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SHARING EXPERTISE

HANDLING OF HAZARDOUS DRUGS

RISK PREVENTION BY PERSONAL PROTECTIVE EQUIPMENT

HANDLING OF HAZARDOUS DRUGS

INTRODUCTION

CONTENT

INTRODUCTION

Antineoplastic drugs (ANPD) have been introduced for cancer treatment since the 1940s. More than 12 million patients are treated with ANPDs each year. Nowadays the number of cancer diagnoses is continuously increasing.

This brochure addresses the hazardous effects of antineoplastic drugs, the importance of risk assessment and standard precautions of personal protection as recommended by the 2004-NIOSH (National Institute for Occupational Safety and Health)-Alert and corresponding updates in 2010/2012 and 2016.[1, 2, 3]

As per February, 14, 2018 a newly updated "NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings: Proposed Additions to the NIOSH Hazardous Drug List 2016" has been presented for comments with deadline for comments per April, 16, 2018.[79]

The expression "antineoplastic drug" (ANPD) is often used synonymously together with "cytostatics" or "chemotherapeutics", however, these terms normally describe an overarching category to which other drug-classes belong. These types of drugs belong to drug-specialties summarized under the term "Hazardous Drugs", according to the CDC's (Centers for Disease Control and Prevention) NIOSH[4] alert in 2004. The term ANPD describes in general the activity of these drugs against a neoplasm, characterizing an abnormal growth of tissue. In a recent systematic review and meta-analysis of the literature[5] the expression "ANPD" is used in a general manner, therefore it is applied in this review, too.

ANPDs represent a broad and non-homogenous group of chemicals with a variety of structures, origins, activities and effects at the cellular level. They are categorized according to their specific potential of toxicity or to their mechanisms of action, described in more detail in the chapter "Definition of risks". Currently, the list encompassing ANPDs used in daily clinical practice contains more than 115 special drugs[1].

During the 1970's first concerns with respect to toxic side effects were raised further to cases that had been reported and documented where healthcare workers (HCW) were exposed to ANPDs. Meanwhile 8 million HCW working with and being unnecessarily exposed to these highly toxic drugs may therefore experience adverse effects that negatively impact their health.[1, 3, 6, 7, 8, 9]

A number of health risks associated with HCWs' occupational exposure to ANPD have been described since many years[10], varying from acute effects[11], reproductive toxic effects[12, 13] and DNA-interference[14].

Today, the association between HCWs' occupational exposure to ANPDs and their adverse effects are still a matter of increasing awareness and a safety concern, for the following reasons:

- The incidence rate of cancer is increasing worldwide and the use of ANPDs is consequently growing.
- Even when the personnel is specifically trained and ANPDs' handling complies with issued guidelines and/or safety recommendations, accidental contamination in the workplace and thus exposure risk is still identifiable.
- The number of HCWs potentially exposed to ANPDs is growing due to the increasing use of these agents, also for the treatment of non-cancer pathologies.

New developments in the field of oncology will lead to more treatment options and more safety issues with respect to new medicines. The EMA (European Medicines Agency) annual report 2016 documents that "most applications for PRIME (priority medicines) received in 2016 were for cancer medicines" and most of the scientific advice requests were related to ANPDs.

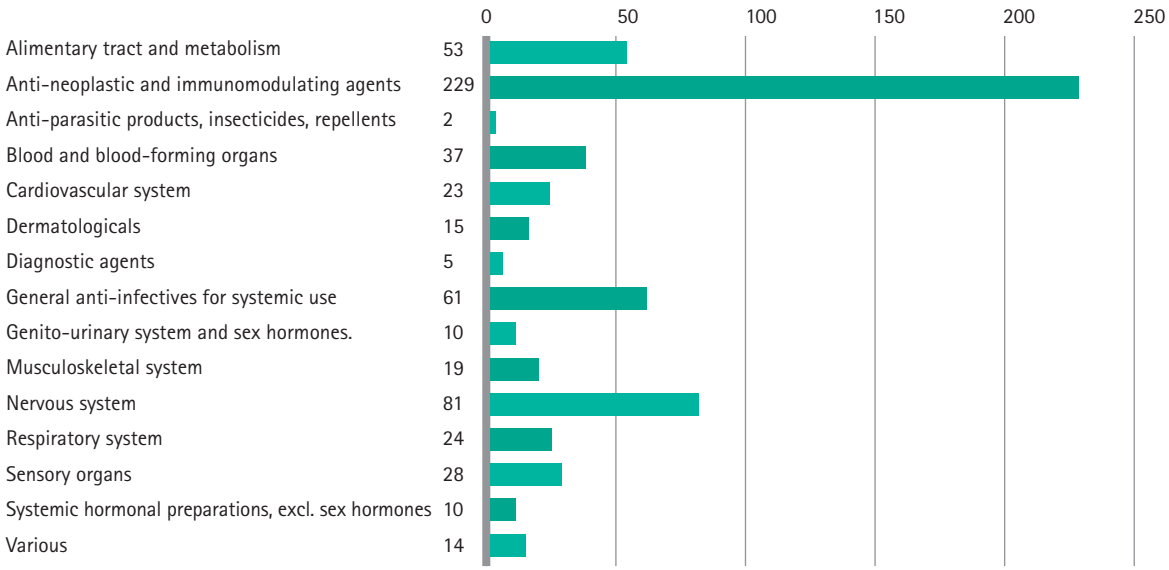

Figure 1: Scientific advice requests by therapeutic area; Source: EMA annual report 2017[15]

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DEFINITION RISKS

DEFINITION OF RISKS

After the first clinical applications of ANPDs more than 40 years ago, quite a number of studies and surveys have been executed in order to increase the level of related evidence. Meanwhile the toxicity of and health risks associated with ANPDs are well known and understood.[9, 16]

The related health risks caused by ANPDs are mainly defined by the following facts:

- Exposure of HCWs to these drugs without any precautions, e.g. Personal Protective Equipment (PPE).
- The toxicity and health risks of ANPDs due to their particular modes of action.

