



Postulating a Dermal Pathway for Exposure to Anti-Neoplastic Drugs among Hospital Workers. Applying a Conceptual Model to the Results of Three Workplace Surveys

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Dermal exposure to anti-neoplastic drugs has been suggested as a potentially important route of exposure of hospital workers. Three small-scale workplace surveys were carried out in several hospitals focusing on contamination by leakage from IV infusion systems; contamination by spilled urine of patients treated with anti-neoplastic drugs and particulate phase anti-neoplastic drugs in the air of outpatient and nursing clinics. A new visual scoring technique using a fluorescent tracer was developed. The method showed a very low limit of detection (0.02 µl of contamination) and a very high inter-observer agreement (ICC=0.99). Evaluation of IV systems and connectors showed distinct differences between the systems. It was estimated that 0.5–250 µg of a drug can become available for contamination during each infusion. Differences in average contamination between nurses were negligible in the experimental set-up. Widespread and frequent contamination due to spillage of contaminated urine was revealed and appeared not to be restricted to the patient's room. Airborne particulate concentrations went undetected for 80% of the measurements. However, in a few cases concentrations up to 2 ng/m³ of cyclophosphamide were measured predominantly in a room of a patient treated with this anti-neoplastic drug.

Based on these results and a recently proposed conceptual model for dermal exposure a most likely exposure scenario was postulated both for nurses involved in administering drugs and nurses caring for treated patients. Estimation of all relevant mass transport rates will be a challenge for the near future. © 2000 British Occupational Hygiene Society. Published by Elsevier Science Ltd. All rights reserved.

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INTRODUCTION

Several epidemiological studies of hospital workers have shown that occupational exposure to anti-neoplastic (cytogenic) drugs can result in reproductive toxic effects (Selevan *et al.*, 1985; Stücker *et al.*,

1990; Taskinen *et al.*, 1986, 1994). Actual exposure to anti-neoplastic drugs in the work environment of hospital workers has been described for two decades (Falck *et al.*, 1979; de Werk Neal *et al.*, 1983; Cloak *et al.*, 1985; Stücker *et al.*, 1986). Biomonitoring of hospital workers has proven that pharmacists, nurses and even cleaners are exposed to these hazardous drugs (Sessink *et al.*, 1992, 1994; McDevitt *et al.*, 1993; Ensslin *et al.*, 1994). It has also become clear that exposure must be infrequent, since only 20–40% of daily spot and 24 h urine samples taken generally

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contain anti-neoplastic agents in quantifiable concentrations (Sessink *et al.*, 1992). The actual pathway through which the agent reaches the worker and results in actual uptake is still largely unknown. Several authors have pointed out that the dermal route could be important (Sessink *et al.*, 1994; Sorsa and Anderson, 1996; Peelen *et al.*, 1999). Uptake of aerosols through the respiratory tract has been proposed as another pathway especially during the preparation in pharmacy departments (McDiarmid *et al.*, 1986).

In three small-scale experimental studies exposure to anti-neoplastic agents during and after application were studied. By using a fluorescent tracer the importance of several tasks and sources of contamination was assessed for nurses. In order to do so a visual scoring technique was developed and validated.

With the results of these studies and the conceptual model developed by Schneider *et al.*, (1999) a most likely exposure scenario for nurses involved in administering of anti-neoplastic drugs and caring for treated patients was hypothesised.

METHODS

Visual scoring technique with a fluorescent tracer

A panel consisting of 10 students and staff of the Environmental and Occupational Health Group at Wageningen University was used to assess the limit of detection (LOD) and the accuracy of the method. One of the panel members had previous experience with fluorescence techniques and three were experienced in subjective estimation of (historical) occupational exposure. Tinopal-CBS was used as a fluorescent agent and cellulose filter paper (Whatman high volume air sampling filters grade 41) without whitening agent was used as a background. The experiment took place in a darkened room, in which fluorescence was visualised by lightening with u.v. blacklight.

