Ann. Occup. Hyg., Vol. 51, No. 3, pp. 231–239, 2007

doi:10.1093/annhyg/mel081

A Pooled Analysis to Study Trends in Exposure to Antineoplastic Drugs Among Nurses

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Received 12 July 2006; in final form 6 December 2006; published online 2 March 2007

Objectives: Several studies have shown that exposure to antineoplastic drugs can cause toxic effects on reproductive health as well as carcinogenic effects. Numerous studies have corroborated that hospital workers are exposed to these drugs. This study focused on trends in exposure to antineoplastic drugs since the introduction of guidelines in The Netherlands.

Methods: Data from three cross-sectional exposure surveys conducted in The Netherlands were pooled to examine trends in occupational exposure to cyclophosphamide. Nurses' 24 h urine samples were analyzed in separate fractions, surface contamination was determined and gloves used during preparation or while handling patient urine were collected. The difference in detectable urine samples between 1997 and 2000 was determined by a generalized estimating equations (GEE) binomial regression model. Mixed models were used to study the time trend in surface and glove contamination levels.

Results: The percentage of nurses' urine samples with detectable cyclophosphamide had decreased 4-fold between 1997 and 2000. Median cyclophosphamide levels in the positive urine samples were 3-fold lower in 2000 than in 1997. Surface and glove contamination had statistically significantly decreased between 1997 and more recent years.

Conclusions: Nurses working at outpatient clinics or oncology wards are still being exposed to cyclophosphamide, but their exposure decreased considerably between 1997 and 2000, presumably due to the introduction of detailed guidelines and regulations in The Netherlands, the subsequent increased use of LuerLock connections and infusion systems prefilled with saline, and growing hazard awareness of nurses working with antineoplastic drugs.

Keywords: antineoplastic drugs; cyclophosphamide; nurses; occupational exposure; time trend

INTRODUCTION

Studies of hospital workers have shown that exposure to antineoplastic drugs can have toxic effects on reproductive health (Selevan *et al*., 1985; Stücker *et al*., 1990) and cause mutagenic activity in urine and chromosomal aberrations and sister chromatid exchange (SCE) in lymphocytes (Falck *et al*., 1979; Waksvik *et al*., 1981; Pohlová *et al*., 1986; Milkovic-Kraus and Horvat, 1991; Sardas *et al*., 1991; Goloni-Bertollo *et al*., 1992). Numerous biomonitoring studies have confirmed that nurses and pharmacy personnel working in hospitals are exposed to these drugs (Sessink *et al*., 1992b; Sessink *et al*., 1994; Ensslin *et al*., 1997; Burgaz *et al*., 1999; Pethran *et al*., 2003). Surveys focusing on the identification of the relevant exposure pathways are scarce, but the dermal route of exposure is considered to be the major route of exposure to antineoplastic drugs (Kromhout *et al*., 2000; Fransman *et al*., 2004, 2005). Surface contamination with antineoplastic drugs was found in several places where preparation or administration had taken place or even further from the handling site (Sessink *et al*., 1992a; McDevitt *et al*., 1993; Connor *et al*., 1999; Rubino *et al*., 1999; Kromhout *et al*., 2000; Schmaus *et al*., 2002). Therefore, contact with contaminated surfaces might play a role in dermal exposure to antineoplastic drugs. Due to the introduction of guidelines in

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1992 (and of enhanced guidelines in 1997) and legal regulations in 2001 for working with antineoplastic drugs in The Netherlands, the subsequent implementation of control measures and growing awareness of hospital personnel regarding exposure to antineoplastic drugs over the past decade, exposure levels and surface contamination might have decreased consequently.

In this paper, we present results from three cross-sectional exposure studies aimed at assessing exposure in 1997, 2000 and 2002. In the first two surveys, internal exposure was evaluated by analyzing urine samples of nurses at outpatient clinics and oncology wards in several Dutch hospitals. Wipe samples were taken to assess surface contamination levels. In the surveys in 1997 and 2002, gloves used for preparing antineoplastic drugs or handling patient urine were collected to estimate possible direct contact with antineoplastic drugs. Our aim was to determine whether internal exposure to antineoplastic drugs, surface contamination levels and glove contamination levels have decreased over time.

