



TOXICOLOGY PROFILE

METHOTREXATE IN THE HEALTH CARE INDUSTRY

Prepared by Hanchen Chen, *Disease Prevention Team*.

Submitted to Dr. George Astrakianakis



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Summary

This report focuses on methotrexate (MTX) in the healthcare industry, including basic properties, use in healthcare settings, exposure routes, health effects, regulations and control measures.

Methotrexate is a widely used anti-neoplastic, anti-inflammatory and immunosuppressive drug, administered via oral or injection. Healthcare workers may be exposed to methotrexate through dermal contact, inhalation and unintentional swallowing or injection during drug preparation, drug administration, waste handling and spills.

Methotrexate has negative effects on pulmonary system, bone, and liver. It is not classifiable as carcinogen by IARC, and there are contradictory conclusions concerning its carcinogenicity in animal and human studies. However, MTX showed carcinogenicity in one epidemiology study and co-carcinogenicity in two animal studies. MTX has shown to be cytotoxic as it can induce chromosome aberrations. MTX has negative reproductive effects and was evaluated as a “human teratogen” by IARC.

Currently, there is no occupational exposure limit established for methotrexate in Canada or any other international bodies.

Methotrexate exposure can be reduced or eliminated by substitution or using pharmacy isolators, or vertical laminar ventilation hood. One study showed a significant reduction of MTX in the urine after the use of a laminar ventilation hood in one pharmacy unit. PPE such as gloves, respiratory protection, gowns and eye protection should be used as a last resort.

Part I General Information

I) Name

Methotrexate

II) Formula

$C_{20}H_{22}N_8O_5$

III) CAS Number

59-05-2

IV) Synonyms and trade names

4-Amino-10-methylfolic acid

4-Amino-N10-methylpteroylglutamic acid

Antifolan

CL-14377

N-[p-[(2,4-Diamino-6-pteridiny)methyl]methylamino]-benzoyl L-(+)-glutamic acid

N-(4-[[[(2,4-Diamino-6-pteridiny)methyl]methylamino]-benzoyl]-L-glutamic acid

N-[p-[(2,4-Diaminopteridin-6-yl-methyl)methylamino]benzoyl]-L-glutamic acid

L-(+)-N-(p-[[[(2,4-Diamino-6-pteridiny)methyl]methyl-amino]benzoyl]glutamic acid

Ledertrexate

a-Methopterin

A-Methopterin

Methotrexate specia

Methotrexatum

Methylaminopterin

MEXATE

MTX

Methotrexate Sodium

V) Properties and Use

The chemical structure of methotrexate is similar to folic acid. Methotrexate inhibits the enzyme dihydrofolate reductase, which decreases DNA and RNA synthesis [1]. Consequently, growth of cancer cells is stopped. Therefore, it is used in treating cancers such as choriocarcinoma, leukemia in the spinal fluid, osteosarcoma, breast cancer, lung cancer, non-Hodgkin lymphoma, and head and neck cancers [7]. In addition, methotrexate is an immunosuppressive and anti-inflammatory medicine, which can reduce the activity of the immune system and body metabolism [8]. In rheumatoid arthritis, this action helps to reduce inflammation in the joints and thus reduce pain and swelling; it also limits damage to the joints and helps to prevent disability in the long term [8]. More recently, methotrexate has been used in women of reproductive age for treatment of ectopic pregnancy [67].

Methotrexate has been widely used in oncochemotherapy at high doses (1000mg~5000mg a day) [1,2] and in the treatment of other non-neoplastic diseases at much lower doses and longer durations [34], such as psoriasis [3], rheumatoid arthritis [4], and steroid-dependent asthma [5]. Methotrexate may be taken by mouth as a tablet or given by injection either into the muscle or under the skin. Injections may be used instead of tablets if the medicine is not being absorbed well, or if the patient may feel sick (nausea) or vomit when taking the tablets [1].

VI) Side-effects

The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress [6]. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection [6].

