<tr>
<td>Refrigerator door</td>
<td>424</td>
<td>209</td>
<td>49</td>
<td>0.007</td>
</tr>
<tr>
<td>Total</td>
<td>1269</td>
<td>774</td>
<td>61</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\)Below LOQ. 
\(^b\)One pharmacy had chosen the wrong sampling position in sampling cycles 1–3.

**Table 5.** Results of the study Group A and the control Group B.

<table>
<thead>
<tr>
<th>Study group</th>
<th>Group A (55 pharmacies)</th>
<th>Group B (75 pharmacies)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Area contamination</td>
<td>Area contamination</td>
</tr>
<tr>
<td></td>
<td>Total samples</td>
<td>Number of positive samples</td>
</tr>
<tr>
<td>Monitoring cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>164(^a)</td>
<td>103</td>
</tr>
<tr>
<td>2</td>
<td>164(^a)</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>164(^a)</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>165</td>
<td>104</td>
</tr>
<tr>
<td>5</td>
<td>165</td>
<td>82</td>
</tr>
<tr>
<td>Total</td>
<td>822</td>
<td>479</td>
</tr>
</tbody>
</table>

\(^a\)One pharmacy had chosen the wrong sampling position in sampling cycles 1–3. 
\(^b\)Below LOQ. 
\(^c\)One pharmacy of Group B was closed down before the fifth monitoring cycle.
A compared with Group B is significant for cyclophosphamide ($P = 0.019$), when the results of the first two cycles (which were not affected by the submission of results) are compared with the last monitoring cycle (cycle 1/2 versus cycle 5). The same applies to the percentage of positive samples for 5-fluorouracil ($P = 0.043$) and cyclophosphamide ($P = 0.001$). The decrease of the part of contaminated samples in Group A when compared with Group B from the first to the fifth monitoring cycle (cycle 1 versus cycle 5) is significant for 5-fluorouracil ($P = 0.027$) and cyclophosphamide ($P = 0.002$).

**Fig. 2.** (a) Trend of the percentage of positive samples in the study Group A and the control Group B in the course of the study. (b) Trend of the contamination levels (90th percentile) in the study Group A and the control Group B in the course of the study.

Correlations between work practice and contamination level

Positive correlations between details of the working procedures and the contamination level were only detectable regarding few points. In most cases, the multitude of different answers allowed no statistically based evaluation of the effects. A more comprehensive presentation of the results of the questionnaires is given in the MEWIP final report (Institution for Statutory Accident Insurance and Prevention in the Health and Welfare Services, 2008).

The eight analyzed compounds are among the 20 most frequently prepared antineoplastic drugs.
According to the preliminary questionnaire, these substances are present in >95% of the 254 interviewed pharmacies, except ifosfamide (72%), which is predominantly prepared in hospital pharmacies. Comparison between the years 2005, 2006, and 2007 showed no clear change of the amounts handled and the number of applications prepared in the participating pharmacies (see Table 6).

Correlations between the amounts handled or the number of applications (530 to 32,500/year) on the one hand and the frequency and height of contamination on the other hand are not present (Spearman’s coefficients range from −0.2229 to 0.5523 for the amounts handled and from −0.1631 to 0.5474 for the number of preparations). The same applies to the intensity of preparation on the day of sampling and within the five previous days. Besides no correlation can be seen between the analytical results and the stated intervals of cleaning of the respective surfaces, which in some cases varied enormously (refrigerator door: daily up to >100 days). The Spearman’s coefficients for this correlation range from −0.118 to 0.164.

A tendency toward higher contamination levels was observed where safety cabinets that re-circulate filtered air into the work room were used. This was the case in 19% of the participating pharmacies.
A difference due to disinfection methods was observed in Group B. Disinfection by spraying of the solvent onto the vials (performed by 31% of the pharmacies) resulted in higher contamination compared with wiping of the containers with wetted tissues (27%) or no disinfection outside the safety cabinet (39%) (total contamination level: \(P = 0.015\); cyclophosphamide: \(P = 0.003\)).

A possible influence of external drug contamination on vials from different suppliers in correlation to the total level of contamination was investigated for 5-fluorouracil. No significant relationship was detectable.