In order to determine the *limit of detection* each panel member had to score a range of cards (cellulose filter paper) with a number of spots. The number of spots varied randomly between zero and five. Two different solutions of Tinopal-CBS were used: Tinopal in distilled water (0.1 g/l) and Tinopal (0.1 g/l) in a NaCl solution (0.9%). The reason for this was that both solutions are generally used as infusion fluid during the administering of anti-neoplastic drugs. Three different spot diameters were used: 0.02, 0.04 and 0.06 μl . Each panel member scored 60 cards after being familiarised with the scoring method by showing reference cards. Distance from and positioning relative to the u.v.-light were standardised.

The *accuracy* was assessed in a second session in which each panel member was asked to estimate the amount of Tinopal solution on a card. The panel members used a reference card on which the following amounts of Tinopal solution had been applied: 0.02, 0.04, 0.06, 0.08, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 10.0, 15, 20, 25

and 50 μl . Two types of reference cards were used: one for which Tinopal was dissolved in water and another for which Tinopal was dissolved in NaCl (0.9%). Scoring was done based on spot surface area and not on the emitted fluorescence intensity. Solution, number of spots per card and diameter of the spots were varied: distilled water versus NaCl solution, single spot versus compound spots (consisting of three spots) and 0.02–0.5 versus 0.5–5.0 and 5.0–40 μl . The cards were administered in series of 10 grouped by solution, while number of spots and quantity ranges were varied randomly. Five cards of each combination of solution, type of spot and quantity range were scored, so each panel members scored 60 cards in total. Two different reference cards were used depending on the solution in which Tinopal was dissolved.

In both experiments Tinopal was administered onto the cards with a micro-injection pipette (Esgé, 1 and 5 μl , Hamilton, 25 and 100 μl). The smallest quantity that could be placed on a card was 0.02 μl .

Contamination by IV infusion systems

The visual scoring technique was consequently used to study exposure to anti-neoplastic agents while administrating these drugs by different IV infusion systems in two oncology departments (outpatient clinic and nursing clinic) of a university hospital. In the outpatient clinic two IV infusion systems were in use. Both systems used Add-a-flex infusion bags, a NPBI connector system and an infusion system of NPBI with one spike point. Some of the bags were delivered from the pharmacy department with the connection tube (filled with NaCl 0.9% solution) already in place, while for others the nurse connected the connection tubes to the bags immediately before administration. In addition two other systems were evaluated, one with an Intraflex infusion bag (used previously) and one with four injector points.

In the outpatient clinic 10 nurses, while mimicking daily practice in a simulation without actual administration of the drug to a patient, performed all operations except for the system with Intraflex infusion bags. The tests with the Intraflex infusion bags were performed by one of the authors (FH).

The contamination of the worker, infusion system and the environment were assessed before (blank) and during administration of the infusion (preparation, administration and detaching). To estimate the total amount of released solution the following monitoring strategy was chosen:

- all observations were done in a fluorescent-free environment, that could be darkened completely
- floor surface was covered with fluorescent-free paper
- to estimate personal contamination every subject wore a fluorescent-free apron and latex gloves
- three standard potential contaminated surfaces of

the IV infusion system were wiped with fluorescent-free cellulose filter paper (spike, septum and needle of connection point or male and female connection points of a Luer–Lock system with connector)

- using the visual scoring technique two observers (FH, RU) assessed independently contamination of the wipes of the IV infusion system, apron, gloves and floor paper; value of contamination (μl) reached by consensus was retained

All procedures were carried out under normal artificial light, while for visual scoring the light was switched to u.v. blacklight.

In the clinic the infusion system was connected to the infusion bag with anti-neoplastic drugs through the spike point. A second bag with NaCl was connected via a permanent connection to this main line. Detaching and reconnecting a new bag with anti-neoplastic drugs through the spike point could lead to contamination. An alternative via a Luer–Lock system was evaluated. Four different systems (SmartSite™, CLAVE®, Safesite and Codan Red) and the original 'Add-a-flex spike connection' were compared. All tests with the different connectors were performed by one of the authors (FH). Scoring was done as described before.