VII) Analytical Methods

HPLC

Reverse Phase HPLC with UV detector has been used as an analytical method in most environmental and biological monitoring studies. Limit of detection can be as low as 0.07 $\mu\text{g}/\text{m}^3$ for air samples [28], 18ng/glove for glove samples [31], 0.001ng/cm² for surface wipe samples [33], and 2nmol/L for urine samples.

Radioimmunoassay

Fluorescence polarization immunoassay and other analytical methods are used to quantify methotrexate concentration. However, this approach is susceptible to several interfering substances, such as methotrexate metabolite 7-hydroxymethotrexate [29].

Part 2 Exposure among healthcare workers

I) Healthcare workers at risk

Both clinical and nonclinical workers may be exposed to anti-neoplastic drugs not only when they prepare and administrate drugs, but also when they clean up spills, touch contaminated surfaces during the preparation, or dispose of hazardous drugs and medical waste [9, 10]. Job tasks with potential exposure to methotrexate can be categorized into three groups: “drug preparation”, “drug administration” and “waste and spills handling and disposal” [11]:

DRUG PREPARATION

- Withdrawal of needles from drug vials [11].
- Breaking open of ampoules [11].
- Reconstituting powdered or lyophilized drugs and further diluting either the reconstituted powder or concentrated liquid forms of hazardous drugs [12].
- Expelling air from syringes filled with hazardous drugs [11].
- Counting out individual, uncoated oral doses and tablets from multi-dose bottles or unit-dosing uncoated tablets in a unit-dose machine.
- Crushing tablets to make oral liquid doses [13-15].
- Compounding potent powders into custom-dosage capsules.
- Contacting measureable concentrations of drugs present on drug vial exteriors, work surfaces, floors, and final drug products, such as bottles, bags, cassettes, and syringes [16-19].

DRUG ADMINISTRATION

- Administering hazardous drugs by intramuscular, subcutaneous, or intravenous (IV) routes.
- Generating aerosols during the administration of drugs, either by direct IV push or by IV infusion.
- Clearing of air from the syringe [11].
- Priming the IV set with a drug-containing solution at the patient bedside.
- Leakage at the tubing, syringe or stopcock [11].
- Performing certain specialized procedures in the operating room, such as intraoperative intraperitoneal chemotherapy [20, 21].

WASTE & SPILLS HANDLING AND DISPOSAL

- Handling wastes of patients who receive antineoplastic drugs, such as urine, feces and sweat [11].
- Handling body fluids or body-fluid-contaminated clothing, dressings, linens, and other materials [22,23].
- Handling contaminated wastes generated at any step of the preparation or administration process.
- Handling unused hazardous drugs or hazardous-drug-contaminated waste.
- Decontaminating and cleaning drug preparation or clinical areas.
- Transporting infectious, chemical, or hazardous waste containers.
- Removing and disposing of personal protective equipment (PPE) after handling hazardous drugs or waste.

II) Monitoring Data

There are both environmental and biological (urine) monitoring studies of methotrexate among healthcare workers. Air and wipe samples were collected to assess MTX levels in the working environment, and urine samples were collected as biological indicators of exposure. Results of the **environmental** and **biological** monitoring studies are summarized in **table 1** and **table 2** respectively.

