Evidence-based Series Special Report IN REVIEW

Safe Handling of Parenteral Cytotoxics

Authors (in alphabetical order):

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: April 13, 2007

An assessment conducted in September 2011 placed the Evidence-based Series (EBS) Cytotoxics Special Report IN REVIEW, which means that it is undergoing assessment for currency and relevance.

The PEBC has determined that it is still appropriate for this document to continue to be available while this updating process unfolds.

The full EBS is comprised of 3 sections and is available on the CCO website (http://www.cancercare.on.ca)
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http://www.cancercare.on.ca/toolbox/qualityguidelines/other-reports/collaborative-pr-ebs/

Section 1: Recommendations
Section 2: Systematic Review
Section 3: Development and External Review of Recommendations - Methods and Results

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Purpose
The purpose of this report is to provide recommendations regarding the safe handling of parenteral cytotoxics by health care workers. To accomplish this mandate, the Expert Panel:

a) Examined evidence regarding the risk of cytotoxic exposure to health care workers. The questions of interest were:
   1. Are health care workers who work with cytotoxic drugs at an increased risk of developing cancer compared to a control group of unexposed health care workers?
   2. Are health care workers who work with cytotoxic drugs at an increased risk of teratogenic births/stillbirths/miscarriage compared to a control group of unexposed health care workers?
   3. Are health care workers who work with cytotoxic drugs at an increased risk of developing an acute toxic effect (skin rash, nausea, etc.) compared to a control group of unexposed health care workers?
   4. Are the children of health care workers who work with cytotoxic drugs at an increased risk of developmental delays compared to children of a control group of unexposed health care workers?

b) Examined the evidence regarding closed systems for handling cytotoxic drugs and their effectiveness for protecting health care workers from these risks.

c) Reviewed guidelines that have addressed the safe handling of cytotoxics by health care workers.

d) Created an ethical foundation on which to frame recommendations on handling cytotoxics.
e) Developed recommendations for precautions that should be taken in the workplace to minimize the risk of adverse effects among staff who work in health care facilities and may be exposed to cytotoxic drugs.

**Target Population**

Any employee of a health care facility in Ontario who may be involved in handling cytotoxic drugs, related waste, or bodily fluids from patients undergoing treatment with cytotoxic drugs. This will generally include staff in the following departments: medicine, nursing, pharmacy, housekeeping, environmental services, transportation and portering, materials management, clinical laboratory, research, and clinical trials.

**Recommendations**

When interpreting and applying the specific recommendations listed below, emphasis should be placed on minimizing exposure to cytotoxic drugs for all staff at all times.

**Policies & Procedures**

- Each institution where cytotoxic drugs are used needs to have written policies and procedures for handling cytotoxic drugs, related waste, and bodily fluids from patients undergoing treatment with these agents.
- The development of policies and procedures needs to be collaborative and consultative. Policies and procedures should be developed with input from all departments where there may be exposure to cytotoxic drugs (e.g., medicine, nursing, pharmacy, housekeeping, environmental services, transportation and portering, materials management, clinical laboratory, research, and clinical trials), as well as employee health, risk management, industrial hygiene and safety officers, and Joint Health and Safety Committees, where applicable.
- These policies and procedures must be readily accessible and must be the focus of training for all relevant employees. Anyone who may be required to handle cytotoxic drugs, related waste, or bodily fluids from patients undergoing treatment with cytotoxic drugs (such as staff associated with nursing, pharmacy, housekeeping, environmental services, transportation and portering, materials management, medical care, research or clinical trials) should be aware of the policies and procedures.
- Policies and procedures must be reviewed and updated annually, in consultation with the appropriate stakeholders as defined above.

**Personal Protective Equipment (PPE)**

- Personal protective equipment is provided by the health care facility for all staff identified above.
- Staff are required to wear PPE in accordance with the written policies.
- PPE must be used when preparing or administering cytotoxic drugs, handling waste, or cleaning up spills, and needs to include at least:
  - double gloves (use powder-free, high-quality gloves made of latex, nitrile, polyurethane, neoprene, or other materials that meet the ASTM * standard for chemotherapy gloves) or gloves that are 7-9 mil thick (Note: 7–9 mil = 0.18–0.23 mm). All gloves must meet ASTM D6978-05 standards.
  - a disposable gown (made of appropriate materials designated to be protective against cytotoxic drugs) or a reusable gown that is designed to be non-permeable (where there is a mechanism for isolating the used gowns and procedures for cleaning).

*American Society for Testing and Materials*
- a fluid-resistant mask when there is a risk of aerosolization (not required when using a Class II, Type A2, B1 or B2 biological safety cabinet),
- eye and face protection (except when using a Class II, Type A2, B1 or B2 biologic safety cabinet for drug preparation).

- Staff who change linen, empty bedpans, or clean urine spills in settings where cytotoxic drugs are administered should wear gloves.
- Certain circumstances also warrant the use of a respirator appropriate to the hazard. A National Institute for Occupational Safety and Health (NIOSH)-certified (e.g., N100 or P100) respirator or Self Contained Breathing Apparatus (SCBA) is appropriate when there is a risk of aerosol generation in a space without engineering controls, such as cleaning out the biologic safety cabinet, cleaning up a spill, or other emergency situations (e.g., fire or major system failure).

**Ventilated Cabinets**
- A Class II (Type B2 is preferred but Types A2 and B1 are acceptable under certain conditions), Class III biologic safety cabinet (BSC) or an aseptic containment isolator is required for preparing cytotoxic drugs.
- The BSC must be equipped with a continuous monitoring device to allow confirmation of adequate airflow and cabinet performance.

**Closed Systems**
- Each health care facility will need to assess the need for closed systems in their environment.
- The issue of closed systems should be addressed in the institutional policies and procedures for handling cytotoxic drugs.
- A closed system (e.g., PhaSeal) is not an acceptable substitute for appropriate ventilation or engineering controls (e.g., Class II or III biological safety cabinets or isolators) used along with PPE.
- Closed systems may provide an additional layer of protection for staff involved in the preparation, administration, or disposal of cytotoxic drugs.
- Closed systems may be used for selected cytotoxic drugs. Drug packaging may be incompatible with closed system sets in some instances.

**Syringes and Intravenous (IV) Sets**
- A needleless vascular access system with Luer lock connections should be used for administration of cytotoxic drugs. When starting an IV, a Safety Engineered Medical Sharps (SEMS) (or needleless) catheter is preferred.

**Transport and Labelling**
- Cytotoxic drugs must be transported in containers designed to contain leakage and spills.
- Containers must be clearly labelled as containing hazardous drugs.

**Education and Training**
- Everyone who works with or may be exposed to cytotoxic drugs must have appropriate hands-on and educational training during orientation and at least annually thereafter.
- Training should cover the potential health risks of cytotoxics, safe practice, containment systems and sources of information, appropriate personal protective equipment, and procedures to handle spills.
Orientation and ongoing training is the responsibility of the employer, who will cover the associated costs.

**Pregnancy**
- Alternative duty should be offered to individuals who are pregnant or breast-feeding, because possible reproductive risks have been associated with exposure to cytotoxic drugs.
- All staff should be fully informed of the reproductive hazards.

**Surveillance**
- Medical surveillance is not recommended because adequate tests are not available for monitoring exposure to cytotoxics or assessing the level of risk associated with exposure.
- The panel strongly urges further research to determine if there are adverse health effects that result from health care workers’ exposure to cytotoxic drugs and to develop sensitive specific surveillance tests to detect any adverse health effects. Health care facilities in Ontario that provide cytotoxic therapy should participate in this research.

**Ethics**
- Health care facilities have a moral and ethical obligation to people who handle cytotoxic drugs to minimize exposure.

**Foundation for Recommendations**
The recommendations above are based on:
- systematic reviews of the evidence on adverse effects and closed systems,
- evidence and recommendations in eight recent guidelines from the United States, Australia, the United Kingdom and Germany, and
- the expert opinion of the multidisciplinary panel.

**Adverse Effects**
- The link between exposure of health care workers to cytotoxic drugs and adverse outcomes is biologically plausible. Some cytotoxic drugs in clinical use (e.g., some anthracyclines, epipodophyllotoxins, and alkylating agents) are associated with an increased risk of secondary malignancies among cancer patients receiving cytotoxic therapy. Several studies have shown detectable levels of cytotoxic drugs in the urine of pharmacists, pharmacy technicians, and nurses who prepare and administer cytotoxic drugs, which may have resulted from surface contamination in the workplace. Neither the dose-response relation between chemotherapy nor the long term effects of this exposure are known.
- A systematic review found evidence from 15 retrospective studies (one cohort study, four case-control studies, and ten surveys) that compared health care workers exposed to cytotoxic agents with those who were not exposed. This review found that:
  - Health care workers exposed to cytotoxic agents may be at increased risk for miscarriage, but the quality of the evidence available is poor. Meta-analysis of data from five retrospective studies detected an excess of spontaneous abortions among subjects exposed to cytotoxic drugs (pooled odds ratio [OR], 1.46; 95% confidence interval [CI], 1.11 to 1.92).
  - The association between workplace exposure to cytotoxics and congenital malformation, ectopic pregnancy and stillbirth is unclear. Meta-analysis of data from four studies failed to detect a statistically significant association for congenital malformations (pooled OR, 1.64; 95% CI, 0.91 to 2.94). Two studies, in each case, failed to detect an association with ectopic pregnancy or stillbirth.
There is insufficient evidence from published studies at present to determine if health care workers who work with cytotoxic drugs are at an increased risk of acute toxic effects or cancer, or if their children are at increased risk for learning disabilities.

**Effectiveness of Precautions to Reduce Risk of Adverse Effects**

- There is general agreement across guideline development groups in North America, Europe, and Australia that many of the precautions recommended in this report (related to policies and procedures, personal protective equipment, ventilated cabinets, syringes and IV sets, transport and labelling, and education and training) are appropriate.
- No studies have examined the effectiveness of these precautions to reduce rates of cancer, adverse reproductive outcomes or acute adverse effects associated with exposure to cytotoxic drugs among health care workers.
- There is evidence that some types of gloves and gowns offer protection against penetration and permeation by hazardous drugs.
- There is limited evidence from poor quality studies to suggest that closed systems may reduce surface contamination with hazardous drugs during preparation.
- Available tests for measuring occupational exposure to cytotoxic drugs have inadequate sensitivity and specificity. They would expose workers to unnecessary anxiety without providing useful information on the level of risk for adverse effects.

**Medical Surveillance**

- Biologic monitoring for occupational diseases requires an identified hazard and an accepted and detectable clinical outcome that can be reliably identified by clinical tests. All of these elements are lacking in the current research on health effects of cytotoxic drugs on exposed health care workers.
- There are no identified medical conditions known to result from exposure of health care workers to cytotoxic drugs, no exposure limits set for cytotoxic drugs, and no standards for interpretation of test results of exposed health care workers to enable meaningful interpretation or action based on biological monitoring results.

**Funding**

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775
Safe Handling of Cytotoxics: Systematic Review

Authors for the Systematic Review (in alphabetical order):

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: April 13, 2007

SYSTEMATIC REVIEW QUESTIONS
1. Are health care workers who work with cytotoxic drugs at an increased risk of developing cancer compared to a control group of unexposed health care workers?
2. Are health care workers who work with cytotoxic drugs at an increased risk of teratogenic births/stillbirths/miscarriage compared to control group of unexposed health care workers?
3. Are health care workers who work with cytotoxic drugs at an increased risk of developing an acute toxic effect (skin rash, nausea, etc.) compared to a control group of unexposed health care workers?
4. Are the children of health care workers who work with cytotoxic drugs at an increased risk of developmental delays compared to children of a control group of unexposed health care workers?
5. Do closed systems for handling cytotoxic drugs protect health care workers from these risks?
6. Are there existing guidelines that can inform practice in Ontario with respect to the safe handling of cytotoxics?

INTRODUCTION
Chemotherapy has an important role in cancer treatment, being potentially curative when used as adjuvant therapy in patients with early stage tumours and offering effective palliation in patients with metastatic disease. However, some patients who are cured of their cancer develop secondary malignancies believed to be linked to exposure to their initial chemotherapy regimens (1,2). Well-known examples of cancer-causing regimens include the MOPP (nitrogen mustard, vincristine, procarbazine and prednisone) chemotherapeutic regimen used in the treatment of Hodgkin’s disease and, more recently, CEF (cyclophosphamide, epirubicin, and fluorouracil), when used in patients with early-stage lymph node-positive breast cancer (3,4). Long-term follow-up data in breast cancer patients treated with adjuvant CEF identified a 1.7% absolute risk for the development of secondary leukemias (4). Among the many antineoplastic agents
currently in clinical use, some anthracyclines, epipodophyllotoxins (e.g., etoposide) and alkylating agents are associated with an increased risk of secondary malignancies (2-5).