Contamination by spilled urine

In a second survey a fluorescent tracer technique was used in a university hospital to estimate contamination by spilled urine. To each urinal and bedpan, prior to use, Tinopal-CBS was added (respectively 25 and 50 ml of a Tinopal-CBS water solution 10 g/l.) for a two-week period. Subsequently, patients used the urinals/bedpans as usual. Bedpans and urinals were stored in the patients' toilet. Full urinals and bedpans were emptied in the 'utility room' in order to weigh the amount of excreted urine. After that the urinals/bedpans were placed in a washer in the same room. Places where urine was spilled were subsequently identified by using u.v.-light (blacklight). Observations took place during nine days of two consecutive weeks. Patient rooms, utility room, toilets (both in the patients' rooms and in the corridors) and corridors were checked for contamination. In addition shoes, skin of arms and hands of patients and nurses and other potential contaminated surfaces were inspected.

During the last two days of observations recordings were made with a video camera. Resulting video images were digitised with the help of a computer and transformed into graphic computer files (tif-files).

Exposure to anti-neoplastic agents in airborne particulate

In a third survey the oncology departments of both the outpatient and nursing clinic were surveyed in two

hospitals. Stationary sampling for 8 or 24 h of hospital air was performed during 19 days of a 5-week period around Christmas 1997 with medium flow inhalable dust samplers (PAS-6 and GSP sampler) (Kenny *et al.*, 1997). Samplers and sampling times varied in order to cover a wide range in limits of detection.

Samples were analysed for cyclophosphamide (CP), isophosphamide (IP) and 5-fluorouracil (5FU) depending on the anti-neoplastic drug being handled. Analyses were done with GS-MSMS (gas chromatography–tandem mass spectrometry) according to previously published methods (Sessink *et al.*, 1992, 1999; Bos *et al.*, 1998).

RESULTS

Scoring method

The small quantities used (0.02–0.06 μl) were clearly detectable. Only three panel members did not correctly score four out of in total 600 cards. Three times one spot too many was scored (0.02 μl and two times 0.06 μl). This occurred when Tinopal was dissolved in distilled water. The most likely explanation for this was counting a fluorescent dust particle. Once one spot too few was observed (NaCl solution; 0.04 μl). All panel members judged the spots in distilled water as more clearly visible.

Arithmetic means of scored and administered quantities were quite similar for spots of Tinopal dissolved in distilled water. For Tinopal dissolved in NaCl solution 20–30% higher amounts were scored than were actually administered (Table 1). An analysis of variance enabled estimation of the intra-class correlation coefficient. Combining all scores the ICC was 0.99 (Table 2), indicating almost perfect agreement between panel members. Agreement between panel members was lowest for spots of Tinopal dissolved in NaCl solution (ICC=0.95).

The overall average accuracy was high with an intercept close to 0 and an average regression coefficient of 0.89. Explained variance (R^2) ranged from 92 to 98%. When individual scenarios were studied it appeared that single spots were more accurately scored than multiple spots, Tinopal in distilled water was better scored and correlation was lower for the middle quantity range of 0.5–5 μl (Table 3).

Contamination by IV infusion systems in outpatient clinic

In Table 4 total (environmental) contamination is presented for four different IV infusion systems in the outpatient clinic. The system with the Intraflex infusion bag showed on average a factor of 40 higher contamination compared to a similar configuration with an Add-a-flex bag. Although this was the test which was not performed by a nurse we believe that the results are due to the system rather than the oper-

Table 1. Average administered and scored quantities of Tinopal. Presented are arithmetic means of the individual mean (5 cards) of 10 panel members

| Quantity range (µl) | Administered quantity (µl) | NaCl single spot | NaCl multiple spots | Distilled water single spot | Distilled water multiple spots |
|---------------------|----------------------------|------------------|---------------------|-----------------------------|--------------------------------|
| 0.02–0.5 | 0.18 | 0.22 | 0.20 | 0.17 | 0.16 |
| 0.5–5.0 | 2.94 | 3.76 | 3.95 | 2.65 | 3.13 |
| 5.0–50 | 26.40 | 31.02 | 34.82 | 25.84 | 27.60 |
| 0.02–50 | 29.52 | 35.00 | 38.98 | 28.66 | 30.90 |

Table 2. Intra-class correlation coefficients for 10 panel members for different experimental conditions

| Combination | ICC |
|-----------------|------|
| All | 0.99 |
| Distilled water | 1.00 |
| NaCl | 0.95 |
| Single | 0.97 |
| Multiple | 0.98 |

ator. The system with four injector points and a connector showed no contamination above the LOD (0.02 µl). Contamination occurred predominantly at the IV infusion system. The floor, gloves and apron hardly showed any contamination.