METHODS

Because cyclophosphamide is widely used in Dutch hospitals and sensitive analytical techniques are available, exposure to this specific antineoplastic drug was chosen as a measure of exposure to antineoplastic drugs. Exposure to cyclophosphamide was measured in outpatient clinics and oncology wards in seven hospitals in 1997 and in three hospitals in 2000. One hospital (hospital 3) was included in both surveys. Tasks performed in outpatient clinics primarily involved administration of antineoplastic drugs to the patient, while, in oncology wards, the patient stayed in the ward for additional nursing care after administration. Main difference between the situation in 1997 and 2000 was that the preparation of antineoplastic drugs in 2000 was only performed in hospital pharmacies. In 2000, the connections between the infusion bag and tube (prefilled with saline) were already made in hospital pharmacies and LuerLock connections were used, which reduced the possibility of cyclophosphamide-leakage during administration in oncology wards and outpatient clinics. In both exposure surveys, no major differences in work activities or use of personal protective equipment were observed between hospitals. Urine and glove samples were collected from a nurse that worked around not more than one patient treated with cyclophosphamide, and wipe samples were collected around not more than one patient treated with cyclophosphamide. In all three surveys, cyclophosphamide was administered intravenously to patients in doses that were comparable across surveys [mean_{1997} = 1951 mg (range: 675–7200 mg); mean_{2000} = 2088 mg (range: 390–5443 mg); mean_{2002} = 2199 mg (range: 150–6000 mg)]. The samples collected in 1997 were part of a large epidemiological questionnaire survey among all Dutch hospitals to study the relation between reproductive outcomes and exposure to antineoplastic drugs (Fransman *et al*., 2007).

Monitoring

In the exposure survey in 1997, starting at the beginning of a work shift, urine samples were collected for 24 h in separate fractions in seven hospitals. Urine samples were analyzed as separate fractions. In total, 14 nurses from outpatient clinics and 12 nurses from oncology wards collected urine samples during two to six workdays and recorded work activities in a diary. Questions were asked about the administration of cyclophosphamide, disconnecting patients' infusion systems and nursing care (washing the patient and urine collection), and about the use of personal protective equipment during those activities. In the 2000 survey, five nurses from outpatient clinics and eight nurses from oncology wards collected urine samples during three workdays in separate fractions for 24 h in three hospitals, starting at the beginning of a work shift. Urine samples were analyzed as separate fractions. Nurses recorded work activities using the same diary as in 1997 (see above). Based on information derived from the self-recorded diaries, a nurse was classified as 'having worked with cyclophosphamide' during a particular workday if she/he: (i) administered cyclophosphamide to a patient, or (ii) disconnected a cyclophosphamide infusion system, or (iii) performed nursing tasks with cyclophosphamide treated patients (washing patients or collecting patient urine). If none of these tasks with cyclophosphamide were performed, the nurse was classified as 'not having worked with cyclophosphamide'. Cleaning activities were reported in the diary, but because we could not be sure which antineoplastic drug (or mix of drugs) was cleaned (and if cyclophosphamide was one of them), these cleaning activities were not used in classifying nurses.

In the 1997 survey, wipe samples were taken from 12 different surfaces using 5 ml of a 0.03 M sodium hydroxide solution and two tissues. In the exposure survey in 2000, wipe samples were taken from 14 different surfaces using 20 ml of a 0.03 M sodium hydroxide solution and two tissues. Nine surfaces matched those measured in 1997. The wiped surface area was predefined for each type of surface.

In the 1997 survey, 19 pairs of gloves were collected, of which 8 were used during cyclophosphamide preparation at hospital pharmacies and 11 were used for handling cyclophosphamide treated patient urine. Because glove samples were not collected in the 2000 survey, an extra survey was

performed in 2002, in which gloves were collected in four hospitals as part of a cross-sectional exposure survey to determine dermal exposure to cyclophosphamide (Fransman *et al*., 2005). In total, 61 glove pairs were collected, of which 30 were used during cyclophosphamide preparation and 31 were used for handling cyclophosphamide treated patients' urine. No major changes in work practices were observed between 2000 and 2002 that could influence glove contamination levels.

Analysis of samples

All samples were stored at −20°C prior to analysis and analyzed for cyclophosphamide using gas chromatography tandem mass spectrometry (GC-MSMS). Samples were analyzed on a Varian Saturn GC-MS ion-trap system with a Varian 8100 autosampler (Sessink *et al*., 1993). The deuturated analytical standard cyclophosphamide was used, which was purchased from Asta-Medica and was of the highest purity obtainable (>97%). Results of glove samples were corrected for a recovery estimated at 58% in an earlier study (Sessink *et al*., 1992a). The described analytical method had an instrument detection limit (IDL) of 0.1 ng/ml for cyclophosphamide.