Table 1. Environmental monitoring of methotrexate in healthcare settings

	Area	Sampling Size	Exposure Level	Analysis Method	Reference
Air	Drug preparation area	17	All samples below LOD.	HPLC ^a	[17]
	Drug preparation area	4	MTX was detected in only one sample during drug preparation (0.3 µg/m ³)	HPLC	[26]
	Pharmaceutical plant	8	Mean: 10µg/m ³ Range: 0.8–182 µg/m ³	FPIA ^b , LOD ^c 0.07µg/m ³	[28]
	Clinical pharmacy department	2	Both samples under LOD	HPLC/UV, LOD: 0.3µg/m ³	[30]
Glove	Clinical pharmacy department, outpatient department (preparation)	10	Among the 10 pairs of gloves, 4 pairs were contaminated, ranging from below LOD to 49 µg/glove	HPLC/UV, LOD: 6µg/glove	[30]
	Drug preparation area	17	MTX was detected in only 2 samples, with the level of 220 and 1900 µg/pair.	HPLC	[17]
	Oncology department	18	MTX were detected on 9 pairs of gloves, ranging from 18 to 49.3 ng/glove.	Enzyme-linked immunoassay, LOD 18ng/glove	[31]
Surface	Drug preparation area	4	Contamination of the laminar airflow hood ranged from 2–633 ng/cm ² , while contamination of floor was not found.	HPLC	[26]
	Drug preparation area	8	Only 3 samples detectable inside the isolator (ranged from 1.81 to 8.61 ng/cm ²)	HPLC/UV	[27]
	Clinical pharmacy department,	N/A	Contamination of floor and hoods with MTX was found	HPLC/UV,	[30]

outpatient department (preparation and administration), and oncology department		in the outpatient department (administration) and oncology department, ranging from 5.5 to 5.9 ng/cm ²	LOD: 0.4~1 ng/cm ²	
Oncology department	8	Contamination with MTX was detected among all sampling spots (mean: 14.8 ng/sample, range 11~19 ng/sample).	Enzyme-linked immunoassay	[31]
Drug preparation area	28	MTX was detected on the hood, floors, door handles and taps, ranging from below LOD to 251ng/cm ² .	HPLC/EITMS ^e , LOD: 1.1µg/L	[32]
Drug preparation area	34	Contamination of surfaces of hood, telephone, handles, table board and shelves was found, with range from below LOD up to 64.5 µg/m ² .	HPLC/UV, LOD: 0.001ng/cm ²	[33]

a. High Performance Liquid Chromatography

b. Fluorescence polarization immunoassay

c. Limit of Detection

d. High Performance Liquid Chromatography/Electrospray Ionization Tandem Mass Spectrometry

Table 2. Biological monitoring (urine) of methotrexate among healthcare workers

Job Category	Sampling Size	MTX Level	Analysis Method	Ref.
Pharmaceutical plant worker	11	Mean ^a : 13.4 µg Range: 6.1-24 µg	FPIA	[28]
Oncology ward staff	20	All samples below LOD	Enzyme-linked immunoassay, LOD: 2nmol/L	[31]

a. MTX-equivalent, which was adjusted for background fluorescent levels. Total urine was collected in portions during the period of about 72-96 h starting from the beginning of the working day

III) Route of Occupational Exposure and Elimination

Primary routes for exposure among healthcare workers are inhalation and dermal absorption [9,11]. Inadvertent ingestion from hand to mouth contact and unintentional injection through needle-sticks or sharps are possible but less common routes of exposure [24, 25].

Inhalation

Inhalation of antineoplastic drugs may occur during aerosolization of powder or liquid during reconstitution or from inhalation of vapors from accidental spillage, which may occur during drug preparation or administration to the patients.

Dermal

Administering the drugs to the patients, and handling the patients directly may expose health care workers to antineoplastic drugs through dermal contact. For example, nurses may come into contact with bodily excretions such as urine, feces, sweat and saliva in caring for the patients who receive antineoplastic drugs.

One environmental contamination study suggested that methotrexate might permeate through cotton or latex gloves, but the permeation rate is much slower compared with cyclophosphamide and 5-fluorouracil [17]. One possible reason

for the difference might be that methotrexate has a higher molecular weight and polarity than the other two substances, both of which will prevent quick permeation of gloves.

Biological half life

Methotrexate can be eliminated through sweat and urine [88]. Using pharmacokinetic analysis, the elimination half-life was calculated to be 11.1 hours [88].

Part 3 Health Effects

I) Pulmonary Effects

Methotrexate can be associated with a variety of acute toxic reactions when given in a relatively large dose over a short period of time [38]. In one study, after giving an extremely large dose of methotrexate ($15\text{mg}/\text{m}^2/\text{i.v.}/\text{day}\times 5\text{days}$), children with lymphocytic leukemia developed acute drug reactions consisting of inflammation of the vaginal, pleural, pulmonary, and bladder epithelium, as well as skin and conjunctive surface, and severe ulceration of the gastrointestinal tract [38]. Pulmonary reactions were the site of the most serious reactions [38], including episodes of pneumonia reported to occur approximately 12 days after the first dose of intravenous methotrexate.

