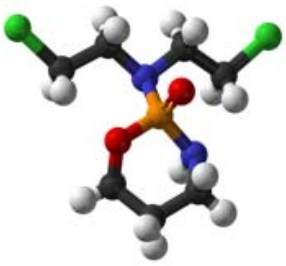

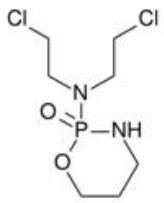

TOXICOLOGY PROFILE

CYCLOPHOSPHAMIDE IN THE HEALTH CARE INDUSTRY

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Summary

This report focuses on cyclophosphamide in healthcare industry, including basic properties, use as a cytotoxic drug, exposure and metabolizing routes, health effects, regulations and control measures.

Cyclophosphamide is used as a drug to treat cancer and other medical conditions. Healthcare workers may be exposed to cyclophosphamide through dermal and inhalation routes. High-risk occupations include pharmacist, pharmacy technician, oncology nurse and so on. Cyclophosphamide is known to be a human carcinogen based on sufficient evidence of carcinogenicity in humans, and it is listed as "1, carcinogen to human" by IARC. In addition, it has definite cytotoxicity, teratogenicity, as well as potential reproductive effects.

Currently there are no occupational exposure limits set up for cyclophosphamide by jurisdiction systems of Canada, U.S. or international agencies. Cyclophosphamide exposure can be reduced or eliminated by substitution or using pharmacy isolators, laminar ventilation hoods. Contamination and permeation of gloves and other personal protective equipment showed that use of PPE alone cannot provide sufficient protection.

Part 1 General Information

I) Name
Cyclophosphamide

II) Synonyms
Cyclo, CP, CPA, CPM, CTX, CYC, CYT

III) Common trade names
Procytox®, Cytoxan®, Neosar®

IV) CAS Number
50-18-0

V) Description
Cyclophosphamide is a white crystalline powder with the molecular formula $C_7H_{15}Cl_2N_2O_2P$ (anhydrous) or $C_7H_{15}Cl_2N_2O_2P \bullet H_2O$ (hydrous) and a molecular weight of 279.1 (hydrous).

VI) Use of cyclophosphamide in the healthcare industry

Cyclophosphamide is a synthetic antineoplastic drug chemically related to the nitrogen mustards, which can be used to treat cancer and some non-neoplastic diseases as well [1].

It is estimated that cyclophosphamide was utilized to treat both neoplastic and non-neoplastic disease in 500,000 patients worldwide each year[7]. As one of the most widely used antineoplastic agents, cyclophosphamide itself does not possess alkylating effect *in vitro* and requires activation *in vivo* to become therapeutically effective [2]. The activation is carried out by hepatic microsomal mixed function oxidases [3]. The products of the biochemical process can express their cytotoxicity by interaction with the DNA of tumor cells, thus interfere with the growth of susceptible rapidly proliferating malignant cells [4].

Diseases that can be treated with cyclophosphamide include: **1)** Malignancies such as malignant lymphoma, multiple myeloma, leukemia, breast and ovarian cancer, neuroblastoma, retinoblastoma, and mycosis fungoides [60~63]. **2)** An immunosuppressive agent following organ transplants or to treat autoimmune disorders such as rheumatoid arthritis, Wegener's granulomatosis, and nephrotic syndrome in children [64].

Cyclophosphamide is given by intravenous injection, as well as given in repeated short courses of oral therapy in conjunction with other cytotoxic agents as part of a chemotherapeutic schedule [2]. Each tablet for oral administration contains cyclophosphamide (anhydrous) 25 mg or 50 mg. In addition, each tablet contains other ingredients such as acacia, FD&C Blue No. 1, lactose monohydrate, magnesium stearate, and microcrystalline cellulose [1].

VII) Sampling and Analysis Methods

There is no standard analytical method of cyclophosphamide established by WorkSafe BC, OSHA or NIOSH. Thus, instead, analysis methods used in several monitoring studies were summarized in **table 1**.