No systematic difference in average contamination was seen between the 10 nurses (inter-nurse variability was zero).

Contamination of different connectors in the nursing clinic

The SmartSite™ and CLAVE® connector showed on average a 40-fold lower contamination than the

Table 3. Average and range of intercept and regression coefficients for 10 panel members by different experimental conditions

| Combination | Intercept | | Regression coefficient | |
|-----------------|-----------|------------|------------------------|-----------|
| | AM | Range | AM | Range |
| All | −0.08 | −0.19–0.13 | 0.89 | 0.83–0.98 |
| Distilled water | −0.01 | −0.30–0.20 | 0.99 | 0.91–1.08 |
| NaCl | −0.42 | −0.56–0.20 | 0.83 | 0.74–0.92 |
| Single | 0.12 | −0.31–0.35 | 0.92 | 0.84–1.05 |
| Multiple | −0.32 | −0.48–0.11 | 0.87 | 0.82–0.93 |
| 0.02–0.5 | 0.02 | −0.00–0.05 | 0.90 | 0.54–1.10 |
| 0.5–5 | 1.16 | 0.60–1.84 | 0.53 | 0.29–0.70 |
| 5–50 | −0.87 | −2.00–2.63 | 0.92 | 0.77–1.03 |

Table 4. Contamination (µl) after administration and detaching four infusion systems in the outpatient clinic

| System ^a | N ^b | K ^c | AM | GM | GSD _{bn} ^d | GSD _{wn} ^e |
|---------------------|-----------------|----------------|-------|------|--------------------------------|--------------------------------|
| II-NaCl/I | 10 | 1 | 13.23 | 3.74 | — ^f | — ^f |
| II-NaCl/A | 20 | 10 | 0.30 | 0.09 | 1.00 | 3.55 |
| II+NaCl/A | 19 ^g | 10 | 0.15 | 0.08 | 1.00 | 3.09 |
| 4I+NaCl/A | 20 | 10 | 0.02 | 0.02 | 1.00 | 1.00 |

^aII-NaCl/I=1 Injector point, Intraflex infusion bag, without connector; II-NaCl/A=1 Injector point, Add-a-flex infusion bag, without connector; II+NaCl/A=1 Injector point, Add-a-flex infusion bag, with connector; 4I+NaCl/A=4 Injector points, Add-a-flex infusion bag, with connector.

^bNumber of procedures.

^cNumber of persons.

^dGSD_{bn}=between-nurses variability.

^eGSD_{wn}=within-nurses variability.

^fGSD_{tot}=13.4.

^gOne outlier (22 µl) due to erroneous handling of one of the nurses was excluded.

Table 5. Average contamination (μl) after administration and detaching five infusion systems with connectors in the clinic

| System ^a | N ^b | S ^c | Direct contamination | | | Potential contamination | | |
|---------------------|-----------------|----------------|----------------------|------|------|-------------------------|-------|------|
| | | | AM | GM | GSD | AM | GM | GSD |
| Spike/Add | 10 | 1 | 5.40 | 5.32 | 1.20 | 75.05 | 42.48 | 2.76 |
| SmartSite™ | 100 | 10 | 0.22 | 0.12 | 2.35 | 0.35 | 0.15 | 2.95 |
| CLAVE® | 100 | 10 | 0.22 | 0.13 | 2.59 | 0.25 | 0.13 | 2.76 |
| Safesite | 50 ^d | 10 | 1.00 | 0.47 | 3.95 | 4.27 | 2.64 | 3.08 |
| Codan Red | 32 ^d | 10 | 1.02 | 0.71 | 2.38 | 13.06 | 10.95 | 2.07 |

^aSpike/add=Add-a-flex infusion bag with connection by spike; SmartSite™=connection via Luer–Lock connector SmartSite™; CLAVE®=connection via Luer–Lock connector CLAVE®; Safesite=connection via Luer–Lock connector Safesite; Codan Red=connection via unnamed connector of Codan.

