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Occupational exposure to anti-cancer drugs: A review of effects of new technology

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Abstract
Because anti-cancer drugs are non-selective, they affect both cancerous and non-cancerous cells. Being carcinogenic and mutagenic, many anticancer drugs therefore present a major health risk to healthcare staff working with them. This paper reviews the means by which exposure to anti-cancer drugs in the workplace may be monitored, assessed and reduced. Both biological monitoring, using non-selective methods or compound-selective methods, and environmental monitoring have provided information on the nature and degree of exposure in the workplace. Pharmaceutical isolators, used for the compounding of cytotoxic IV infusions and the preparation of injectable drugs, provide a physical barrier between pharmacists and cytotoxic drugs and reduce direct exposure. However, the interior of isolators and the contents thereof (e.g. infusion bags and syringes) are readily contaminated by aerosols and spillages and afford a secondary source of exposure to pharmacists, nurses and cleaning staff. Closed system transfer devices (CSTDs), designed to prohibit the transfer of contaminants into the working environment during drug transfer between the vial and syringe, have been successful in further reducing, but not eliminating surface contamination. Given that the number of patients requiring treatment with chemotherapeutic agents is predicted to increase, further efforts to reduce occupational exposure to anti-cancer drugs, including the refinement and wider use of CSTDs, are recommended.

Keywords
Anti-cancer drugs, biological monitoring, environmental monitoring, closed system drug transfer device, pharmaceutical isolator

Introduction
Anti-cancer drugs are known to be toxic to cancerous as well as non-cancerous cells, making them both carcinogenic and mutagenic. These particular properties make anti-cancer drugs hazardous to patients (resulting in secondary malignancies) as well as to healthcare staff, and in particular nurses, pharmacists, pharmacy technicians and cleaners who may come in contact with these anti-cancer drugs during their day-to-day duties.

One of the earliest reports of occupational hazards presented by anti-cancer drugs was published in 1979, showing the mutagenic effects of anti-cancer drugs in urine samples collected from nurses working with...
the drugs. Since then, a number of other studies have reported the toxic effects of anti-cancer drugs on healthcare workers around the world. Acute symptoms that have been reported include headaches, hypersensitivity, hair loss, nausea and vomiting; long-term effects include increased mutagenic activity, increased risk of spontaneous abortions, congenital malformations and infertility.

A programme to evaluate the carcinogenic potential of various chemicals, including anti-cancer drugs, was initiated by the International Agency for Research on Cancer (IARC) in 1969. The IARC subsequently produced a number of monographs and divided various drugs according to their carcinogenic potential (see Table 1 for a selection of results). The combined evidence generated by studies on the toxic effects of anti-cancer drugs and monographs published by the IARC have led to the publication of a number of guidelines on the safe handling of anti-cancer drugs. Despite following safety protocols, a risk is still posed to healthcare staff regularly handling anti-cancer agents (Table 2 shows the conditions in which healthcare staff may be exposed to these anti-cancer drugs).

**Measurement of occupational exposure**

The measurement of occupational exposure may be performed by biological monitoring of staff or by environmental monitoring of the workplace. A brief description of methods employed for both biological and environmental monitoring is given below.

**Table 1. Classification of anticancer drugs by the IARC.**

<table>
<thead>
<tr>
<th>Carcinogenic to humans (Group 1)</th>
<th>Probably carcinogenic to humans (Group 2 A)</th>
<th>Possibly carcinogenic to humans (Group 2B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>busulfan</td>
<td>adriamycin</td>
<td>bleomycin</td>
</tr>
<tr>
<td>chlorambucil</td>
<td>azacitidine</td>
<td>dacarbazine</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>cisplatin</td>
<td>mitomycin</td>
</tr>
<tr>
<td>etoposide</td>
<td></td>
<td>mitoxantrone</td>
</tr>
<tr>
<td>melphalan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tamoxifen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>thiopeta</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Conditions of staff exposure to anticancer drugs.**

- Reconstitution of drugs
- Contact with contaminated vials
- Cleaning pharmaceutical isolators/LFC
- Handling contaminated body fluids
- Aerosols generated during drug manipulations
- Administering drugs to the patients
- Cleaning spills

**Biological monitoring**

Biological monitoring of healthcare staff may be performed using non-selective methods, such as urinary mutagenicity and cytogenetic monitoring, or compound-selective methods, such as urinary monitoring of specific anti-cancer drugs.