Statistical analysis

The data were analyzed using SAS statistical software (version 8.02; SAS institute, Cary, NC). The difference in the proportion of detectable urine samples between 1997 and 2000 was determined by a generalized estimating equations (GEE) binomial regression model (Zeger and Liang, 1986) using the GENMOD procedure in SAS. The number of detectable urine fractions divided by the total number of urine fractions per workday was treated as the dependent variable. The comparison between 1997 and 2000 was adjusted for department (outpatient clinic or oncology ward) and whether or not nurses had worked with cyclophosphamide on that day (as previously defined), with a repeated worker (nurse) effect. Average cyclophosphamide levels in the 24 h urine samples were calculated by using only samples with detectable levels of cyclophosphamide. Average surface and glove contamination levels were calculated by substituting sample values below the limit of detection (LOD), with 0.5× LOD (Hornung and Reed, 1990). Log-transformed data were modelled in the MIXED procedure in SAS that was used to study time trends in surface contamination levels adjusted for surface area, with a random hospital effect. The MIXED procedure in SAS was used to study the time trend in glove contamination levels, using log-transformed data adjusted (and stratified) for the performed task, with a random worker (nurse) effect.

RESULTS

Biological monitoring

Table 1 shows the frequency of cyclophosphamide-related task performance, the use of gloves, and the infusion system that was used during urine collection

Table 1. Frequency of cyclophosphamide-related task performance, the use of gloves, and the use of LuerLock connections and infusion systems prefilled with saline during urine collection days in the 1997 and 2000 survey in outpatient clinics and oncology wards

	Outpatient clinics				Oncology wards			
	1997 Survey (N = 70)		2000 Survey (N = 15)		1997 survey (N = 40)		2000 survey (N = 24)	
	n	%	n	%	n	%	n	%
Administering CP	32	45.7%	6	40.0%	20	50.0%	10	41.7%
Glove use	32	100%	6	100%	20	100%	9	90.0%
'Closed' infusion system used	11	34.4%	5	83.3%	6	30.0%	10	100%
Administered CP dose	29	1124 mg	6	1176 mg	18	3285 mg	9	2695 mg
Disconnecting CP	32	45.7%	4	26.7%	18	45.0%	6	25.0%
Glove use	28	87.5%	3	75.0%	18	100%	6	100%
'Closed' infusion system used	11	34.4%	3	75.0%	6	33.3%	5	83.3%
Washing CP-treated patients	0	0.0%	0	0.0%	3	7.5%	3	12.5%
Glove use	—	—	—	—	3	100%	3	100%
Handling CP-treated patient urine	0	0.0%	0	0.0%	11	27.5%	6	25.0%
Glove use	—	—	—	—	11	100%	4	66.7%
Worked with CP[a]	39	55.7%	6	40.0%	25	62.5%	14	58.3%

N = number of urine collection days; n = number of urine collection days on which the CP-related task was performed, gloves were used, 'closed' infusion system was used; CP = cyclophosphamide.
[a]Performed one of the CP-related tasks: administering CP, disconnecting CP, washing CP-patient, or handling CP-patient's urine.

in both exposure surveys. Washing cyclophosphamide treated patients was slightly more performed in 2000 (12.5% of urine collection days) than in 1997 (7.5%), while the frequency of handling cyclophosphamide treated patient urine was similar in 2000 (25.0%) and 1997 (27.5%). The frequency of both cyclophosphamide administration and disconnection seemed to have been lower in 2000 than in 1997. Therefore, mainly at outpatient clinics the classification of nurses on whether or not they had worked with cyclophosphamide (as previously defined) was somewhat lower in 2000 than in 1997 (Table 1). Unexpectedly, gloves appeared to have been used less frequently in 2000 than in 1997 during most cyclophosphamide-related tasks. In 2000, considerably more LuerLock connections and infusion systems prefilled with saline were used than in 1997 at both outpatient clinics and oncology wards during administration and disconnection of cyclophosphamide (Table 1). The average cyclophosphamide dose administered to patients was not statistically significantly different in 1997 (1951 mg) compared with 2000 (2088 mg), but the average administered cyclophosphamide dose in outpatient clinics was statistically significantly ($P < 0.01$) lower than in oncology wards when adjusted for calendar year (Table 1).