The exposure to these drugs may be extremely hazardous even at very low concentration levels upon contact of these agents with the human body.

The action on tumor cells of most ANPD are only partially targeted to be selective, and impacts on healthy (non-tumour) cells may also occur resulting in acute (e.g. skin irritation, sore throat, dizziness, cough, headache, hair loss, allergic reaction, diarrhea, nausea, vomiting) and delayed adverse effects due to long term exposure (DNA-damaging / -alterations in gene patterns /organ damage). These properties of ANPDs are considered the most hazardous, and may lead to e.g. acute leukemia, impact on the bone marrow, fetal malformation and abortion, negative effects on the reproductive function in either sexes.[17]

Many studies provide evidence that HCWs who are continuously and increasingly exposed to these drugs have to face the above mentioned risks, particularly when they are involved in the "supply – and procedural chain" for these drugs e.g. manufacture, transport to distribution, administration preparation for patients, before and after administration and finally the procedures of cleaning and waste disposal.

Risk categories of ANPDs

More than 115 antineoplastic drugs used in healthcare setting have been listed by the US-CDC's Federal Authority for Occupational Safety and Health Research "NIOSH" (2016)[1]. Many of these drugs react very rapidly and are associated with high risks of carcinogenicity and a number of identified risks have been addressed in studies. Hazardous drugs have been reported as carcinogenic, teratogenic, mutagenic and toxic to the reproductive system, DNA ("genotoxic") or organs. The combination of at least two of the above mentioned criteria fulfills the requirement that corresponding drugs are classified as "hazardous".

HCWs are therefore confronted to a variety of potential risks during their occupational activities in administration, handling, transportation and disposal of cytotoxic drugs.[5]

Highly protective measures and detailed caution practices are meanwhile recommended during administration and handling of all types of antineoplastic drugs where these show more than one or two characteristic patterns of a hazardous drug to humans or animals.

Risk categories	Definition
Carcinogenicity	Ability or tendency to produce cancer (impact on cellular metabolism or DNA-damage)
Teratogenicity	Capability of producing fetal malformation (malformation of embryo or fetus)
Mutagenicity	Ability to increase the spontaneous mutation rate by causing changes in the DNA
Reproductive toxicity	Ability of causing effects on the male or female reproductive system (infertility)
Genotoxicity	Ability to damage or mutate DNA (genotoxic substances are not necessarily carcinogenic)
Organ toxicity	Process how organ systems may be affected by toxic exposure (e.g. Hepatotoxicity or damage of liver)[20]

Table 1: Risks of Antineoplastic agents / Cytotoxic drugs[18, 19]

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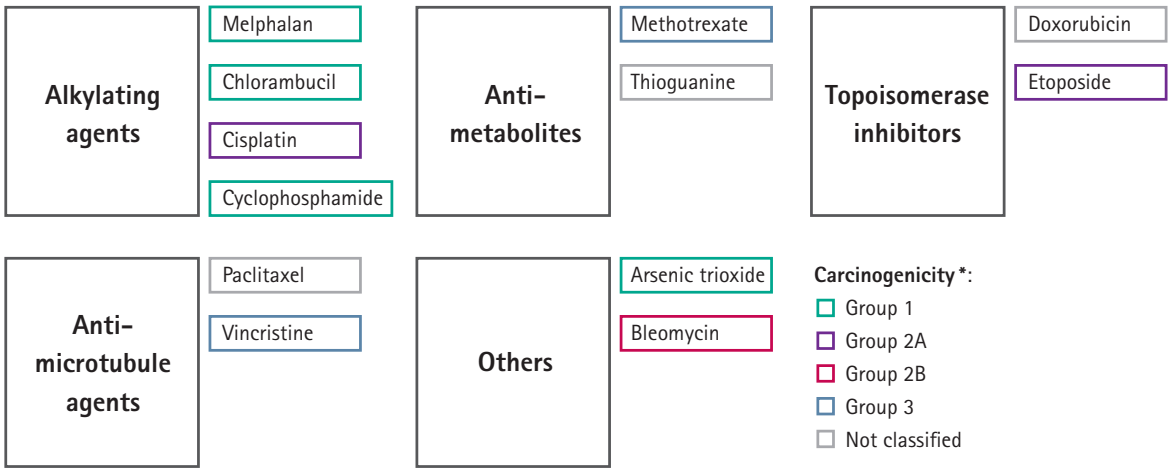
The International Agency of Research on Cancer (IARC)-Monographs categorized these drugs as to their carcinogenicity as group 1, 2 A, 2 B, 3 and 4[21].

The US FDA (Food and Drug Administration) established studies targeted to adverse effects of different hazardous drugs on pregnant women (among them nurses) where risks are categorized as A, B, C, D and X. These categories indicate affects like birth defect or fetal problems and are described as follows.