**Urinary mutagenicity assay.** A test of urinary mutagenicity has been commonly used as an indicator of exposure to cytotoxic drugs. The determination of urinary mutagenicity may be performed by using techniques such as the Ames test or thioether assay. The Ames test was initially described by B.N. Ames in the early 1970s and is commonly used to determine the mutagenic potential of various pharmaceutical agents.

The test uses strains of *Salmonella typhimurium* which cannot synthesise histidine and are unable to grow in histidine-free media. On exposure to the mutagenic chemical, the *Salmonella* strains mutate to start producing histidine. The thioether assay is a non-selective method for the determination of exposure to hazardous chemicals based on the detection of thioether in the urine. Anti-cancer agents, such as alkylating agents, are neutralised by conjugation with glutathione which are then excreted in the urine as thioether. Several studies have demonstrated an increase in urinary mutagenicity as an indicator of exposure to anti-cancer drugs in healthcare staff. However, other research has shown no increase in urinary mutagenicity, even in staff working with anti-cancer agents on a regular basis. Because of the relatively low sensitivity of these techniques, coupled with the general limitations of biological monitoring outlined below, they are no longer favoured for the detection of the effects of occupational exposure to anti-cancer drugs.

**Cytogenetic monitoring.** Cytogenetic monitoring methods detect changes or damage to the genetic material in healthcare staff members working with anti-cancer drugs. According to a review by Suspiro and Prista, the most common methods of cytogenetic monitoring are the analysis of chromosomal aberrations (CA), sister chromatid exchanges (SCE), micronuclei tests, COMET assay and mutation tests. CA is the most frequently used method to detect exposure to cytotoxic agents through changes in chromosome numbers or chromosome structures, especially in blood lymphocytes. CA may be divided into two types: the first may affect both sister chromatids on chromosomes caused by double strand breaks, while in the second just one sister chromatid is affected. All studies included in the above review reported an increase in CA in the cells of exposed healthcare staff, emphasising the effectiveness of this test to detect DNA damage. SCE arise from the exchange of genetic material between sister chromatids.
in cells exposed to cytotoxic agents without causing any alteration in the numbers or structure of the affected chromosomes. Although this test appears to be one of the most sensitive tests for identifying DNA damage, the significance of increased frequency of SCE in relation to increased risk of cancer is not well established and the application of this test is declining.\textsuperscript{16} The COMET test was first introduced by Osteling and Johanson as a technique to visualise DNA strand breaks due to exposure to anti-cancer drugs and is highly sensitive.\textsuperscript{17} The test is able to measure both primary and secondary DNA strand breaks, is simple and cheap to carry out and requires a small sample. However, because it may produce false positives, it requires peripheral blood samples rather than epithelial buccal cells. In the micronucleus test, the numbers of micronuclei are used as a measure of the extent of DNA damage. Micronuclei are cytoplasmic bodies formed during the anaphase of mitosis or meiosis. In cells exposed to hazardous chemicals, including anti-cancer drugs, there is an increased likelihood of the presence of more than one micronucleus.\textsuperscript{18} The micronuclei are counted using a technique called cytokinesis-block micronucleus test (CBMN). This test may be applied to peripheral blood lymphocytes as well as to epithelial buccal cells, making it more convenient.\textsuperscript{16} Mutation tests, such as the hypoxanthine-guanine phosphoribosyltransferase (HPRT) assay, have also had some use in detecting mutations caused by exposure to cytotoxic agents.\textsuperscript{16} However, the relationship between positive mutation and increased cancer risk is yet to be established.

There are numerous studies in the literature that show a direct relationship between exposure to anti-cancer drugs and DNA damage. For example, Sasaki et al.\textsuperscript{1} used the COMET test to demonstrate increased DNA damage in nurses handling anti-cancer drugs at three Japanese hospitals ($n=121$) compared with control subjects (female clerks; $n=46$) from the same hospitals, while Cornetta et al.\textsuperscript{18} used both COMET and micronucleus tests to demonstrate increased DNA damage in oncology nurses at two Italian hospitals ($n=83$) compared with office workers at the same institutes ($n=73$). A study among Hungarian nurses ($n=717$) used both analysis of CA and SCE to determine the effects of exposure to anti-cancer drugs, an anaesthetic gas (halothane) and sterilising agents (ethylen and formaldehyde).\textsuperscript{19} The results were compared against age-matched, unexposed control subjects working in medical care ($n=93$) and revealed that the group of nurses exposed to anti-cancer drugs had the highest incidence of both CA and SCE.