Table 2 presents percentages of urine fractions positive for cyclophosphamide in the 1997 and 2000 survey, adjusted for department and 'worked with cyclophosphamide' during the day of urine collection. The percentage of positive urine fractions had decreased by a factor of 4 between 1997 and 2000 ($e^{\beta} = 0.24$; 95% CI = 0.10–0.57; Table 2; Figure 1). This reduction in positive urine samples was similar for outpatient clinics ($e^{\beta} = 0.27$; 95% CI = 0.07–1.06) and oncology wards ($e^{\beta} = 0.21$; 95% CI = 0.07–0.63). In both surveys, the percentage of detectable urine samples did not statistically significantly ($P < 0.05$) differ between oncology wards and outpatient clinics (Table 2). The percentage of detectable urine samples did not statistically significantly ($P < 0.05$) differ between nurses who reported having performed one of the cyclophosphamide-related tasks and nurses who reported not having performed one of the cyclophosphamide related tasks. In addition to the fact that the percentage of positive urine samples was lower in the 2000 than in the 1997 survey, the cyclophosphamide level in the positive 24 h urine samples was three times lower in 2000 (geometric mean = 24.1 ng/24 h) than in 1997 (geometric mean = 71.8 ng/24 h) (Table 3). However, because a relatively small proportion of urine samples contained detectable levels of cyclophosphamide, we

Table 2. Number of urine collection days, number of urine samples collected during those days, percentage of urine samples with detectable cyclophosphamide levels in outpatient clinics and oncology wards for nurses who did or did not work with cyclophosphamide in the 1997 or 2000 survey, and the factor difference between 1997 and 2000 (e^{β}) with 95% confidence intervals (95% CI)

	1997 Survey (7 Hospitals)				2000 Survey (3 Hospitals)				Binomial regression (2000 versus 1997)[a]	
	Urine days	Urine samples	Samples >LOD	% Samples >LOD	Urine days	Urine samples	Samples >LOD	% Samples >LOD	e^{β}	95% CI
All measurements	110	717	61	8.5%	39	294	7	2.4%	0.24[b]	0.10–0.57
Outpatient clinics	70	483	32	6.6%	15	119	2	1.7%	0.27[c]	0.07–1.06
Not worked with CP	31	223	13	5.8%	9	69	1	1.4%		
Worked with CP	39	260	19	7.3%	6	50	1	2.0%		
Oncology wards	40	234	29	12.4%	24	175	5	2.9%	0.21[c]	0.07–0.63
Not worked with CP	15	95	10	10.5%	10	77	2	2.6%		
Worked with CP	25	139	19	13.7%	14	98	3	3.1%		
Only hospital 3	30	182	12	6.6%	18	118	4	3.4%	0.49	0.15–1.61
Outpatient clinic	16	103	6	5.8%	9	62	1	1.6%	0.39	0.03–4.57
Not worked with CP	5	33	1	3.0%	5	32	0	0.0%		
Worked with CP	11	70	5	7.1%	4	30	1	3.3%		
Oncology ward	14	79	6	7.6%	9	56	3	5.4%	0.67	0.25–1.77
Not worked with CP	6	36	2	5.6%	3	19	1	5.3%		
Worked with CP	8	43	4	9.3%	6	37	2	5.4%		

CP = cyclophosphamide; LOD = limit of detection; e^{β} = factor difference in surface contamination between 1997 and 2000.
[a]GEE binomial regression model using the number of detectable urine samples divided by the total number of urine samples as the dependent variable, with a repeated worker effect.
[b]Factor difference (e^{β}) between 1997 and 2000 is adjusted for department and having worked with CP, with a repeated worker effect.
[c]Factor difference (e^{β}) between 1997 and 2000 is adjusted for having worked with CP, with a repeated worker effect.

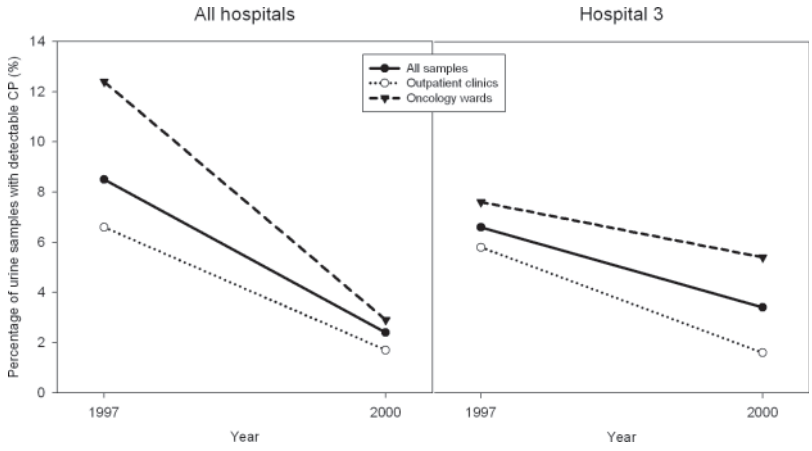

Fig. 1. Percentage of nurses' urine samples with detectable cyclophosphamide levels in outpatient clinics and oncology wards in 1997 and 2000.