If patients receiving potentially curative chemotherapy are at an increased risk of developing secondary cancers, then what is the risk to health care workers who prepare and administer these agents? Nurses, pharmacists, pharmacy technicians, and porters who deliver cancer drugs to chemotherapy units and physicians may be exposed to cytotoxic agents during the care of cancer patients. In addition to being at risk for cancers, those individuals might also develop acute toxic effects following accidental spills of cytotoxic agents. In female health care workers who become pregnant, there is also the potential hazard of spontaneous abortions, stillbirths, or teratogenic effects on the unborn fetus. Occupational exposure to cytotoxic drugs was recognized as a potential hazard for health care workers in the 1970s when Falck et al, studying the mutagenicity of urine samples, first demonstrated the potential risk to nurses handling these drugs (6). Subsequent examination of the workplace documented detectable levels of drugs in airborne samples and on work surfaces (7,8), confirming that exposure is possible even in the absence of obvious direct contact. No long-term adverse effects of occupational exposure had been conclusively demonstrated, but the potential risk was deemed serious enough to warrant the issuing of several drug-handling guidelines during the 1980s and 1990s (9-20). These guidelines promoted the control of exposure through the implementation of stringent procedures, use of specialized equipment and personal protective gear, and education of those handling these drugs or at risk of exposure. As a result, many institutions introduced and implemented policies and procedures designed to minimize occupational exposure and the consequent risks associated with handling cytotoxic drugs.

Prior to the development of international standards for the preparation and administration of cancer drugs, it was not uncommon for nurses to prepare cancer agents on the nursing unit with minimal protective gear or equipment. In the mid-1980’s, international standards were developed that specified that cytotoxic agents could only be prepared in an accredited pharmacy with a specially equipped preparation suite containing a biological safety cabinet to minimize cytotoxic exposure (9,16). Pharmacists and pharmacy technicians preparing cytotoxic drugs are now required to wear personal protective equipment (PPE) consisting of a gown, two pairs of chemotherapy gloves, and a head cover. In addition to these established precautions, all cytotoxic drugs should be prepared in a biological safety cabinet—preferably vented 100% to the outside. Nurses involved in the handling of cytotoxic drugs are also required to wear appropriate PPE. In the event of cytotoxic spills, predefined cleanup and decontamination protocols have become policy in any health care facility that prepares and administers cytotoxic drugs. Given these changes in the preparation and administration of cancer drugs over time, the risk of acute and long-term toxic effects in health care workers may have declined over the past 20 years. Nevertheless, health hazards may still exist for hospital staff as suggested by environmental contamination studies that have demonstrated measurable levels of contamination in the workplace despite the standards of practice in place (21). Detectable levels of cytotoxic drugs have been reported in the urine of pharmacists, pharmacy technicians, nurses, and workers in drug manufacturing plants (22).

As part of a review of safe-handling practices for chemotherapy delivery, Cancer Care Ontario formed the Cytotoxic Safe Handling Task Force\(^2\) in 2003 to examine the evidence on adverse effects among health care workers from exposure to cytotoxic agents. An Expert Panel\(^3\) was assembled to review the evidence on adverse effects and on closed handling systems for handling cytotoxics, as well as available guidelines on this topic, and to develop recommendations for use in Ontario.

\(^2\) Susan Poirier (chair), George Dranitsaris, Mary Johnston, Julie Makarski, Tim Savage, Trudi Schueller

\(^3\) Esther Green (co-chair), Maureen Trudeau (co-chair), Michelle Barton, Mary Johnston, Gail Macartney, Debbie Milliken, Susan Poirier, Paula Reynolds, Tim Savage, Lisa Schwartz.
METHODS

This set of three systematic reviews was developed by Cancer Care Ontario’s Program in Evidence-Based Care (PEBC). Evidence was selected by a Research Coordinator and reviewed by members of the Cytotoxic Safe Handling Task Force and/or the Cytotoxic Safe Handling Expert Panel. The Task Force was responsible for preparing a systematic review on the risks from handling cytotoxic drugs in 2003/2004. The Expert Panel updated the systematic review and reviewed the evidence on closed systems and recent guidelines on safe handling in 2006.

These systematic reviews provide a convenient and up-to-date source of the best available evidence on the adverse effects of handling cytotoxics and published guidelines on safe handling of hazardous drugs. Because there is little high-quality evidence on the effectiveness of practices for minimizing risk (such as personal protective equipment) but wide acceptance of ideal standards for these practices, the expert panel did not conduct a systematic search on these topics. Rather, they reviewed the recommendations made in existing guidelines on safe handling. This was supplemented by a systematic review for evidence on the effectiveness of closed systems for handling cytotoxic drugs, a relatively new technology that is not currently standard practice. The systematic reviews and recommendations are intended to promote evidence-based practice in Ontario, Canada.

The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

For the reviews on adverse effects and closed systems, MEDLINE (Ovid), CINAHL (Ovid), EMBASE (Ovid), the Cochrane Central Register of Controlled Trials, and HealthStar (Ovid) were searched from inception of each database to July 2006. The proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) for 2001-2005, the American Society of Hematology (ASH) for 2005, the Oncology Nursing Society (ONS) for 2003-2006, and the Canadian Society of Hospital Pharmacists (CSHP) for 2005-2006 were searched for studies published in abstract form but not yet available as full reports.

The MEDLINE search for primary studies on adverse outcomes from handling cytotoxic drugs used the following search terms: exp health personnel/; oncologic nursing/; oncology service, hospital/; pharmacy/; pharmacy service, hospital/; exp occupational diseases/; exp environmental exposure; abnormalities, drug included/; carcinogens/; teratogens/; exp “attention deficit and disruptive behavior disorders”/; exp child behavior disorders/; exp child development disorders, pervasive/; exp communication disorders/; developmental disabilities/; exp learning disorders/; mental retardation/; motor skills disorders/; developmental delay:.tw.; exp drug toxicity/; hazardous substances/; exp antineoplastic substances/ad,ae.po,st,sp,to/; exp epidemiologic study characteristics/; cohort.mp.; control.mp.

For studies of closed systems for handling cytotoxics, search terms included exp antineoplastic agents/, cytotoxic:.mp., closed system.mp., phaseal.mp., oncovial.mp. and securmix.mp. A bibliography provided by one of the manufacturers was also searched (www.phaseal.com/. Accessed 25 January 2006).

The National Guideline Clearinghouse database (http://www.guideline.gov/), CMA Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), MEDLINE (Ovid), CINAHL (Ovid), and EMBASE (Ovid) databases were searched for existing guidelines in January 2006. Google (http://www.google.ca/) was also used to search the Web for documents that included the text “safe handling” or “hazardous drugs.”

Reference lists of eligible studies and published reviews were scanned to identify additional papers.
Study Selection Criteria

Adverse Effects

Before conducting the search for evidence on risks of adverse events among health care workers, the reviewers identified the following eligibility criteria for studies evaluating the risk of toxic events in health care workers exposed to cytotoxic drugs. Studies were eligible if they:

- were available as full reports or meeting abstracts in the public domain;
- were conducted in North America, Western Europe, Australia, or New Zealand (These jurisdictions were expected to have health care practices similar to Canada);
- reported risk ratios (relative risk, odds ratio, likelihood ratio, etc.) for cancer, teratogenic births, stillbirths, miscarriage, developmental delays, or acute toxic effects;
- included nurses, pharmacists, or pharmacy technicians/assistants exposed to cytotoxic drugs;
- had control groups that may have included health care workers not exposed to cytotoxic drugs or members of the general population.

Practice Guidelines from Other Developers

The expert panel reviewed related guidelines from other groups that were published in English between January 2003 and June 2006. They examined recommendations related to the following aspects of handling cytotoxic or other hazardous drugs:

- development of local policies and procedures,
- collaboration and consultation with affected staff and departments in developing policies and procedures,
- personal protective equipment,
- ventilated cabinets for drug preparation,
- closed systems for drug preparation and administration,
- type of syringes and intravenous (IV) sets used for preparation and administration,
- procedures for transport and labelling drugs,
- staff education/training,
- special considerations for pregnant staff members, and
- medical surveillance of staff.

They also reviewed guideline reports for discussion of ethical issues by the guideline developers. A document from the Joint Center for Bioethics (51), which describes ethical principles and values that can be extended to all risk related health care provision, was used as a framework for thinking about the ethical considerations that can be drawn from the guidelines.

Closed Systems

The expert panel reviewed reports of all studies that evaluated closed systems in the clinical setting.

Synthesizing the Evidence

For the initial (2003) literature review, there was sufficient data to examine the relationship between exposure to cytotoxic agents and two outcomes only: spontaneous abortion and congenital malformation. The MetaView analysis component of the Cochrane Collaboration’s Review Manager 4.2 software (Review Manager (RevMan) [Computer program]. Version 4.2 for Windows. Oxford (England): The Cochrane Collaboration, 2000.) was used for statistical pooling. Most papers reported both raw and adjusted data. In order to investigate the consistency of results arising from these two approaches, two sets of meta-analysis were conducted, and the results were compared in the following manner:

1. Data for the meta-analysis were obtained by constructing two-by-two tables, based on raw data abstracted from study reports, and analyzed using a random-effects model (23).
2. Adjusted odds ratios, reported in published study reports, were pooled using the generic inverse variance approach. Standard errors for input into the analysis were based on published confidence intervals (24,25).

Before embarking on the systematic review, the working group identified studies of health care workers exposed after 1985 as being most relevant to contemporary clinical practice. For this reason, they planned to:

a) do subgroup analysis to examine studies that included only subjects exposed after 1985, when modern handling methods were introduced (using MetaView, see above),
b) perform meta-regression with time of exposure as a predictor, using fixed effects regression analysis, weighted by study variance (24,25).

Because only two studies were restricted to workers exposed after 1985 and these studies measured different outcomes, we could not investigate the effects of timing of exposure.

In all cases, the results of the meta-analysis were expressed as odds ratios (OR) with corresponding 95% confidence intervals (CI). The odds ratio (also known as the relative odds) is a measure of the association between exposure (in this case to cytotoxic drugs) and outcome (e.g., miscarriage). The odds ratio is calculated by dividing the odds of exposure among those with the outcome of interest by the odds of exposure among the control group. Odds ratios >1.0 indicate an excess of adverse outcomes associated with exposure to cytotoxic drugs. Odds ratios were chosen over risk ratios for the pooled analysis primarily because the investigators for the studies included in this review reported odds ratios.

Statistical heterogeneity among studies was assessed using the \(I^2\) test statistic (26), considered to be a superior measure of study heterogeneity than the Q-statistic because the latter is often underpowered when evaluating homogeneity in meta-analysis. The p-values associated with the Q-statistic (chi-square with k-1 degrees of freedom, where k is the number of studies) are also reported.

There were insufficient data to pool results from studies of closed systems.

RESULTS

Literature Search Results

Adverse Effects

The original literature search identified 14 studies evaluating the outcomes of interest (27-41), seven of which were suitable for statistical pooling, and update searching found one additional study (70), for a total of 15 (Table 1). The studies differed in their design and outcome of primary interest. Three studies evaluated cancer risk, twelve focused on reproductive outcomes, and two addressed acute toxicity. Two studies contributed evidence on two risks, cancer and reproductive outcomes (33,70). Peelen et al presented their study results in a report prepared for the Dutch Ministry of Social Affairs and Employment (40), Martin’s work was reported in a doctoral dissertation and meeting abstract (52,70), and the other studies were published in health care or occupational health journals.

Some results for an unpublished study by Martin were included in a meeting abstract in 2005 (52). The limited information available from the abstract was added to the review in early 2006 and additional information was requested from the author without success. In mid-November 2006, the reviewers located a copy of the doctoral dissertation reporting on this study (70) that had been posted in ProQuest’s Dissertations and Theses database (accessed through the McMaster University Library: http://proquest.umi.com.libaccess.lib.mcmaster.ca/ on November 17, 2006). The primary purpose of Martin’s study was to identify the association between the handling of chemotherapy drugs by oncology nurses and disabilities among their children. This very large and recent survey collected data from 3,627 members of the Oncology Nursing Society (ONS) in 2002. Fifty percent of those who were sent the mailed questionnaire responded. It should be noted that 89% of respondents reported handling chemotherapy at some point in their nursing careers.
No prospective studies were found. Retrospective studies use data that has already been collected for reasons other than the research question posed by the investigators and thus, can be prone to bias because of variability and gaps in the exposure and/or outcome data available. For example, the cytotoxic drugs used and levels of exposure will have changed over time and may be very difficult to determine in retrospect. Furthermore, women who have had adverse outcomes, such as a miscarriage, may recall their exposure to cytotoxics differently from the control group.