**Urinary monitoring.** The direct measurement of anti-cancer drugs in urine samples of healthcare staff may also be used to study the impact of exposure to these drugs. In a study by Turci et al.,\textsuperscript{20} urine samples from staff working in oncology units were tested for cyclophosphamide, ifosfamide, methotrexate (MTX) and platinum (Pt). Cyclophosphamide was most frequently detected in the range of 50–10,000 ng L$^{-1}$, ifosfamide was detected in one sample at 153 ng L$^{-1}$ and Pt was detected in the range of 920–1300 ng L$^{-1}$; MTX was not detected in any of the samples. According to a review of biological monitoring studies,\textsuperscript{21} measurable levels of anti-cancer drugs, such as cyclophosphamide, MTX, anthracyclines and Pt based drugs, have been detected in urine samples of various healthcare workers. Cyclophosphamide is the most frequently observed drug in urine samples of staff involved in its preparation and administration and has been found in the range of 0–50 μg L$^{-1}$. Despite its common use as a bio-marker, however, it is not the most suitable drug for monitoring studies. Cyclophosphamide itself is an inactive pro-drug and is extensively metabolised in the liver into active metabolites. The urinary excretion of the unchanged drug is no more than 20% of the administered dose,\textsuperscript{22} meaning that the risk of occupational exposure is underestimated.

Unlike cyclophosphamide, MTX and Pt-based drugs are excreted mainly through the kidneys, either unchanged or as metabolites. The ranges detected in the literature are 0.5–40 μg L$^{-1}$ of MTX and 0.6–34.4 μg L$^{-1}$ of Pt.\textsuperscript{21} Studies involving these drugs have been mostly undertaken in hospitals where either Biological Safety Cabinets (BSC) or Laminar Flow Cabinets (LFC) were being used for the preparation of anti-cancer drug infusions. An increased exposure to pharmacists is likely when working in these facilities compared with staff working in pharmacy aseptic manufacturing units, as in the UK, where chemotherapy infusions are prepared in pharmaceutical isolators.

Biological monitoring studies are an important tool for understanding the occupational risks to healthcare professionals working with anti-cancer drugs. Such studies not only provide an actual measurement of the drugs that the healthcare workers are exposed to but also the type and extent of DNA damage that exposure may incur. However, non-selective biomonitoring has certain limitations in that it may produce false positives arising from DNA damage caused by external factors (e.g., vehicular exhaust, smoking and ageing). On the other hand, compound-selective biomonitoring provides an accurate measure of the occupational exposure, but the detection levels depend on factors such as the extent of drug metabolism, drug assay, sensitivity and selectivity of the assay and the equipment used to test the samples. As there are no safe exposure levels of anti-cancer drugs, measures must be taken to reduce the work surface contamination to ALARA (as low as reasonably achievable).\textsuperscript{23}
Environmental monitoring

Although biological monitoring has provided evidence of the exposure of healthcare staff to anti-cancer drugs, this approach does not address the causes or likely routes of exposure to anti-cancer drugs. Environmental monitoring of the pharmacy aseptic manufacturing units (where anti-cancer drug IV infusions are prepared) and drug administration areas provide a baseline level of contamination that staff are exposed to on a regular basis. Specifically, studies have been published which have demonstrated measurable quantities of various anti-cancer drugs within pharmacy manufacturing units, storage shelves, prepared IV bag surfaces, LFCs and isolators and ward administration areas.\textsuperscript{21, 24-29}

Methods used to determine work surface contamination usually involve wipe and air sampling, but collection of contaminated gloves, operator pads and swabs has also been employed. Wipe samples are taken from various work surfaces using moistened, low linting wipe tissues, while air sampling involves sucking air from drug preparation areas through a micron-sized (0.5-1.2 μm) filter. The marker drugs are then extracted from wipe tissues and filters using suitable solvents or reagents and analysed for the particular marker drug. Table 3 shows examples and typical quantities of drugs detected in these environments. The data obtained from these studies can be used to tailor approaches towards reducing work surface contamination with anti-cancer drugs, which in turn reduces the risk of exposure to healthcare staff. Means of reducing occupational exposure include use of personal protection equipment (PPE), preparation of anti-cancer drug IV infusions in pharmaceutical isolators and use of closed system transfer devices (CSTDs) for the manipulation of hazardous drugs.