Table 1. Sampling and Analysis Method for Cyclophosphamide

Sample	Sampling and Analysis Method	Limit of Detection (LOD)	Ref.
Urine Sample	Collect urine for 24 hrs. Then urine samples were analyzed using Gas Chromatography with Electron Captures Detector (GC/ECD).	2.5µg/day urine	[15]
	Collect urine for 24 hrs. Then urine samples were analyzed using GC/MS.	0.1g/l urine	[19]
	Collect urine for 24 hrs. Then urine samples were analyzed using GC/MS.	1g/l urine	[17]
	Collect urine for 24 hrs. Then urine samples were analyzed using GC/MS.	0.5µg/day urine	[21]
	Collect urine for 24 hrs. Then urine samples were purified and analyzed using High Performance Liquid Chromatography/Tandem Mass Spectrometry (HPLC/TMS).	0.05 mg/l urine	[26]
Air Sample	Air samples and airborne particulate samples were taken using PAS-6 sampler and polytetrafluoroethyiene filters respectively. Then CP of the air sampler and filter were analyzed. Instrumentation not mentioned.	N/A	[16, 19]
		2 ng/m^3	[26]
Gloves Permeation/ Contamination	The permeation of the latex gloves used during preparation was determined by wearing cotton gloves. After preparation of the drugs, the latex and the cotton gloves were collected separately. The cotton gloves were extracted and analyzed in the same manner as were the latex gloves.	N/A	[16]
	After preparation of the drugs, the left and the right glove were collected together, then extracted, and analyzed by GC/MS.	0.1µg/glove	[19]
	After preparation of the drugs, left and right gloves were collected separately and put in glass pots with the possibly contaminated side outside. Then the contaminated gloves using sodium hydroxide solution.	N/A	[17]
Wipe Test of Surfaces	Spot samples of floors and hood surfaces were taken, then extracted with sodium hydroxide solution, and analyzed using GC/MS.	N/A	[17]
	Spot samples of floors and hood surfaces were taken, then extracted with sodium hydroxide solution, and analyzed using HPLC/TMS.	1 ng/dm^2	[26]

Part 2 Exposure among healthcare workers

I) Healthcare workers at risk

In Canada, cyclophosphamide is marketed for human use as an intravenous injection or tablets for oral consumption, thus occupational exposure among healthcare workers may occur in multiple scenarios.

Nurses

In 2007, a study of cancer risks among nurses in British Columbia found cyclophosphamide to be the most frequently used alkylating agent. Of the units polled in this research, 44% of oncology, 80% of pharmacies and 5% of other departments reported using cyclophosphamide [23]. In 2007, CIHI (the Canadian Institute for Health Information) estimated that 416 Registered Nurses (RNs) worked in the oncology areas of BC hospitals, while there were 3,129 RNs in the oncology area nationwide [24], and thus may have been exposed to chemotherapeutic drugs (including cyclophosphamide).

Pharmacist and Pharmacy technicians

Pharmacists and pharmacy technicians are potentially exposed to chemotherapeutics when they prepare the drugs for patient use. According to a report developed by Eli Lily [25], which is a leading pharmaceutical corporation, there were 94 pharmacists across Canada working in hematology/oncology outpatient pharmacies, and 91 in inpatient pharmacies. Pharmacy technicians compose approximately 47% of the average hospital pharmacy staff, ahead of pharmacists at 40% [25]. Therefore, the number of pharmacy technicians exposed to chemotherapeutic drugs can be estimated as being slightly higher than the number of pharmacists.

Other healthcare workers, such as animal caretakers and stuff involved with medical waste disposal may also be exposed to cyclophosphamide.

II) Monitoring Data

Monitoring data of cyclophosphamide is summarized in **table 2** as below. The main method of evaluating cyclophosphamide exposure is biological monitoring (urine), as there are multiple routes of exposure. Air samples were collected in some studies to evaluate the effectiveness of the ventilation. In addition, gloves samples and wipe samples were collected to show contamination of the work place.