Regarding the material of the work tops, on metal surfaces—mainly stainless steel (in 37% of the pharmacies)—tendentiously lower contamination levels were found compared with coated chipboard or wood (61%).

### Impact of monitoring

In each sampling cycle, approximately three quarters of the members of the study group reported changes of the working procedure (study accompanying questionnaire). During the whole study, 36 pharmacies of the Group A changed their cleaning protocols, some of them more than once. The changes included more frequent cleaning, change of applied detergents, alteration of responsibilities etc. Approximately, one-third of the Group A pharmacies contacted persons responsible for the study to inform themselves about possible explanations for contamination and recommendations for improvements. In addition, in the feedback questionnaire (return quote 48%), two-thirds (67%) of all participants stated that they have or will change their work procedures for the future as a consequence of their monitoring results. Most frequently mentioned were revisions of cleaning protocols, more frequent changes of the use of gloves, and other change of other equipment as well as more intensive training of employees. Approximately, half (46%) of the participants are planning to implement regular environmental monitoring in their safety concepts. Further, 50% consider carrying out monitoring in the future. Overall, the participants were highly satisfied and marked the whole monitoring process, the sampling kit, and organization as good to very good. Many participants expressed the need of guidance or trigger values for antineoplastics in order to assess the monitoring results and to decide about future actions.

### DISCUSSION

Approximately, 16% of the antineoplastic drug preparing pharmacies in Germany participated in MEWIP. Therefore, the study provides a unique overview on the present situation of drug handling and the resulting contamination level. However, because the participation was voluntary, it has to be assumed that pharmacies with a better safety level will probably have been over-represented. In Fig. 4, an overview of earlier monitoring studies is presented, where each data point represents one individual value of the surface contamination with cyclophosphamide. Compared with earlier monitoring studies, the MEWIP results are in the middle range. The 90th percentile of MEWIP ranges close to that of the previous German monitoring project. However, if different studies are compared, influences by the applied methods, such as different recovery rates due to sampling procedures and the analytical limits of determination, need to be considered.

In MEWIP, especially the two investigated taxanes have comparable low recovery rates and high LOQ (see Table 1). Thus, it has to be assumed that a number of paclitaxel and docetaxel contaminations have
not been detected. The same applies to 5-fluorouracil, which has a three times higher limit of detection (LOD) compared with cyclophosphamide and ifosfamide. Therefore, the prominent position of this drug (amounts handled and numbers of preparations) is only reflected in the observed high area concentration, whereas the rate of contaminated surfaces is probably underestimated.

The detectable concentration can also be lowered by irreversible absorption of the compound on the surface material as well as by chemical or physical decomposition. Thus, the known photosensitivity of methotrexate could be one reason for the small number of positive results obtained for this compound.

Apart from analytical procedures, the frequency of positive findings as well as the detectable amounts is influenced by several factors. In general, the surface contamination is expected to depend on the handled amounts, the intensity, and the type of preparation activity (e.g., reconstitution of powders versus dilution of concentrated solutions). In accordance, 5-fluorouracil, which is mainly responsible for the total area contamination, is handled in the highest amounts followed by gemcitabine, cyclophosphamide, and ifosfamide, which are mainly supplied as dry substance.

Overall, the results show that not only 5-fluorouracil but also cyclophosphamide, ifosfamide, and gemcitabine are suited as marker compounds in regular environmental monitoring using the MEWIP method. If the range of substances to be analyzed is restricted, the respective procedures can be optimized and better recoveries and/or sensitivities for the individual compounds are achievable. Besides the eight antineoplastic drugs analyzed by multimethod in MEWIP, selected compounds, such as the also frequently applied platinum-based antineoplastics and cytarabine are of interest for monitoring studies and routine surveillance. Sampling routines and analytical procedures for these compounds are available but differ from those applied in MEWIP.