Technology designed to reduce exposure

Personal protection equipment

The use of PPE remains the first line of protection against exposure to anti-cancer drugs. PPE used in pharmacy aseptic units include gloves, disposable chemo-protect gowns and masks. According to guidelines issued by NIOSH and the American Society of Health-System Pharmacists, operators must use double gloves and change them every 30 min when dealing with anti-cancer drugs.\textsuperscript{30} Special attention must be paid to the gloves and their material and permeability characteristics. A number of factors may increase the permeation of drugs through the gloves, such as the concentration and hydrophobicity of the drug and its molecular weight, ambient temperature and exposure to alcohol during the infusion preparation stage. Assessments of various glove materials have concluded that vinyl is most permeable to anti-cancer drugs whereas nitrile and neoprene afford much better protection.\textsuperscript{31, 32}

Disposable chemo-resistant gowns must be worn at all times while preparing, handling and administering anti-cancer drug infusions. Harrison and Kloos\textsuperscript{33} evaluated the commercially available gowns for splash protection against anti-cancer drugs and found that gowns laminated with polyethylene or vinyl provided better protection than those bonded with polypropylene.

Sessink et al.\textsuperscript{34} compared the levels of cyclophosphamide in the urine of pharmacy technicians after the introduction of additional protective measures (including special masks and a down-flow laminar flow cabinet) to the levels reported in a previous study in which no such measures were employed. The results indicated that there was a reduction in the mean daily quantity of cyclophosphamide in the urine of technicians from 1.44 μg per day to 0.16 μg per day.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Location</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>methotrexate</td>
<td>Wipe sample (pharmacy)</td>
<td>0.05–6 ng cm(^{-2})</td>
</tr>
<tr>
<td></td>
<td>Gloves (preparation)</td>
<td>0.023–1900 μg/²pair</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>Wipe sample (pharmacy)</td>
<td>0.72–208.6 ng cm(^{-2})</td>
</tr>
<tr>
<td></td>
<td>Gloves (preparation)</td>
<td>21–620 μg/²pair</td>
</tr>
<tr>
<td>Pt-based drugs</td>
<td>Wipe sample (pharmacy)</td>
<td>0.55–92.3 ng cm(^{-2})</td>
</tr>
<tr>
<td></td>
<td>Gloves (preparation)</td>
<td>0.02–0.193 μg/²pair</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>Wipe sample (pharmacy)</td>
<td>0.2–8240 μg cm(^{-2})</td>
</tr>
<tr>
<td></td>
<td>Gloves (preparation)</td>
<td>0.002–113.98 μg/²pair</td>
</tr>
<tr>
<td>ifosfamide</td>
<td>Wipe sample (pharmacy)</td>
<td>0.2–9100 μg cm(^{-2})</td>
</tr>
<tr>
<td></td>
<td>Gloves (preparation)</td>
<td>6.5–60 μg/²pair</td>
</tr>
</tbody>
</table>

Pharmaceutical isolators

A pharmaceutical isolator (Figure 1) may be defined as follows:

"An arrangement of physical barriers that are integrated to the extent that the isolator can be sealed in order to carry out a routine leak test based on pressure to meet specified limits. Internally it provides a workspace which is separated from the surrounding environment. Manipulations can be carried out within the space from the outside without compromising its integrity."\textsuperscript{35}

Isolators may be constructed using either rigid or flexible material and provide an enclosed working area. Common construction materials are flexible...
film, stainless steel, coated steel, glass and plastics. The general design is of an enclosed workspace, interlocking transfer chambers on each side of the isolator and access devices such as gauntlets or sleeves and gloves.\textsuperscript{36, 37} The isolators are maintained at either a negative or positive pressure to the surrounding environment depending on the type of protection needed. Negative pressure isolators are used to manipulate hazardous drugs, including anti-cancer agents, whereas positive pressure isolators are used to protect products, such as total parenteral nutrition (TPN). The work zone is maintained to EU GMP Grade A standard and full laminar air flow over the work zone is provided via an inlet high-efficiency particulate air (HEPA) filter. The air leaving the work zone is returned to the down-flow fan system via the main HEPA filter located underneath the work tray. The exhaust fan is mounted on the top of the isolator, which in most cases is vented outside of the clean-room facility.