Table 2. Monitoring data of cyclophosphamide among healthcare workers

Ref.	No. of wks	Job category	CP level	Note
[15]	21	Nurses and pharmacy personnel	**Urine** *mean*:11.4μg/day *range*: 3.5~38 μg/day	Standard safety precautions were applied in the hospital pharmacies, including vertical laminar air flow safety cabinet, protective clothing (disposable gown or cotton gown) and Latex gloves. So the detection of cyclophosphamide in urine put the effectiveness of PPE into question.
[16]	9	Pharmacy technicians	**Urine** *median*: 0.6μg/day *range*: <LOD~19.4 μg/day **Air** 0.04~10.1 μg/m^3	1) CP was present in the urine of technicians who did not prepare CP. 2) The study found high CP permeation of latex and cotton gloves, as well as the presence of CP on gloves when CP was not prepared. 3) CP presented in the air, which showed inefficacy of the hood.
[17]	2	Pharmacy technician	**Urine** All samples under LOD of 1μ/L. **Air** <LOD **Spot** spot samples of the hood ranged from 1 to 160ng/cm2, while most of floor spot samples were below LOD.	From the contamination of the laminar airflow hood, floor and gloves, it can be concluded that release of drugs during preparation did happen.
[19]	25	Female pharmacy technicians and nurses.	**Urine** *mean*: 0.06 μg/day *range*: <LOD to 0.5μg/day **Air** <LOD **Spot** Contamination of the floors of the administration rooms and gloves were found.	1) No significant correlations were observed between the amounts of CP excreted in urine and the amount of CP prepared or administered. 2) CP was found not only in the urine of pharmacy technicians and nurses actively handling it, but also in the urine of pharmacy technicians and nurses not directly involved in the preparation and administration.
[26]	24	Pharmacy technicians, pharmacists and nurses preparing or administrating antineoplastic drugs	**Urine** 50% samples were positive for CP, ranged from 0.1~ 2.1 mg/L. **Air** Area samples all below LOD, personal samples may range up to 240ng/m^3 **Wipe** ranged from <LOD to	1) Pad samples showed that workers preparing the drugs were at higher risk than administrating the drugs. For individuals, it also showed that arms, legs and chest were the most contaminated parts 2) In the wipe samples taken from different locations in the preparation rooms, high amounts of CP was detected even when it had not been prepared on the day of the sampling. 3) Airborne drug levels were always below LOD (2ng/m^3). Thus inhalation cannot be considered as the main exposure route. While permeation of CP through both latex and vinyl gloves suggested that dermal uptake is

			383.3 μg/dm²	possibly the main exposure route. 4) Environmental and biological monitoring, together with the evaluation of the efficiency of the laminar flow hoods, may be considered as a recommended approach to risk assessment so as to minimize occupational exposure to hazardous drugs.
[20]	2	Nurses	**Urine** *mean*: 0.47 μg/day *range*: 0.43~0.51 μg/day	
[22]	8	Nurses	**Urine** *mean*: 0.79 μg/day *range*: <LOD to 2.9 μg/day	
[18]	4	Animal caretakers	**Urine** *mean*: 0.05μg/day *range*: <LOD to 0.2 μg/day **Gloves** ranges from 2~199 mg/pair	The result showed that in this particular study, animal caretakers were exposed to CP during their work.
[21]	20	Hospital workers (not specified)	**Urine** *mean*: 0.39 μg/day *range*: <LOD to 2.5 μg/day	A clear relationship between cyclophosphamide handling and detectability of excretion existed.

III) Exposure Route

Inhalation

During drug preparation, a variety of manipulations are performed which may result in aerosol generation, spraying, and splattering. Examples of these manipulations include: the withdrawal of needles from drug vials; the use of syringes and needles or filter straws for drug transfer; the opening of ampoules; and the expulsion of air from the syringe when measuring the precise volume of a drug [55].