^bTotal number of observations.

^cNumber of specimen.

^dNo repeats were done after a specimen was no longer airtight after detachment.

Add-a-flex spike connection, which showed by far the highest contamination (GM =5.3 μl) (Table 5). The ‘Safe’ and ‘Codan’ connectors had contamination levels of respectively a factor 11 and 7.5 lower than the Add-a-flex spike connection. The four connectors and their repeatedly assessed contamination are depicted in Fig. 1.

It was also shown that contamination increases for the ‘Safe’ and ‘Codan’ with the number of times the connector is being used (respectively 24% and 11% for each time used). For the SmartSite™ no time-trend was seen, while the CLAVE® connector showed an 8% decrease in contamination after each time it was used.

Potential contamination (including environmental contamination by tapping the spike and bag after detachment) was considerably higher for all systems except for the systems with the SmartSite™ and CLAVE® connectors.

Contamination by spilled urine

Observations prior to the administration of Tinopal to the bedpans and urinals showed widespread fluorescence by cleaning agents. Using the u.v. blacklight at a wavelength of 255 nm eliminated the fluorescence of the cleaning agents, while Tinopal fluorescence was still clearly visible.

Main results are summarised in Table 6. Video registrations are shown in Figs. 2–5. Frequent and widespread contamination was seen in toilets used by patients and in the utility room. Toilets used by visitors did not show contamination. The corridor itself showed also contaminated spots during a third of the observation days. Contamination was also identified on shoe soles and the skin of nurses and patients. Patients showed contamination of the skin more often, while the nurses had more often contamination of the shoe soles. Cleaning wipes in use in the utility room showed frequent and large-scale contamination.

Exposure to anti-neoplastic agents in airborne particulate

The limits of detection for CP and IP were respectively 1.56, 0.52 and 0.89 ng/m^3 for PAS-6 8-h TWA, PAS-6 24-h TWA and GSP 8-h TWA measurements. For 5FU the limits of detection were 313, 104 and 179 ng/m^3 for the three different sampling methods.

Table 7 gives the results of the inhalable particulate measurements. For IP and 5FU no measurable airborne concentrations were found even though it was being administered during the measurement period. CP was present in 16% of the inhalable airborne particulate measurements. In the outpatient clinic of one hospital and the nursing clinic of the other hospital

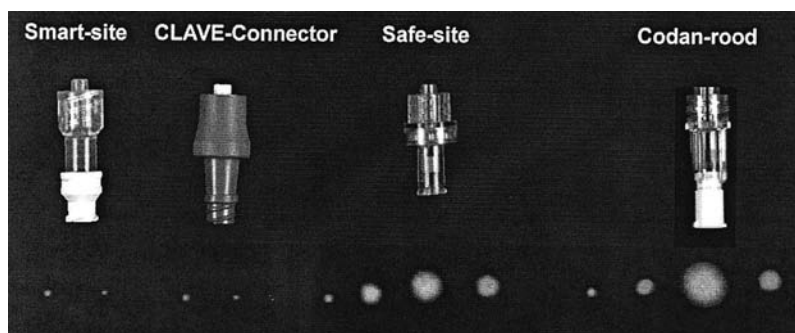


Fig. 1. Tested connectors and their repeatedly measured contamination.

Table 6 Total amount and size of contamination spots in several rooms during nine observation days