Pharmaceutical isolators have been in use for aseptic processing since the 1980s in hospital pharmacies and for various purposes in the pharmaceutical industry.\textsuperscript{39} Applications in the pharmaceutical industry include keg sampling, weighing and dispensing of active pharmaceutical ingredients (APIs), and the mixing and blending of APIs.\textsuperscript{36} In hospital pharmacies, isolators are primarily used for the compounding of cytotoxic IV infusions and the preparation of other hazardous injectable drugs. Other applications in the hospital environment include sterility testing, research and radio-pharmacy. The major advantage of using an isolator is that it provides a physical barrier between the operator and the hazardous substance (e.g. cytotoxic drug), thereby reducing the risk of exposure to staff. Isolators also provide an aseptic environment for the product, thus reducing the risk of microbial contamination of the IV infusions. The main problems with isolators are that (i) technicians may find it uncomfortable to work in such a restrictive setting and (ii) contamination may arise during the compounding of cytotoxic drugs which is difficult to trace and clean.

A recent UK study\textsuperscript{35} examined contamination levels within hospital pharmacy manufacturing units and in the urine samples provided by pharmacy workers engaged in the preparation of anti-cancer drug IV infusions. This study was conducted in two pharmacy units which both used pharmaceutical isolators for the compounding of cytotoxic IV infusions. Wipe samples were taken from isolator surfaces and the drug preparation room floor, while pre- and post-shift urine samples were collected from staff. The results showed measurable amounts of cyclophosphamide (22–1596 ng m\textsuperscript{-2}), ifosfamide (undetected to 1503 ng m\textsuperscript{-2}), MTX (20–674 ng m\textsuperscript{-2}) and platinum (5–130 ng m\textsuperscript{-2}) in the wipe samples, and higher levels of platinum in post shift urinary samples (6–82.4 nmol mol\textsuperscript{-1} creatinine) when compared to a control group consisting of office-based hospital workers (undetected to 14.5 nmol mol\textsuperscript{-1} creatinine). Crauste-Manciet et al.\textsuperscript{38} conducted a study in hospital pharmacies in France and evaluated surface contamination in their positive pressure pharmaceutical isolators by cyclophosphamide, ifosfamide, MTX and 5-fluorouracil (5-fu). The contamination ranges for wipe samples from isolator surfaces were 0.16–6.55 ng cm\textsuperscript{-2} for cyclophosphamide, 0.03–0.85 ng cm\textsuperscript{-2} for ifosfamide, 9.73–83.76 ng cm\textsuperscript{-2} for 5-fu and undetected to 8.61 ng cm\textsuperscript{-2} for MTX.

Contamination from isolator surfaces may be readily transferred to the external surface of infusion bags and syringes prepared for patient use, subsequently resulting in an additional, secondary exposure of healthcare staff to cytotoxic drugs. In most aseptic manufacturing units in the UK, pharmaceutical isolators are cleaned at the start of each working day and then at the end of each session. The most common cleaning agents used for this purpose are sterile, neutral detergent, followed by 70% denatured ethanol. Roberts et al.\textsuperscript{39} have shown that this cleaning regime, while effective against viable organisms, does not remove all traces of cytotoxic contamination.

**Closed system drug transfer devices**

The contamination of pharmaceutical isolators with hazardous drugs is mainly the result of contaminated vials, aerosols generated during the compounding process or spillages, and is an important source of exposure of anti-cancer drugs to pharmacy staff. To reduce the risk of aerosol generation and spillages, CSTDs have been introduced for use during the compounding process. CSTDs have been in use in North America and Europe since the late 1990s. There are a limited number of Food and Drug Administration-approved CSTDs...
available on the market; these include Phaseal, Chemoclave, Texium IV and Onguard with Tevadaptor. According to the National Institute of Occupational Health and Safety (NIOSH), a closed system is defined as 'a device that does not exchange unfiltered air or contaminants with the adjacent environment' and a closed system device as 'a drug transfer device that mechanically prohibits the transfer of environmental contaminants into the system and the escape of hazardous drug or vapour concentrations outside the system'. Although CSTDs are designed differently to each other, they all act by maintaining a 'closed' connection between the vial and the transfer device (syringe). The major advantage of CSTDs is that they reduce the production of aerosols during the compounding process, which are generally considered to be a major cause of occupational exposure to hazardous drugs. CSTDs are also needle-free systems (with the exception of the Phaseal device, which has a needle-safe design) and therefore reduce the risk of needle stick injuries to staff manipulating cytotoxic drugs.