IARC	FDA
Group 1 i.e., "carcinogenic to humans", e.g. busulfan, chlorambucil and cyclophosphamide	**Category A:** Sufficient studies were successful to prove risk in fetus during first 3 months of pregnancy.
Group 2 A i.e., "probably carcinogenic to humans", e.g. cisplatin, etoposide, N-ethyl-and N-methyl-N-nitrosourea	**Category B:** Adequate studies done on animal reproductionfailed to show any risk during pregnancy and there are insufficient studies on pregnant women.
Group 2 B i.e., "possibly carcinogenic to humans", e.g. bleomycin and mitomycin-C	**Category C:** Significant adverse effects were found in animal fetus and reproduction system. However, there is inadequate evidence on human studies, but cautious strategies need to be implemented due to possible risks to pregnant women.
Group 3 proved as "carcinogenic but limited to animals"	**Category D:** Authentic evidence on fetal risk found in human studies from the data, basis on investigation or marketing. But conditionally potential benefits of this drug may acceptable in pregnant women rather then it's risk consideration.
Group 4 represent substances with a lower degree of evidence of carcinogenicity in animals / humans	**Category X:** Significantly positive evidence found in human and animal studies, where fetal abnormalities and fetal risks were revealed on the basis of corresponding investigations.[22, 23]

Table 2: Classification of IARC and FDA



* Based on classification of the International Agency for Research on Cancer (IARC); see table 2 on page 6.
Source: PAHO (Pan American Health Organization), WHO, CAREX Canada et al.: [24]

Figure 2: Examples of different types of antineoplastic agents and their carcinogenicity

Other types of ANPDs for so-called "targeted therapies" (s. table 2 – part 2) are angiogenesis inhibitors (e.g.: bevacizumab, sorafenib, sunitinib). These drugs tend to inhibit new blood cell growth which suppress growth in tumor cells. Potential adverse effects are found in animal reproduction system and recommended to follow the FDA risk category C. There are other side effects like gastrointestinal perforation, fistulas, bleeding, clots in arteries, hypertension may arose during administration of these drugs.[25] Gene expression modulators, apoptosis inducers and cancer vaccines are also used in different cancer treatments.[26]

NIOSH later on highlighted that misclassification of drugs as "hazardous" may occur which could influence the credibility of hazardous drug lists.[27, 33]

For a long time monoclonal antibodies (Mabs) have been assessed as hazardous.[4, 27, 28, 29, 30, 31, 32] Recent re-evaluations of risks revealed that monoclonal antibodies are non-hazardous drugs.[27, 32] Their specific targeted mechanisms do not lead to severe side effects. Due to the high molecular weight there is no risk of skin penetration and accidental inhalation, standard gloves as a protective measure for the handling is sufficient.

HANDLING OF HAZARDOUS DRUGS

DEFINITION RISKS

Specification of ANPDs' functionality- and risk-profiles

ANPD Group	Example	Functionality in cancer therapy
Alkylating Agents	**Nitrogen Mustard:** Cyclophosphamide, Ifosfamide, Melphalan, Chlorambucil **Ethylenamine and Methylenamine derivatives:** Altretamine, Thiotepa **Alkyl Sulfonates:** Busulfan **Nitrosoureas:** Carmustine, Lomustine **Triazenes:** Dacarbazine, Procarbazine **Platinum containing Antineoplastic agents:** Cisplatin, Carboplatin, Oxaliplatin	DNA-/RNA-alkylation » inhibiton of cell divison
Antimetabolites	**Antagonists of Purine/ Pyrimidines Base:** 5-Fluorouracil (5-FU), 6-Mercaptopurine (6-MP) Capecitabine, Cytarabine, Fludarabine, Gemcitabine **Folic acid antagonists:** Methotrexate, Pemetrexed	Replacing metabolites » malfunctions Blockage of vital enzymes of the cancer cell » cell death
Antitumor Antibiotics	**Anthracyclines:** Doxorubicin, Daunorubicin, Epirubicin, Idarubicin **Other anti-tumor antibiotics:** Actinomycin-D, Bleomycin, Mitomycin-C	Binding to DNA » inhibition of RNA synthesis Intercalation in DNA » inhibiting nucleic acid synthesis
Topoisomerase Inhibitor	**Group 1:** Topotecan, Irinotecan **Group 2:** Etoposide, Teniposide, Mitoxantrone	Interference with Topoisomerase-enzymes » DNA strands break
Mitotic Inhibitor (Plant Alkaloids)	Paclitaxel, Vinblastine	Inhibition of cell division

Table 3 – part 1: Functionalities and Risks of ANPD-groups[1, 34, 35, 36, 37, 38, 39]

Therapy	Example	Functionality on cancer treatment
Targeted therapy	Afatinib, Imatinib, Gefitinib, Bortezomib (proteosome inhibitors)	Effect on specific cancer cell, blockage of enzymes, proteins and other molecules involved in growth of cancer cells, less harmful to normal cells
Differentiating agents	Bexarotene	Binding to intracellular receptors » inhibition of tumor cell proliferation
Hormone therapy	**Anti-estrogens:** Fulvestrant, Tamoxifen **Aromatase inhibitors:** Anastrozole, Exemestane Letrozole **Progestin:** Megestrol acetate **Estrogens** **Anti-androgens:** Bicalutamide, Flutamide **Gonadotropin**-releasing hormone (GnRH)[35] Leuprolide, Goserelin	Inhibition of hormone activities required for cancer cells growth
Immunotherapy	**Monoclonal antibody therapy (Mab)[44]** Rituximab and Alemtuzumab **Non-specific immunotherapies and adjuvants** Interleukin-2 / Interferon-α	Direct binding to cancer cells or growth factor for cancer cells » inhibition of cell proliferation Interleukin-2 / Interferon-α: Boost of immune system to identify and attack cancer cells