Table 3. Cyclophosphamide levels (in nanograms) in nurses' 24 h urine samples in outpatient clinics and oncology wards in the 1997 and 2000 survey (only urine samples > LOD)

	1997 Survey				2000 Survey			
	N	AM [ng]	GM [ng]	Range	N	AM [ng]	GM [ng]	Range
All measurements	32	170.8	71.8	10–1250	7	26.1	24.1	14–45
Outpatient clinics	17	83.5	56.9	10–395	2	32.5	31.6	25–40
Not worked with CP	7	55.4	41.4	10–100	0	—	—	—
Worked with CP	10	103.2	71.0	20–395	2	32.5	31.6	25–40
Oncology wards	15	269.8	93.4	10–1250	5	23.6	21.6	14–45
Not worked with CP	5	222.1	93.3	10–707	4	24.0	21.5	14–45
Worked with CP	10	293.6	93.5	15–1250	1	22.0	22.0	—

CP = cyclophosphamide; N = number of urine collection days with detectable urine samples; AM = arithmetic mean, calculated by only using the detectable urine samples; GM = geometric mean, calculated by only using the detectable urine samples.

could not justifiably perform any formal statistical analyses on these data.

When only urine data from the hospital that was measured in both surveys (hospital 3) were included in the analysis, a similar reduction in the proportion of positive urine samples by year, type of department, and subcategories were observed, with a 2-fold decrease between 1997 and 2000 (e^{β} = 0.49; 95% CI = 0.15–1.61) for all measurements, a 2.5-fold decrease (e^{β} = 0.39; 95% CI = 0.03–4.57) for the outpatient clinic, and a 1.5-fold decrease (e^{β} = 0.67; 95% CI = 0.25–1.77) for the oncology ward (Table 2; Figure 1).

Surface contamination

In the 1997 survey, all 12 surface areas (except for the patient bed) were contaminated at least 60% of the times a surface was wiped. In the 2000 survey, the majority of samples for each surface area were non-detectable. The more frequently and higher contaminated surface areas in the 2000 survey appeared to be surface areas that were situated in the direct surroundings of treated patients, including infusion poles, patient beds, bedside tables and the floor alongside patient bed, urinals or bedpans and bedpan washers (Table 4). Although not all surface areas were measured in both surveys, a statistically significant 3.7-fold reduction (e^{β} = 0.27; 95% CI = 0.12–0.61) in overall surface contamination levels was found between 1997 and 2000, when adjusted for department and type of surface area. This reduction in surface contamination was somewhat stronger in oncology wards (e^{β} = 0.21; 95% CI = 0.07–0.59) than outpatient clinics (e^{β} = 0.35; 95% CI = 0.11–1.07). In oncology wards, the variation between hospitals (S^2_{bh} = 1.34) appears to be smaller than the variation within hospitals (S^2_{wh} = 2.80). In outpatient clinics however, variation between hospitals (S^2_{bh} = 2.06) and within hospitals (S^2_{bh} = 2.07) was similar (Table 5). When only data from the hospital measured in both surveys were included in the analysis (N_{1997} = 24; N_{2000} = 53), a similar reduction in surface contamination was observed between 1997 and 2000 (adjusted for department and the type of surface area) with a factor (e^{β}) of 0.16 (95% CI = 0.07–0.33). This reduction was again stronger in the oncology ward (e^{β} = 0.11; 95% CI = 0.03–0.32) than the outpatient clinic (e^{β} = 0.31; 95% CI = 0.10–0.95; data not shown).

Table 4. Cyclophosphamide surface contamination levels per surface area (in ng/cm^2) for the 1997 and 2000 survey

Sampling area	1997 Survey (7 Hospitals)				2000 Survey (3 Hospitals)			
	N	N > LOD	Median	Range	N	N > LOD	Median	Range
Inside cyclophosphamide-transport bin	—				10	4	<LOD	<LOD–0.04
Outside cyclophosphamide-transport bin	6	4	0.04	<LOD–0.14	10	4	<LOD	<LOD–0.05
Outside cyclophosphamide infusion bag or syringe	1	1	0.07	—	11	0	<LOD	—
Worktop in medicine room	28	18	0.01	<LOD–0.46	—			
Nurses' writing desk	20	15	0.003	<LOD–0.62	9	2	<LOD	<LOD–0.01
Infusion pole	1	1	0.13	—	13	9	0.05	<LOD–1.67
Control panel infusion pump	—				3	0	<LOD	—
Garbage bin for antineoplastic agents	22	18	0.07	<LOD–29.5	16	5	<LOD	<LOD–0.11
Pedal bin for antineoplastic agents	9	6	0.01	<LOD–12.0	—			
Cupboard for garbage bin	—				2	0	<LOD	—
Patient's bed	2	0	<LOD	—	13	9	0.005	<LOD–0.07
Bedside table	4	4	0.11	0.06–0.15	2	2	0.02	0.02–0.02
Floor alongside the patient's bed	37	36	0.10	<LOD–20.6	16	14	0.01	<LOD–2.23
Door	1	1	0.14	—	—			
Outside urinal/bedpan (before washing)	—				2	1	0.02	<LOD–0.04
Outside urinal/bedpan (after washing)	—				2	0	<LOD	—
Outside bedpan/urinal-washer	11	7	0.03	<LOD–4.00	6	3	0.03	<LOD–0.61
Total	142	111 (78%)	0.05	<LOD–29.5	115	53 (46%)	<LOD	<LOD–2.23

