



**Preventing occupational and
environmental exposure to cytotoxic drugs
in veterinary medicine**

**Document of the European College of Veterinary Internal
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Introduction

Cytotoxic drugs, sometimes known as antineoplastic, anticancer or cancer chemotherapy drugs, include any drug that inhibits or prevents the function of cells. Cytotoxic drugs are used to treat cancer and in some cases, to treat immunologic diseases. However, their actions are not specific to tumour cells and normal cells may also be damaged. As a result these drugs can produce significant side effects in patients or others exposed.

Reasons for concern

There is concern over the potential of cytotoxic drugs to harm workers who are at risk at exposure. This includes workers who prepare, administer, or handle the drugs. The concern is based on:

- toxic side effects seen in patients treated with these drugs
- evidence that these drugs can produce chromosome changes, cancer, and reproductive abnormalities in animal experiments
- even adverse effects in workers exposed to these drugs

When therapeutic doses are given to patients, cytotoxic drugs produce toxic side effects due to their poor selectivity between target (e.g., cancer cells) and normal cells.

There is ample evidence that many of these drugs cause serious adverse effects in cancer patients receiving long-term therapy. These adverse effects include:

- neoplasms and leukemias
- testicular and ovarian dysfunction — including permanent sterility
- cumulative chromosome damage
- other organ damage

Animal studies confirm the potential of these agents to induce malignancy and to cause chromosomal damage and reproductive abnormalities. *Appendix 1* lists antineoplastic or anti-cancer drugs that have been classified by the International Agency for Research on Cancer (IARC) as possible or probable cancer-causing agents.

Not all cytotoxic drugs are carcinogenic. In particular, antimetabolites such as methotrexate (amethopterin), cytarabine (cytosar), and 5-fluorouracil (5-FU) have not caused cancer in animal studies or in humans receiving therapeutic treatments, despite their use by a large number of patients over many years. On the other hand, the alkylating agents (in particular nitrogen mustards, ethylenimine derivatives, and nitrosoureas) have been shown repeatedly to be carcinogenic in laboratory systems and in cancer patients.

Studies of worker exposure to cytotoxic drugs have shown:

- detectable levels of cytotoxic drugs in the air of hospital areas where parenteral cytotoxic drugs are prepared without the use of biological safety cabinets (BSC)
- detectable amounts of various cytotoxic drugs in the urine of health care workers preparing the drugs without adequate precautions

There is also evidence that exposure to cytotoxic drugs can cause adverse effects in workers.

There are reports that exposure to cytotoxic drugs:

- can cause an increased frequency of chromosome damage in exposed workers
- can produce some acute effects in workers which include skin, eyes, and mucous membrane irritations, allergic reactions upon contact with the skin, as well as subjective symptoms including nausea, headache, and dizziness
- has been associated with adverse reproductive outcomes (including higher incidences of spontaneous abortions and a higher risk of delivering malformed babies)

Repeated, long term occupational exposure to small amounts of cytotoxic drugs has not been identified as a cause of cancer. However, because of the above mentioned concerns, precautions must be followed to limit occupational exposure to all cytotoxic drugs.

Veterinary Practice

In veterinary medicine the use of cytotoxic drugs as antineoplastic agents and immunosuppressive treatment is expanding. Persons at risk here are the veterinarian, the technician, the pharmacist, the cleaner, and the owner and his family. The potential therapeutic benefits of hazardous drugs usually outweigh the risks of side effects. However people exposed to these drugs because of their animal being treated, risk side effects without any therapeutic benefit.

Control of Exposure

In order to diminish the risk of exposure to persons the speciality of Oncology of the European College of Veterinary Internal Medicine – Companion Animals (ECVIM-CA) makes the following recommendations:

- Only use chemotherapy in animals if there is a proof for Evidence-Based Medicine¹ efficacy of that drug/protocol for the type of cancer concerned
 - If efficacy has not been proven:
 - No “trial and error”!
 - Only investigational use in controlled clinical trials

Note:

As efficacy of cytotoxic drugs in human medicine is no guarantee for success in veterinary medicine, these drugs/protocols should also be evaluated in a controlled clinical trial.

- Start treating animals with immune mediated diseases with non-cytotoxic agents e.g. prednisone, in view of
 - lack of proof of efficacy of cytotoxic immunosuppressive agents in veterinary medicine
 - potential hazards to environmental and occupational exposure
- Protocols for handling cytotoxic drugs and related waste have been developed and are included in this document. These protocols are based on present human protocols of among others the NIOSH and the MARC.

Sources:

- *International Agency for Research on Cancer* (<http://www.iacr.com.fr>)
- *National Institute for Occupational Safety on Health* (<http://www.cdc.gov/niosh/>)
- *Management and Awareness of Risks of Cytotoxic Handling* (<http://www.marchguidelines.com>)
- *Module Kankerverwekkende Stoffen, KNMvD, March 2005.*

1 Evidence-based medicine (EBM): "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. David Sackett, et al. "Evidence Based Medicine: What It Is and What It Isn't," *BMJ* 312, no. 7023 (1996).

Literature:

Anwar WA, Salama SI, Serafy MM, Hermida S and Hafez AS. Chromosomal aberrations and micronucleus frequency in nurses occupationally exposed to cytotoxic drugs. *Mutagenesis*. 1994;9:315-317.

Ensslin AS, Huber R, Pethran A, Pethran A, Rommelt H, Schelerl, Kulka U and Fruhmann G. Biological monitoring of hospital pharmacy personnel occupationally exposed to cytostatic drugs: urinary excretion and cytogenetics studies. *Int Arch Occup Environ Health* 1997 70:205-208.