Several monitoring data [16, 26] show that airborne cyclophosphamide does exist in the drug preparing room, consequently inhalation is one possible route of exposure. However, unlike most kinds of other substances (formaldehyde or glutaraldehyde), there are controversies concerning whether inhalation was the major route of exposure. For example, in the study by Sessink [16], the author calculated the “inhaled amount” of cyclophosphamide by multiplying air concentration with a respiration volume of 10m3/8h and a retention factor of 100%, and by comparing the “inhaled amount” with “excreted amount through urine”, they found that the amounts of CP inhaled were generally lower compared with the amounts of CP excreted, and it was expected that the inhaled amount will be much less than the “total amount” as only 1~5% CP was excreted un-metabolized [20]. However, there are other scholars who consider inhalation is the main risk factor in handling cytotoxic drugs [53].

Dermal

Direct skin contact may result in systematic absorption [54]. Glove and body cover-up contamination among pharmacy technicians and oncology nurses in several monitoring studies indicates that dermal maybe one important route of

exposure. Results of a recent study using a fluorescent tracer technique indicated the spills may also occur during administration of antineoplastic drugs and handling of patient's urine, and hand area is most likely to be exposed [27]. Oncology nurses and cleaning personnel may be exposed to cyclophosphamide since these antineoplastic drugs are present in the patient's excreta [28]. In addition, disposal of cytotoxic drugs and trace contaminated materials presents a possible source of exposure to pharmacists, nurses and physicians as well as to ancillary personnel, especially the housekeeping staff [55].

One pilot study assessed dermal exposure of cyclophosphamide among hospital personnel, and they found that exposure predominately occurred on the hands and sporadically on forehead and forearms [29]. This study also found that gloves used during preparation of cyclophosphamide were more contaminated than gloves used in other tasks, however, actual exposure of the hands (underneath the gloves) was highest during decanting of urine of treated patients.

Part 3 Pharmacokinetics and Metabolism

Cyclophosphamide is well absorbed after oral administration with a bioavailability greater than 75%. The unchanged drug has an elimination half-life of 3 to 12 hours [5]. It is eliminated primarily in the form of metabolites, but from 5% to 25% of the dose is excreted in urine as unchanged drug [5]. Several cytotoxic and noncytotoxic metabolites have been identified in urine and in plasma. Concentrations of metabolites reach a maximum in plasma 2 to 3 hours after an intravenous dose. Plasma protein binding of unchanged drug is low but some metabolites are bound to an extent greater than 60%.

Part 4 Health effects

I) Carcinogenicity

As discussed above, alkylating agents express their cytotoxicity by interacting with the DNA of tumor cells. Since the desired cytotoxicity is not specific for cancer cells, normal cells may also be damaged, resulting in toxic side-effects [4]. According to International Agency for Research on Cancer (IARC), there is sufficient evidence of carcinogenicity in humans and animals, so it is listed as "1, carcinogen to humans"[5].

Bladder cancer

One epidemiology study with the largest investigation group concerning secondary bladder cancer following cyclophosphamide therapy showed a dose-dependent relationship between bladder cancer and cyclophosphamide [6]. Cohort of the study was 6171 two-year survivor of non-Hodgkin's lymphoma (NHL) in U.S., the Netherlands, Canada, and Sweden, which included 48 patients with secondary cancer of the urinary tract identified, and the control group of 136 subjects with NHL but did not develop a second malignancy. The study also looked into other possible cancer inducing factors, including radiotherapy and other chemotherapy regimens, such as vincristine and prednisone (CVP); doxorubicin, vincristine and prednisone (CHOP); vincristine, procarbazine, and prednisone (COPP); and bleomycin, doxorubicin, vincristine and prednisone (BACOP). The study found a significant 4.5-fold risk of bladder cancer followed cyclophosphamide therapy, while radiotherapy without cyclophosphamide was associated with a non-significantly increased risk of bladder malignancy (RR=2.8), and treatment with other cytotoxic agents or prednisone did not contribute to bladder cancer risk. The study also found a cumulative-dose dependent risk of bladder cancer, which was independent of the route of cyclophosphamide administration (oral or intravenous). The dose-response relationship was summarized in **table 3**, and from the table, we can see an increase in RR of bladder cancer corresponding the increase of cumulative dose or duration of chemotherapy.