Regarding the three investigated spots, the floors have shown to be both most frequently and most highly contaminated. However, the lower substance

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**Fig. 4.** Comparison of the monitoring results for cyclophosphamide in drug preparing units in different countries. IUTA 2000–2008: data from unpublished commercial wipe sample monitoring in pharmacies. (Sessink et al., 1992b; McDevitt et al., 1993; Connor et al., 1999; Minoia et al., 1999; Kiffmeyer et al., 2000; Pethran et al., 2001; Soave et al., 2003; Schierl, 2004; Hedmer et al., 2005; Schulz et al., 2005; Türk, 2007; R. Schierl, personal communication; Harrison et al., 2006; Institution for Statutory Accident Insurance and Prevention in the Health and Welfare Services, 2008).
levels on the work tops and the refrigerator doors should be considered as more serious regarding possible exposure because these surfaces are directly touched by personnel. The fact that 5-fluorouracil, a substance that has to be stored at room temperature, had over all the highest concentrations (90 percentile) on the refrigerator doors, astonished many study participants. It is assumed that this finding is a result of spread of the compound via contaminated gloves. In addition, inadequate cleaning procedures may spread or accumulate traces of substances.

A number of reasons are discussed to influence the release and spread of antineoplastic agents in the work environment. Although it was not the main objective of MEWIP, the acquired data have been utilized in order to review selected factors and the corresponding level of contamination. The resulting correlations are mainly categorized as ‘exploratory significant,’ i.e. indicating that a targeted study might be justified to investigate those factors. However, it is worth noting that in accordance to our results, the throughput is not linked with the contamination level. Despite of the discussion about the influence of the handled amounts on the one hand and the higher standards and greater routine in large units on the other hand, ‘clean’ working is possible in both large (>10 000 preparations/year) as well as in small units (500–1000 preparations/year). In general, it has become evident that there are a number of pharmacies that kept a low level of contamination over the whole study, whereas certain units had comparatively frequent and high values.

The effects of regular wipe sample monitoring on the surface contamination could be shown for part of the investigated compounds.

It has to be considered that some of the members of the Group A already had a zero contamination level at the beginning of the study (11% in the first and 20% in the second cycle). In these cases, no additional measurable effect of the monitoring could be achieved in the course of the study. Because pharmacies that were already using regular environmental monitoring at the beginning of the study have been inserted in monitoring Group B, this may contribute to the lower starting results of this group.

Therefore, a regular repetition of the monitoring is recommended. The workplace contamination with antineoplastic drugs in German pharmacies is very low (90th percentile 0.1 ng cm$^{-2}$). During the study, a constant reduction of the contamination level was achieved, whereas the percentage of contaminated spots remained more or less unchanged above 50%. This indicates that a zero level of exposure is hardly achievable. However, as often remarked by the participants, some kind of threshold or trigger values are required in order to assess the individual result and to decide whether counter measures are required. Because no official threshold limits are defined for antineoplastic drugs, we propose a technical guidance value based on the percentiles of the 10 152 MEWIP analyses. As a substance-independent guideline, we suggest 0.1 ng cm$^{-2}$ (1 µg m$^{-2}$) based on the 90th percentile of the compound found in the highest concentrations in MEWIP (fluorouracil with 0.117 ng cm$^{-2}$).

The surface contamination with fluorouracil was below this level in 90% of the MEWIP results and can, therefore, be achieved with the state-of-the-art of contamination control. Stricter values such as the 50th or 75th percentile, as suggested by Schierl et al. (2009), may be aspired to in the future in accordance with harmonized exposure-risk relationship descriptions for occupational carcinogens. However, at the present time, it is considered as more urgent to improve the situation at those workplaces, in pharmacies and elsewhere, where higher contamination levels occur.

In addition, the MEWIP study has shown that the 75th percentiles of most substances fall below the analytical limit of determination and thus are not well suited to be controlled by wipe sample monitoring.

An environmental monitoring as in MEWIP can be applied in many other relevant sectors such as hospital wards. In addition, it can be adapted to further relevant substances, e.g. monoclonal antibodies or antibiotics. Future investigations of the correlation between outer and inner exposure are regarded as useful. Likewise of interest are comparative studies with other countries in order to extend the database and identify best practice of drug handling under different conditions. Finally, follow-up studies will have to show whether the effect of the monitoring on the contamination level is sustainable.

CONCLUSION

The developed monitoring procedure has proven to be suitable as a reliable and affordable tool for routine monitoring of workplace contamination with antineoplastic agents. The results also suggest that a repeated monitoring has a stronger effect on the contamination level than a singular measurement.
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