Ensslin AS, Pethran A, Schierl R and Fruhmann G. Urinary platinum in hospital personnel occupationally exposed to platinum-containing antineoplastic drugs. *Int Arch Occup Environ Health*. 1994a; 65:339-342.

Ensslin AS, Stoll Y, Pethran A, Pfaller A, Rommelt H and Fruhmann G. Biological monitoring of cyclophosphamide and ifosfamide in urine of hospital personnel occupationally exposed to cytostatic drugs. *Occup Environ Med* 1994;51:229-233.

Favier B, Gilles L, Gesage M and Latour JF. Analysis of cyclophosphamide in the urine of antineoplastic drug handlers. *Bull Cancer*. 2003; 90:905-909.

Favier B, Gilles L, Latour JF, Desage M, Giammarile F. Contamination of syringe plungers during the sampling of cyclophosphamide solutions. *J Oncol Pharm Practice*. 2005; 11:1-5.

Favier B, Gilles L, Ardiet C and Latour JF. External contamination of vials containing cytotoxic agents supplied by pharmaceutical manufacturers. *J Oncol Pharm Practice*. 2003; 9:15-20.

Goloni-Bertollo EM, Tajara EH, Manzato AJ and Varella-Garcia M. Sister chromatid exchanges and chromosome aberrations in lymphocytes of nurses handling antineoplastic drugs. *Int J Cancer*. 1992;50:341-344.

Grummt T, Grummt H-J and Schott G. Chromosomal aberrations in peripheral lymphocytes of nurses and physicians handling antineoplastic drugs. *Mutat Res*. 1993; 302: 19-24.

Labuhn K, Valanis B, Schoeny R, Loveday K and Vollmer WM. Nurses' and pharmacists exposure to antineoplastic drugs: Findings from industrial hygiene scans and urine mutagenicity tests. *Cancer Nursing*. 1998;21:79-89.

Lassila O, Toivanen A and Nordman E. Immune function in nurses handling cytostatic drugs. *Lancet*. 1980;2:482.

Lovejoy N, Powers L, Flessel P, Lecocq G, Guirguis G and Chang K. Mutagenicity in urine of hospital workers who prepare and administer chemotherapy agents. *EMS Abstracts*. 1985;7.

Niklasson B, Bjorkner B and Hansen L. Occupational contact dermatitis from antitumor agent intermediates. *Contact Dermatitis*. 1990;22:233-235.

Peelen S, Roeleveld N, Heederik D, Krombout H and de Kort W. Toxic effects on reproduction in hospital personnel. 1999;Dutch Ministry of Social Affairs and Employment.

Sessink PJM, Verplanke AJW, Herber RFM and Bos RP. Occupational exposure to antineoplastic agents and parameters for renal dysfunction. *Int Arch Occup Environ Health*. 1997;69:215-218.

Sessink PJM, Kroese ED, van Kranen HJ and Bos RP. Cancer risk assessment for health care workers occupationally exposed to cyclophosphamide. *Inter Arch Occup Environ Health*. 1993;67:317-323.

Sotaniemi EA, Sutinen S, Arranto AJ, Sutinen S, Sotaniemi KA, Lehtola J and Pelkonen RO. Liver damage in nurses handling cytostatic agents. *Acta Med Scand*. 1983;214:181-189.

Stücker I, Caillard J-F, Collin R, Gout M, Poyen D and Hémon D. Risk of spontaneous abortion among nurses handling antineoplastic drugs. *Scand J Work Environ Health*. 1990; 16:102-107.

Valanis BG, Vollmer WM, Labuhn KT and Glass AG. Acute symptoms associated with antineoplastic drug handling among nurses. *Cancer Nurs*. 1993;16:288-295.

**Protocols for handling cytotoxic drugs and related waste in
veterinary medicine**

1. General guidelines

1.1 Cytotoxic agents (chemotherapy drugs) are potentially hazardous to health. It is therefore essential to take precautions to prevent contamination of personnel. Employees involved (cleaners, animal caretakers, veterinarians) must be provable informed of:

- the risks of working with cytotoxic agents
- the work in a safety cabinet
- potential methods of preventing aerosol forming and spread of contamination
- the instructions in case of an emergency and contamination
- principles of good personal protection and hygiene practice

Note:

(1) Provable informed means that of every employee involved personally signed papers of information, training procedures and instructions must be present.

(2) As an employer you have the moral and in most countries legal duty to protect the health of your employees and anyone else, e.g. the public, who may be affected by your work.

1.2 There must be a procedure for use of personal protection equipment to minimise cytotoxic exposure. These means of protection should be according to the addendum.

1.3 There must be a clear procedure and adequate materials (cytotoxic spill kit) for cleaning of spilled cytotoxic agents and there must be a clear procedure how to handle after an injection accident.

Note:

(1) An example of such a procedure is given in Appendix 6.

1.4 All potential contaminated material should be discarded in special waste disposal containers that can be opened with a foot pedal or has another mechanism to prevent direct contact with hands/gloves..

1.5 Material that is potentially contaminated should be discharged as special hospital waste.

1.6 All areas where cytotoxic agents are being prepared and/or administered or where animals are being nursed who have received cytotoxic drugs, are identified by a clear warning sign that contamination with cytotoxic drugs is possible. These areas are only open to persons who are directly involved in the process. After the preparation and/or administration or after the nursing of the animal, the area is closed and is cleaned before other activities can taken place in this area.

1.7 There should be a special protocol for cleaning of facilities where cytotoxic agents are being prepared, handled and/or administered, and for areas where animals are being nursed who have received cytotoxic drugs. In this protocol among others, the following items should be covered:

- Spread of contamination should be prevented by using new cleaning material for every new area.
- The person who cleans the area should be protected by wearing gloves.
- The efficacy of the cleaning should be checked on a regularly base with wipe tests.