Table 3 – part 2: Functionalities and Risks of ANPD-groups » targeted and other therapies [25, 26, 40–46]

HANDLING OF HAZARDOUS DRUGS

RISKS CAUSES

CAUSES FOR RISKS

The world's population is expected to grow rapidly with the consequence of a rising prevalence for cancer-related diseases and enhanced need for treatment procedures. This will trigger the demand and development of oncology drugs driving the risk of exposure for HCWs in healthcare setting.[2, 3] The Centers of Disease Control and Prevention (CDC) reported that today in the US about 8 million HCWs are exposed to hazardous drugs.[47] Among these, hospital nurses and pharmacists are most frequently exposed to ANPDs, but also e.g. physicians, workers in research laboratories, and workers involved in logistics are at risk of exposure.[48]

Hospitals, pharmacies, manufacturer's premises, research or analytical laboratories, patient home, transport vehicles (patient ambulance, pharmacy transportation couriers, waste collectors), waste disposal areas are potential areas for antineoplastic drug exposure carrying major risks.[49, 50]

Many questionnaire-based surveys conducted with oncology nurses and pharmacists identified the causes of exposure as risks in occupational settings and emphasized needs for improvements and for implementation of a "safety – culture" in the medical institutions as given in table 1.[17, 9, 51] Non-compliant working procedures and notable refusal of PPE have been observed during preparation, administration and handling situations of hazardous drugs during patients' treatment.

Overall, risk causes may generally be categorized related to:

- **Organizational structure, workplace**, facilities and processes incl. communication / surveillance
- **Safety culture**, awareness / behavior
- **Knowledge** / training
- Availability / utilization of **PPE** (personal protective equipment) & **safety devices** / -tools

Workplace / processes	Safety culture	Knowledge / training	PPE / safety devices and tools
Lack of separated preparation area with proper aspiration and ventilation[17, 52, 53]	Risky behavior Smoking, drinking and food consumption in the working area[52]	Lack of knowledge and training[9, 17, 52, 53]	PPE not or only partly used[52, 59]
Working place contaminated[54]	Lack of adherence to defined standard procedures[55]	Poor participation in training programs[52]	Lack of spill management tools[55]
Improper disposal of contaminated waste and spill management[52, 55]	Decreasing caution and awareness of risks[9]	Discrepancy between knowledge and compliance[56]	Lack of awareness of different types, qualification and functions of PPE[9]
Improper hand hygiene practice[54, 56]	Lack of surveillance programs and related knowledge in hospital management[9]		Double gloving practice not implemented[9, 57]
Improperly validated procedures[54]			Inappropriate glove changing practice[58]

Table 4: Causes of risks (=exposure), identified via survey-studies

See also: Connor T.H. (2016) - Surface Wipe Sampling for Antineoplastic (Chemotherapy) and Other Hazardous Drug Residue in Healthcare Settings: Methodology and Recommendations - J Occup Environ Hyg. 2016 Sep; 13(9): 658–667. doi: 10.1080/15459624.2016.1165912; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5138855/

HANDLING OF HAZARDOUS DRUGS

RISKS CAUSES

Activity	Healthcare personnel	Route of exposure
Drug receipt	Warehouse or pharmacy workers	Drug residue contact on containers, boxes, vials, work surface, floor
Drug transportation	Pharmacy technicians and transport staff	Transport and movement of drugs from one area to another.
Drug dispensing	Pharmacy workers	Transferring drugs
Compounding	Pharmacists, nursing personnel	Manipulating drugs, transferring and mixing liquids Removal of drug-contaminated air from syringes Disinfection and cleaning process Maintenance of equipment
Spill management	Environmental service worker, nurses and pharmacists	Clean up of emergency spill, waste disposal
Drug administration	Nurses, doctors	In exceptional cases: Oral exposure and inhalation of aerosols drug contact during intra-operative injection/infusion or bladder installation
Patient care	Hospital and home care nurses, family care provider personnel	Handling of drug contaminated body fluids, clothing, dressing and infusion lines Administration of IV and oral chemotherapy agents at home
Patient movement	Ambulance service, patient transportation services	Transferring patients from hospital to home or specialized treatment and care organizations
Waste disposal	Nurses, cleaning staff, environmental service workers	Unprotected drug waste handling
Post-mortem management	Mortuary staff	Dead body transfer, washing of dead body
Research and development	Research laboratory personnel	Drug and equipment handling, cleaning process
Veterinary care	Veterinary doctors and co- workers, animal owners	Application of the drugs to affected animals

Table 5: Routes of Exposure dependent on type of ANPD-handling[32]

Exposure may occur during handling of cytotoxic drugs, administration, distribution, transportation and on the way of waste disposal. Preparation of the drug solution, unsecure contact with treated patient's body, bed cover, cloths, urine bottles, catheter bags, ostomy bags, napkins, excreta, vomitus bowls are very common "transmitters" of exposure. Unsafe cleaning of leakages and spills present also potential sources of occupational exposure in healthcare workers.[50]