N = number of measurements; LOD = limit of detection.

Table 5. Average surface contamination levels in the 1997 and 2000 survey in outpatient clinics and oncology wards, and the factor difference between 1997 and 2000 (e^{β}) with 95% confidence interval (95% CI)

	1997 Survey (7 Hospitals)					2000 Survey (3 Hospitals)					Mixed effects model (2000 versus 1997)			
	N	N> LOD	AM [ng/cm^2]	GM [ng/cm^2]	Range	N	N> LOD	AM [ng/cm^2]	GM [ng/cm^2]	Range	e^{β}	95% CI	S^2_{bh}	S^2_{wh}
All measurements	142	111	0.70	0.03	0.001–29.5	115	53	0.06	0.01	0.001–0.80	0.27[a]	0.12–0.61	1.10	2.67
Outpatient clinics	78	62	1.11	0.04	0.001–29.5	37	17	0.02	0.01	0.001–0.11	0.35[b]	0.11–1.07	2.06	2.07
Oncology wards	64	49	0.21	0.02	0.001–3.99	78	36	0.08	0.01	0.001–2.23	0.21[b]	0.07–0.59	1.34	2.80

N = number of measurements; LOD = limit of detection; AM = arithmetic mean, 0.5× LOD was substituted for sample values <LOD; GM = geometric mean, 0.5× LOD was substituted for sample values < LOD; e^{β} = factor difference in surface contamination between 1997 and 2000; S^2_{bh} = between hospital variance component (log-transformed data); S^2_{wh} = within hospital variance component (log-transformed data).
[a]The factor (e^{β}) is adjusted for department, type of surface area (fixed effects) and hospital (random effect).
[b]The factor (e^{β}) is adjusted for type of surface area (fixed effect) and hospital (random effect).

Glove samples

Cyclophosphamide contamination levels found on gloves show that hands of pharmacy technicians and nurses were potentially exposed to cyclophosphamide during performance of their daily duties. Gloves used during cyclophosphamide preparation in hospital pharmacies were statistically significantly more contaminated with cyclophosphamide than gloves used while handling cyclophosphamide treated patient urine in the 1997 survey ($P < 0.0001$) and in the 2002 survey ($P = 0.001$; Table 6; Figure 2). Contamination levels on the gloves were reduced 20-fold between 1997 and 2002 for all samples ($e^{\beta} = 0.05$; 95% CI = 0.01–0.25), when adjusted for task. This reduction over time was much stronger for the preparation of cyclophosphamide ($e^{\beta} = 0.008$; 95% CI = 0.0003–0.22) than for handling cyclophosphamide treated patient urine ($e^{\beta} = 0.19$; 95% CI =

Table 6. Average glove contamination levels (in nanograms per pair of gloves) for the 1997 and 2002 survey for cyclophosphamide preparation or handling cyclophosphamide treated patient urine, and the factor difference (e^{β}) between 1997 and 2002 with 95% confidence intervals (95% CI)

Task	1997 Survey					2002 Survey					Mixed effects model (2002 versus 1997)			
	N	N> LOD	**AM** [ng]	GM [ng]	Range	N	N> LOD	AM [ng]	GM [ng]	Range	e^{β}	95% CI	S^2_{bw}	S^2_{ww}
All samples	19	15	31 403	1136	<LOD–207 434	61	23	3094	49.7	<LOD–97 754	0.05[a]	0.01–0.25	2.47	2.63
Preparation of CP	8	8	72 890	27 041	1793–207 434	30	15	6260	122.9	<LOD–97 754	0.008	0.0003–0.22	4.56	3.41
Handling CP-treated patient urine	11	7	1230	113.3	<LOD–8448	31	8	29.1	20.7	<LOD–126.9	0.19	0.06–0.61	0.34	1.72

CP = cyclophosphamide; N = number of measurements; LOD = limit of detection; AM = arithmetic mean, 0.5× LOD was substituted for sample values <LOD; GM = geometric mean, 0.5× LOD was substituted for sample values <LOD; e^{β} = factor difference in glove contamination between 1997 and 2002; S^2_{bw} = between worker variance component (log-transformed data); S^2_{ww} = within worker variance component (log-transformed data).
[a]The factor (e^{β}) is adjusted for the task (preparation or handling urine), with a random worker (nurse) effect.