Retrospective data were available from one cohort study (33), four case-control studies (27,28,37,41), and ten surveys (29-32,34-36,38-40,70). Exposure and outcome data were obtained differently in these three types of studies, but there was potential for bias in all of these retrospective designs. In the comparative cohort study by Skov et al, hospital records were used to identify two groups of nurses, those who had worked in departments where cytotoxic drugs were administered (exposed group) and those who worked in other departments (control group). Outcomes were then ascertained from the same databases for both groups. In the case-control studies, potential exposure to cytotoxic agents was determined by questionnaire for two groups of hospital staff identified from health registries: those who had experienced the outcome of interest (cases) and those who had not (controls). In the survey-based studies, both exposure and outcome were established in the analysis of questionnaire responses. Survey data were analyzed using outcome-based comparisons for two surveys (38,70) and exposure-based comparisons for the other eight surveys (29-32,34-36,39,40). For data collected using questionnaires, bias can arise if the respondent’s recall is selective or response rates are inadequate. Incomplete records could bias results from studies using data from registries or databases.

Outcome data were obtained from registries and hospital discharge databases for the cohort and case-control studies and from study subjects in the survey-based analyses. For most studies, informants were not asked directly about exposure to cytotoxic drugs but were considered exposed if they worked in an oncology setting. Only two studies appear to have been restricted to subjects exposed to cytotoxic drugs after 1985, the year in which new standards of practice were introduced (40,41). The most recent study, by Martin (70), was based on a survey conducted in 2002; many of the nurses surveyed would have been exposed after 1985. Nine studies included only nursing staff (27,28,32,33,35-37,40,70), one included only pharmacy staff (34), and the others included a range of health care workers.
Table 1. Studies included in the systematic review (sorted by year of publication).

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Provides evidence related to:</th>
<th>Cancer</th>
<th>Reproductive events</th>
<th>Acute effects</th>
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<td><strong>Exposure before 1985</strong></td>
<td></td>
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<tr>
<td>Hemminki, 1985 (27)</td>
<td>case-control</td>
<td>spontaneous abortion congenital malformation*</td>
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<td>spontaneous abortion</td>
<td>--</td>
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<td>Selevan, 1985 (28)</td>
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<td>spontaneous abortion*</td>
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<td>Valanis, 1987 (29)</td>
<td>survey</td>
<td></td>
<td>--</td>
<td>spontaneous abortion</td>
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<td>McDonald, 1988 (30,31)</td>
<td>survey</td>
<td>spontaneous abortion stillbirth congenital malformation</td>
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<td><strong>Exposure may have occurred before or after 1985</strong></td>
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<td>Stucker, 1990 (32)</td>
<td>survey</td>
<td>spontaneous abortion*</td>
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<td>Skov, 1992 (33)</td>
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<td>spontaneous abortion* congenital malformation*</td>
<td>cancer</td>
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<td>Valanis, 1993 (34)</td>
<td>survey</td>
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<td>Saurel-Cubizolles, 1993 (35)</td>
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<td>ectopic pregnancy</td>
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<td>McAbee, 1993 (36)</td>
<td>survey</td>
<td>spontaneous abortion/stillbirth congenital malformation*</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gunnarsdottir, 1997 (37)</td>
<td>nested case-control</td>
<td>breast cancer</td>
<td>--</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>Bouyer, 1998 (38)</td>
<td>survey</td>
<td>ectopic pregnancy</td>
<td>--</td>
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<td>--</td>
</tr>
<tr>
<td>Valanis, 1999 (39)</td>
<td>survey</td>
<td>spontaneous abortion*</td>
<td>--</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>Martin, 2003 (70)</td>
<td>survey</td>
<td>spontaneous abortion learning disabilities</td>
<td>cancer</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td><strong>Exposure after 1985</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peelen, 1999 (40)</td>
<td>survey</td>
<td>spontaneous abortion*</td>
<td>--</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>Lorente, 2000 (41)</td>
<td>case-control</td>
<td>congenital malformation (oral clefts only)</td>
<td>--</td>
<td></td>
<td>--</td>
</tr>
</tbody>
</table>

* data from published report used for meta-analysis

**Addendum:** Further data from the study by Peelen et al (40) were published by Fransman et al (71) in January 2007, while this systematic review and draft recommendations were undergoing external review by practitioners in Ontario. The new report of the Dutch study, focuses on reproductive outcomes in nurses exposed to cytotoxic drugs and provides a clearer description of study methods and results than the original paper, which was not published in a peer-reviewed journal. The 2007 paper also reports outcomes separately for four levels of exposure.
to cytotoxic drugs: “background” (nurses who did not work with cytotoxic drugs but worked in departments where cytotoxic drugs were frequently handled), “low” (exposed to ≤0.20 μg/week), “medium” (exposed to 0.21-0.74 μg/week), and “high” (exposed to >0.74 μg/week). Exposure levels were estimated using frequencies of key nursing tasks and glove wearing reported on the survey and dermal exposure levels from another study. There were a total of 1259 pregnancies among 1519 nurses surveyed. The new report includes data from 425 pregnancies between 1990 and 1997 among nurses exposed to cytotoxics, 279 among those with background exposure and 663 among those without exposure.

**Outcomes**

Outcome data on risks of adverse effects among nursing and pharmacy staff are presented in Table 2 below and the text that follows.
### Table 2. Odds ratios for adverse events.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Total # of events</th>
<th>Odds Ratio* (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gunnarsdottir (37)</td>
<td>case-control</td>
<td>7</td>
<td>1.22 (0.41 to 3.62)</td>
</tr>
<tr>
<td>Skov et al (33)</td>
<td>comparison to national cancer rates survey</td>
<td>14</td>
<td>1.20 (0.65 to 2.01)</td>
</tr>
<tr>
<td>Martin (70) [unpublished]</td>
<td></td>
<td>332</td>
<td>3.27 (1.11 to 9.58)</td>
</tr>
<tr>
<td><strong>Spontaneous Abortion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skov (33)</td>
<td>retrospective cohort</td>
<td>83</td>
<td>0.74 (0.40 to 1.38)</td>
</tr>
<tr>
<td>Selevan (28)</td>
<td>case-control</td>
<td>124</td>
<td>2.30 (1.21 to 4.39)</td>
</tr>
<tr>
<td>Hemminki (27)</td>
<td>case-control</td>
<td>163</td>
<td>0.8 (CI not reported)</td>
</tr>
<tr>
<td>Peelen (40)</td>
<td>survey</td>
<td>70</td>
<td>1.40 (0.75 to 2.60)</td>
</tr>
<tr>
<td>Stucker (32)</td>
<td>survey</td>
<td>90</td>
<td>1.70 (1.03 to 2.80)</td>
</tr>
<tr>
<td>Valanis (39)</td>
<td>survey</td>
<td>791</td>
<td>1.50 (1.25 to 1.80)</td>
</tr>
<tr>
<td>McAbee (36)</td>
<td>survey</td>
<td>49**</td>
<td>0.67 (0.01 to 5.5)**</td>
</tr>
<tr>
<td>McDonald (31)</td>
<td>survey</td>
<td>13</td>
<td>0.97 (observed/expected)</td>
</tr>
<tr>
<td>Martin (70) - unpublished</td>
<td>survey</td>
<td>530</td>
<td>Odds ratio not reported</td>
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<tr>
<td><strong>Congenital Malformation</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Skov (33)</td>
<td>retrospective cohort</td>
<td>59</td>
<td>1.00 (0.55 to 1.81)</td>
</tr>
<tr>
<td>Lorente (41)</td>
<td>case-control</td>
<td>100</td>
<td>3.35 (0.37 to 3.12)*****</td>
</tr>
<tr>
<td>Hemminki (27)</td>
<td>case-control</td>
<td>38</td>
<td>2.54 (1.17 to 5.49)</td>
</tr>
<tr>
<td>Peelen (40)</td>
<td>survey</td>
<td>35</td>
<td>1.05 (0.45 to 2.42)</td>
</tr>
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<td>survey</td>
<td>18</td>
<td>3.28 (1.28 to 8.38)</td>
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<td>McDonald (30)</td>
<td>survey</td>
<td>8</td>
<td>1.98 (observed/expected)</td>
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<td><strong>Stillbirth</strong></td>
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<td></td>
<td></td>
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<td>Peelen (40)</td>
<td>survey</td>
<td>4</td>
<td>1.20 (0.65 to 2.20)</td>
</tr>
<tr>
<td>Valanis (39)</td>
<td>survey</td>
<td>62</td>
<td>1.10 (0.55 to 2.20)</td>
</tr>
<tr>
<td>McDonald (31)</td>
<td>survey</td>
<td>0</td>
<td>0.48 (observed/expected)</td>
</tr>
</tbody>
</table>

* Lower limit of 95% CI >1.0 indicates an excess of adverse outcomes associated with exposure
** includes stillbirths; *** odds ratio for cleft lip; NR, not reported
Cancer
Limited data were available to address cancer risk in health care workers (Table 2). Only three studies reported on cancer outcomes (33,37,70). Gunnarsdottir et al found seven cases of breast cancer among nurses who specialized in cancer care, but the number exposed to cytotoxic drugs and the length of time since exposure were not clear, making it difficult to assess risk (37). Skov et al reported 14 cancers, including three hematologic cancers, among 794 nurses who were reported by head nurses to have prepared and administered cytotoxic drugs (33). Effect-size estimates had wide confidence intervals for both studies. Skov et al did detect an excess of hematologic cancers among exposed nurses compared to national rates (standardized incidence ratio, 5.37; 95% CI, 1.11 to 15.7), but this result was based on only three cases. Skov noted that two nurses developed leukemia within five years of preparing chemotherapy. In an unpublished study by Martin, 332 members of the ONS reported a diagnosis of cancer on a survey questionnaire completed by 3,627 nurses (70). After adjusting for age, residence and work setting, those who reported handling chemotherapy had a significantly higher probability of cancer than those who had not handled chemotherapy (OR, 3.27; 95% CI, 1.11 to 9.58).

Spontaneous Abortions
Eight published studies (27,28,31-33,36,39,40) and one unpublished study (70) provided evidence on spontaneous abortion rates (Table 1). Data were pooled from five studies (Skov, Selevan, Peelen, Stucker, and Valanis) but not from the other three (McAbee, Hemminki, and Martin).

Three studies (McAbee, Hemminki, Martin) were not included in the meta-analysis (27,36,70). The study by McAbee is different from the others in that it did not present separate results for spontaneous abortions and stillbirths (36). This survey-based study, which included 318 oncology nurses (exposed), 477 non-oncology nurses (controls) and 338 university employees (controls) did not detect a statistically significant association between the exposure to cytotoxic drugs and the composite outcome spontaneous abortion/stillbirth (OR, 0.67; 95% CI, 0.01 to 5.5).

The study by Hemminki et al (27) was also not included in the meta-analysis, because there was some overlap in the study population with the Selevan et al study (28). The two studies were carried out independently, but 189 nurses (56 cases and 133 controls) were included in both (personal e-mail communication with Dr. Marja-Liisa Linbohm, Finnish Institute of Occupational Health; November 28, 2003). The two studies differed from each other in the method used for collecting data on exposure. In the Hemminki study (27), head nurses reported the exposure to cytotoxic drugs, while Selevan et al (28) used self-reported data on exposure. Although there was reasonable agreement between the head nurse reports and self-reports (kappa = 0.66 for cases and 0.52 for controls), selective reporting could not be excluded as a potential source of bias. The studies also used different eligibility criteria for selecting the study population. The Hemminki study was designed primarily to investigate the effects of anaesthetic gases on spontaneous abortion and malformation rates. As a result, subjects were selected from nurses working in departments where cytotoxic-drug use was relatively uncommon. Unlike the Selevan study, Hemminki et al did not find an association between spontaneous abortion and the handling cytotoxic drugs (27). The investigators postulated that the discrepancy between the two studies might be due to differences in exposure levels. The Selevan study was designed specifically to examine the effects of cytotoxic drugs on pregnancy outcomes and focused on nurses employed in hospitals that used significant amounts of these drugs and in departments where cancer chemotherapy was administered (28). It is likely that the level of exposure was higher among nurses working in these departments. Given these considerations, only the Selevan study was included in the meta-analysis on spontaneous abortion conducted in this systematic review.
The abstract and unpublished report by Martin did not report data in a format suitable for inclusion in our meta-analysis (52,70). The full report states that there was no significant difference in spontaneous abortion rate between those who handled chemotherapy and those who did not, but did not report an odds ratio (70).