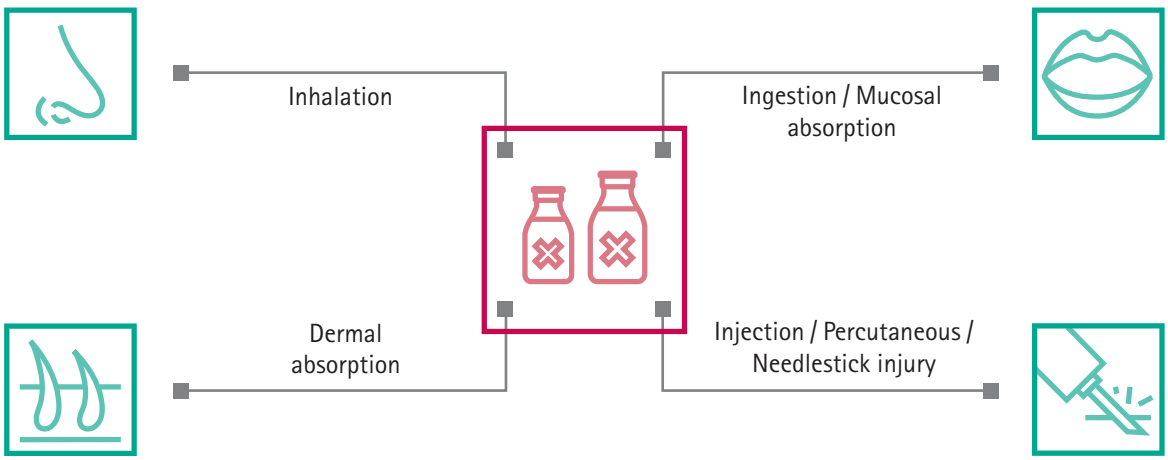


Figure 3: Routes of exposure

Inhalation exposure occurs due to droplets, particles and vapors of antineoplastic drugs, a probable route that may occur during drug preparation.

Dermal exposure may occur when spiking or unspiking intravenous solution bags and tubing's with conceivable leakages. Spill or leakage are crucial responsible factors of direct skin contact from ANPDs. Surface contamination of vials, biological safety cabinet, countertop, floor, equipment may lead to dermal exposure. Handling body fluids, excreta of treated patient or bed covers and contact with other used products by patient may further lead to exposure.[49, 50, 60]

Ingestion / mucosal exposure may occur due to consumption of food and beverages in preparation area.

Needle stick injuries by drug contained needles may cause injection exposure.

HANDLING OF HAZARDOUS DRUGS

CONSEQUENCES

CONSEQUENCES

The consequences – in a worst case-scenario – of a lifelong exposure to hazardous drugs like ANPD are to be discussed in two (inter-related) aspects:

- Burden of illness to HCW's, particularly to women
- Burden of costs to the health system

BURDEN OF ILLNESS TO HCW'S

As extreme consequences carcinogenic, teratogenic, mutagenic and reproductive effects have been identified and studied. "The excess lifetime leukemia risk at age 80 of an exposed oncology nurse after 40 years of dermal exposure to cyclophosphamide was estimated to be 1.04 per million oncology nurses. This risk could potentially increase to a maximum of 154 per million if a nurse performs all cyclophosphamide-related tasks with the maximum frequency (as observed in this population) and is exposed to maximum exposure intensities for each task without using protective gloves for 40 years."[61]

A number of investigations/surveys reveal a variety of information of adverse health effects on HCW's due to antineoplastic drugs exposure. A review described various reproductive consequences are associated with hazardous drug exposure in healthcare workers[64]: ANPDs' presence in breast milk, women treated with or are exposed to these drugs may face adverse effects by ovarian volume decrease, ovarian follicles damage, ovarian fibrosis resulting in amenorrhea and menopausal symptoms. Certain ANPDs can penetrate the placenta. Alkylating agents and anti-metabolites show higher rates of adverse pregnancy outcomes. Adverse effects of reproductive outcomes, infertility, miscarriage, stillbirth and congenital malformations in exposed healthcare workers have been found from numerous reproductive studies.

Maternal occupational exposure in association with ANPDs showed congenital anomalies and a higher reproductive risk in the first trimester. In men secondary hormone changes have been observed and some ANPDs may produce prolonged azoospermia. Interestingly, it is underlined as a limitation that all studies published up to 2013/2014 refer to data published before 2002, and most data were collected in the 1980s. Additionally, most of these studies investigated small sample sizes and small numbers of exposed cases which is the reason why the studies were often unable to adjust for confounding factors and report wide confidence intervals. In todays research results it is reported that stillbirths, congenital abnormalities, abortion diarrhea, hair loss, allergic reactions, infertility in both sexes, genotoxic damage and leukemia are the common effects of occupational exposure to ANPDs.[51, 52, 54, 63]

Several studies report that ANPD-handling nurses show a higher frequency of binucleated micronucleated cells [62] and significant chromatid and chromosomal aberrations.[54] ANPDs reduce fetal body weight, cause skeletal and visceral abnormalities and head and limb defects. [63]

In summary, according to a "Workshop on the Safe Handling of Hazardous Drugs Cohosted by the National Institute for Occupational Safety and Health and the American Society of Clinical Oncology" authored by Thomas H. Connor (NIOSH) and Robert Zon (ASCO) "approximately 60 % of 100 published studies show significant association between genetic damage and antineoplastic drug exposure."[65]

BURDEN OF COSTS TO THE HEALTH SYSTEM

Economic studies directly targeted to cost evaluations do obviously not yet exist but will appear to be necessary in the future: Scientific investigations on the burden of illness and their related costs to the health system will further trigger awareness-campaigns and profound implementation measures to close the still existing gaps.

It is postulated that stakeholders should support development of large-scale epidemiologic data registries on occupational exposure to antineoplastic drugs, and professional societies can play a role in the development of such a database.