Notes:

(1) Because of the current lack of availability of wipe tests for those cytotoxic drugs often used in veterinary medicine this obligation is not yet applicable.

(2) An example of a cleaning protocol is given in the appendices.

- 1.8 Areas where cytotoxic agents are being prepared or administered should be easy to clean: walls and floors should fit seamless; in the immediate proximity there should be an emergency shower and an eyewash facility. In the case that an animal that has received cytotoxic drugs is being hospitalised in a veterinary practice, these demands are also applicable for the ward area.
- 1.9 Only infusion sets and syringes with luer-lock fittings will be used to administer cytotoxic drugs. However, the use of closed system is to be preferred.
- 1.10 As a general rule pregnant women should not be involved in the process of preparing and/or administration of cytotoxic agents, caretaking of animals that have been treated with cytotoxic drugs, or cleaning of these areas. It is also the responsibility of the employee to warn the line management immediately if she is pregnant or trying to conceive.
- Note:*
- (1) *See Appendix 2 for discussion on pregnancy in employees handling cytotoxic drugs.*
- (2) *Exceptions to this rule can be made only in accordance with local procedure and after proper informed and signed consent.*

2. Guidelines for the preparation

- 2.1 The work area should be clearly designated for drug preparation and access restricted to authorised staff.
- 2.2 Preparation is most appropriately undertaken by trained staff using a negative pressure pharmaceutical isolator with externally ducted exhaust filters. If such an isolator is not present than a suitably modified Class 2B Biological Safety Cabinet (BSC) may be used. These facilities should at least be annually validated. (For details on BSC see Appendix 5)

Notes:

- (1) *Select a ventilated cabinet depending on the need for aseptic processing. Aseptic technique is important for protecting hazardous drugs from possible contamination. However, it is also important to consider worker protection and to assure that worker safety and health is not sacrificed. Therefore, when asepsis is required or recommended, use ventilated cabinets designed for both hazardous drug containment and aseptic processing.*
 - (2) *When asepsis is not required, a Class I BSC or an isolator intended for containment applications (a “containment isolator”) may be sufficient.*
 - (3) *Regardless of type, equip each ventilated cabinet with a continuous monitoring device to confirm adequate air flow before each use*
 - (4) *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.*
 - (5) *Install the outside exhaust so that the exhausted air is not pulled back into the building by the heating, ventilating, and air conditioning (HVAC) systems or by the windows, doors, or other points of entry.*
 - (6) *Place fans downstream of the HEPA filter so that contaminated ducts are maintained under negative pressure.*
 - (7) *Do not use a ventilated cabinet that recirculates air inside the cabinet or exhausts air back into the room environment unless the hazardous drug(s) in use will not volatilize (evaporate) while they are being handled or after they are captured by the HEPA filter. Information about volatilization should be supplied by the drug manufacturer.*
 - (8) *Let a certified company check the safety cabinet annually to ensure proper working order.*
- 2.3 Eating, drinking, smoking, chewing gum, applying cosmetics and storing food in or near the preparation area should be prohibited.
- 2.4 Closed or semi-closed systems should be used to prevent aerosol forming and control exposure to carcinogenic compounds.
- Note:*
- (1) *Special spike systems (like those of Codan and Braun) can be used. Other systems specially developed for the use of cytotoxic agents are recommended (e.g. Tevadaptor[®], Oncovial[®] and PhaSeal[®]).*
- 2.5 Manipulation of oral or topical medicines containing cytotoxic drugs should be avoided if possible. If unavoidable, tasks such as dividing or crushing tablets should be restricted to a controlled environment such as a BSC, ideally within a pharmacy department. Carrying out these procedures on wards or in clinics should not be allowed.
- From experience there is little need in dividing or crushing tablets. Usually smaller size of tablet or an adjustment of the dosage scheme is sufficient.*

- 2.6 During the preparation personal protection should include disposable special chemoprotect gloves, disposable protective clothing, and eye and face protection.
Note:
(1) For personal protective equipment see Appendix 4.
- 2.7 If working in a facility that has a recirculating isolator/cabinet, respiratory protection should be worn.
- 2.8 There should be clear procedures for dealing with any spillages and for the safe disposal of waste.
- 2.9 When drug preparation is complete, seal the final product in a plastic bag or other sealable container for transport before taking it out of the ventilated cabinet. Clearly label it as containing cytotoxic drugs.
- 2.10 Seal and wipe all waste containers inside the ventilated cabinet before removing them from the cabinet.
- 2.11 Remove all outer gloves and sleeve covers and bag them for disposal.
- 2.12 All potential contaminated material should be discarded in special waste disposal containers that can be opened with a foot pedal or has another mechanism to prevent direct contact with hands/gloves.
- 2.13 Wash hands with soap and water immediately after removing gloves.

3. Guidelines for administration

- 3.1 Administration should be carried out in clearly designated areas.
- 3.2 Take all necessary measures to ensure tranquillity and cooperative behaviour of the animal treated and for non-disrupted administration of cytotoxic agents. If the temperament of the animal is such that a safe administration is not to be expected the veterinarian has the right not to treat these animals.
- 3.3 Administration of a bolus injection will be done through a catheter system, which can be flushed with 0.9% NaCl before it will be removed from the animal. Only infusion sets and syringes with luer-lock fittings will be used to administer these drugs. Preferable closed infusion systems are used (e.g. Tevadaptor[®], Oncovial[®] and PhaSeal[®]).
- 3.4 Employees should protect themselves with disposable, powder free, latex gloves and special disposable protective clothing.
- 3.5 Administer drugs safely by using protective medical devices (such as needleless and closed systems) and techniques (such as priming of IV tubing by pharmacy personnel inside a ventilated cabinet or priming in-line with nondrug solutions).
- 3.6 Never remove tubing from an IV bag containing a hazardous drug.
- 3.7 Do not disconnect tubing at other points in the system until the tubing has been thoroughly flushed.
- 3.8 Remove the IV catheter, tubing and bag intact when possible.
- 3.9 Dispose gloves and protective gown.
- 3.10 All potential contaminated material should be discarded in special waste disposal containers that can be opened with a foot pedal or has another mechanism to prevent direct contact with hands/gloves..
- 3.11 Wash hands with soap and water before leaving the drug administration site.
- 3.12 Procedures should be in place for dealing with any spillages that occur and for the safe disposal of waste.
- 3.13 Owners of animals can be present as long as they are informed of the hazards.