There was no statistically significant heterogeneity among the five studies that were pooled (P=0.14; $I^2=42\%$) (28,32,33,39,40). Very similar results were obtained from pooling raw data to obtain crude odds ratios (overall OR, 1.45; 95% CI, 1.12 to 1.88) and reported adjusted odds ratios (overall OR, 1.46; 95% CI, 1.11 to 1.92), with both indicating an excess of spontaneous abortions among subjects exposed to cytotoxic drugs. The adjusted odds ratios, which may be more accurately abstracted from published reports than raw numbers of events, are illustrated in Figure 1.

### Table: Summary of Adjusted Odds Ratios for Spontaneous Abortion

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Exposed N</th>
<th>Unexposed N</th>
<th>logOdds Ratio (SE)</th>
<th>Odds Ratio (random)</th>
<th>Weight</th>
<th>Odds Ratio (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skov</td>
<td>281</td>
<td>809</td>
<td>-0.3011 (0.3180)</td>
<td>13.38</td>
<td>0.74</td>
<td>[0.40, 1.38]</td>
</tr>
<tr>
<td>Selevan</td>
<td>46</td>
<td>399</td>
<td>0.8329 (0.3298)</td>
<td>13.11</td>
<td>2.30</td>
<td>[1.21, 4.39]</td>
</tr>
<tr>
<td>Peelen</td>
<td>249</td>
<td>1010</td>
<td>0.3680 (0.3559)</td>
<td>13.06</td>
<td>1.40</td>
<td>[0.79, 2.40]</td>
</tr>
<tr>
<td>Stucker</td>
<td>139</td>
<td>357</td>
<td>0.5366 (0.2564)</td>
<td>13.08</td>
<td>1.75</td>
<td>[1.03, 2.90]</td>
</tr>
<tr>
<td>Valanis</td>
<td>1448</td>
<td>5297</td>
<td>0.4055 (0.0930)</td>
<td>40.48</td>
<td>1.50</td>
<td>[1.25, 1.80]</td>
</tr>
</tbody>
</table>

Total (95% CI): 2163 7872

Test for heterogeneity: Chi² = 6.89, df = 4 (P = 0.14), $I^2 = 41.9\%$
Test for overall effect: Z = 2.71 (P = 0.007)

The crude OR for the study by Peelen et al (40), the only study of exposure after 1985 that reported data on spontaneous abortions, was 1.44 (95% CI, 0.80 to 2.60), compared to a pooled crude OR of 1.45 (95% CI, 1.05 to 2.00) for the four studies that included exposures before 1985.

Investigators used the following sets of variables, some of which might be considered confounders because they could increase risk for the outcomes of interest, to adjust odds ratios:
- age in the study by Skov et al (33);
- exposure to anaesthetic gases and x-rays, previous fetal loss, previous abortion, alcohol consumption, and contraception in the study by Selevan et al (28);
- other relevant occupational exposures such as physical strain and exposure to disinfectants and/or ionising radiation in the study by Peelen at al (40);
- age, pregnancy order, and smoking in the study by Stucker et al (32);
- age, gravidity, smoking, and prior adverse pregnancy outcomes in the study by Valanis et al (39).

Confounders are variables that are related to both exposure (cytotoxics) and outcome (e.g., miscarriage). For example, if nurses working with cytotoxics tended to be older than those who did not and older women tended to have a higher rate of miscarriage, this might bias the estimate of the risk for miscarriage associated with cytotoxic exposure.

In addition to nurses and nurse’s aids, the large study by Valanis et al included pharmacists and pharmacy assistants, as well as the spouses of male nurses and pharmacy staff (39).

**Addendum:** The overall unadjusted odds ratio for spontaneous abortion in the recent publication of the Dutch study, originally reported by Peelen et al (40), was 1.01 (95% CI, 0.93 to 1.10) (71). This result appears to be based on the same survey as the original paper, but...
includes data from a much larger number of nurses. The number of spontaneous abortions was not reported. Unadjusted (and adjusted) odds ratios for different exposure levels were: 1.2 (1.0) for background exposure, 1.3 (1.2) for low exposure, 1.0 (0.8) for medium exposure, and 1.3 (1.2) for high exposure.

**Congenital Malformation**

Six studies reported on congenital malformations (Table 2). Four of these (Skov, Peelen, Hemminki, McAbee) provided data suitable for statistical pooling (27,33,40). Pooled raw data from these four studies are presented in Figure 2. The 95% CI for the pooled OR contains 1.0 (OR, 1.64; 95% CI, 0.91 to 2.94), indicating no statistically significant incremental risk. Although the magnitude of the observed odds ratio is similar to that for spontaneous abortion, the confidence interval is larger and includes 1.0, which may be due, in part, to the smaller number of events available for analysis.

There was heterogeneity among the four studies (p=0.07, I²=59.8%), but no obvious association between observed effect size and study design. There were, however, differences among studies that may have contributed to heterogeneity. The stated objective of the study by Skov et al was to evaluate the risks among nurses handling cytotoxic drugs (33). Peelen et al and McAbee et al also presented malformation data for exposure groups consisting solely of oncology nurses (36,40). Hemminki et al examined the adverse reproductive outcomes associated with a number of occupational exposures (including anaesthetic gases, cytotoxic drugs, sterilizing agents, shift work, and radiation) in nurses working in a variety of clinical settings (27). Only the study by Peelen et al, which did not detect an association between work on an oncology ward and malformations, was restricted to exposure after 1985 (40).

**Figure 2: Odds ratio for congenital malformation (raw data pooled).**

Two studies (McDonald, Lorente) did not provide sufficient data for pooling (30,41). In a study of exposure before 1985, McDonald et al reported twice the expected rate of congenital defects among the children of 152 physicians and nurses who had administered cytotoxic drugs during the first month of pregnancy, compared to working women in the same community (p=0.05) (30). In a study conducted after 1985, Lorente et al found that 3% of 100 working women who gave birth to children with oral clefts had workplace exposure to cytotoxic drugs during the first trimester of pregnancy, compared to 1% of 751 working women whose children did not have these abnormalities (41). The ORs were 3.35 for cleft lip with or without cleft palate (95% CI, 0.37 to 3.12) and 11.2 for cleft palate only (95% CI, 1.98 to 63.7).

**Addendum:** The overall unadjusted odds ratio for congenital malformation in the recent publication of the Dutch study, originally reported by Peelen et al (40), was 0.97 (95% CI, 0.86 to 1.09) (71). This result appears to be based on the same survey as the original paper, but
includes data from a much larger number of nurses. The number of congenital malformations was not reported. Unadjusted (and adjusted) odds ratios for different exposure levels were: 1.9 (1.9) for background exposure, 1.3 (1.5) for low exposure, 1.1 (1.2) for medium exposure, and 0.9 (0.9) for high exposure.

**Stillbirths**

Only three studies provided evidence on stillbirths (31,39,40). Neither the large study by Valanis et al (OR, 1.1; 95% CI, 0.5 to 2.2) nor the more recent but smaller study by Peelen et al (OR, 1.2; 95% CI, 0.6 to 2.2) detected an association between occupational exposure to cytotoxic drugs and stillbirths (39,40). In the study by McDonald et al, there were no stillbirths among 63 nurses and physicians who were involved in the administration of chemotherapy (31).

**Addendum:** The overall unadjusted odds ratio for stillbirth in the recent publication of the Dutch study, originally reported by Peelen et al (40), was 1.20 (95% CI, 0.98 to 1.47) (71). This result appears to be based on the same survey as the original paper, but includes data from a much larger number of nurses. The number of stillbirths was not reported. Unadjusted (and adjusted) odds ratios for different exposure levels were: 1.0 (0.9) for background exposure, 3.8 (3.3) for low exposure, 3.9 (4.3) for medium exposure, and 2.1 (1.8) for high exposure.

**Ectopic Pregnancy**

Three studies reported ectopic pregnancy rates (33,35,38). As part of a survey to study the risks associated with working in operating theatres, Saurel-Cubizolles et al observed that 7% of hospital staff exposed to cytotoxic drugs had an ectopic pregnancy versus 1% of unexposed staff (OR, 10.0; 95% CI, 2.1 to 56.2) (35). The same group of investigators then carried out a case-control study to confirm these results, which were based on only six ectopic pregnancies in each group. The second study found that 18% of 140 cases and 20% of 279 controls had been exposed to cytotoxic drugs, leading Bouyer et al to conclude that there was no association between exposure and ectopic pregnancy (38). In a retrospective cohort study, Skov et al also failed to detect a difference in ectopic pregnancy rates between an exposed (1.8% of 281 pregnancies) and an unexposed group (1.7% of 809 pregnancies) (33).

**Learning Disabilities**

The only information available on learning disabilities among the children of health care workers exposed to cytotoxics appeared in an unpublished report of a retrospective survey by Martin (70). After adjustment for sex of offspring, gestation, premature birth and anoxia, children whose mothers rarely used gloves when handling chemotherapy were more likely to have learning disabilities that those who usually wore gloves (OR, 2.56; 95% CI, 1.75 to 3.72).

**Acute Toxic Effects**

Only two studies examined the acute effects of handling cytotoxic drugs (29,34). Both assessed exposure before 1985 and suffered from low participation rates. Interpretation was hampered by a failure to adjust the univariate analysis for multiple comparisons and the inadequate reporting of risk ratios. In 1987, Valanis et al compared 134 exposed nurses with 43 not exposed and reported that “significantly more exposed than control nurses reported” symptoms. In a later study of 533 pharmacists and pharmacy technicians, the same investigators did not detect increased symptoms in the exposed group compared to the control but did detect more symptoms among exposed subjects who had skin contact with cytotoxic drugs. Symptoms reported in these two studies included nausea and vomiting, dizziness, headache, eye irritation, chronic cough, sore throat, and viral/other infections.
Closed Systems
Although seven studies of closed systems for handling hazardous drugs were located, they provided little evidence to inform a decision about the effectiveness of this technology to reduce exposure among health care workers preparing or administering cytotoxic drugs (53-59). All studies measured surface contamination, and two also measured cytotoxics in the urine of pharmacy staff and nurses. All of the studies were descriptive in nature. Although five studies compared open and closed systems, they were not designed to evaluate differences between groups. None of the studies were randomized and none included statistical analysis of results. Nevertheless, the observed results suggest the potential for contamination to be reduced with closed systems and point to a need to test this hypothesis in well-designed studies.

Guidelines from Other Groups
Eight guidelines on safe handling of hazardous drugs have been published since 2003 (60-67). They were produced for use in the United States, Australia, the United Kingdom, and Germany. The most recent guideline, which was published in June 2006, was developed by the American Society of Hospital Pharmacists (ASHP) (60). None of the guidelines were evidence-based (i.e., based on a systematic review of the evidence), but the ASHP guideline does provide narrative summaries the evidence related to each recommendation. Because none of the guidelines were evidence-based (i.e., included a systematic review of the literature, with a full description of the literature search and eligibility criteria for the review), we did not undertake a formal quality assessment of the guidelines (69).

The guidelines by the American Society of Health-System Pharmacists (ASHSP) and an Australian guideline by WorkSafe Victoria covered all of the areas of interest to the Expert Panel and the others included recommendations related to most of these issues (Table 3). The relevant recommendations and related text from each guideline are summarized in Appendix A.
### Table 3. Topics included in each guideline.

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Policies</th>
<th>Collaboration/consultation</th>
<th>PPE</th>
<th>Ventilated cabinets</th>
<th>Closed systems</th>
<th>Syringes &amp; IV sets</th>
<th>Transport</th>
<th>Education/training</th>
<th>Pregnancy</th>
<th>Medical surveillance</th>
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</tbody>
</table>

- = This guideline did not include recommendations directly related to this topic.
X = There are recommendations related to this topic in the guideline – see Appendix A.

PPE, personal protective equipment.

ASHP, American Society of Health-System Pharmacists
SHPA, Society of Hospital Pharmacists of Australia
NIOSH, National Institute for Occupational Safety and Health (US)
ONS, Oncology Nursing Society (US)
HSE, Health & Safety Executive (UK)
Marc, project of Mayne Pharma (UK)
WorkSafe, WorkSafe Victoria (Australia)
DGOP, German Society of Oncology Pharmacy
DISCUSSION
Evidence to address the questions posed by the expert panel was limited in terms of quantity, quality, and generalizability. In addition to the evidence on adverse effects and closed systems found by systematic reviews, the panel considered recent guidelines from other developers, current practices in Ontario, ethical issues, and available methods for risk assessment and medical surveillance.