A further key driver to more systematic research (particularly focused on implementation) will be triggered by the implementation of the "USP general Chapter <800>" titled "Hazardous Drugs-Handling in Healthcare Settings" – this campaign is accompanied by guidance for a healthcare institutions' "self assessment tools" in order to achieve readiness to meet Chapter <800> standards.[66]

HANDLING OF HAZARDOUS DRUGS

PREVENTIVE STRATEGIES

PREVENTIVE STRATEGIES

In contrast to patients with cancer where the benefit of an ANPD-therapy normally outweighs the risk of a secondary malignancy in the future, the occupational risk of exposure to ANPDs for HCWs appears to be unacceptable.

THEREFORE, "PREVENTIVE STRATEGIES" FOR HCW MUST FOCUS ON "PREVENTION OF EXPOSURE RISK".[3]

Institutional policies for safe handling of ANPDs have to be implemented within the scope of "Preventive strategies"-programs.

Organizations are obliged to enforce safe handling practices in oncological settings. These include controlled preparation, presence of separate administration areas and proper emergency waste handling. For all procedures, **Personal Protective Equipment** and Safety Devices must be provided.

Educational programs need to be established ensuring compliance with defined safety procedures which shall be surveilled through internal audits.

In order to support implementation processes, **guidelines and recommendations** have been established since the very early phases of recognized safety concerns and have undergone a continuous improvement-process as is shown in the following table:

Title	Editor	Source
Guidelines for safe handling of cytotoxic drugs in pharmacy departments and hospital wards	Society of Hospital Pharmacists of Australia (SHPA)	**1981**[69] Hosp Pharm. 1981 Jan; 16 (1):17-20. https://www.ncbi.nlm.nih.gov/pubmed/10249749
Recommendations for Safe Handling of Hazardous Drugs	Oncology Nursing Society (ONS)	**1982 – Update 2017**[70] https://voice.ons.org/news-and-views/safe-handling-of-hazardous-cancer-drugs
ASHP Guidelines on Handling Hazardous Drugs	American Society of Health-System Pharmacists (ASHP)	**1985 – Revision 2006**[71] American Journal of Health-System Pharmacy June 2006, 63 (12) 1172-1191; DOI: https://doi.org/10.2146/ajhp050529, http://www.ajhp.org/content/63/12/1172?sso-checked=true
Controlling Occupational Exposure to Hazardous Drugs	US Occupational Safety and Health Administration (OSHA)	**1986 – Update 2016**[72] https://www.osha.gov/SLTC/hazardousdrugs/controlling_occex_hazardousdrugs.html
A Report on the National Commission on Cytotoxic Exposure	National Study Commission on Cytotoxic Exposure (NSCCE)	**1987 – Update 1992**[73] Gallelli et al. J. Pharm. Tech. Vol. 8 March/April 1992 http://journals.sagepub.com/doi/abs/10.1177/875512259200800205
NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings	National Institute for Occupational Safety and Hazards (NIOSH)	**2004 – Updates 2010, 2012, 2014 and 2016**[1] https://www.cdc.gov/niosh/topics/antineoplastic/pdf/hazardous-drugs-list_2016-161.pdf
Guidelines for the safe handling of hazardous drugs: Consensus recommendations	Michigan Experts: University of Michigan	**2010**[74] Chaffee et al. (2010) American Journal of Health-System Pharmacy, 67(18), 1545-1546. DOI: 10.2146/ajhp100138 https://experts.umich.edu/en/publications/guidelines-for-the-safe-handling-of-hazardous-drugs-consensus-rec
UHC consensus statement: model hazardous drug safety plan for institutions	University HealthSystem Consortium (UHC)	**2010**[75] University HealthSystem Consortium (UHC): UHC consensus statement: model hazardous drug safety plan for institutions. Am J Health-Syst Pharm 2010; 67:1545-6
"PSHSA-Whitepaper" Safe handling of hazardous drugs in healthcare	Canada: PSHSA (Public Services Health and Safety Association), Ontario	**2013**[76] Safe handling of hazardous drugs in healthcare https://www.pshsa.ca/wp-content/uploads/2013/11/PSHSA-White-paper-Safe-Handling-of-Hazardous-Drugs-in-Healthcare.pdf
"Practice Guideline" Safe handling of cytotoxics: guideline recommendations	Canada: "Cytotoxic Handling Expert Panel / Working Group" / Centre for Global eHealth Innovation, Toronto General Hospital	**2015**[77] Easty, A. C., Coakley, N., Cheng, R., Cividino, M., Savage, P., Tozer, R., & White, R. E. (2015) - Safe handling of cytotoxics: guideline recommendations - Current Oncology 2015, 22(1), e27-e37 doi: http://dx.doi.org/10.3747/co.21.2151 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4324350/

Table 6: History of Guidelines / (Consensus-) Recommendations on Safe Handling of ANPDs / Cytotoxic Drugs

HANDLING OF HAZARDOUS DRUGS

GUIDELINES, (CONSENSUS-BASED) RECOMMENDATIONS AND STANDARDS REFLECT THE PROCESSES IN THE SUPPLY CHAIN PATHWAY FOR HAZARDOUS DRUGS AS ALREADY MENTIONED ABOVE.

Legislations and regulations in handling these drugs offer "graduated" categories of recommendations, i.e. whether a certain measure is "(strongly / ...) recommended". And it is clearly communicated that reductions in attention to the administration and surveillance of antineoplastic drugs by intention or accidentally may enhance adverse effects in healthcare setting and any related risks.

PREVENTIVE STRATEGIES

Preventive strategies are related to the four defined categories for causes of risks:

1 ORGANIZATIONAL STRUCTURE

In general it is postulated that in the future workplace safety needs a higher priority.[3] Within the main responsibility of the pharmacies, in purchasing cytotoxic drugs, a full integrity of the whole packaging has to be ensured and checked.