4. Guidelines for nursing animals within the clinic

- 4.1 Special wards or designated kennels with clear identification of the use of cytotoxic agents are used for the hospitalisation of animals treated with cytotoxic agents.
- 4.2 Excreta of treated animals (saliva, urine, vomit, faeces) are a potential risk after the animal has been treated. As long as there is no information available for the period of risk for the used cytotoxic agent in this animal human data should be used.

Note:

(1) A list of periods of risk for different cytotoxic agents in humans is given in appendix 3.

- 4.3 During the period of risk personal protective means, like disposable gloves and protective clothing is being used during taking care of the animal.
- 4.4 All materials that have been in contact with the animals during the period of risk should be considered as potentially contaminated.
- 4.5 After the animal has left the ward, the cage should be cleaned according to a cleaning protocol (see Appendix 7)

5. Guidelines for information for the owner

5.1 Written information on the potential hazards of the cytotoxic drugs must be available for the owner.

Note:

(1) An example of written information is given in Appendix 8

5.2 Written information on the administration of oral cytotoxic drugs must be available for the owner.

Note:

(1) An example of written information is given in Appendix 9

5.3 Written information on how to deal with the patient's excreta, like saliva, urine and faeces, must be available for the owner.

Note:

(1) An example of written information is given in Appendix 8

Antineoplastic drugs classified by the International Agency for Research on Cancer (IARC)

Antineoplastic or anti-cancer drugs are used to treat cancer. Most antineoplastic drugs are also cytotoxic. The following is a list of antineoplastic drugs that have been classified by the International Agency for Research on Cancer (IARC) as known, probable, or possible **cancer-causing agents**. It is not a complete listing of all carcinogenic antineoplastic drugs, since not all antineoplastic drugs have been reviewed and classified by IARC.

Some of the following antineoplastic drugs that are classified as potentially carcinogenic are not cytotoxic. Despite this, the precautions outlined in this guide and guides on antineoplastic drugs should be used.

Group 1 – Drugs which are carcinogenic (sufficient human evidence of carcinogenesis)

- Azathioprine (Imuran)
- Busulfan (Myleran)
- Certain combined chemotherapy for lymphomas:
(e.g., procarbazine, vincristine, prednisone, and nitrogen mustard)
(e.g., mechlorethamine, vincristine, procarbazine, prednisone)
- Chlorambucil (Leukeran)
- Cyclophosphamide (Cytoxan, Procytox)
- Melphalan (Alkeran)
- Thiotepa
- Tamoxifen citrate (Apo-Tamox, Gen-Tamoxifen, Nolvadex, Nolvadex-D, Novo-Tamoxifen, Tamofen, Tamone)

Group 2A – Drugs which are probably carcinogenic to humans (generally, limited human evidence, but sufficient animal evidence)

- Bischloroethyl nitrosourea or carmustine (BiCNU)
- 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea or lomustine (CCNU)
- Cisplatin (Platinol)
- Doxorubicin (Adriamycin)
- Nitrogen mustard (Mustargen)
- Procarbazine (Natulan)
- Etoposide

Group 2B – Drugs which are possibly carcinogenic to humans (generally, limited human evidence, but absence of animal evidence)

- Bleomycin sulfate (Blenoxane)
- Dacarbazine (DTIC)
- Mitomycin (Mutamycin)
- Streptozocin (Zanosar)
- Daunorubicin (Cerubidine)
- Mitoxantrone

Discussion on pregnancy in staff handling cytotoxics

(Source: www.marchguidelines.com)

Aim:

To establish the specific areas of concern for staff handling cytotoxics who are pregnant, or trying to conceive, and to provide guideline principles to inform the development of local policies for the handling of cytotoxics during pregnancy.

Status:

This is a particularly complex and emotive issue, which is of extreme importance to staff and managers in areas predominantly staffed by females of childbearing age.

Various studies have demonstrated links between occupational exposure to cytotoxic drugs and menstrual dysfunction (Shortridge et al 1995), infertility (Valanis et al 1997), miscarriages and stillbirths (Valanis et al 1999), low birth weight and congenital abnormalities (Scheepers 1999). However when considering the evidence it should be taken into consideration that these studies were mostly carried out either in the 1980's, or based on staff exposure in the 1980's, a time when the use of personal protective equipment and safe handling techniques were not well established. These studies do not on the whole reflect current working practices.

Other studies have failed to find a statistically significant association with spontaneous abortion and congenital malformation (Skov et al 1992). This may be due to the increased awareness of the risk, leading to the use of protective clothing and equipment, or the avoidance of cytotoxic handling by staff if they are pregnant. A recent review of chemotherapy administered to 376 patients during pregnancy concluded that the "use of chemotherapy in the second and third trimesters seems to be safe" (Cardonick and Iacobucci 2004, p289).

The time of greatest risk to the unborn child is during the first three months of pregnancy, being the time of most rapid cell division and differentiation. As most staff will not disclose their pregnancy until well into this period any policy for the handling of cytotoxics by pregnant staff should therefore consider the needs of staff trying to conceive and indeed those who may not be aware that they are pregnant. Guidance from the Health and Safety Executive for new and expectant mothers emphasises that "a safe level of exposure cannot be determined for these drugs, so you should avoid exposure or reduce it to as low a level as is reasonably practicable" (HSE 2002).