| | Diameter (\varnothing) \leq 5 cm | | 5 cm $<$ \varnothing \leq 10 cm | | \varnothing $>$ 10 cm | |
|---|--|-----------------|-------------------------------------|-----------------|-------------------------|-----------------|
| | # Spots | # Positive days | # Spots | # Positive days | # Spots | # positive days |
| Other rooms (<i>N</i> =3) | – | – | – | – | – | – |
| Visitors' toilet in corridor (<i>N</i> =2) | – | – | – | – | – | – |
| Patients' room (<i>N</i> =9) | 5 | 3 (33%) | – | – | – | – |
| Toilet in patients' room (<i>N</i> =5) | 13 | 7 (78%) | 5 | 3 (33%) | 1 (11%) | 1 (11%) |
| Corridor (<i>N</i> =1) | 8 | 3 (33%) | 4 | 3 (33%) | 1 (11%) | 1 (11%) |
| Patients' toilet in corridor (<i>N</i> =2) | 7 | 4 (44%) | 1 | 1 (11%) | 2 (22%) | 2 (22%) |
| Utility room (<i>N</i> =1) | 13 | 7 (78%) | 5 | 3 (33%) | 1 (11%) | 1 (11%) |
| Sole shoe patient (<i>N</i> =6) | 2 | 2 (22%) | – | – | – | – |
| Sole shoe nurse (<i>N</i> =24) | 7 | 4 (44%) | – | – | – | – |
| Skin nurse (arm) (<i>N</i> =24) | 2 | 2 (22%) | – | – | – | – |
| Skin patient (hands) (<i>N</i> =8) | 5 | 4 (44%) | – | – | – | – |
| Portable chair toilet (<i>N</i> =1) | 3 | 1 (11%) | – | – | – | – |
| Cleaning wipes (<i>N</i> =18) | >20 | 3 (33%) | – | – | – | – |



Fig. 2. Cleaning wipes at counter in the utility room. The fluorescent has come onto the wipes after cleaning the counter on which urine has been spilled.

measurable concentrations were found ranging respectively from 1.50–1.64 to 0.46–1.66 ng/m³. At both places IV infusion with CP had taken place.

In the outpatient clinic of hospital 1 a patient was treated with 1450 mg CP via an IV infusion. On one day only one of the four samples taken in the room where infusion with the drug had taken place, showed a detectable level of 1.50 ng/m³. The other positive

sample was taken on the same day in a personnel room (1.64 ng/m³).

In hospital 2 measurable concentrations of CP were found in and around a room of a patient receiving 1800 mg CP during four consecutive days. Nine out of 16 samples were positive for CP. In the room of the patient all samples taken (*N*=7) had quantifiable amounts of CP and the range in concentration was

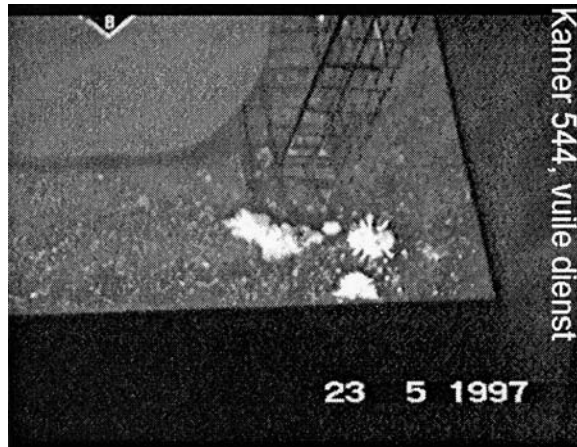


Fig. 3. Elevation between counter and urinal washer in the utility room. Urine has been spilled during transport of the urinal/bedpan from the counter to the washer.

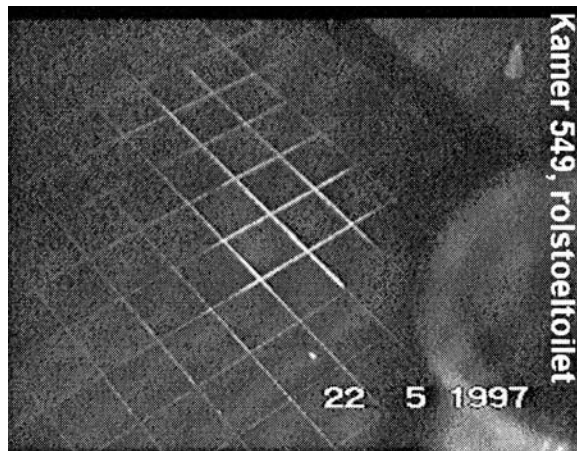


Fig. 4. In the joints of the floor surface of a patient's toilet a remainder of spilled urine is visible. A few days before this picture was taken a large spill from a urinal caused by a patient was identified. This spill had consequently been dispersed over a larger surface by cleaning activities.