Adverse Effects
Very little evidence was available to address questions 1 (cancer) and 3 (acute toxic effects). The task force was aware that it is important, in situations like this, to differentiate between no evidence of risk and insufficient evidence to determine risk. Although 14 studies provided evidence on reproductive outcomes from comparisons of health care workers exposed to cytotoxic agents and those who were not exposed, these were all retrospective. Pooled analysis of the data available indicates an excess of spontaneous abortions among health care workers exposed to cytotoxic drugs. Heterogeneity among the studies that examined the association between the exposure to cytotoxics and congenital malformations makes interpretation difficult, but no statistically significant excess of malformations was detected. There was limited evidence to determine an association between exposure to cytotoxic drugs and ectopic pregnancy or stillbirth.

Many studies ascertained exposures or outcomes from indirect and, therefore, potentially biased sources. There were few attempts to connect differences in handling practices and exposure levels to outcome. The most important impediment to generalizing the evidence from the available literature to current practice in Ontario arises from the fact that the majority of subjects studied were exposed to cytotoxic agents before 1985. Numerous changes in practice and procedure have taken place over the last 20 years with regard to safe handling of cytotoxic agents. It is also important to note that epidemiological studies only established an association between exposure and outcome variables and not causation. For causation to be established, several conditions, such as a dose response effect and consistency of association among similar studies, must be demonstrated.

The Cytotoxic Safe Handling Task Force interpreted the evidence found by the systematic review from a number of different perspectives. They agreed on an overall conclusion that there is insufficient evidence to determine if health care workers who work with cytotoxic drugs are or are not at an increased risk for cancer, teratogenic births, stillbirths or acute toxic effects, but there is evidence that they may be at increased risk for miscarriage. However, the group was unable to reach consensus as to how significant this increased risk might be. All perspectives considered whether the available evidence allowed for the determination of the direction and magnitude of risk and how much risk was acceptable. These discussions were inevitably coloured by consideration of how much expenditure was reasonable to minimize risk. In addition to a professional perspective (health care worker, policy analyst, health care administrator, or occupational safety manager), interpretation of the evidence may be influenced by gender.

Information on the potential impact of occupational exposure to cytotoxics was provided by one member of the Cytotoxic Safe Handling Task Force (GD) who used the results of this meta-analysis, available epidemiological data (42), and an estimate of the number of female health care workers exposed to cytotoxic agents in Ontario in 2004 (n=897) to calculate that the potential number of additional miscarriages per year secondary to cytotoxic exposure would be approximately 1.3 (95% CI, 0.32 to 2.66) (68).

Although statistically significant, the observed increase in risk for spontaneous abortion was relatively small (OR, 1.46; 95% CI, 1.11 to 1.92). For the reasons outlined above, the OR may well be a biased estimate, and the real association between occupational exposure and risk could be smaller or larger. This presents difficulties for health care workers who want to
assess their personal risk and for policy makers who want to assess interventions for minimizing risk. Nurses and pharmacists providing cancer care may draw a parallel between exposure to low levels of cytotoxics and exposure to low levels of radiation (43,44). Low-level radiation exposure has not been linked to specific ill effects. Rather, the risk of low-level exposure is extrapolated from the known risks of high-dose exposure. With radiation, the approach used is “to reduce the occupational exposure to levels as low as reasonably achievable (ALARA) by means of good radiation protection planning and practice, as well as by management commitment to policies that foster vigilance against any departure from good practice...”(45,46). Health care workers may argue that knowing that patients treated with cytotoxic agents develop second cancers, there is no reason to believe that they would not also be at risk of cancer. While there is almost certainly a dose-response relationship between chemotherapy and risk, the magnitude and nature of the relationship is unknown. The risk to workers ingesting low doses of cytotoxics, however, is likely to be correspondingly small.

The occupational health and safety perspective may compare the health care setting with industrial settings, where worker exposure to known carcinogens is closely regulated (47). For the health care sector, the Occupational Safety and Health Administration (OSHA) guidelines state that the “preparation, administration and disposal of hazardous drugs may expose pharmacists, nurses, physicians and other health care workers to potentially significant workplace levels of these chemicals” and give advice to “minimize exposure and reduce occupational risks in handling antineoplastic agents” (48). In Ontario, under the Occupational Health and Safety Act and O.Reg. 67/93 sections 93(1)(2)(3), health care facilities are required to have programs to protect workers from exposure to antineoplastic drugs. The ALARA approach has traditionally been taken in order to protect health care workers from exposure to cytotoxic agents.

The policy analyst considers the relative magnitude of the risk compared with other known risks. Most individuals attempt to identify the large risks among all the risks experienced in their everyday lives and to respond appropriately. Extending this argument, governments and health policy decision makers also face the same challenges when confronting the many risks to public and employee health. Decision makers must be aware of the dangers associated with misinterpreting the magnitude of the various risks within the public health debate. Underestimating a true and substantial risk can have major consequences for human health. However, overestimating the importance of a small and perhaps unproven risk can also have major negative consequences to public health because it may redirect limited resources away from a larger risk that has been conclusively demonstrated through rigorous scientific techniques.

Managers of health care facilities must deal with strategies to communicate with staff at risk and to introduce policies or technologies to reduce risk. The simple dissemination of an odds ratio or relative risk to the target population is usually not enough. Several years of research in risk perception have suggested that people are typically more afraid of relatively small risks and less afraid of those that could potentially cause them more harm (49,50). As a result, hospital administrators must develop successful risk communication strategies when disseminating the results of such studies to their staff. Unfortunately, effective risk communication remains a neglected tool in public health policy. In addition to using biological safety cabinets and following existing guidelines related to personal protective equipment and education, strategies to reduce risk range from reassigning female staff to less hazardous duties to expensive closed systems for handling cytotoxics drugs. A review of the feasibility and potential effectiveness of each intervention considered should be conducted before adopting it.

**Closed Systems**
Appropriately designed studies are needed to evaluate the effectiveness of closed systems for handling hazardous drugs.
Ethics
In the absence of strong evidence, the expert panel used the following ethical framework invoking the following principles, which emerged from review of the research on risks associated with handling cytotoxics and existing guidelines on safe handling, to inform their recommendations:

- Recognition that there is a duty to provide care, even if it includes risk, and that trained supported professionals are the best people to provide this care.
- Appropriate recognition and support for those who take risks for others.
- As far as reasonably possible, mitigation of risks for those who take risks to help others.
- Employer support of workers and recognition that risks must be attended to and mitigated, as far as possible.
- Alertness to the need for extra caution and safety measures, and responsiveness to the reported needs and concerns of staff and knowledgeable others.
- Access to, and appropriate use of, safety measures and equipment.
- Timely implementation of safety improvements and encouragement of research that will improve safety measures.
- Equal access to care when harm has occurred.
- Equal opportunity to avoid risks for reasonable situations (e.g., pregnancy).
- Availability of ongoing education and updates.

These principles were not intended to directly address the systematic review questions, but to provide a framework for formulating recommendations.

Guidelines
None of the recent guidelines found were based on a systematic review of the evidence or developed for use in Canada. Nevertheless, they provided a framework, along with the ethical principles described above, for making expert-opinion-based recommendations for use in Ontario. In the absence of strong evidence on the potential harms from handling cytotoxic drugs and mechanisms to reduce exposure, review of the guidelines from other groups helped the expert panel to reach consensus on the structure and content of their recommendations.

ONGOING TRIALS
Expert panel members are not aware of relevant ongoing studies on topics such as adverse events, closed systems, or PPE.

CONCLUSIONS
- There is insufficient evidence to determine if health care workers who work with cytotoxic drugs are at an increased risk of cancer or acute toxic effects. Female health care workers may, however, be at increased risk for miscarriage. The association between the exposure to cytotoxics and congenital malformation or stillbirth is unclear.
- There is insufficient evidence to determine if closed systems do or do not protect health care workers from exposure to cytotoxic drugs during preparation and administration.
- Recommendations for the safe handling of cytotoxics are needed for use in Ontario and the rest of Canada.

CONFLICT OF INTEREST
The members of the Cytotoxic Safe Handling Task Force declared no potential or actual conflicts of interest.
JOURNAL REFERENCES
A draft of the systematic review on adverse events from cytotoxics among health care workers was published in 2005 by one of the Working Group members (GD), with a personal version of the meta-analysis, interpretation, and conclusions (68).

The following recommendations article (© 2009 American Society of Clinical Oncology) has been published by the Journal of Oncology Practice (http://jop.ascopubs.org):


ACKNOWLEDGEMENTS
The Cytotoxic Safe Handling Working Group, which was chaired by Susan Poirier and included George Dranitsaris, Mary Johnston, Julie Makarski, Tim Savage, and Trudi Schueller, performed the original systematic review and meta-analysis on adverse effects, with assistance from Steven Hanna, of the Dept. Clinical Epidemiology and Biostatistics and CanChild Centre for Childhood Disability Research at McMaster University, (statistical advice and assistance with the meta-analysis) and Christina Woodward, Library & Information Services at the London Regional Cancer Centre (preliminary PubMed literature search).

For a complete list of the Cytotoxic Safe Handling Expert Panel members, please visit the CCO Web site at http://www.cancercare.on.ca/

Funding
The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at: Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775
REFERENCES

18. Guidelines for the handling and disposal of hazardous pharmaceuticals (including cytotoxic drugs). Ottawa (Canada): Canadian Society of Hospital Pharmacists; 1993.


## Appendix A. Existing guidelines on safe handling of cytotoxic chemotherapy – summary of recommendations.

### Table 1. Policies & procedures.

<table>
<thead>
<tr>
<th>Producer, date, country</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>ASHP, 2006 US</td>
<td>Policies and procedures for the safe handling of hazardous drugs must be in place for all situations in which these drugs are in use throughout a facility… <em>(page 1175)</em></td>
</tr>
<tr>
<td>SHPA, 2005 Australia</td>
<td>Precise operating and safety procedures for the handling of cytotoxic drugs and equipment must be established, documented and regularly reviewed. <em>(page 44)</em></td>
</tr>
<tr>
<td>NIOSH, 2004 US</td>
<td>Implement a program for safely handling hazardous drugs at work and review this program annually on the basis of the workplace evaluation. <em>(page 11)</em></td>
</tr>
<tr>
<td>ONS, 2003 US</td>
<td>No recommendations</td>
</tr>
<tr>
<td>HSE, 2003 UK</td>
<td>…as an employer you have a legal duty to protect the health of your employees … You must have a health and safety policy… <em>(page 2)</em></td>
</tr>
<tr>
<td>Marc, 2003-2005 UK</td>
<td>No recommendations</td>
</tr>
<tr>
<td>WorkSafe, 2003 Australia</td>
<td>The first priority in protecting the health of employees is to eliminate or reduce the risks to health so far as is practicable. This may be implemented through: • establishment of written policies and protocols to ensure the safe handling of cytotoxic drugs… <em>(page 4)</em>.</td>
</tr>
<tr>
<td>DGOP, 2003 Germany</td>
<td>Written working rules must be prepared for each particular workplace. <em>(page 11)</em> the working rules must contain: • description of the workplace / activity • name of hazardous substance • designation of the hazardous substance at the workplace • hazards for persons and the environment • protective measures and rules of behaviour • action in case of danger • first aid emergency telephone number / poisons centre telephone number • organisational rules at the workplace • restrictions • proper disposal • date of posting, signature of the employee. <em>(page 15)</em></td>
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Table 2. Collaboration/consultation in developing policies & procedures.

<table>
<thead>
<tr>
<th>Producer, date, country</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>ASHP, 2006 US</td>
<td>This program must be a collaborative effort with input from all affected departments, such as pharmacy, nursing, medical staff, housekeeping, transportation, maintenance, employee health, risk management, industrial hygiene, clinical laboratories, and safety officers. (page 1175).</td>
</tr>
<tr>
<td>SHPA, 2005 Australia</td>
<td>No recommendations</td>
</tr>
<tr>
<td>NIOSH, 2004 US</td>
<td>Seek ongoing input from workers who handle hazardous drugs and from other potentially exposed workers regarding the quality and effectiveness of the prevention program. (page 11)</td>
</tr>
<tr>
<td>ONS, 2003 US</td>
<td>No recommendations</td>
</tr>
<tr>
<td>HSE, 2003, UK</td>
<td>You must have a health and safety policy and should consult employees and safety representatives on the risks identified in the workplace and the measures needed to prevent or control these risks. (page 2)</td>
</tr>
<tr>
<td>Marc, 2003-2005 UK</td>
<td>No recommendations</td>
</tr>
</tbody>
</table>
| WorkSafe, 2003 Australia | Employers are required to consult with the relevant health and safety representative(s) when assessing and controlling risks arising from the handling of cytotoxic drugs. Consultation directly with employees will draw on their experience and knowledge. Consultation should occur:  
  • when identifying cytotoxic drugs  
  • during the risk assessment process  
  • when determining which control strategies should be applied to eliminate or reduce risks associated with the handling of cytotoxic drugs, and  
  • when reviewing the effectiveness of control measures. (page 5) |
| DGOP, 2003 Germany       | No recommendations |
Table 3. Personal protective equipment.