The following recommendations are based on the available literature and expert opinion. They are general principles, which should be used when devising local protocols for the safe handling of cytotoxics by staff during pregnancy or when planning a pregnancy.

The emphasis should be on clear guidelines to reduce occupational exposure to all staff at all times.

Recommendations:

1. Identification of those at risk of occupational exposure to cytotoxics through:
 - Preparation / reconstitution of cytotoxics
 - Administration of cytotoxics
 - Handling cytotoxic waste
 - Handling patient excreta / body fluids
 - Receipt, storage and transportation of cytotoxics
2. COSHH (Control of substances Hazardous to Health) assessments should be carried out for each activity involving the handling of cytotoxics to assess the level of risk and the adequacy of control measures in place.
3. 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
4. Staff choice:
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
5. 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
 - A comprehensive documented method of staff education and assessment in safe handling of cytotoxics must be in place
 - Safe handling procedures must be audited and documented on a regular basis to ensure staff compliance to reduce risks to as low a level as is reasonably practicable.

References:

1. Cardonick, E. and Iacobucci, A. Use of chemotherapy during human pregnancy. *The Lancet Oncology*, 2004; 5: 283- 291
2. 'New and Expectant Mothers at Work: a guide for employers'. HSG 122. Health and Safety Executive 2002.
3. Peelen S, Roeleveld N, Heederik D, Krombout H and de Kort W. Toxic Effects on Reproduction in Hospital Personnel. Cited by Scheepers P. in *The Pharmaceutical Journal*, 1999; 263: 65
4. Skov T, Maarup B, Olsen J, Rorth M, Wihereik H, Lynge E. Leukaemia and reproductive outcomes among nurses handling antineoplastic drugs. *British Journal of Industrial Medicine*, 1992; 49: 885-861.
5. Shortridge L, LeMasters G, Valanis B, Hetzberg V. Menstrual cycles in nurses handling antineoplastic drugs. *Cancer Nursing*, 1995; 18: 439-444
6. Valanis B, Vollmer W, Labuhn K, Glass A. Occupational exposure to antineoplastic agents and self reported infertility among nurses and pharmacists. *Journal of Occupational and Environmental Medicine*, 1997; 39 (6): 574-580.
7. Valanis B, Vollmer W, Steele P. Occupational exposure to antineoplastic agents: self reported miscarriages and stillbirths amongst nurses and pharmacists. *Journal of Occupational and Environmental Medicine*, 1999; 41 (8) : 632-638.
8. Clark C. Occupational exposure to cytotoxic drugs. *The Pharmaceutical Journal*, 1999; 263: 65-67

List of periods of risk

In the table cytotoxic agents often used in veterinary medicine are listed with expected period of risk of potential contamination after injection in a dog or cat. As no information is known in these species, data has been taken from the human.

Cytotoxic drug	Period of risk after last administration Of cytotoxic drug
5-Fluorouracil	3 days
Carboplatin	5 days
Chlorambucil	2 days
Cisplatin	8 days
Cyclophosphamide	4 days
Cytarabine	3 days
Doxorubicin	7 days
Gemcitabine	7 days
Lomustin (CCNU)	3 days
Mitoxantrone	8 days
Vincristine	3 days
Vinblastine	3 days

Selection and use of personal protective equipment (PPE) to minimise cytotoxic exposure

(Source: www.marchguidelines.com)

Aim:

To assist Healthcare professionals to:

- recognise the risks and causes of exposure
- minimise exposure by appropriate means
- take appropriate action if exposure occurs

To promote the use of effective personal protective equipment (PPE) in order to maximise protection when preparing, administering or disposing of cytotoxics.

Background:

Although there are a wide variety of commercially available PPE, not all has the evidence to support use in the workplace. This guideline aims to ensure that equipment being used in the workplace is appropriate for the job for which it has been selected.

Recommendations:

- Staff should not handle cytotoxic drugs or waste unless they understand the risks, consequences and appropriate techniques for avoiding exposure.
- Appropriate Personal Protective Equipment should be agreed by local protocol, and made readily available to all relevant staff.
- Drugs supplied in safety-orientated packaging should be selected over those in standard packs.
- Where possible select a route of administration that avoids or minimises aerosols, spraying, splashing and facial or skin exposure.
- For oral preparations, use tablets in blister or foil packs in preference to solutions.
- Adopt a "no touch" approach to handling cytotoxics, i.e., wear disposable gloves and other appropriate PPE.
- Disposable gloves
 - Wear them at all times when contact with cytotoxic drugs is possible
 - Do not assume that your chosen glove is impermeable; study the literature
 - Change gloves regularly and always change between patients
 - Damaged gloves should be changed immediately
 - Wash hands properly before and after use of gloves
 - For spillages, industrial thickness gloves (>0.45mm) made of latex and neoprene, nitrile, synthetic rubber or similar materials are recommended. Alternatively double latex or nitrile gloves can be used.
 - Gloves with no powder are preferred since the powder may absorb cytotoxic contamination
 - Individual practitioner's preferences should be considered in regard to sensation and dexterity