Table 3. Relationship between CP dose and bladder cancer rate

cumulative dose, (g)	Median	No. of cases	No. of controls	Matched RR	95% CI
<20	10.0g	8	22	2.4	0.7-8.4
20-49	34.0g	5	6	6.3	1.3-29
≥50	87.7g	5	2	14.5	2.3-94
Duration of therapy, y					
<1	6mo	8	20	2.5	0.7-9.0
1-2	18mo	3	6	3.7	0.6-22
≥2	51mo	7	4	11.8	2.3-61

There are other studies concerning the potential risk of bladder cancer after administration of cyclophosphamide, which are summarized in **table 4** as below.

Table 4. Studies indicating potential risk of bladder cancer following cyclophosphamide administration

Description of the study	result	comments	Ref.
Case report	Two cases of carcinoma of the bladder, who had been on cyclophosphamide treatment for 2 and 4 years respectively.	just description of the two cases	[8]
A prospective study in UK of 1,634 patients treated with immunosuppressive medicines (azanthioprine and cyclophosphamide).	13.0- and 12.8- fold relative risk were found for non-Hodgkin's lymphoma and bladder cancer respectively among patients treated with cyclophosphamide.	No dose-response evaluation. No adjustment of possible confounders.	[9]
The cohort consists of 471 patients treated for non-Hodgkin's lymphomas with cyclophosphamide, and the case group consists of nine patients with transitional cell carcinoma of urinary bladder.	Mean cumulative risk of bladder cancer was 3.5% and 10.7% respectively among patients with 8 years and 12 years of cyclophosphamide treatment.	Revealed dose-response relationship. Small case group.	[10]

Leukemia

A highly increased risk of acute nonlymphocytic leukemia has been observed in patients treated for malignant diseases with alkylating agents [11~13]. Studies revealed the potential of inducing leukemia specifically for cyclophosphamide are summarized in **table 5** as below.

Table 5. Studies indicating the potential risk of leukemia after cyclophosphamide administration

Description	Result	Ref.
602 patients treated for non-Hodgkin's lymphomas, and 498 patients treated with alkylating agents, predominantly CP.	9 patients developed overt acute nonlymphocytic leukemia or pre-leukemia with refractory cytopenia and cytogenetic abnormalities of the bone marrow, and they all had received alkylating treatment. A Kaplan-Meier estimate of the cumulative probability of leukemic complications was 6.3 ± 2.6% (mean ± SE) 7 years after the start of treatment.	[14]
1,474 patients with stage II or III breast cancer receiving adjuvant chemotherapy.	The 10-year estimated leukemia rate 0.5% (95% CI, 0.1% to 2.4%) for the chemotherapy-only group.	[30]
3,363 1-year survivors of ovarian cancer who were treated with alkylating agents, and 333 of them were treated with CP.	The 10-year cumulative risk (mean+SE) of acquiring a leukemic disorder was 8.5%±1.6% for the overall group, while 5.4%±3.2% for the CP treated group.	[31]

II) Reproductive effects

Human Studies

Cyclophosphamide is associated with reproductive toxicities in both males and females [35, 36]. Both spermatogenesis and oogenesis are interrupted following treatment with cyclophosphamide [35]. Cyclophosphamide induced sterility is dependent upon dose, duration of exposure, and the state of gonadal function at the time of exposure [35]. In females, amenorrhea has been associated with cyclophosphamide exposure due to decreased estrogen and increased gonadotropin secretions; while in males, testicular atrophy [37], as well as oligospermia or azoospermia associated with increased gonadotropin release may develop [35].