II) Effects on Bone

Clinical research has verified the detrimental effects of methotrexate chemotherapy on bone through increased fracture incidence [38-40]. Quantitative studies using single photo absorptiometry demonstrated a reduction in bone mineral content between 6 and 9 months after methotrexate treatment [41]. In addition, it is well documented that one course of methotrexate will induce osteopenia and depress bone formation 14 days following treatment [42]. One animal study with Sprague-Dawley rats focused on whether the alternation in bone was reversible or not, and they found that methotrexate alters both cortical and cancellous bone, and recovery from osteoblast and osteoclast was not observed [43]. Another animal study with female Sprague-Dawley rats found that prolonged administration of low-dose methotrexate in rats caused significant osteopenia and increased bone resorptions [37].

III) Hepatotoxicity

Methotrexate is metabolized into a polyglutamated form, then the metabolite is retained within the liver cell long term, which may be the major cause of hepatotoxicity [48,49]. There are several case reports of hepatic fibrosis at autopsy in leukemia patients who received antimetabolite therapy, including methotrexate [44, 45]. For patients receiving low-dose methotrexate therapy, advanced hepatic fibrosis is much less frequent [50]. Abnormal liver function tests have been noted in women receiving methotrexate for choriocarcinoma [46], and increased mortality from hepatic disease was found among psoriatics receiving methotrexate [60]. One study focusing on hepatotoxic effects among 22 patients receiving intensive methotrexate therapy found that values for SGOT, SGPT, LDH and BSP were significantly higher in cases than the control group; in addition, liver biopsies revealed inflammation of chronic portal appearing in 7 cases [47]. A retrospective analysis of 104 psoriasis and psoriatic arthritis patients treated with methotrexate found different outcomes: In most cases, adverse drug reactions (ADR) were mild, and liver changes and serum enzyme level increases were not a major problem in the patients [51].

IV) Carcinogenicity

Animal studies

Animal studies concerning the carcinogenicity, mutagenicity, cytotoxicity and clastogenicity of methotrexate are summarized in **table 3** below. From the results we can see that there was no increased tumor rate among methotrexate treated rats, mice and hamsters.

Table 3. Animal studies concerning the carcinogenicity of methotrexate

Study group	Dose	Conclusion	Ref.
Sprague-Dawley rats	0.1, 0.2 and 0.4mg/kg MTX as dietary admixtures on a 5 days on, 9 days off for 23 mo.	No evidence of either early onset or increased incidence of any tumor type was found in the MTX-treated group. In addition, no significant increase in chromosomal aberrations was seen in any dose group relative to the control group. Thus it is concluded that MTX has no oncogenic potential in rats.	[34]
Swiss mice and Syrian golden hamsters	The mice were administered 10, 8, 5, or 3 ppm of MTX in the diet on alternate weeks for life, while the dose of the hamsters was 20, 10, or 5 ppm.	The incidence of tumors was not increased in either species.	[55]
Mice and rats	0.15~1.0mg/kg/dose, 3 times weekly for 6 mo.	The incidence of tumors was not increased in either species.	[56]

Human studies

There are human studies concerning the carcinogenic risk of methotrexate treatment, including one epidemiological study and several case reports of patients who develop malignancies during or following methotrexate treatment, and the results are summarized in **table 4**. 5 out of 6 studies did not reveal elevated incidence of cancer among methotrexate treated patients, and the remaining one study found a 2-fold relative risk after adjusting for possible confounders.