Since the introduction of CSTDs a body of evidence has been provided by various comparative studies on the efficacy of CSTDs in reducing work surface contamination, aerosol production and occupational exposure to healthcare staff working with hazardous drugs. Connor et al. evaluated a CSTD (Phaseal) using cyclophosphamide and ifosfamide as marker drugs and 5-fluorouracil as a control in a renovated pharmacy unit with new BSCs. The marker drugs were prepared using a CSTD and 5-fluorouracil was prepared using standard practice (needle-syringe). The samples were collected from various locations within the pharmacy unit over a period of 168 days. Results showed that the contamination by cyclophosphamide and ifosfamide was considerably lower than that incurred by 5-fluorouracil and suggested that the use of the CSTD in conjunction with a BSC effectively contained contamination from the marker drugs.

Wick et al. examined the efficacy of a CSTD (Phaseal) by collecting surface wipe samples as well as urine samples from the healthcare staff involved in preparation or administration of anti-cancer drugs. Cyclophosphamide and ifosfamide were used as marker drugs for the study, and samples were collected before and after the introduction of a CSTD (Phaseal). The results showed a marked reduction in surface contamination with the marker drugs after the use of the CSTD, and none of the urine samples was found to be contaminated with the marker drugs compared with 10 positive samples for ifosfamide and 18 positive samples for cyclophosphamide in samples collected prior to use of the CSTD.

Harrison et al. evaluated the use of a CSTD (Phaseal) within and outside a BSC. The marker drugs used for the study were cyclophosphamide and 5-fluorouracil. Baseline samples from workplace surfaces were taken for 12 weeks and the CSTD was then introduced. Cyclophosphamide was prepared using the CSTD within a BSC and 5-fluorouracil was prepared using the CSTD outside the BSC on a counter top. The results showed that use of the CSTD within the BSC significantly reduced surface contamination by cyclophosphamide, but that use of the CSTD outside the BSC did not measurably reduce contamination by 5-fluorouracil. Spivey et al. used fluorescein to determine the source of surface contamination in the work place and the effectiveness of a CSTD (Phaseal) in reducing contamination. When the CSTD was used for the reconstitution of fluorescein, no leakage was observed; in contrast, standard practice (needle-syringe) resulted in leakage during each step of reconstitution.

Recent studies conducted in Japan and Australia also confirm the efficacy of CSTDs in reducing workplace contamination. Yoshida et al. used cyclophosphamide to detect work surface contamination and exposure to healthcare staff by comparing results from samples taken before and after the use of a CSTD (Phaseal). The samples were collected for five days during the conventional drug preparation phase and then operators were trained in the use of the CSTD for two weeks and samples were taken again while IV infusions were prepared using the device. Twenty-four hour urine samples from pharmacists preparing the drug infusions were also collected and analysed during both phases. The results revealed that during the baseline phase, the concentration range of cyclophosphamide on the working surface was 0.0095–27 ng cm⁻² and during the CSTD phase the range was undetected to 4.4 ng cm⁻²; urinary cyclophosphamide ranged from undetected to 170 ng day⁻¹ during the baseline phase and undetected to 15 ng day⁻¹ during the CSTD phase. Sidirov et al. used a similar approach, employing cyclophosphamide as a marker drug and taking wipe samples pre- and post-introduction of a CSTD (Phaseal). The authors concluded that there was a reduction of 75% in positive samples of cyclophosphamide and a reduction of 68% in total contamination on using the CSTD.

A recent study in 22 US hospital pharmacies examined the effect of introducing a CSTD (Phaseal) on work surface contamination over a five-year period. Cyclophosphamide, ifosfamide and 5-fluorouracil were used as marker drugs for the study and wipe samples were collected from BSC surfaces before and after the introduction of the CSTD. The percentage of pre-CSTD samples found to be positive for cyclophosphamide, ifosfamide and 5-fluorouracil was 78%, 54% and 33%, respectively, and the percentage of positive sample post-CSTD was 68% for cyclophosphamide, 45% for ifosfamide and 20% for 5-fluorouracil. Median concentrations of cyclophosphamide,
ifosfamide and 5-fu were reduced by 95%, 90% and 65%, respectively, on introduction of the CSTD.