- Nitrile gloves may be used, but not with etoposide
- Follow manufacturers' recommendations, if any
- Gowns
 - Saranex / Tyvek laminated demonstrated to be most effective against 15 antineoplastic drugs (Harrison and Kloos, 1999).
 - Laboratory coats are porous – do not use them
 - Disposable gowns should have:
 - Closed front
 - Long sleeves
 - Elastic or knit cuffs
 - The following materials have been shown to offer protection in order of effectiveness:
 - Codan "Chemoprotect" gowns and sleeves are made of spun-bonded polypropylene laminated with polyethylene. These are commonly used within the UK and a similar product performed well in a US study, which compared penetration and splash protection of six disposable gown materials against fifteen cytotoxic drugs.
 - The "Chemoplus" gown included in cytotoxic spillage kits supplied by Sage performed very poorly in the Gross et al study and is not recommended for use with cytotoxics.
- Eye and facial protection
 - Eye protection should fully enclose the eyes.
 - Know the location and proper usage of eye and face protection equipment, eyewash and spillage kits.
- 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
 - 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

References:

1. Clinical Practice Guidelines. The administration of cytotoxic chemotherapy. Recommendations and Technical Report, 1998. Royal College of Nursing.
2. Gross ER and Groce DF. An evaluation of nitrile gloves as an alternative to natural rubber latex for handling chemotherapeutic agents. *J Oncol Pharm Practice*, 1998; 4 (3): 165-168.
3. Singleton LC and Connor TH. An evaluation of the permeability of chemotherapy gloves to three cancer chemotherapy drugs. *Oncology Nursing Forum*, 1999, 26 (9): 1491-1496.
4. Harrison BR and Kloos MD. Penetration and splash protection of six disposable gown materials against fifteen antineoplastic drugs. *J Oncol Pharm Practice*, 1999; 5 (2): 61-66.
5. Sessink PJM et al. Evaluation of the PhaSeal hazardous drug containment system. *Hospital Pharmacy*, Nov 1999; 34 (11): 1311-1317.

6. Delporte JP et al. Chemical Contamination of the Primary Packaging of 5-Flourouracil RTU Solutions Commercially Available on the Belgian Market. *European Hospital Pharmacy* 1999; 5 (3): 119-121.
7. Sewell GJ. Pharmaceutical issues: preparation and handling. *J Oncol Phar Practice*, 1995; 1 (Suppl 1): 6-12.
8. NIOSH Alert. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Healthcare Settings. 2004
9. Klein et al. Permeation of cytotoxic formulations through swatches from selected medical gloves. *Am J Health Systems Pharm* 2003; 30 (10): 1006-11.
10. Allen, Loyd. Basics of Compounding for Hazardous Drugs Part 3. Safe Handling and Personal Protection. *International Journal of Pharmaceutical Compounding* 2007; 11 (1): 50

Classification of Biological Safety Cabinets

NIOSH Publication No. 2004-165:

Preventing Occupational Exposure to Antineoplastic and Other Hazardous Drugs in Health Care Settings

BSC (biological safety cabinet): A BSC may be one of several types, as described here

Class I BSC: A BSC that protects personnel and the work environment but does not protect the product. It is a negative-pressure, ventilated cabinet usually operated with an open front and a minimum face velocity at the work opening of at least 75 ft/min (23m/min). A Class I BSC is similar in design to chemical fume hood except all of the air from the cabinet is exhausted through a HEPA filter (either into the laboratory or to the outside).

Class II BSC: A ventilated BSC that protects personnel, product, and the work environment. A Class II BSC has an open front with inward airflow for personnel protection, downward HEPA-filtered laminar airflow for product protection, and HEPA-filtered exhausted air for environmental protection.

Type A1 (formerly, Type A): These Class II BSCs maintain a minimum inflow velocity of 75 ft/min (23m/min), have HEPA-filtered downflow air that is a portion of the mixed downflow and inflow air from a common plenum, may exhaust HEPA-filtered air back into the laboratory or to the environment through an exhaust canopy, and may have positive-pressure contaminated ducts and plenums that are not surrounded by negative-pressure plenums. They are not suitable for use with volatile toxic chemicals and volatile radionuclides.

Type A2 (formerly, Type B3): These Class II BSCs maintain a minimum inflow velocity of 100 ft/min (30m/min), have HEPA-filtered downflow air that is a portion of the mixed downflow and inflow air from a common exhaust plenum, may exhaust HEPA-filtered air back into the laboratory or to the environment through an exhaust canopy, and have all contaminated ducts and plenums under negative-pressure or surrounded by negative-pressure ducts and plenums. If these cabinets are used for minute quantities of volatile toxic chemicals and trace amounts of radionuclides, they must be exhausted through properly functioning exhaust canopies.

Type B1: These Class II BSCs maintain a minimum inflow velocity of 100 ft/min (30m/min), have HEPA-filtered downflow air composed largely of uncontaminated, recirculated inflow air, exhaust most of the contaminated downflow air through a dedicated duct exhausted to the atmosphere after passing it through a HEPA filter, and have all contaminated ducts and plenums under negative pressure or surrounded by negative-pressure ducts and plenums. If these cabinets are used for work involving minute quantities of volatile toxic chemicals and trace amounts of radionuclides, the work must be done in the directly exhausted portion of the cabinet.

Type B2 (total exhaust): These Class II BSCs maintain a minimum inflow velocity of 100 ft/min (30m/min), have HEPA-filtered downflow air drawn from the laboratory or the outside, exhaust all inflow and downflow air to the atmosphere after filtration through a HEPA filter without recirculation inside the cabinet or return to the laboratory, and have all contaminated ducts and plenums under negative pressure or surrounded by directly exhausted negative-pressure ducts and plenums. These cabinets may be used with volatile toxic chemicals and radionucleotides.

Class III BSC: A BSC with a totally enclosed, ventilated cabinet of gas-tight construction in which operations are conducted through attached rubber gloves and observed through a nonopening view window. This BSC is maintained under negative pressure of at least 0.50 inch (1.3 cm) of water gauge, and air is drawn into the cabinet through HEPA filters. The exhaust air is treated by double HEPA filtration or single HEPA filtration/incineration. Passage of materials in and out of the cabinet is generally performed through a dunk tank (accessible through the cabinet floor) or a double-door pass-through box (such as an autoclave) that can be decontaminated between uses.