Fig. 5. Spilled urine beneath a sink in a patient's toilet. Careless handling by a patient will be the most likely cause of this contamination. At the right from the spot, the patient's urinal with the fluorescent is visible.

Table 7 Inhalable particulate concentrations (ng/m³) of CP, IP and 5FU for outpatient clinics and nursing clinics of two hospitals

| Department (hospital) | Sampler | N ^a CP (# pos.) | Concentration range | N IP (# pos.) | N 5FU (# pos.) |
|-----------------------|------------|----------------------------|---------------------|---------------|----------------|
| Outpatient clinic (1) | PAS-6 | 12 (2) | 1.50–1.64 | – | 39 (0) |
| | GSP | – | – | – | 6 (0) |
| Nursing clinic (1) | PAS-6 | – | – | 7 (0) | – |
| | GSP | – | – | 1 (0) | – |
| Outpatient clinic (2) | PAS-6 | 34 (0) | – | – | 39 (0) |
| | GSP | 5 (0) | – | – | 5 (0) |
| Nursing clinic (2) | PAS-6 | 7 (2) | 1.62–1.66 | – | – |
| | PAS-6 24-h | 6 (6) | 0.46–0.78 | – | – |
| | GSP | 2 (1) | 0.94 | – | – |
| Total | All | 66 (11) | 0.46–1.66 | 8 (0) | 89 (0) |

^aNumber of measurements.

0.46–0.94 ng/m³. Samples were taken on the second ($N=1$), third ($N=2$), and fourth ($N=2$) day of treatment, but also two days after the final administration ($N=2$). On this particular day also measurable concentrations were found in the washer room where urine was weighed and urinals cleaned (respectively, 1.62 and 1.66 ng/m³). In this room no measurable concentrations were found on two earlier occasions when the drug was actually administered. On one of the days the patient moved from one patient's room to another room. In both rooms airborne concentrations of CP were measured. In the shower/toilet no measurable quantities were present.

DISCUSSION

The visual scoring technique based on fluorescence of Tinopal-CBS was shown to be highly reproducible and very accurate for assessing the volume of contamination by liquids. These findings are in agreement with the high inter-observer agreement reported for another visual scoring technique by Fenske (1988), when evaluating exposure to pesticides. However, since the intensity of the fluorescence was not taken into account, our method did not result in accurate estimates of mass of contamination. Nevertheless, based on the successful evaluation of contamination during the handling of an IV infusion system, the method could be labelled 'a poor man's VITAE technique'. The use of fluorescence imaging in this way represents a useful occupational hygiene training-tool both for hospital workers and other personnel who deal with hazardous materials. The VITAE technique (computer-based video imaging system) developed by Fenske *et al.*, (1986) does not suffer from the above-mentioned limitations, but will never be widely used given the high capital costs.

The three surveys have shown that during administering of anti-neoplastic drugs and handling of contaminated urine, measurable and observable contamination of hospital air, surfaces and skin both of patients and nurses can occur in the outpatient and

nursing clinics. The surveys have also indicated that these events occur very irregularly. This coincides well with earlier reported results of anti-neoplastic agents in urine of nurses and other hospital workers. For instance, Sessink *et al.*, (1992) reported contaminated urine for 25%, 40%, and 20% of the days monitored among respectively hospital pharmacy technicians, outpatient clinic nurses and oncology clinic nurses.

It can be estimated that with a typical anti-neoplastic drug concentration of 20 g/l., 0.5–250 µg of the drug is available for skin contamination during each infusion, the actual contamination largely depending on the type of IV system used. The contamination was predominantly present on the IV infusion system and not on the skin, gloves or clothing (apron). Using appropriate gloves during administering of the drugs will further reduce the likelihood of skin contamination considerably.

Contamination due to spilled urine appeared to be more widespread than originally believed. Contamination of patients' toilets, surfaces near the patient's bed, contamination of utility rooms (urinal washer) and corridors appeared to happen frequently (30–80% of observed days). However, the visualisation method applied, underestimated total contamination with contaminated urine, since only spilled urine from the bedpans/urinals was visualised. Additional spills during filling of the urinals and bedpans are however likely to occur as well. In addition, contamination from other contaminated excreta like sweat and vomit might also occur. Unfortunately, identified spots were not subsequently wiped in order to quantify the amounts of anti-neoplastic agents present in the spots. Sessink *et al.*, (1992) reported levels of CP of 0.9 ng/cm² on the floor in front of a washer in a utility room and levels of methotrexate (MTX) of 5.5–5.9 ng/cm² in three wipe samples from two patient rooms. CP was also detected on one of nine urinals (8.3 µg). These spots are comparable to spots identified in our study, but in addition we also identified contamination of nurses and patients' shoes, arms and hands.