<table>
<thead>
<tr>
<th>Producer, date, country</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>ASHP, 2006 US</td>
<td><strong>Gloves</strong></td>
</tr>
</tbody>
</table>
|                         | Gloves must be worn at all times when handling drug packaging, cartons, and drug vials… (*page 1178*).  
|                         | During compounding in a Class II BSC, gloves and gowns are required… (*page 1178*).  
|                         | See Appendix C of the ASHP guideline for detailed recommendations.  
|                         | **Gowns**      |
|                         | Personal protective gowns are recommended during the handling of hazardous drug preparations… (*page 1179*).  
|                         | See Appendix D of the ASHP guideline for detailed recommendations.  
|                         | **Other**     |
|                         | Eye and face protection should be used whenever there is a possibility of exposure from splashing or uncontrolled aerosolization of hazardous drugs… a face shield, rather than safety glasses or goggles, is recommended… (*page 1180*).  
|                         | Similar circumstances also warrant the use of a respirator. (*page 1180*)  
|                         | Shoe and hair coverings should be worn during the sterile compounding process… (*page 1180*).  
| SHPA, 2005 Australia    | Protective clothing must be worn by all personnel preparing cytotoxic drugs, cleaning cytotoxic preparation facilities, or cleaning cytotoxic spills… Coveralls are preferable to gowns. Boots or overshoes, head covering, masks and gloves are also compulsory. Safety glasses are strongly recommended for wearers of contact lenses but are otherwise optional.  
|                         | Specific recommendations are provided on page 46 of the SHPA guideline.  
| NIOSH, 2004 US          | Wear PPE (including double gloves and protective gowns) while reconstituting and admixing drugs…(*page 13*). Detailed recommendations given in NIOSH report.  
| ONS, 2003 US            | **Gloves**     |
|                         | Gloves should be worn during all hazardous drug-handling activities (*page 17*). Detailed recommendations given on page 18 of the ONS guideline.  
|                         | **Gowns**      |
|                         | Gowns that provide adequate protection from hazardous drugs are disposable, made of lint-free, low-permeability fabric. They should have a solid front and knot or elastic cuffs. (*page 18*)  

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### Eye and Face Protection
A plastic face shield should be worn in situations where eye, mouth, or nasal splashing or aerosolization is possible... *(page 19)*.

### HSE, 2003 UK

**Gloves**
Where contact with cytotoxic drugs is possible, and methods of control other than protective gloves are not reasonably practicable, protective gloves must be provided for employees. *(page 3)*

**Gowns**
Protective clothing such as gowns and aprons can help prevent contamination of clothes and subsequently, the skin. The choice of material is important as their absorptive properties may vary. Standard laboratory coats are unsuitable as cytotoxic drug solutions may soak through them. Consider the comfort of staff wearing protective clothing. *(page 3)*

**Eye and Face Protection**
Eye and face protection is relevant, particularly where cytotoxic drugs are being handled outside an enclosed system and there is a risk of splashing. A number of options are available including a face shield or visor, goggles and safety spectacles. *(page 3)*

**Respiratory protection**
...if it is not reasonably practicable to control exposure using total enclosure/local exhaust ventilation, you will need to consider respiratory protective equipment (RPE) if exposure to powders or aerosols is possible. Surgical masks will not protect against the inhalation of fine dust or aerosols. *(page 3)*

### Marc, 2003-2005 UK

**Gloves**
Wear them at all times when contact with cytotoxic drugs is possible ... There is evidence that nitrile and latex gloves offer good protection to the operator from cytotoxic contamination.

**Gowns**
- Saranex / Tyvek laminated demonstrated to be most effective against 15 antineoplastic drugs.
- Laboratory coats are porous – do not use them
- The following materials have been shown to offer protection in order of effectiveness:...

**Eye and facial protection**
Eye protection should fully enclose the eyes, meeting British Standard EN 166.

**Respiratory protection**
- Surgical masks do not offer protection against aerosols
- Appropriate respiratory protection is required wherever total enclosure / local exhaust ventilation cannot control exposure
- When solid or liquid particles may be a risk, an FFP2 or FFP3 filtered face piece respirator should be used
<table>
<thead>
<tr>
<th>Source</th>
<th>Text</th>
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<tbody>
<tr>
<td><strong>WorkSafe, 2003 Australia</strong></td>
<td>• For cytotoxics in powdered form, a biological safety cabinet is recommended. Where a biological safety cabinet is not available, a temporary measure may be the use of a THP3 powered respirator. (Handling: Selection and use of personal protective equipment…)</td>
</tr>
</tbody>
</table>
|                 | The following personal protective equipment should be provided, in conjunction with other control measures, to personnel who prepare cytotoxic drugs:  
|                 | • coverall or gown  
|                 | • head covering  
|                 | • closed footwear and overshoes  
|                 | • protective gloves – long enough to cover the elasticised cuffs of gowns or coveralls  
|                 | • protective eyewear  
|                 | • respiratory protective device (where an inhalation risk exists, for example, a large cytotoxic drug spill).  
|                 | For further information on personal protective equipment, refer to Appendix 9 – Personal Protective Equipment. (page 21)  
|                 | Using the following personal protective equipment is recommended during the administration of cytotoxic drugs (where there is an assessed exposure risk):  
|                 | • gown  
|                 | • closed footwear  
|                 | • protective gloves  
|                 | • protective eyewear (where there is a risk of eye splash)  
|                 | • respiratory protective device (where an inhalation risk exists, for example, after a large cytotoxic drug spill). (page 23)  
| **DGOP, 2003 Germany** | The directives, regulations and guidelines currently in force … stipulate the use of protective equipment by every employee of a cytostatics department deriving from evaluation of the hazards involved...In the case of cytostatics preparation, this also applies to those employees who put together the finished drugs for the preparation and package the ready-to-administer solutions. Personal protective equipment includes:  
|                 | • overall or protective gown (possibly in combination with cuffs)  
|                 | • protective gloves  
|                 | and in special cases  
|                 | • respiratory protective equipment  
|                 | • protective eyewear  
|                 | • overshoes. (page 58)  
|                 | Very detailed descriptions appear on pages 63-86 of the DGOP guideline. |
Table 4. Ventilated cabinets.

<table>
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<tr>
<th>Producer, date, country</th>
<th>Recommendation</th>
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| ASHP, 2006 US          | When asepsis is not required, a Class I BSC or a containment isolator may be used to handle hazardous drugs. When sterile hazardous drugs are being compounded, a Class II or Class III BSC or an isolator intended for asepsis and containment is required. *(page 1176)*  
*See Appendices A, B and E of the ASHP guideline for detailed recommendations.* |
| SHPA, 2005 Australia   | Cytotoxic drugs may be prepared in wither a CDSC [cytotoxic drug safety cabinet] or in a pharmaceutical isolator cabinet.  
*Detailed recommendations are given on standards for CDSCs and isolator cabinets, maintenance, and cleaning (pages 44-45)* |
| NIOSH, 2004 US         | Mix, prepare, and otherwise manipulate, count, crush, compound powders, or pour liquid hazardous drugs inside a ventilated cabinet designed to prevent hazardous drugs from being released into the work environment.  
When aseptic technique is required, use one of the following ventilated cabinets:  
— Class II BSC (Type B2 is preferred, but Types A2 and B1 are allowed under certain conditions)  
— Class III BSC  
— Isolators intended for asepsis and containment (aseptic containment isolators)  
Use a high-efficiency particulate air filter (HEPA filter) for the exhaust from these controls, and where feasible, exhaust 100% of the filtered air to the outside. *(page 15)* |
<p>| ONS, 2003 US           | A class II type B or class III vertical flow BSC is necessary to minimize exposure of personnel to cytotoxic agents during preparation and mixing of the agents. <em>(page 15).</em> |
| HSE, 2003 UK           | Aseptic preparation of cytotoxic drugs can be carried out using a suitable safety cabinet or a pharmaceutical isolator. There is a distinction between measures designed to protect sterility of the product and those designed to provide operator protection. HSE and the Medicines Control Agency (now known as the Medicines and Healthcare Products Regulatory Agency) have jointly produced guidance on factors to consider when selecting a negative or positive pressure isolator for aseptic reconstitution of drugs <em>(page 3).</em> |</p>
<table>
<thead>
<tr>
<th>Reference</th>
<th>Description</th>
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<tbody>
<tr>
<td>Marc, 2003-2005 UK</td>
<td>Preparation is most appropriately undertaken … using a negative pressure pharmaceutical isolator with externally ducted exhaust filters. If a pharmaceutical isolator is not available, then a suitably modified Class 2 Microbiological Safety cabinet may be used. (Handling: Cytotoxic drug preparation: facilities and good practice)</td>
</tr>
<tr>
<td>WorkSafe, 2003 Australia</td>
<td>Engineering controls are plant or processes that reduce the generation of substance, suppress or contain substances, or limit the area of contamination in the event of spills and leaks. For example: • install ventilation and air-filtering systems such as laminar-flow cytotoxic drug safety cabinets (page 11)</td>
</tr>
<tr>
<td>DGOP, 2003 Germany</td>
<td>A cytostatics workbench of type H must be used, type tested in accordance with DIN12980 as laminar air flow (LAF). Cytostatics workbenches with an additional HEPA cassette filter stage beneath the work surface are to be preferred. An exhaust air system should be installed as an additional safety measure. (page 48)</td>
</tr>
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Table 5. Closed systems

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<tr>
<th>Producer, date, country</th>
<th>Recommendation</th>
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| ASHP, 2006 US           | Several studies have shown reduction in environmental contamination with marker hazardous drugs during both compounding and administration when comparing standard technique for handling hazardous drugs to use of PhaSeal. It should be noted, however, that PhaSeal components cannot be used to compound all hazardous drugs. (page 1178)  
  
  As other products become available, they should meet the definition of closed-system drug-transfer devices established by NIOSH and should be required to demonstrate their effectiveness in independent studies. (page 1178)  
  
  Closed-system drug-transfer devices (or any other ancillary devices) are not a substitute for using a ventilated cabinet. (page 1178) |
| SHPA, 2005 Australia    | No recommendations. |
| NIOSH, 2004 US          | Consider using devices such as closed-system transfer devices... when transferring hazardous drugs from primary packaging (such as vials) to dosing equipment (such as infusion bags, bottles, or pumps). (page 13)  
  
  Remember that a closed-system transfer device is not an acceptable substitute for a ventilated cabinet and should be used only within a ventilated cabinet.  
  
  Use appropriate PPE and work practices even when you are using a closed system. (page 14) |
| ONS, 2003 US            | When a closed system (such as PhaSeal) is used properly, it may reduce the release of hazardous drugs into the environment when withdrawing them from vials.  
  
  ...using a closed system eliminates the exposure risk associated with spiking and priming tubing. (page 22) |
| HSE, 2003 UK            | Measures to control exposure should be applied in the following order:  
  • use totally enclosed systems as the first choice for controlling exposure to carcinogens, unless this is not reasonably practicable;… (page 2)  
  
  Totally enclosed systems should be used to control exposure to carcinogenic compounds. (page 3) |
| Marc, 2003-2005 UK      | These guidelines come from the manufacturer of the ONCO-TAILN vial system.  
  A closed system (OncoVial) has been developed for the preparation, administration and disposal of parenteral drugs. The system is designed to prevent leakage of drug into the environment thus protecting health care workers from potential exposure. |
<table>
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<tr>
<th>Source</th>
<th>Information</th>
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</thead>
<tbody>
<tr>
<td>WorkSafe, 2003 Australia</td>
<td>Equipment used for preparing drugs should incorporate a closed system, where possible (page 20)</td>
</tr>
</tbody>
</table>
| DGOP, 2003 Germany             | The preparation of cytostatics requires the following technical equipment: … 
  • PhaSeal®, Securmix® (page 87) |

Such devices may have a role in minimising staff exposure, however, it cannot be recommended that they replace the role undertaken by trained pharmacy staff using a Class II Type Microbiological Safety Cabinet or Pharmaceutical isolator sited in an appropriate environment. (Handling: Cytotoxic handling and containment in preparation areas)
Table 6. Syringes & IV sets.