Cytotoxic drugs accident and spillage protocol

Objective:

Prevention of contamination with cytotoxic agents after spillage or accidents.

Instruction

Emergency boxes (Cytotoxic spill kits) are present in the preparation room, in the room where drugs are administered, and in the special area of the ward where chemotherapy patients are hospitalized.

Content of Cytotoxic Spill Kit:

Disposable protective gowns (e.g. Chemoprotect L+XL)	2x
Disposable latex powderfree chemotherapy gloves (size 8)	2 pair
Disposable latex powderfree chemotherapy gloves (size 9)	2 pair
Full Face Respirator	1x
Filters for Full Face Respirator	2x
pH 5 soap tablet	1x
Plastic bag	4x
Red and white plastic ribbon	10 meter
Plastic tweezers (182 mm)	2x
Plastic shoe coverings	2 pair
Chemosorbs pads	3x
Absorbent disposable towels	several

Contamination of clothes and/or skin

- Carefully take off protective clothes and then the protective gloves and dispose them in the special waste disposal container.
- Rinse your skin with large amounts of tap water and wash it with soap afterwards
- Leave the room. In case of contamination of large parts of the body take a shower (use if available the emergency shower).
- Consult the pharmacist

Contamination of the eyes

- Ask help of other people if possible
- Remove contacts, if present
- Rinse the eyes with large amounts of tap water (use the eyewash facility if present) for at least 20 minutes, while holding back the eyelid(s)
- Consult the pharmacist

Accidental injection with cytotoxic drug

(due to contaminated needles or contaminated broken glass)

- Bleed the wound for a while
- If the glove is penetrated, take off the glove

- Rinse the wound with tap water
- Consult the pharmacist

Spillage of cytotoxic drugs

1) In safety cabinet

- Observe carefully where the cytotoxic drugs are spilled
- Absorb first the fluid with a dry-absorbent towels
- Clean contaminated area 3 times: take a dry tissue in one hand and a tissue with 70% Alcohol in other hand. Clean area with alcohol tissue and immediately thereafter with dry tissue. Repeat this two times.
- Always start with most contaminated area first
- Dispose all contaminated material in the special waste disposal container.

2) On the floor

- In the Cytotoxic Spill Kit you will find all necessary items
- Call for assistance and warn others. Do not leave spill site unguarded.
- Protect your self with special Chemoprotec latex gloves, disposable protective gown, disposable protective shoe coverings and Full Face Respirator
- Identify area of spillage with special plastic ribbon
- Absorb fluid with dry absorbent towels. Start with most contaminated area first.
- Carefully remove broken glass (special cards, tweezers)
- Clean contaminated and a reasonable area around it three times (with both a dry TORK? and with a with 70% alcohol TORK?)
- Always start with most contaminated area first
- Dispose all contaminated material in the special waste disposal container.
- Wash hands thoroughly and record spill

Contamination with chemotherapy powder

- Beware that draught and passing people can further spread the powder
- Protect your self with special disposable chemotherapy latex gloves, disposable protective gown, disposable protective shoe coverings and Full Face Respirator
- Identify area of spillage with special plastic ribbon
- Call for assistance and warn others. Do not leave spill site unguarded.
- Cover the powder with moisted absorbent towels and remove the powder. Start with most contaminated area first. Repeat until no powder is seen anymore
- Carefully remove broken glass (special cards, tweezers, forceps)
- Clean contaminated and a reasonable area around it three times (with both a dry TORK? and with a with 70% alcohol TORK?)
- Dispose all contaminated material in the special waste disposal container.
- Wash hands thoroughly and record spill

Miscellaneous

- Always report accidents to pharmacist
- Prepare new Cytotoxic Spill Kit

Protocol Cleaning of chemotherapy facilities

Objective: To prevent exposure of cleaners, employees and other people to cytotoxic agents, taking into account hygienic aspects.

Instruction:

The cleaning will be entered into a log book: date and person responsible will be noted. In addition, the areas cleaned will be noted.

Areas:

- | | |
|---|--|
| A | Cytotoxic drug preparation facility in Pharmacy |
| B | Cytotoxic drug administration facility in Hospital |
| C | Special Chemotherapy cage in the ward |

Recommendations:

- All areas where cytotoxic drugs are stored, prepared, administered and disposed of (including handling of patient excreta) should be regarded as potentially contaminated
- Staff involved in cleaning (including agency staff) should have received training and education on the health risks associated with cytotoxics and the consequences of ineffective cleaning.
- Personal protective clothing must be worn by staff undertaking cleaning duties in potentially contaminated areas. As a minimum this should include disposable gloves and gown designed for chemotherapy handling. Wear face shields if splashing is possible.
- Written procedures should be available for cleaning of pharmacy and clinical areas and also for items of equipment in these facilities. In these procedures details should be listed of the areas and equipment to be cleaned, when cleaning should be done and how.
- When designing cleaning procedures the solubility of cytotoxic agents must be considered. In general, all cytotoxics can be considered to be water-soluble. Therefore, aqueous solutions should be used for cleaning (e.g., sterile water for irrigation or sterile aqueous concentrates of surfactants/ bactericides for aseptic areas and aqueous detergent solutions for non-aseptic areas). Critical areas in aseptic units (e.g., base of isolator) may be wiped with sterilized 70% IMS after cleaning
- Any obvious spillages of cytotoxic solutions should be mopped up with disposable absorbent material before cleaning. Cytotoxic powders or residues should be absorbed onto disposable toweling moistened with water prior to cleaning
- Contaminated disposable items (e.g., absorbent towel and protective clothing) used in cleaning should be disposed of as cytotoxic waste
- After each cleaning
- Cleaning procedures should be validated and then regularly monitored using deliberate contamination with fluorescent dye
- Cleaning of electrical equipment that may be contaminated with cytotoxics (e.g., infusion pumps) is particularly difficult and potentially hazardous. Seek advice from the Medical Physics/ Medical Electronic Department and draw up cleaning procedures with them