Animal Studies

There are several animal studies showing the adverse reproductive effects following administration of cyclophosphamide, and some of them are summarized in **table 6** as below.

Table 6. Animal studies concerning reproductive effects of cyclophosphamide

Description of material	Dose	Reproductive effects	Ref.
Rabbits (female, pregnant)	Intravenous doses of 30 mg/kg for 9 days.	Increased number of embryonic deaths, The embryotoxic effect of CP administration was particularly evident in the early periods of embryonic development.	[38]
Mice (females at different stages of follicle maturation)	Pregnancies were established 1~4 weeks after administration of CP at a dose of 75mg/kg.	Conceptions attributable to follicles exposed to CP at a mature stage had a significantly lower number of implantation sites and a high resorptions rate. Malformation rate was more than 10 times higher in treated groups.	[39]
Mice (male)	Rats were administered CP (1.4, 3.4, and 5.1 mg/kg) daily for 11 wk by gavage, then mated with female rats.	No significant effects on male reproductive function such as reproductive organ weights, serum testosterone, luteinizing hormone or follicle-stimulating hormone, epididymal sperm counts or fertility were observed. However, dose-dependent pregnancy outcome were observed, such as increase rate of preimplantation loss and malformed/growth-retarded fetuses were observed.	[40]
Rats (male)	Rats of different age groups were administered different levels of CP, and then mated with female rats.	Fertility trials demonstrated that there was a dramatic fall in the number of fetuses per female. A significant decrease in epididymal sperm was observed in the high-dose group (100mg/kg for 10d).	[41]
Rats (male)	The rats received chronic CP treatment by gavage-feeding: 1, 3, 6 and 9 wk with saline (control), or 5.1 (low dose) or 6.8 (high dose) mg/kg/day of CP.	Chronic low-dose treatment of male rats with CP not only had early and striking effects on the bone marrow and the pregnancy outcome but also affected the male reproductive system in a clear time- and dose-dependent manner.	[42]

III) Teratogenic effects

Cyclophosphamide is one of the best studied teratogens: **1)** Toxicology experiments with multiple laboratory animal species showed clearly teratogenicity[32], it primarily produces central nervous system, skeletal, or facial anomalies [33]. **2)** In addition, cyclophosphamide is a known human teratogen with a recognizable pattern of malformation known as "Cyclophosphamide Embryopathy", which includes growth deficiencies (pre- and postnatal) and central nervous system, facial, and skeletal anomalies [34].

IV) Cytotoxicity

Cytotoxicity of cyclophosphamide generally considered to be the result of DNA crosslink formation through covalent bonding of highly reactive alkyl groups of the alkylating nitrogen mustards [43]. As mentioned in the "Use of cyclophosphamide in the healthcare industry" of part I, the alkylation of the 7-nitrogen atom of guanine in DNA molecules takes place by phosphoramide mustard resulting from cyclophosphamide activation. At alkaline or neutral pH condition, nitrogen mustard is converted to chemically reactive carbonium ion through imonium ion. Carboinium ions react with the N^7 of guanine residues in DNA to form a covalent linkage. The second arm in the phosphoramide mustard can react with a second guanine moiety in an opposite DNA stand or in the same stand to form crosslinks [44, 45]. Following crosslink formation, the cells will undergo apoptosis initiated by DNA damage and inhibition of DNA replication, modulation of cell cycle, and other anti-proliferative effects [46~49].

Part 5 Regulations and guidelines

I) Exposure limit

Currently, no occupational exposure limit of cyclophosphamide for Canada or any other international bodies were established.

II) Hazard classification

Information on classification of cyclophosphamide by multiple systems as an occupational or environmental hazard was summarized in **table 7**.