Although the product literature of each CSTD claims that microbiological sterility is maintained during the compounding process as well as during the storage of prepared infusions, there is a paucity of published data confirming these assertions. In a study comparing four CSTDs (Phaseal, Chemoprotect Spike, Clave connecter and Securmix) in maintaining sterility during manipulations, the rubber stoppers of vials containing saline were contaminated with Pseudomonas aeruginosa and the devices were then connected to the artificially contaminated vials. The cells transferred during the manipulations were counted using solid-phase cytometry. The results showed that Phaseal was the most effective device in preventing microbial contamination of the contents of the vial. In a second study, Phaseal devices were connected to vials containing sterile culture media and stored at room temperature; at day 7 there was a 98.2% probability that the vials were not contaminated. In an extension of this study, sterile test culture media were transferred from vials into IV bags using Phaseal devices and the bags were then incubated for 14 days. The results showed that at day 7, the probability of uncontaminated samples was 99.7%.

It is therefore clear that CSTDs are highly effective in reducing the surface contamination within pharmacy aseptic manufacturing areas. However, it should also be noted that even though pharmaceutical isolators provide a high level of protection to pharmacy operators, the exterior surfaces of infusions prepared in isolators are likely to be contaminated with anti-cancer drugs which in turn results in contamination of ward surfaces and poses an exposure risk to nurses. The use of CSTDs along with pharmaceutical isolators would provide a higher level of protection to nursing staff as the outer surfaces of IV infusion bags prepared using CSTDs are less likely to be contaminated with anti-cancer drugs. NIOSH also recommends the use of CSTDs in conjunction with BSCs or pharmaceutical isolators in order to reduce the risk of occupational exposure to anti-cancer drugs. Despite this recommendation and clear evidence that CSTDs reduce contamination, such devices are not used regularly in the UK National Health Service (NHS) hospital pharmacy aseptic manufacturing units, perhaps, at least partly, due to the added costs involved.

**General discussion and future perspectives**

Since the introduction of guidelines for the safe handling of anti-cancer drugs, there has been a profound change in the way anti-cancer drug infusions are compounded in hospital pharmacies across Europe and North America. The practice of compounding anti-cancer drug IV infusions on the wards has given way to centralised pharmacy aseptic units, where trained pharmacy technicians prepare anti-cancer infusions in BSC or pharmaceutical isolators placed in clean rooms. The use of PPE, such as double gloves, chemo-protect gowns and masks, has also become standard practice. These changes have not only reduced the likelihood of healthcare staff exposure to anti-cancer drugs, but have also resulted in a reduction of the overall contamination of the work place.

Despite changes in practice and the introduction of various protective and containment measures, contamination of both the working environment and health care employees is still reported when compared with corresponding control environments or control groups. Clearly, healthcare staff remain at risk of routine exposure to low levels of anti-cancer drugs. The clinical significance of low level exposure to anti-cancer drugs is not fully understood, especially when workers are exposed to a combination of anti-cancer drugs over long periods of time. Due to the lack of this understanding and a paucity of data in this respect, it is difficult to quantify the risk of low level exposure. A meta-analysis published in 2005 identified 14 studies from 1966 to 2004 where health risks in staff following occupational exposure to cytotoxic drugs were evaluated; of these, however, only seven were suitable for statistical pooling. The analysis concluded that there was no significant association between occupational exposure and congenital malformation and still birth, but there was a small incremental risk of spontaneous abortion in female staff handling cytotoxic drugs.

More recently, and especially in the UK, hospitals have begun to outsource the production of batches of anti-cancer drug infusions to commercial aseptic units. This is likely to further reduce work surface contamination, especially in hospital pharmacies, provided that chemotherapy infusions themselves are free from surface contamination. Standardised monitoring of the workplace in UK hospitals has also been proposed by Quality Control North West (QCNW), a quality control laboratory based in North West England. Thus, in an ongoing attempt to establish levels of contamination ALARA (as low as reasonably achievable), customised surface wipe kits are used to sample the work place. Wipe samples are then returned to QCNW and analysed for various anti-cancer drugs using liquid chromatography/mass spectrometry (LC/MS). Levels are used as a guideline and if a sample exceeds ALARA, the specific area is cleaned to reduce surface contamination.
Table 4. Recommendations for the safe handling of oral chemotherapy.