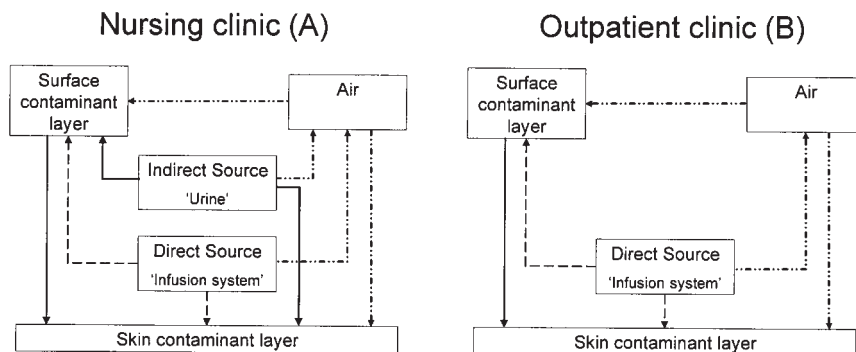


Fig. 6. Mass transport pathways for skin contamination with anti-neoplastic agents for nurses in the nursing clinic (A) and outpatient clinic (B). Transfer between compartments is graphically depicted by arrows according to likelihood of occurrence: → most likely; - - → likely; ···· → unlikely.

Actual contamination of nurses (and cleaners) directly due to contact with contaminated excreta or indirectly due to unprotected contact with contaminated surfaces (floor, urinals, linen, etc.) is therefore most likely.

Finally, uptake of anti-neoplastic drugs by inhalation cannot be ruled out. In our study the air in a room of a patient treated with CP showed low but measurable concentrations of CP (range 0.5–1.7 ng/m³). Earlier reports of air concentrations have shown much higher concentrations during the preparation of anti-neoplastic drugs in pharmacy departments (range 0.1–10 µg/m³) (de Werk Neal *et al.*, 1983; Sessink *et al.*, 1994). Recently, also gaseous exposure concentrations up to 130 ng/m³ have been measured in the exhaust outlet of a biological safety cabinet (Opiolka *et al.*, 2000). Based on the results and a conceptual model proposed by Schneider *et al.* (1999) a model with relevant compartments and likely transfer processes for dermal exposure can be hypothesised for nurses working in oncology departments. This model is graphically shown for nurses in the outpatient and in the nursing clinic in Fig. 6. The 'infusion system containing the agent' and 'contaminated urine' are clearly sources for skin contamination. Deposition of particulate anti-neoplastic agents from the air onto the skin contaminant or surface contaminant layer is unlikely, but cannot be ruled out. Direct transfer of contamination to surfaces and skin due to splashes and spilling of contaminated urine is most likely to occur. Also the indirect route from initial transfer to the surface contaminant layer followed by transfer from the surface to the skin is most likely to be present. Transfer from the IV infusion system to the surface and skin is less likely to happen, especially since gloves are most likely worn during this process. A recent study among 32 nurses from seven hospitals in The Netherlands showed fewer positive urine samples in the outpatient clinics (administering of the drugs) when compared to nursing clinics (both administering and handling of excreta and patients) (25 versus 38%) (Peelen *et al.*,

1999). This coincides very well with the proposed model and consequent use of gloves during administration (Fig. 6).

The challenge will be to complete the hypothesised model for exposure to anti-neoplastic agents among nurses. This will include estimation of all relevant mass transport rates. Also, similar models for dermal exposure will have to be developed for other groups of workers for whom exposure to these agents has been proven (pharmacy technicians and cleaners) or members of the general public (visitors) who might be exposed as well given the widespread contamination of anti-neoplastic drugs in hospital settings.

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