<table>
<thead>
<tr>
<th>Producer, date, country</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>ASHP, 2006 US</td>
<td>Luer-Lok syringes and connections must be used whenever possible for manipulating hazardous drugs, as they are less likely to separate during compounding. <em>(page 1180)</em> Use needleless systems whenever possible. <em>(Appendix G)</em></td>
</tr>
<tr>
<td>SHPA, 2005 Australia</td>
<td>Luer lock syringes and fittings must be used in the preparation and administration of cytotoxic drugs… All cytotoxic drugs supplied as pre-filled syringes must have luer lock needleless closures attached. <em>(page 47)</em></td>
</tr>
<tr>
<td>NIOSH, 2004 US</td>
<td>Consider using devices such as … needleless systems when transferring hazardous drugs from primary packaging (such as vials) to dosing equipment (such as infusion bags, bottles, or pumps). <em>(page 13)</em></td>
</tr>
<tr>
<td>ONS, 2003 US</td>
<td>Use syringes with Luer lock connections…<em>(page 21).</em></td>
</tr>
<tr>
<td>HSE, 2003 UK</td>
<td><em>No recommendations</em></td>
</tr>
<tr>
<td>Marc, 2003-2005 UK</td>
<td><em>No recommendations</em></td>
</tr>
<tr>
<td>WorkSafe, 2003 Australia</td>
<td>Drug preparation equipment … Specific methods of control include: • use of Luer-lock syringes and fittings to keep connections together <em>(page 20)</em> The use of the following equipment is recommended to reduce risks: • needleless administration system <em>(page 22)</em></td>
</tr>
<tr>
<td>DGOP, 2003 Germany</td>
<td>The standards for syringes used in the preparation of cytostatics are: … Luer lock connection. <em>(page 89)</em></td>
</tr>
</tbody>
</table>
### Table 7. Transport and labelling.

<table>
<thead>
<tr>
<th>Producer, date, country</th>
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</thead>
<tbody>
<tr>
<td>ASHP, 2006 US</td>
<td>Drugs that have been identified as requiring safe handling precautions should be clearly labeled at all times during their transport and use (page 1175). The packaging (cartons, vials, ampules) of hazardous drugs should be properly labeled by the manufacturer or distributor with a distinctive identifier that notifies personnel receiving them to wear appropriate personal protective equipment (PPE) during their handling. Policies and procedures must be in place for handling damaged cartons or containers of hazardous drugs. (page 1175) Hazardous drug packages must be placed in sealed containers and labelled with a unique identifier... (page 1175).</td>
</tr>
<tr>
<td>SHPA, 2005 Australia</td>
<td>Cytotoxic drugs must be packaged so as to provide adequate physical and chemical protection for the drug during storage and transportation, and allow for easy identification of the contained drugs... (page 48).</td>
</tr>
<tr>
<td>NIOSH, 2004 US</td>
<td>Store and transport hazardous drugs in closed containers that minimize the risk of breakage. (page 12)</td>
</tr>
<tr>
<td>ONS, 2003 US</td>
<td>Do not transport drug-filled syringes with needles attached. (page 22)</td>
</tr>
<tr>
<td>HSE, 2003 UK</td>
<td>Once prepared, a drug should be clearly labelled as cytotoxic and packaged to ensure it will not spill or leak when transported to the area where it will be administered. (page 4)</td>
</tr>
<tr>
<td>Marc, 2003-2005 UK</td>
<td>For all cytotoxics being transported between pharmacy and wards ensure: The label indicates to the porter that the contents of the container are Cytotoxic ... Cytotoxics should be double wrapped in polythene bags, and placed in a rigid, sealable, leak-proof container. (Support: Transport of cytotoxic drugs)</td>
</tr>
<tr>
<td>WorkSafe, 2003 Australia</td>
<td>Cytotoxic drugs should be packaged in a labelled, sealed, leak-proof container, with outer bags heat-sealed where possible,...(page 20)</td>
</tr>
<tr>
<td>DGOP, 2003 Germany</td>
<td>the finished preparations be transported in unbreakable, liquid-tight, closeable containers. The transport containers must also carry a warning label such as “Caution Cytostatics.” (page 161)</td>
</tr>
</tbody>
</table>
### Table 8. Education/training.

<table>
<thead>
<tr>
<th>Producer, date, country</th>
<th>Recommendation</th>
</tr>
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</table>
| ASHP, 2006 US          | All workers who work with or around hazardous drugs must be trained to appropriately perform their tasks using the established precautions and required PPE. *(page 1176)*  
All staff members who handle hazardous drugs should receive safety training that includes recognition of hazardous drugs and appropriate spill response. *(page 1176).*  
All staff who will be compounding hazardous drugs must be trained in stringent aseptic and negative-pressure techniques necessary for working with sterile hazardous drugs… *(page 1182).* |
| SHPA, 2005 Australia   | All personnel must be trained in the safe handling of cytotoxic drugs and related wastes before working in the cytotoxic preparation facility.  
Personnel handling cytotoxic drugs should be provided with appropriate up-to-date information on all aspects of the safe handling of cytotoxic drugs, as well as the reported hazards of low-level exposure to these agents. *(page 49)* |
| NIOSH, 2004 US         | Provide training for handling hazardous drugs safely, cleaning up spills, and using all equipment and PPE properly.  
Conduct regular training reviews with all potentially exposed workers in workplaces where hazardous drugs are used. *(page 11)* |
| ONS, 2003 US           | Programs for the training of employees who handle hazardous agents must be developed. The initial program should include safety procedures for personnel, based on their specific roles related to hazardous drug handling, such as  
Use of engineering controls  
Use of PPE  
Drug preparation  
Drug transport  
Drug administration  
Disposal of hazardous materials  
Management of hazardous drug spills  
Management of acute exposure. *(page 43)*  
Annual reviews of policies, procedures, guidelines, and updates regarding safe handling must be mandatory for all personnel involved in handling hazardous drugs. *(page 44)* |
<table>
<thead>
<tr>
<th>Source</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSE, 2003 UK</td>
<td>Employers need to ensure that employees handling cytotoxic drugs are given suitable and sufficient information, instruction and training that is relevant to their work. This should be enough to make employees aware of the risks of working with cytotoxic drugs and the precautions they should take when handling them. (<em>page 5</em>)</td>
</tr>
</tbody>
</table>
| Marc, 2003-2005 UK | Structured training should take place before exposure to risk, and should cover:  
* the potential health risks of cytotoxics  
* safe practice and containment systems  
* sources of information  
* personal protective equipment, and  
* emergency procedures  
All staff who work with, or may be required to work with, cytotoxic drugs should receive training. This will include: pharmacy staff, nurses, doctors, support staff (e.g., porters, cleaning staff and maintenance staff), and relevant agency staff.  
...  
Education and training should be on-going, with regular updates to any advice, and tests of staff competency.  
(Education: Education on cytotoxic risks and safe handling) |
| WorkSafe, 2003 Australia | Employers should ensure that only employees who have received appropriate training, and have obtained the required level of proficiency, handle cytotoxic drugs and related waste. Training should occur:  
* at induction  
* prior to commencement of duties where cytotoxic drugs and related waste are involved  
* when new equipment is introduced or procedures change  
* on an ongoing basis, with a review every two years.... (*page 16-17*) |
| DGOP, 2003 Germany | All persons directly or indirectly handling cytostatics must receive instruction... (*page 16*)  
Both theoretical knowledge and practical skills are imparted during the education, training and further training of the staff...(*page 28*)  
Training new employees in the cytostatics preparation sector must be performed very carefully since the workplace involved is potentially very hazardous for person and product...(*page 30*)  
Training and further training is intended to ensure that the knowledge possessed by the employees is kept constantly up to date with the latest scientific and technological developments... (*page 35*) |
<table>
<thead>
<tr>
<th>Producer, date, country</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>ASHP, 2006 US</td>
<td>Because reproductive risks have been associated with exposure to hazardous drugs, alternative duty should be offered to individuals who are pregnant, breast-feeding, or attempting to conceive or father a child... (page 1185)</td>
</tr>
<tr>
<td>SHPA, 2005 Australia</td>
<td>Personnel who are pregnant or breastfeeding must be excluded from working with cytotoxic drugs. Personnel planning imminent parenthood must also be permitted exclusion from preparing cytotoxic drugs. (page 49)</td>
</tr>
<tr>
<td>NIOSH, 2004 US</td>
<td>No recommendations</td>
</tr>
<tr>
<td>ONS, 2003 US</td>
<td>No recommendations but states under surveillance Special consideration should be given to the reproductive history of employees handling hazardous drugs. General questions regarding problems in conceiving and poor reproductive outcomes (spontaneous abortions and fetal malformations) should be included. Male employees should provide information about the reproductive histories of their partners... (page 38).</td>
</tr>
<tr>
<td>HSE, 2003 UK</td>
<td>decide who might be harmed and how...Pay attention to groups of workers who may be at particular risk, e.g. young workers, trainees and new and expectant mothers. Pregnant workers are especially relevant, as some drugs may be harmful to the unborn child. Further guidance is contained in New and expectant mothers at work: A guide for employers. (page 2)</td>
</tr>
</tbody>
</table>
| Marc, 2003-2005 UK     | All staff should be fully informed of the reproductive hazards by:  
  - Receiving verbal and written information upon induction  
  - Having access to relevant literature  
  - Signing to say they have read and understood the relevant COSHH assessments  
  - Providing opportunity for discussion of any concerns  
  
  Pregnant staff or those trying to conceive should:  
  - always be offered alternative duties if they choose not to work with cytotoxics at this time  
  - managers should have consideration for their staff's perception of the risk of exposure to cytotoxics  
  
  Reducing the risk:  
  - As some pregnancies are unplanned, or staff unwilling to discuss plans for conception, the emphasis should be on clear guidelines to reduce exposure to all staff at all times  
  - Staff should be encouraged to discuss plans for pregnancy with their manager in confidence  
  - Staff should be advised to inform their manager as soon as a pregnancy is suspected / confirmed  
  - Staff who chose not to work with cytotoxics at this time must be offered |
alternative duties
• To comply with HSE guidance all pregnant staff or those trying to conceive should be removed from duties involving the preparation of cytotoxic drugs (HSE, HSG 122, 2002)
• Areas with a perceived high risk of occupational exposure, may wish to consider moving all pregnant staff or those trying to conceive from handling cytotoxics (Handling: Pregnancy in staff handling cytotoxics)

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<tr>
<th>Source</th>
<th>Description</th>
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| WorkSafe, 2003  | The appointed medical practitioner should provide medical advice and counselling to the employee, including:
• the potential risks to employees planning parenthood, or those who are breast-feeding or pregnant. *(page 49)*
  - conduct a medical review as soon as possible in the following situations:…
    - if an employee advises she is pregnant, or is breast-feeding *(page 50)* |
| DGOP, 2003      | As long as the pregnant woman is not exposed to these hazardous substances while handling them in the prescribed way, she may continue to be employed.
  In order to exclude all recognisable risks the following measures must be taken in the order given:
  1. Working conditions must be modified to exclude any danger. If this is not possible,
  2. transfer must be made to a different workplace. If this is either impossible or unreasonable,
  3. the employee must be released from work. *(page 17-18)* |
Table 10. Medical surveillance.