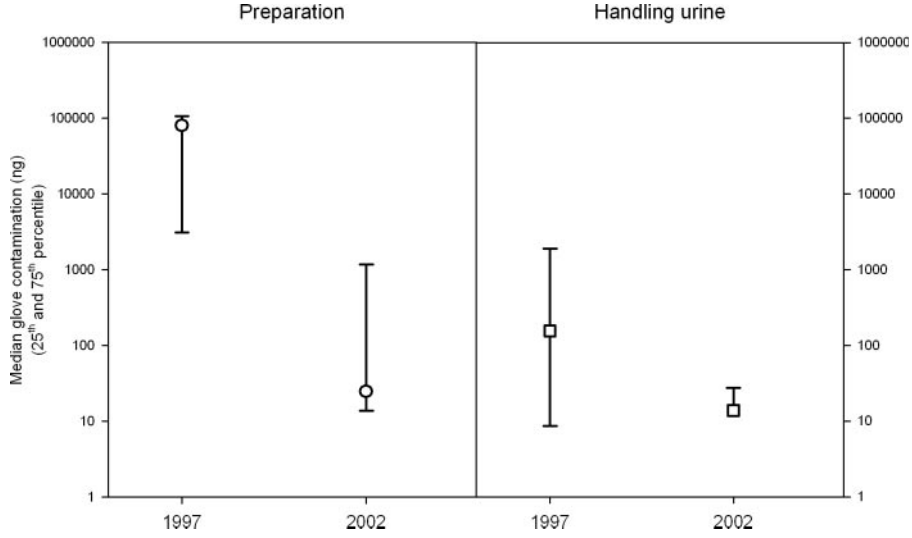

Fig. 2. Median glove contamination levels (in nanograms per pair of gloves) in 1997 and 2002 for cyclophosphamide preparation or handling cyclophosphamide treated patient urine.

0.06–0.61; Table 6; Figure 2). For the preparation of cyclophosphamide, the variation in glove contamination levels between nurses was very large ($S^2_{bw} = 4.56$) and appeared to be larger than the variation within nurses from day to day ($S^2_{ww} = 3.41$). For handling cyclophosphamide treated patient urine the variation in glove contamination levels between nurses was very small ($S^2_{bw} = 0.34$) and considerably smaller than the variation within nurses from day to day ($S^2_{ww} = 1.72$).

DISCUSSION AND CONCLUSIONS

In this study, we demonstrated that the percentage of oncology nurses' urine samples with detectable levels of cyclophosphamide, cyclophosphamide levels in 24 h urine samples, and glove and surface contamination levels have decreased dramatically between 1997 and more recent years. This reduction is likely due to the introduction of enhanced guidelines and regulations for working with antineoplastic drugs in The Netherlands and subsequent implementation of control measures and growing awareness of oncology nurses regarding exposure to antineoplastic drugs.

A 4-fold (statistically significant) reduction in percentage of oncology nurses' positive urine samples was found between 1997 and 2000. Furthermore, the cyclophosphamide levels in the nurses' positive urine samples decreased 3-fold between 1997 and 2000. This not only supports the decrement in frequency of exposure to cyclophosphamide over time, but also indicates that levels of contamination to which nurses were exposed have decreased between 1997 and 2000. The percentage of detectable urine samples and cyclophosphamide levels in detectable

urine samples appears to be somewhat higher in oncology wards than outpatient clinics, which suggests that nurses working in oncology wards were more exposed to cyclophosphamide than nurses working in outpatient clinics. Nurses who reported not having performed one of the cyclophosphamide-related tasks nevertheless appeared to have detectable cyclophosphamide levels in their urine. This suggests that there are other sources of exposure than those defined and that contact with contaminated surfaces might play a role in exposure to cyclophosphamide, in addition to the direct contact with cyclophosphamide during performance of cyclophosphamide-related tasks.