Cytotoxic Drug waste containers must be labeled as such with a cytotoxic sign, be rigid and leak-proof and sharps waste should be collected separately. Further processing should be done before disposal.[58, 60]

Dedicated (separated) preparation areas with controlled temperature, ventilation and air condition systems must be taken into consideration by hospital administration or the entrepreneur of a medical institution.

In case of contamination there must be a separated area and workers should wear two pairs of gloves during cleaning of cytotoxic drugs.[60]

2 SAFETY CULTURE

All staff-members including receiving and transport-personnel in medical institutions must be informed by their employers about the reproductive hazards of ANPDs and related hazardous drugs, be made aware of the potential exposure to these drugs and adequately trained. Particularly, it should be part of the program that the pregnant workers should be offered alternative duties.[60]

As already emphasized in the chapter "Definition of Risks" these measures do not necessarily have to be applied for MABs due to their specific target mechanisms and higher molecular weight. A recent re-assessment of risks revealed that MABs in general do not have to be classified as hazardous drugs.

All institutions should install "task force"-committees who compile, review and monitor policies and standardized processes for all personnel employed in administration and preparation of these drugs, and also implement risk prevention management-programs for handling ANPDs/cytotoxic drugs.

Feasible, effective control measures in healthcare setting can and must ensure targeted exposure control in healthcare workers. The NIOSH re-emphasizes an appropriate "hierarchy of (industrial hygiene) control" in order to avoid exposure which is e.g. engineering control, administrative control and appropriate PPE use. (2016_NIOSH, 2006_Connor, based on 1978_Skov)

During patient care the safe handling of body fluids and excretions, as well as diapers and patient clothing is crucial. Chemotherapy drugs may be present in the body for several days after the last dose of the chemotherapy treatment. Toilets, bed pans, urinals and diapers and also patient clothing are contaminated by ANPDs and their metabolites Patient care procedures, including washing of the patient and cleaning of facilities may bear the risk of unintended contact with the drugs. Specials hygiene standards need to be implemented both for patients and nursing staff.

3 KNOWLEDGE / TRAINING

Hospitals and supervising authorities shall provide continuously updated educational material and adequate training for all staff involved in ANPD/cytotoxic drug handling. Staff members must be made aware of the potential exposure to these drugs related risks and protective measures.

Equipment, training and educational activities shall be in adherence to regulations for cytotoxic drug hazard prevention (see table 6).[42, 57, 60, 62, 63, 64]
It must be ensured that the staff applies the best practice standards when handling these drugs.

In several countries the Aesculap Academy offers local training concepts to ensure a safe handling & application of cytotoxic drugs. The Aesculap Academy is one of the leading medical education forums for all B. Braun customers and provides indication, therapy and process-related courses to all Healthcare Professionals.

With these training activities the academy addresses the training needs and requirements for clinical staff and thus contributes to protect health and improve care.

Based on globally recognized quality criteria, innovative learning methods and technologies more than 75.000 medical professionals are trained annually.

With the website "Ready for <800>" (www.readyfor800.com) B. Braun offers an online educational platform, supported by expert insights, experiences, and recommendations, with focus on awareness and education of the new hazardous drug safety standard, USP <800>.

HANDLING OF HAZARDOUS DRUGS

PREVENTIVE STRATEGIES

4 PPE & SAFETY DEVICES

Healthcare workers should work in compliance with standards, guidelines and recommendations listed above in table 6 and adherently follow the recommendations for PPE-use: appropriate PPE use knowledge and maximizing complete gearing will ensure proper barrier against any general and accidental exposure from cytotoxic drugs.[62]

Spill kits should be available in areas where cytotoxic drugs are stored, transported, handled and administered. It must be ensured that spill kits (see 2017_McGill und 2017_Connor), biological safety cabinets (BSC) personal protective gear and appropriate waste management containers must be functionally installed where ANPDs are stored, transported, handled and administered and that these kits are always accessible.[60, 4]

"Chemotherapy-grade" gloves according to ASTM D-6978 (American Society for Testing and Materials) or EN 374 (European standard) approved gloves should be used and must be powder-free. Nitrile, polyurethane, polychloroprene and latex gloves are recommended. Two pairs of gloves ensure maximum protection against various cytotoxic drugs concentrations and in an emergency spill case. First pair gloves should be put on before wearing protective gown. When handling ANPDs, HCWs should change gloves every 30 minutes and remove gloves immediately in case of torn, puncture or visible contamination appearance.[60]

Protective gowns should be lint-free, should have long sleeves with tight cuff. Gowns should be changed every 3.5 hours and immediately in case of contamination necessary.

Surgical masks are required during drug preparation. Full face protection may be adequate in administration and handling of cytotoxic drugs.[60, 62] For adequate eye protection fluid resistant goggles are recommended. In emergency eye exposure, an at least 15 minute eye wash with isotonic eye wash solution is indicated. Head caps are required in sterile preparation area. Shoe covers can prevent contamination of workers' shoes.[60]

SOPs for clean rooms need to be established and followed. In BSC- class II cabinets HEPA (High-Efficiency Particulate Air)-filters are recommended in cytotoxic drug preparation. After drug preparation it should be cleaned acc. to cleaning and disinfection-SOPs.[54]

The most recent recommendations for safe handling of cytotoxic drugs are published by NIOSH in "General guidance for some of the possible scenarios that may be encountered in healthcare settings where hazardous drugs are handled" (2016_NIOSH, (Tab. 7). The table 7 from NIOSH relates the different types of hazardous drug-formulations and their corresponding hazard potential to recommended protective measures. However, the authors are underlining that not all possible situations may be covered by these recommendations.