Table 7. Hazard classification of cyclophosphamide

System/jurisdiction	Classification/note
Health Canada DSL (Domestic Substances List)	High priority substance (added under the Food and Drug Act)
Canadian Environmental Protection Act (CEPA), 1999	Not listed
U.S. EPA: Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)	Reportable Quantity (RQ) = 10 lb
U.S. EPA: Resource Conservation and Recovery Act	Listed as a hazardous constituent of waste. Listed hazardous waste: waste codes in which listing is based wholly or partly on substance-U058
U.S. FDA	Cyclophosphamide is a prescription drug subject to labeling and other requirements
IARC	1, carcinogen to humans

Part 6 Control Methods

Since no governmental regulatory agencies have established exposure limit for cyclophosphamide, our control methods should eliminate or reduce potential exposure as much as possible..

I) Substitution

Substitution involves using a less hazardous substance or a substance in a less hazardous form. Australian WorkSafe Victoria [49] recommends that substitution can be achieved from the following aspects:

- Purchase single-dose preparations
- Purchase cytotoxic drugs in a liquid form rather than in a powder form
- Use a more dilute form of cytotoxic drug where possible
- Incorporate handling techniques that minimize aerosol generation
- Purchase drugs in vials, not ampoules
- Purchase drugs in plastic vials, or vials reinforced with plastic casings.

II) Engineering Control

Handling techniques and equipment

Equipment used for preparing drugs should reduce the potential of generating high pressure or release of cytotoxic drugs [49]. Engineering control methods for handling of cytotoxic drugs include [49]:

- Use of Luer-lock syringes and fittings to keep connections together
- Use of Luer-slip syringes (only if Luer-lock connections are incompatible) such as intrathecal needles
- Use of syringe-to-syringe connectors when transferring solutions from one syringe to another
- Use of wide bore needles to reconstitute and draw-up cytotoxic drugs
- Use of filter needles only when the cytotoxic drug has been removed from a glass ampoule, or if particulate matter is visible, for example if coring of a vial rubber has occurred
- Use of air-venting devices to equalize pressures and to prevent the passage of powder, aerosols and liquids

Pharmaceutical Isolators

Isolation is one way of reducing the risk of exposure, as it involves separating people from the substance by barriers to prevent or reduce contact [49]. The use of a pharmaceutical isolator was developed out of three main considerations [50]: **(i)** It has to provide a physical barrier and a permanently closed working environment which avoid direct skin contact between handlers and toxic products. **(ii)** The air is released through an air exhaust system outside the preparation room directly into the atmosphere, which avoids inhalation risks of the cytotoxic drugs. **(iii)** It also has to protect the pharmaceutical product from microbiological contamination during drug reconstitution.

Both positive and negative pressure isolators can be used to achieve the above function. The isolators are enclosed systems and rely on a steady flow of filtered air during use. A slight pressure differential is placed on the isolator (either positive or negative), and air entering and leaving the isolator under both pressure conditions, will go through the high-efficiency particulate air (HEPA) filters [51]. However, in case of a leak on the isolator, the positive pressure system will allow air that may be contaminated with cytotoxic drug to enter the workplace; while a negative pressure system will let air which contains bacterial enter the isolator and contaminate the preparation. One study by UK HSE focused on comparing the effectiveness of positive and negative pressure isolator in two pharmacy units, and no significant difference was found in operators' exposure level [52]. In addition, the exposure level and measured absorption were significantly lower than previous studies done in healthcare work environment without isolation systems, which suggests that a correctly designed isolator can reduce the risk to the operator; regardless of the pressure difference is positive or negative.

Vertical laminar flow hood

Horizontal laminar flow work bench which are commonly used in ordinary pharmaceutical department is **not** recommended for preparing cytotoxic drugs. The reason is that while this type of unit provides product protection, it may expose the operator and the other room occupants to aerosols generated during drug preparation procedures [55]. Therefore, a vertical laminar flow biological safety cabinet that provides both product and operator protection is needed for the preparation of cytotoxic drugs. This is accomplished by filtering incoming and exhaust air through a HEPA filter. It should be noted that the filters are not effective for volatile materials because they do not capture vapors and gases. Personnel should be familiar with the capabilities, limitations and proper utilization of the biological safety cabinet selected [55].