Surface contamination levels have significantly decreased almost 4-fold between 1997 and 2000. The reduction in positive urine samples and surface contamination in outpatient clinics demonstrates that the implementation of more LuerLock connections and infusion systems prefilled with saline has been effective in reducing cyclophosphamide exposure and surface contamination. Yet, the stronger reduction in both cyclophosphamide levels in positive 24 h urine samples and surface contamination in oncology wards versus outpatient clinics suggests that introduction of enhanced guidelines and regulations was most effective for nursing tasks. Presumably, nurses in 1997 were already carefully handling the concentrated drug (during preparation, administration and disconnection of infusion system), but the better awareness of nurses handling patient excreta might have caused the stronger reduction in surface contamination and exposure concentrations in oncology wards. Nevertheless, surface areas that were still contaminated in 2000 were all surfaces in direct surroundings of the patient and were most likely contaminated by the patient or patient excreta. Therefore, the main source of (dermal) exposure and surface contamination that still remains after the introduction of LuerLock connections and infusion systems prefilled with saline and safer handling of those systems seems to be the patient and patient excreta contaminated with cyclophosphamide. The cyclophosphamide contamination found on gloves decreased significantly between 1997 and 2002 for both tasks. This reduction in glove contamination was much stronger for the preparation of cyclophosphamide (125-fold) than for handling cyclophosphamide treated patients' urine (5-fold).

None of the three cross-sectional exposure surveys (1997, 2000 or 2002) was originally designed to study time trends in exposure or contamination levels and, therefore, the same hospitals, nurses and surfaces were not selected in the three surveys. Because hospitals and nurses were randomly selected for all three surveys and a similar reduction was observed for the hospital that was studied in all surveys, we do not think that the reduction in exposure and contamination levels found in this pooled analysis can be attributed to the selection of hospitals, nurses and surfaces.

In the 1997 survey, wipe samples were taken using 5 ml of a 0.03 M sodium hydroxide solution, while in the 2000 survey 20 ml of the same solution was used for wipe sampling. Because of the higher quantity of wiping solution, the removal efficiency could have been better in 2000 than in 1997. This could therefore have possibly caused an underestimation of the surface contamination in 1997, which would then further strengthen the decrease in surface contamination between 1997 and 2000.

In conclusion, oncology nurses working in outpatient clinics and oncology wards are still exposed to cyclophosphamide, but their exposure has strongly decreased between 1997 and 2000/2002. The statistically significant decrease in both surface contamination and glove contamination is consistent with decreased cyclophosphamide levels in urine samples and implies that the dermal exposure route is the main route of exposure to cyclophosphamide. Yet, from the results of this study, the exact pathway through which dermal exposure occurs is hard to hypothesize. Still unclear is whether dermal exposure is more likely to occur via direct contact with cyclophosphamide or with patient excreta (contaminated with cyclophosphamide), or via indirect exposure through contact with contaminated surfaces. In addition to dermal absorption, exposure through ingestion of cyclophosphamide at the workplace from hand-to-mouth contact could potentially play a role in total internal exposure to cyclophosphamide among nurses (Cherrie *et al.*, 2006). However, nurses' activities in hospitals require high hygienic standards and nurses are regarded to wash hands regularly during work, especially after contact with drugs or patient excreta. Therefore exposure through ingestion among nurses is considered to be minimal in comparison with the dermal exposure route.

The results of this study strongly suggest that efforts, such as increased use of LuerLock connections, infusion systems prefilled with saline and nurses' growing awareness of the hazard raised by introduction of improved guidelines, have resulted in decreased individual exposure to cyclophosphamide among oncology nurses in The Netherlands. Several good quality efforts have been made in different countries to implement regulations to reduce contamination levels and protect hospital workers from occupational exposure to antineoplastic drugs during preparation, administration and nursing activities with treated patients (Hilhorst *et al.*, 2001; Health&Safety Executive, 2003; Worksafe Victoria, 2003; Ministry of Social Affairs and Employment, 2004; NIOSH-Alert, 2004). Despite the decrease in task-based exposure levels, recent findings show that the median weekly exposure to antineoplastic drugs of the total population of oncology nurses in

The Netherlands has not changed between 1997 and more recent years (Meijster *et al*., 2006) because of an increase in the frequency of task performance related to antineoplastic drugs. This is in accordance with the growing number of patients treated with chemotherapy in the last decade in The Netherlands.

Acknowledgements—The authors are indebted to the management and workers of the hospitals for their participation in this study. The authors thank Rob Anzion of the Radboud University Nijmegen Medical Centre (Nijmegen, The Netherlands) and Paul Sessink of Exposure Control (Wijchen, The Netherlands) for their analytical support. The authors are grateful to Tim Meijster, Bram Woltjer, Daan Bouwman, Natasja Bak and Ellen van der Maarl for their help during data collection. The Dutch Ministry of Social Affairs and Employment and the participating hospitals financed parts of the study.

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