Environmental contamination with cytostatic drugs: past, present and future

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Measuring environmental contamination with cytostatic drugs has become an interesting tool to evaluate preparation techniques in hospital pharmacies. A preliminary model is presented here demonstrating that environmental contamination lower than 0.1 ng/cm² is a safe reference value.

Introduction
Cytostatic drugs have been used for many years in the treatment of cancer and non-neoplastic diseases. However, most cytostatic drugs are not selective in action and healthy cells are also damaged, which results in adverse health effects [1]. For healthcare workers such as pharmacists, pharmacy technicians, nurses, and medical doctors involved in the preparation and administration of these drugs, exposure may also cause adverse effects such as cancer, foetal malformations, and foetal loss during pregnancy even at low exposure levels [1].

To prevent exposure of healthcare workers to cytostatic drugs, biological safety cabinets and isolators have been installed, preparation and administration rooms are ventilated, devices and special mixing techniques are applied, and personal protective equipment (such as gloves, gowns, goggles, and special clothing) is used. All these precautions are well documented in guidelines and regulations set up by national authorities and (inter) national societies of healthcare professionals (pharmacist and nurses) and have the aim of offering maximum protection to the healthcare workers handling these toxic drugs [2, 3].

Monitoring
The first studies to evaluate exposure of healthcare workers to cytostatic drugs were published circa 1980 [4]. At that time, results demonstrated exposure of healthcare workers to cytostatic drugs based mainly on mutagenicity in urine (Ames assay) and the presence of chromsome aberrations and sister chromatid exchanges in blood lymphocytes. The findings of these tests have resulted in worldwide regulations and guidelines [5]. Follow-up studies with these tests have shown a reduction in the exposure of healthcare workers to cytostatic drugs. Professionals involved in this issue were more or less leaning back, thinking that the problem was solved but in fact the opposite was the case. It was found that the tests did not show exposure of healthcare workers despite cyclophosphamide, a carcinogenic cytostatic drug, being detected in their urine. Due to lack of selectivity and sensitivity, these tests became less useful in the 1990s [4].

These new findings have resulted in the development of more sensitive methods for the analysis of individual cytostatic drugs or their metabolites mainly in urine [6-8]. In addition, one was more focused to find out the causes of the exposure [9]. This has resulted in the development of so-called wipe tests to measure environmental contamination. With wipe tests, potential contaminated surfaces are pre-wetted and wiped with a tissue; the tissue is then analysed for the drugs to be monitored and, finally, the amount is calculated for the area wiped. By taking wipe samples, contaminated surfaces can be traced and ranked according to the level of contamination. The causes of the contamination can then be attempted to be elucidated. Wipe tests can be used to evaluate preparation and administration procedures, to test devices, and to check cleaning procedures.

Taking wipe samples has become very popular and, nowadays, many hospitals perform these tests on a frequent basis to evaluate their procedures and routines [10]. Most hospitals which perform these tests see a decline of the environmental contamination over time. In addition, the decline is not only observed for environmental contamination but also for the amounts of cytostatic drugs excreted in the urine of healthcare workers indicating a reduction of occupational exposure.

Developments
It is clear that a reduction of environmental contamination with cytostatic drugs will eventually result in a lower exposure of healthcare workers. Over the last decade, several developments have positively contributed to these results.

A tremendous reduction in environmental contamination has been achieved by the introduction of so-called closed-system transfer devices. With these systems, a leak-free transfer of drugs from vial to infusion bag, syringe or pump can be achieved. Although a number of companies have introduced these devices on the market, long-term clinical studies showing the effectiveness of the devices have not yet been published for the majority [11]. Objective criteria for a device to be considered as a closed-system transfer device are lacking; only a general definition is available, which indicates a closed system as one that mechanically prevents the transfer of environmental contaminants into the system and the escape of drugs or vapour out of the system.
Objective criteria should be set by authorities in collaboration with organisations of healthcare professionals such as American Society of Health-System Pharmacists and the International Society of Oncology Pharmacy Practitioners. It is a pity that, although these devices seem to be very effective in reducing environmental contamination, their use is only recommended and not obliged [1, 12].

Another improvement has been made by the pharmaceutical industry. The production of contained and sleeved vials has substantially reduced the outside contamination of drug vials [13]. However, there are still drugs on the market without such a protection or without information about the contamination on the outside of the vials. Therefore, it is important to stress that vials should only be touched when wearing gloves. The checking of vial contamination by independent authorities in combination with certification could further reduce contamination on the outside of drug vials. Acceptable levels or standards for vial contamination have to be set by authorities in collaboration with the pharmaceutical industry and hospital pharmacist organisations.