Table 4. Human studies concerning the carcinogenicity of methotrexate

Study population/case	Conclusion	Notes	Ref.
1380 patients with severe psoriasis treated with MTX and PUVA.	High-level exposure to methotrexate is a significant independent risk factor for developing squamous cell carcinoma (SCC), with relative risk of 2.1 (95% CI 1.4~2.8).	This study adjusted for confounding factors such as age, sex, geographic residence and level of exposure to PUVA radiation, which is commonly used in combination of MTX to treat psoriasis.	[57]
224 patients received MTX therapy during 1960 to 1965	No increased incidence of total internal malignancy was found, nor did any one type of neoplasm appear predominant.		[60]
1380 patients with severe psoriasis	Case-control analysis showed no increase of the risk of noncutaneous or cutaneous malignancy. Relative risk was 0.96 and 1.2 for noncutaneous and cutaneous malignancies respectively.	No adjustment of confounding factors, including other therapies received by the patients.	[61]
A psoriasis patient taking	The patient developed transitional cell carcinoma of the	Definitive cause-and-effect judgment	[58]

MTX.	nasopharynx with metastasis to the cervical nodes.	cannot be made on the basis of isolated reports	
Patients with chronic obstructive pulmonary disease (COPD), asthma and rheumatoid arthritis receiving low-dose MTX.	There are three cases of malignancies: malignant neoplasm, pneumonitis and pancytopenia.		[59]
18572 patients with rheumatoid arthritis	The study did not show an increased SIR of lymphoma in patients receiving MTX compared with those who were never exposed to MTX. They also did not find a causal relationship between rheumatoid arthritis and the development of lymphoma.	Epidemiology study with largest investigation scale ever.	[76]

In addition, methotrexate has been administered in combination with known carcinogens to test for its co-carcinogenic potential, which are summarized in table as below. 3 out of 5 studies showed negative effects, and the remaining 2 showed positive effects, which indicated that methotrexate may act as a promoter. Studies concerning the co-carcinogenicity of methotrexate are summarized in [table 5](#).

Table 5. Studies concerning co-carcinogenicity of methotrexate

Species	MTX regimen	Carcinogen regimen	Conclusion	Ref.
Syrian hamsters	0.06 mg, 3 times per week, 8 to 12 weeks in total	0.5% DMBA TOP to buccal pouch, 3 times per week, 8 to 12 weeks in total	Compared with the group receiving DMBA alone, MTX together with DMBA accelerated tumor growth, and the tumors occurred earlier and were more anaplastic.	[35]
White Swiss mice	0.2 mg/kg in diet	0.5% methylcholanthrene (MC) TOP for 11 weeks to shaved dermis	Compared with the group receiving MC alone, MTX together with MC resulted in increased tumor rate and decreased tumor latency.	[36]
Syrian hamsters	0.15 mg subcutaneous, 1 time per week, 18~26 weeks in total	0.5 DMBA TOP to tongue 3 times weekly for 18~26 weeks	No co-carcinogenic effects	[52]
Syrian golden hamsters	0.1mg TOP 3 times per week to buccal pouch for 6~12 weeks	0.5% DMBA TOP 3 times per week to buccal pouch	No co-carcinogenic effects	[53]
C3Hf/HeN mice	2mg/kg intraperitoneal, 3 times per week, 23 weeks in total	UV light, 3 times per week	No co-carcinogenic effects	[54]

V) Cytogenetic Toxicity

Methotrexate was reported as a weak clastogen and it induced chromosomal aberrations in bone marrow of mice after multiple treatments [62]. Methotrexate could induce chromosomal aberrations in mice bone marrow, and it was found highly clastogenic in mice bone marrow even after a low dose single treatment [75]. Other studies showed its clastogenicity in human bone marrow of methotrexate treated patients [63,64], but it was nonclastogenic in human lymphocytes *in vivo* [64]. In addition, a progressive accumulation of strand breaks in post-replication DNA arising out of spontaneous and normally repaired DNA lesions that had not been repaired due to shortage of dTTP and purine nucleotides after methotrexate treatment has been reported [76].