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packaging to state if segregation technique used</td>
</tr>
<tr>
<td>Packaging material to be durable, tamper-proof and be able to contain accidental leakage</td>
</tr>
<tr>
<td>Oral cytotoxics to be stored and transported separately from non-toxic drugs</td>
</tr>
<tr>
<td>Tablets or capsules to be packed based on amount needed per cycle</td>
</tr>
<tr>
<td>Cytotoxic drugs to be stored separately from other drugs in pharmacies</td>
</tr>
<tr>
<td>Appropriate PPE to be used while dispensing chemotherapy</td>
</tr>
<tr>
<td>Tablets or capsules not to be dispensed using automated counting machines</td>
</tr>
<tr>
<td>Separate equipment must be used for cytotoxic and non-cytotoxic agents</td>
</tr>
<tr>
<td>All non-disposable equipment to be cleaned after each use</td>
</tr>
<tr>
<td>All healthcare workers dealing with oral chemotherapy must be trained and competency routinely assessed</td>
</tr>
</tbody>
</table>

Table 5. Recommendations for the safe handling of injectable chemotherapy.

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packaging should specify hazardous/cytotoxic drugs</td>
</tr>
<tr>
<td>Drugs should be transported in closed containers to minimise risk of breakage</td>
</tr>
<tr>
<td>Spill training must be provided to all staff according to written policies and procedures</td>
</tr>
<tr>
<td>IV infusions must be prepared in ventilated cabinets</td>
</tr>
<tr>
<td>Appropriate PPE such as chemo resistant gloves, gowns and masks must be worn while preparing chemotherapy infusions</td>
</tr>
<tr>
<td>Gloves must be changed every 30 min or when torn, punctured or contaminated</td>
</tr>
<tr>
<td>After preparation final container should be sealed in a plastic bag in the ventilated cabinet</td>
</tr>
<tr>
<td>All waste containers must be sealed and wiped within the ventilated cabinet</td>
</tr>
<tr>
<td>CSTDs may be considered for the preparation of infusions</td>
</tr>
<tr>
<td>Needle-free, closed systems should be used while drug administrations</td>
</tr>
<tr>
<td>Use PPE while administration of IV cytotoxic drugs</td>
</tr>
<tr>
<td>Use specified chemotherapy waste bins for disposal of contaminated gowns, gloves and IV bags</td>
</tr>
<tr>
<td>Wash hand with soap and water after preparation and administration of chemotherapeutic agents</td>
</tr>
</tbody>
</table>

have concentrated on pharmacy aseptic units and oncology wards where chemotherapy IV infusions are prepared and administered. Less attention, however, has been given to the risks associated with oral chemotherapy. Healthcare staff may be exposed to drugs to be administered orally during their transportation, unpacking, storage and disposal. Oral chemotherapy, as well as injectable chemotherapy, also presents risks of exposure to patients' family members or care providers because it is more likely to be used at home. A team of international pharmacists from North America and Europe recently reviewed existing guidelines on handling oral chemotherapy and recommended measures to fill existing gaps. The recommendations made by the above team (oral chemotherapy) and NIOSH (injectable chemotherapy) to manufacturers, health care providers and patients are summarised in Tables 4 and 5, respectively.

In the future, occupational exposure to anti-cancer drugs is predicted to increase due to the increasing number of patients requiring treatment with chemotherapeutic agents. According to an estimate for the year 2008, 12.7 million new cases of cancer were diagnosed worldwide and 309,500 cases were diagnosed in the UK. It has also been estimated that the number of new patients with cancer in the UK would increase by 55% for men and 35% for women by the year 2030 as compared with 2007, mainly due to the effects of an increasing and aging population. Increasing numbers of patients will, therefore, require treatment with chemotherapeutic agents. Even though the use of newer and potentially less toxic anti-cancer drugs, such as mono-clonal antibodies, has increased, the use of traditional anti-cancer drugs will continue. Accordingly, further efforts to reduce exposure in the working environment, including the refinement and wider use of CSTDs, are recommended.

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**References**