- Re-evaluate the effectiveness of cleaning procedures on a regular basis, taking into account the introduction of new cytotoxic or genotoxic medicines and new formulations/ presentations

Example Information pamphlet for owners of animals who need to make a decision whether to treat their animal with chemotherapy

Although the majority of cancer in our animals are still being treated with surgery, sometimes other treatment modalities are needed. Several tumour types can nowadays be treated with chemotherapy. Usually these agents are being administered according to special protocols. Apart from their effect on the tumour these drugs also have some disadvantages, which are important for you to realize. As owner of the animal you must discuss all advantages and disadvantages with your veterinarian-oncologist and carefully make a decision. As each tumour type has its own special treatment, no specific detailed information can be given in this pamphlet. Some general considerations/remarks are listed below.

Side effects

Although your veterinarian-oncologist will do everything to prevent side effects, some animals may still suffer side effects during the chemotherapy protocol. Vomiting, diarrhoea and increased susceptibility for infection are some of the more frequent side effects. Usually they are seen much less often than in humans. If your animal gets ill after administration of chemotherapy, contact your veterinarian. Your veterinarian can treat these side effects and perhaps must adapt the protocol.

Environmental hazards

The strange thing about cytotoxic drugs is that, although used for treatment of cancer, many of them can also cause cancer. One should therefore always try to prevent direct contact with these drugs. After administration to your animal these drugs are being excreted again. This means that all excreta (vomit, faeces, urine), but also saliva can be contaminated starting right after the administration.

You must be willing to take care of all excreta of your pet during the period of time your veterinarian will tell you: the length of time depends on the drugs your pet has been given. For cats this implies cleaning its box every day; use disposable plastic bags in the box and disposable gloves. Keep all contaminated waste separated and dispose all contaminated material into a trash can.

For dogs, during the risk period you must keep it on the leash all the time when outside, remove all faeces with plastic bags using disposable gloves, and rinse off and dilute all urine with water (take a bottle of water with you every time you walk your dog). You can dispose of the faeces by flushing it in the toilet, or by discarding it by disposing it into a trash can. The resting place(s) of your pet should also be scrutinized every day, and sanitized after each risk period, by washing all clothes slept on, and rinsing with soap all surfaces of sleeping places.

Last but not least: avoid being licked by your pet, and deter stroking it; in this regard pay special attention to children.

Children and pregnant women are especially sensitive for the carcinogenic effects of these drugs. Children should be told to leave the animal alone during the period of risk. In the case of pregnant women in the house extra precautions should be taken and indeed it may be preferable to temporarily re-home the pet or even not to start treatment.

Costs

Chemotherapy drugs are usually expensive drugs. As these drugs have to be prepared in special safety cabinets and all persons involved in preparation and administration must wear protective clothes, and a large amount of time is needed the costs are usually higher than for normal drugs. Additional costs can be made if blood work, X-rays or other diagnostics are indicated.

Example Information pamphlet for owners of animals who are treated with chemotherapy

This information is intended for the caretaker of the animal which is being treated with this drug.

Your dog or cat has been prescribed one of the following drugs:

- Melphalan (Alkeran[®])
- Cyclophosphamide (Endoxan[®])
- Hydroxyurea (Hydrea[®])
- Azathioprine (Imuran[®])
- Chlorambucil (Leukeran[®])

These drugs require your special attention. If handled wrongly these drugs may endanger not only your pet but also yourself. Therefore, please read the following instructions carefully.

- 1) Administer the drug only in the dose prescribed by your veterinarian.
- 2) Prevent direct contact of the drug with your skin. Use disposable gloves for the administration of the drugs and carefully wash your hands afterwards.
- 3) Part of the drug will be excreted by your pet in the saliva, urine, faeces or vomit. Take care that the animal does not urinate or defecate in the area of playing children.
- 4) If vomit, urine, faeces or blood is spilled in your house take immediate precautions. Use disposable gloves to remove the contaminated material with disposable absorptive material and carefully wash your hands afterwards.
- 5) You must be willing to take care of all excreta of your pet during the period of time your veterinarian will tell you: the length of time depends on the drugs your pet has been given. For cats this implies keeping it inside during the risk period, and cleaning its box every day; use disposable plastic bags in the box and disposable gloves. Keep all contaminated waste separated and dispose of it like chemical waste (e.g. paint, organic solvents). For dogs, during the risk period you must keep it on the leash all the time when outside, remove all faeces with plastic bags using disposable gloves, and rinse off and dilute all urine with water (take a bottle of water with you every time you walk your dog). You can dispose of the faeces by flushing it in the toilet, or by discarding it like chemical waste. The resting place(s) of your pet should also be scrutinized every day, and sanitized after each risk period, by washing all clothes slept on, and rinsing with soap all surfaces of sleeping places. Last but not least: avoid being licked by your pet, and deter stroking it; in this regard pay special attention to children.
- 6) During the treatment try to prevent direct contact with your pet. Most likely the drug is being excreted by your animal during 3-5 days after administration.
- 7) Although no information is yet available on the amount of excretion of these potential hazardous drugs by your animal, and therefore the risk it poses, it is advisable that women who are pregnant or lactating are extra careful. Also the presence of little children requires extra precautions to avoid direct contact with the pet..

- 8) Keep the drugs in their original package, outside the reach of children and pets
- 9) Remnants of the drug, that are no longer used, should be brought back to your veterinarian.