The third improvement is the increase of the awareness that handling cytostatic drugs implies a potential health hazard. Continuous education and training have contributed to inform healthcare workers about the risks when handling these drugs.

More recently, robots for the preparation of cytostatic drugs have been developed and some have been implemented in the hospital setting. However, clinical studies evaluating robots have yet to be published. Major concerns regarding environmental contamination and the exposure of healthcare workers are potential cross-contamination and spread of contamination inside the robot area and on the outside of prepared bags. This ultimately results in the transfer of contamination to administration areas. Independent validation studies need to be performed to investigate these potential concerns.

**The Dutch approach**

Nowadays, many hospitals take wipe samples and a question raised frequently is, ‘Does the observed contamination result in exposure of the healthcare workers and, if so, what level of contamination is acceptable in terms of health risk?’ These are legitimate questions because, over time, wipe samples continue to show contamination. More drugs will be prepared in the future due to more cancer patients, drug vials will still be contaminated on the outside, and detection limits of analytical methods will continue to be lowered due to new and more sensitive techniques.

Over the last 20 years, a lot of monitoring studies have been performed in The Netherlands. To evaluate procedures and to check contamination and exposure, the Dutch authorities have obliged hospitals to perform wipe tests regularly. This has resulted in an enormous database in general showing a reduction of environmental contamination over time. In addition, excretion of cyclophosphamide has not been found indicating no measurable exposure to this drug. These findings have resulted in a debate about what is an acceptable level for environmental contamination in terms of health risk for healthcare workers.

Dutch healthcare professionals such as pharmacists, nurses, occupational hygienists, and toxicologists have discussed this issue for many years. A few years ago, a consensus was agreed on the approach of how to set an acceptable level of environmental contamination. A very pragmatic approach was followed based on the marker drug cyclophosphamide. The selection of cyclophosphamide was obvious: it is a highly toxic drug, resistant, with high skin permeability (skin exposure), and is frequently used and monitored (wipe and urine samples) due to sensitive analytical methods. In fact a worst-case scenario was followed (conservative approach). Based on the data set, 90% of the wipe samples show contamination levels < 0.1 ng/cm² and 99% of the wipe samples show contamination levels < 10 ng/cm². In addition, no positive urine samples were found at contamination levels < 0.1 ng/cm² indicating no measurable exposure of the healthcare workers. This has resulted in the reference values 0.1 ng/cm² (‘safe’) and 10 ng/cm² (‘not acceptable’).

Based on these data, Dutch healthcare professionals have agreed on different types of actions to be performed depending on the levels of contamination found after wipe sampling (see Table 1). In addition, these data can also be linked to cancer risk estimates in terms of strive risk level and prohibitory risk level based on the analysis of cyclophosphamide in the urine of healthcare workers [14]. In the final ‘traffic-light’ model, it can easily be seen what levels of cyclophosphamide environmental contamination

| Table 1: Reference values for environmental contamination with cyclophosphamide (CP) in The Netherlands |
| --- | --- | --- |
| **Urine CP (µg/24 h)** | Strive risk level | Prohibitory risk level |
| < 0.02 | 0.02–0.2 | > 2 |
| Contamination CP (ng/cm) | 0.1–1 | 1.0–10 | > 10 |
| Actions | Monitoring once a year | Risk estimate |
| Evaluate after 4 years | Monitoring within 3–6 months | Eventually followed by measures |
| | Take measures | Check by monitoring |

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and urine excretion are acceptable and which actions need to be performed.

This approach is considered as a first step to indicate what can be considered as a ‘safe’ level for environmental contamination with cyclophosphamide. The approach will be evaluated after several years and will, if possible, be expanded to other cytostatic drugs.

**Conclusion**

Over the last thirty years, enormous steps have been set forward to reduce occupational exposure of healthcare workers to cytostatic drugs. The awareness has grown, closed-system transfer devices have been introduced, and cleaner vials have been produced. For the next decade, these developments need to be intensified in order to result in a further lowering of environmental contamination and consequent exposure of healthcare workers to these drugs. To follow and to support these developments, the use of monitoring methods by taking and analysing wipe and urine sample are a must and will remain a permanent tool for measuring contamination and exposure at healthcare sites.

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**References**