III) Administrative control

Training

Employers should ensure that only employees who have received appropriate training, and have obtained the required level of proficiency to perform tasks involving the use of cyclophosphamide. Training should occur on an ongoing basis, with a review every two years or when new equipment is introduced or procedures change [49].

The training should include the following elements:

- Occupational hazards of exposure to cytotoxic drugs and waste
- Legislative requirements for health and safety
- Legislative requirements for waste management
- The risk management process
- Control measures and work practices to be adopted when handling cytotoxic drugs and waste
- Maintenance of equipment
- Correct selection, use, cleaning and disposal of personal protective equipment
- Procedures to be adopted in the event of an accident, injury or spill
- Access to first aid resources
- Storage, transport, treatment and disposal of cytotoxic waste

Spill management

Spills of cytotoxic drugs should be avoided in the first place, as the decontamination of the spill spot may be extradinary difficult. One study indicates that commonly used cleaning agents, such as CaviCide®, Phenokil ™, chlorohexidine and bleach, cannot completely eliminate cytotoxic drug contaminated surfaces, even combined with organic solvents or de-ionized water [57].

If spills of cytotoxic drugs and related waste happen, they must be dealt with immediately as they present a high risk of exposure. People in the immediate vicinity of a spill should be alerted immediately and told to stay clear [56]. Ancillary workers should assist only in the containment of a spill, while alerting trained personnel [56].

Other Administrative Controls

Other administrative control measures include:

- Allocate responsibilities for health and safety
- Reduce the number of employees who work with cytotoxic drugs
- Keep containers of cytotoxic drugs secure and tightly lidded when not in use
- Prohibit eating, drinking and smoking in work areas
- Develop and implement standard operating procedures for all work activities
- Provide appropriate information, education and training to employees
- Use cytotoxic signs and labels to clearly identify all cytotoxic drugs from other waste
- Develop emergency procedures to deal with spills

IV) Personal protective equipment

Specific information for PPE to protect worker from cytotoxic drug exposure is available under Section 6 of WorkSafe BC OHS Regulation. According to section 6.55, personal protective equipment program should include the following elements [59]:

- Medical gloves that are manufactured and designed for use when handling cytotoxic drugs
- A moisture resistant, long-sleeved gown with cuffs
- If there is a risk of contact with aerosols, an approved respirator
- If there is a risk of eye contact, eye and face protection.
- Used gowns and gloves must not be worn outside the preparation, administration or storage area and must be handled as hazardous waste or contaminated linen.

WCB Saskatchewan has the following requirements concerning the use of respirators, gloves, protective gown and eye protection [58]:

*"……Approved **respiratory protective** devices include a reusable facemask with filter cartridges, or a disposable filter mask. The filter cartridges or the filter mask must provide HEPA filtration and carry NIOSH label with either N100, P100, or R100 rating. These respirators are available from most safety equipment suppliers. Surgical masks are neither suitable nor adequate to protect the worker."*

*"……Thicker **gloves** provide better protection, as cytotoxic drugs can permeate most glove materials — including latex. Non-powdered gloves are preferred because powders adsorb the drugs. Powdered latex gloves also adsorb latex proteins. Workers who use powdered latex gloves are exposed to more of the latex proteins that cause latex allergy in some persons. Workers who have developed an allergy to latex proteins must be provided with vinyl or nitrile gloves or glove liners."*

*"……A **gown** made of low permeability fabric with a closed front, long sleeves, and closed cuffs is recommended."*

*"……**Eye protection**, such as splash goggles, should be made available for use in any situation where there is a risk of splashes into the eyes. Eye protection should also be used when cleaning up spills."*

Previous studies showed that one major exposed skin area was hand [17, 19, 29], so gloves are of essential importance in the personal protection equipment system. U.K. HSE recommends wear two sets of gloves ("double gloving") whenever performing tasks involving CPH and other hazardous/antineoplastic drugs [51].

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