<table>
<thead>
<tr>
<th>Producer, date, country</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>ASHP, 2006 US</td>
<td>All workers who handle hazardous drugs should be routinely monitored in a medical surveillance program… (page 1185).</td>
</tr>
<tr>
<td>SHPA, 2005 Australia</td>
<td>Institutions must have a written policy for baseline and regular monitoring of staff involved in the preparation of cytotoxic drugs. Regular monitoring, which includes a full blood examination and differential, should be offered at a minimum of six-monthly intervals. Arrangements must be made for appropriate explanation counselling of staff with results outside the normal range. (page 49)</td>
</tr>
<tr>
<td>NIOSH, 2004 US</td>
<td>If you handle hazardous drugs, participate in medical surveillance programs provided at your workplace. If you handle hazardous drugs but have no medical surveillance program at work, see your private health care provider for routine medical care. Be sure to inform him or her about your occupation and possible exposures to hazardous drugs. (page 18)</td>
</tr>
<tr>
<td>ONS, 2003 US</td>
<td>Limited resources may preclude the implementation of a comprehensive medical surveillance program for health care workers who are exposed to hazardous drugs. For institutions that do not have the means to develop a comprehensive surveillance program, a few key elements may serve to track employees’ exposures. In health care institutions where some form of periodic employee health evaluation is already in place, new elements of surveillance may be added to screen hazardous drug handlers for their specific health risks… (page 41-42).</td>
</tr>
<tr>
<td>HSE, 2003 UK</td>
<td>The results of the risk assessment for staff potentially exposed to cytotoxic drugs should be used to determine whether health surveillance is necessary. Where this has shown that exposure is most unlikely to result in any disease or adverse health effect, health surveillance is not required. …it is recommended that employers keep a health record on all staff potentially exposed to these compounds. … biological monitoring … and biological effect monitoring (measurement and … However, data produced from using these techniques are difficult to interpret in the context of the health of an individual employee and are therefore not recommended for routine use in health surveillance. (page 5)</td>
</tr>
<tr>
<td>Marc, 2003-2005 UK</td>
<td>The COSHH Regulations (1994) require that monitoring or health surveillance should be implemented if a risk cannot be totally eliminated. Methods for staff monitoring: • cytogenetic methods (sister-chromatid exchange rates, micronuclei</td>
</tr>
</tbody>
</table>
formation),
- analysis of drugs/ metabolites in blood, urine
- mutagenicity studies, and
- miscellaneous methods such as white blood cell counts
None of these methods are satisfactory for staff monitoring.*
(Handling: Cytotoxic contamination: staff and environmental monitoring )

<table>
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<tr>
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<th>Description</th>
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</table>
| WorkSafe, 2003    | The ideal test should be sensitive, specific, quantitative, rapid, reproducible and inexpensive, noninvasive and not cause unnecessary duress or anxiety in the individual.  
There is currently no test that meets these requirements.  
Therefore, this guide recommends that biological monitoring should not be part of the health monitoring program. (page 13) |
| DGOP, 2003        | Employees working in the area of cytostatics preparation are constantly handling CMR drugs. They must be offered regular occupational medical check-ups.  
These check-ups should include:  
1. Initial examination before taking up employment.  
2. Follow-up examinations during their employment at intervals of 12 to 24 months.  
3. Examinations at the request of the employee if there is a suspicion of work-related impairment to health.  
Despite its limited meaningfulness, it is recommended that biomonitoring be included in the follow-up examinations as a means of performing spot checks on the effectiveness of the existing protective measures. (page 21) |
Abbreviations:
ASHP, American Society of Health-System Pharmacists
SHPA, Society of Hospital Pharmacists of Australia
NIOSH, National Institute for Occupational Safety and Health
ONS, Oncology Nursing Society
HSE, Health & Safety Executive
WorkSafe, WorkSafe Victoria - Victorian WorkCover Authority
DGOP, German Society of Oncology Pharmacy
Evidence-based Series Special Report: Section 3

Safe Handling of Cytotoxics: Development and External Review of Recommendations - Methods and Results

Authors (in alphabetical order):
E. Green, M. Johnston, G. Macartney, D. Milliken,

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: April 13, 2007

THE PROGRAM IN EVIDENCE-BASED CARE
The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province. Occasionally, ad hoc expert panels are asked to develop recommendations related to specific topics outside the scope of existing DSGs and GDGs.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for which the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information. These methods were used to develop this Special Report.

The Evidence-based Series
This PEBC Special report is formatted as an Evidence-based Series comprised of three sections.

- Section 1: Recommendations. This section contains the recommendations derived from a systematic review of the clinical and scientific literature, examination of existing guidelines,
and consideration of ethical principles concerning risk to health care workers. The final recommendations are based on the expert panel’s interpretation of the evidence and understanding of the clinical environment and on feedback obtained from practitioners in Ontario.

- **Section 2: Systematic Review.** This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the Expert Panel.

- **Section 3: Development and External Review of the Recommendations: Methods and Results.** This section summarizes the process for developing this report and the results of the formal external review by Ontario practitioners of the draft version of the recommendations and systematic review.

**DEVELOPMENT OF THIS EVIDENCE-BASED SERIES**

**Guideline Development**

This evidence-based series was developed by the Cytotoxic Safe Handling Expert Panel of CCO’s PEBC. The series is a convenient and up-to-date source of the best available evidence on safe handling of cytotoxic drugs developed through systematic review, evidence synthesis, expert opinion and input from practitioners in Ontario. The expert panel is comprised of pharmacists, nurses, an ethicist, an oncologist, and an occupational health and safety manager. In addition to reviewing the evidence on adverse effects among health care workers from handling cytotoxic drugs, this report addresses the question “What precautions should be taken in the workplace to minimize the risk of adverse effects among hospital and clinic staff that may be exposed to cytotoxic drugs?” The panel reviewed and discussed the evidence summarized in the systematic review described in Section 2 of this evidence-based series, which included consideration of recent guidelines from other developers. The panel then reached consensus on the target population for the guideline and a set of specific recommendations.

**Internal Review by the Report Approval Panel**

Prior to the submission of this evidence-based series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. The report was revised in response to the following requests from the Report Approval Panel:

- Re-organize the report to make clear the role of expert opinion, ethical principles, guidelines from other groups and evidence in formulating the recommendations.
- Add more guidance to readers on interpreting the methods used in the studies included in the systematic review.

**External Review by Ontario Clinicians**

Following the review and approval of the report by the PEBC Report Approval Panel, the Cytotoxic Safe Handling Expert Panel circulated the recommendations and systematic review to practitioners in Ontario for review and feedback.

**Methods**

Feedback was obtained through a mailed survey of 111 individuals in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved. Written comments were invited. The survey was mailed out on December 15th 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Cytotoxic Safe Handling Expert Panel reviewed the results of the survey.
Results
Thirty-eight responses were received out of the 111 surveys sent (34% response rate). Responses included 33 returned questionnaires, as well as phone, fax and email responses indicating that the practitioner would not be completing the questionnaire. Of the 33 practitioners who completed all or part of the questionnaire, 26 indicated that they were responsible for handling cytotoxic agents and/or ensuring the safety of those who do handle cytotoxics. Seven respondents answered ‘No’ to this item and one of these did not complete the remaining items. Results for eight key items on the feedback survey, completed by 32 respondents, are summarized in Table 1.

Table 1. Responses to eight key items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>The rationale for developing recommendations, as stated in the &quot;Introduction&quot; section of the report, is clear.</td>
<td>31 (97%) 1 (3%) 0</td>
</tr>
<tr>
<td>There is a need for recommendations on the safe handling of cytotoxics.</td>
<td>32 (100%) 0 0</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>23 (72%) 7 (22%) 2 (6%)</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>30 (94%) 2 (6%) 0</td>
</tr>
<tr>
<td>The draft recommendations in the report are clear.</td>
<td>31 (97%) 1 (3%) 0</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>30 (94%) 0 2 (6%)</td>
</tr>
<tr>
<td>If this report were to be approved, how likely would your hospital be to make use of it?</td>
<td>Very likely or likely Unsure Not at all likely or unlikely</td>
</tr>
<tr>
<td>(One respondent did not reply to this item)</td>
<td>21 (66%) 2 (6%) 8 (25%)</td>
</tr>
</tbody>
</table>

Summary of Written Comments
Nineteen respondents (58% of those completing the questionnaire) provided written comments. The main points contained in the written comments are summarized below:

Additional evidence
- An additional relevant publication (Fransman et al), published in January 2007 - after the draft report was sent to reviewers, was identified. This paper provided further analysis of data from one of the studies already included in the systematic review of the evidence on adverse effects among health care workers who handle cytotoxic drugs.

Purpose
- The report should specify if the recommendations include oral cytotoxic agents or just intravenous preparations.

Personal protective equipment
Three respondents made the following comments:
- Double gloving is expensive, uncomfortable and impedes nurses in their work. Only one of the eight practice guidelines from other developers reviewed for this report recommended double gloving (NIOSH). The reviewer suggested revising the recommendation on gloves to read “Gloves are to be 7-9 mil thick and meet ASTMD6978-05 Standards.” Another reviewer asked if the recommendations apply to health care employees with secondary exposure -
i.e., people who change linen for incontinence or diaphoresis or who empty bedpans/clean urine spills.

- The third reviewer agreed that pharmacists and technicians require disposable gowns but did not agree with the recommendation for disposable gowns for nurses, citing two reasons: i) cost and ii) resistance from nurses. There are non-disposal coats that meet standards and are non-permeable. The reviewer’s centre has the regional laundry test permeability each time the coat is laundered.

**Ventilated cabinets**
Two respondents suggested the following changes to the report:
- Add “ventilated to the outdoors or if possible, use a high-efficiency particulate air (HEPA) filter” to the recommendation.
- Add some discussion on the importance/relevance of negative pressure preparation rooms.

**Closed systems**
Three respondents suggested the following changes to the report:
- Add an example of when a closed system should be considered, such as when preparing BCG or interferon for bladder instillation.
- Suggest drugs that should be handled with closed systems.
- Provide guidance to institutions on issues that they should consider, given the limited evidence, when deciding on the use of closed systems.

**Transport and Labelling**
- One respondent suggested specifying that cytotoxic drugs be transported in “puncture proof” containers.

**Education and training**
- One respondent was concerned that the draft report did not reference current “WHIMIS” legislation on handling hazardous materials in Ontario. Hospitals and cancer centres need to work within this legislation when developing policies and procedures and staff must undergo mandatory training.

**Pregnancy**
- Rewording of the recommendation was suggested, so that the recommendation was stated first followed by the rationale.

**Implementation**
Four respondents provided the following comments and questions:
- The recommendations may be difficult to implement at small community hospitals. Provincial standards are needed to provide clear direction to hospitals without pharmacies. Not all hospitals have biomedical support to service the ventilation and air-filtering systems. Furthermore, capital equipment obligations may be very costly for small community hospitals.
- Will this translate into recommendations for family and caregivers at home? Will nurses & physicians recommend double gloving, condoms, etc., as protection against bodily fluid of patients in the home setting?
- Is there a way of extending the recommendations to community health care workers who administer treatment outside the hospital (e.g., FOLFOX and FOLFIRI for colorectal cancer)?
A task force made up of stakeholders from all cancer centres in Ontario was suggested to address the issues related to medical surveillance research. CCO should get CANO and RNAO endorsement for these recommendations.

Additional areas for possible recommendations
Two respondents suggested adding recommendations related to:
- the sterile preparation area (size, type, etc.) - many hospitals are going through renovations and/or re-design of their chemotherapy clinics,
- the provision of pre-primed I.V. chemotherapy bags to RN’s.
- routine environmental testing in chemotherapy areas on a routine basis as a quality measure.

Modifications to Report
After reviewing and discussing the feedback from practitioners, the expert panel made the following changes to the report:

Purpose
The term “parenteral” was added to the purpose statement in Section 1 of the report as well as to the title.

Personal protective equipment
The wording of recommendations related to gloves and gowns was modified to include the options suggested by reviewers.

Ventilated cabinets
The wording of the recommendations was clarified and made consistent with the NIOSH recommendation. Type B2, B1 and A2 biologic safety cabinets (BSC) differ in the amount of air filtered to the outside and the amount of air being recirculated. A Class II Type B2 hood is 100% vented to the outside. A statement was added that the BSC must be equipped with a continuous monitoring device to allow confirmation of adequate airflow and cabinet performance. Use of a high-efficiency particulate air filter (HEPA filter) was not specified because all BSCs have HEPA filters.

Closed systems
No changes were made. The list of drugs that could be used with closed systems is constantly changing and would soon be out-of-date if added to the report. With respect to the last point raised by practitioners, the panel felt that the report already describes the issues that institutions should consider when formulating policies and procedures related to safe handling.

Transport and labelling
No changes were made. Puncture-proof containers are “designed to contain leakage and spills” as covered in the recommendation.

Education
No changes were made. Workplace Hazardous Materials Information System (WHMIS) training is outside the scope of this report.

Pregnancy
The recommendation was reworded as suggested by the reviewer.
Implementation

- The recommendations are intended to apply to all health care institutions in Ontario who administer parenteral cytotoxic drugs. The purpose of the report is to make standards known so that institutions can assess the adequacy of their facilities, polices and procedures.
- Community agencies that administer home chemotherapy should have access to the recommendations and should provide gloves to patients’ families/caregivers to use when changing soiled linen and cleaning up bodily fluids. Cancer Care Ontario will disseminate this report to the appropriate community agencies.
- The last two suggestions from practitioners under Implementation are outside the scope of this special report, which is intended to summarize the evidence and make recommendations for practice. While CCO will disseminate the report to relevant stakeholders, it does not seek formal endorsement from individual groups.

Additional areas for possible recommendations
No changes were made. The intention of this report is to provide fairly broad recommendations to guide practice and policy without being overly prescriptive about the details of implementation.

Funding
The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

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Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775
REFERENCES