VI) Teratogenicity, Reproductive and Developmental Effects

Methotrexate achieves its antineoplastic and anti-inflammatory effects through inhibition of dihydrofolate reductases; this action interrupts the synthesis of thymidylate, purine nucleotides, and the amino acids serine and methionine, thereby interfering with the formation of DNA, RNA and proteins [68]. Thus methotrexate has potential reproductive effects during pregnancy [67].

Most of the reported cases of pregnant women exposed to methotrexate have documented normal pregnancy outcomes [70,71]. However, of the 48 reported cases of methotrexate exposure, three have documented fatal deformities [72-74]. All three exposures were in the first trimester, when the risk for anomalies resulting from exposure to folate antagonists is assumed to be highest. Methotrexate exerts cytotoxicity to trophoblasts and has the potential of inducing early abortion [66]. Anecdotal reports of patients treated with methotrexate for arthritis have implicated methotrexate as either a teratogen or an abortifacient [69].

Consequently, based on those case reports, methotrexate is a human teratogen according to IARC evaluation [65]. US Food and Drug Administration (FDA) has placed methotrexate in risk category D (there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk) based on the fact that it may cause neural defects when used in the first trimester [67].

Part 4 Regulations

I) Exposure Limit

Currently, there is no occupational exposure limit established for methotrexate in Canada or any other international bodies.

II) Hazard Classification

Hazard classification of methotrexate was summarized in [table 6](#) below.

Table 6. Hazard classification of methotrexate

System/Jurisdiction	Classification/Note	Ref.
Health Canada Domestic Substances List (DSL)	NDSL (Non-domestic Substances List). The NDSL is an inventory of substances that are not on the DSL but are accepted as being in use internationally. Substances that are not on the DSL but are listed on the NDSL are subject to the <i>New Substances Notifications Regulations (Chemicals and Polymers)</i> of the <i>Canadian Environmental Protection Act, 1999</i> .	[77]
IARC	Methotrexate is not classifiable as to its carcinogenicity to humans (Group 3)	[65]
IARC	Methotrexate is a human teratogen	[65]
US FDA	Risk category D (there is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk)	[67]
US NIOSH	Registry of Toxic Effects (RTECS) Identification Number: MA1225000	[78]

Part 5 Control Measures

Since no governmental regulatory agencies have established an exposure limit for methotrexate, 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 liquid form rather than in 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 Controls

Handling techniques and equipment

Equipment used for preparing drugs should reduce the potential of generating high pressure or release of cytotoxic drugs [79]. Engineering control methods for handling cytotoxic drugs include [79]:

- 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 to reduce 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 [80]: (i) It has to provide a physical barrier and a permanently closed working environment, which prevent 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 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 that 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 [81]. However, in case of a leak in 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 isolators in two pharmacy units; no significant difference was found in the operators' exposure levels [82]. In addition, the exposure level and measured absorption were significantly lower than previous studies done in healthcare work environments, without isolation systems, which suggest that a correctly designed isolator can reduce the risk to the operator; regardless if the pressure difference is positive or negative.

Vertical laminar flow hood

Horizontal laminar flow work benches, which are commonly used in ordinary pharmaceutical department, are **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 [83]. 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 filtration of the 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. One study found that the urine burden in oncologic nurses decreased after a central pharmacy unit with laminar airflows with outside-air exhaust was installed [88].

Personnel should be familiar with the capabilities, limitations and proper utilization of the biological safety cabinet selected [83].

III) Administrative controls

Training

Employers should ensure that only employees who have received appropriate training, and have obtained the required level of proficiency are performing tasks involving the use of methotrexate. Training should occur on an ongoing basis, with a review every two years or when new equipment is introduced or procedures change [79].

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

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 [84]. Thus, extra precautions to prevent spills of cytotoxic drugs are needed.

If spills of cytotoxic drugs and related wastes occur, 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 [85]. Ancillary workers should assist only in the containment of a spill, while alerting trained personnel [85].

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 on PPE to protect workers from cytotoxic drug exposure is available under Section 6 of WorkSafe BC OHS Regulation. According to section 6.55, a personal protective equipment program should include the following elements [86]:

- 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 [87]:

*“.....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.”*

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