Table 7: Personal protective equipment and engineering controls for working with hazardous drugs in healthcare settings* (Taken from 2016_NIOSH1)

Formulation	Activity	Double chemo-therapy gloves	Protective gown	Eye / face protection	Respiratory protection	Ventilated engineering control
All types of hazardous drugs	Receiving, unpacking, and placing in storage	no (single glove can be used, unless spills occur)	yes, when spills and leaks occur	no	yes, when spills and leaks occur	no
Intact tablet or capsule	Administration from unit-dose package	no (single glove can be used)	no	no	no	N/A
Tablets or capsules	Cutting, crushing, or manipulating tablets or capsules; handling uncoated tablets	yes	yes	no	yes, if not done in a control device	yes†
	Administration	no (single glove can be used)	no	yes, if vomit or potential to spit up†	no	N/A
Oral liquid drug or feeding tube	Compounding	yes	yes	yes, if not done in a control device	yes, if not done in a control device	yes†
	Administration	yes	yes	yes, if vomit or potential to spit up†	no	N/A
Topical drug	Compounding	yes	yes	yes, if not done in a control device	yes, if not done in a control device	yes†, BSC or Compounding aseptic containment isolator (CACI) (Note: carmustine® and mustargen® are volatile)
	Administration	yes	yes	yes, if liquid that could splash†	yes, if inhalation potential	N/A
Subcutaneous/ intra-muscular injection from a vial	Preparation (withdrawing from vial)	yes	yes	yes, if not done in a control device	yes, if not done in a control device	yes, BSC or CACI
	Administration from prepared syringe	yes	yes	yes, if liquid that could splash†	no	N/A

(Continued on the next page)

HANDLING OF HAZARDOUS DRUGS

PREVENTIVE STRATEGIES

Formulation	Activity	Double chemo-therapy gloves	Protective gown	Eye/face protection	Respiratory protection	Ventilated engi-neering control
Withdrawing and/or mixing intravenous or intramuscular solution from a vial or ampoule	Compounding	yes[§]	yes	no	no	yes, BSC or CACI; use of Closed system drug transfer device (CSTD) recommended
	Administration of prepared solution	yes	yes	yes; if liquid that could splash[ǂ]	no	N/A; CSTD required per USP 800 if the dosage form allows
Solution for irrigation	Compounding	yes	yes	yes, if not done in a control device	yes, if not done in a control device	yes, BSC or CACI; use of CSTD recommended
	Administration (bladder, HIPEC, limb perfusion, etc.)	yes	yes	yes	yes	N/A
Powder/solution for inhalation/ aerosol treat-ment	Compounding	yes	yes	yes, if not done in a control device	yes, if not done in a control device	yes, BSC or CACI
	Aerosol admini-stration	yes	yes	yes	yes	yes, when applicable
	Administration	yes	yes	yes; if liquid that could splash[ǂ]	yes, if inhalation potential	N/A
Drugs and metabolites in body fluids	Disposal and cleaning	yes	yes	yes, if liquid that could splash	yes, if inhalation potential	N/A
Drug-contami-nated waste	Disposal and cleaning	yes	yes	yes, if liquid that could splash	yes, if inhalation potential	N/A
Spills	Cleaning	yes	yes	yes	yes	N/A

Even though risks of exposure cannot be completely eliminated [12, 14, 18, 19], technologically more advanced approaches in so called "engineered control"- systems (e.g. "compounding aseptic containment / robotic systems) [17-19, 21-23] can substantially reduce / avoid workplace contamination.

Within the focus "risk and waste minimization for ANPDs", authors from Switzerland[27] established structured "toxicity assessments" to minimize exposure risks in the hospital and pharmacy – these assessments had been accompanied by a definition of protective measures.

Quite similarly, a Turkish author team[68] discusses attempts to reduce and eliminate workplace contamination.

Table 7 addresses the different types of hazardous drug - formulations and their corresponding hazard potential the recommended "activity" in general, necessities for "Double chemo-therapy gloves", "Protective gown", "Eye / face protection", "Respiratory protection" as well as "Ventilated engineering control."

To minimize the risks in the admixture, transportation or administration of cytotoxic drugs, it is recommended to use Safety Devices in addition to the PPE. Safety-enhancing features in the mentioned areas are for example a needle-free admixture in a closed system, supporting the HCW in minimizing spillage and reducing the risk of contamination.

This was also encouraged by a recent NIOSH alert. Sharps disposal containers shall be used for easy and safe disposal of medical sharps. These should be impact- and puncture-resistant.

HANDLING OF HAZARDOUS DRUGS

PREVENTIVE STRATEGIES

Table 8: Summary of Preventive Strategies in HCWs' working areas[58]

Training		Standard procedures and documentation
Human resources management		Drug administration by oncology nurses or appropriately trained personnel only, trained cleaning and environmental workers
Preparation area	Clean environment control	Biological safety cabinet Class II or class III cabinet
	Personal Protective Equipment	Double gloving, change of gloves every 30 minutes. Glove selection: chemical resistance approved according ASTM (American society for testing and materials) and / or by EN 374 (European standers for protective gloves)
		Protective disposable gown with closed front, long sleeves, knit or elastic closed cuff. Cuffs tucked under gloves
		Fluid-resistant eye protection and face mask
		Head cover and shoe cover
Caution in preparation and administration		Avoid needle stick injuries and spillage
		Avoid inhalation
		Minimize exposure during transfer drugs via needles to syringes
Risky behavior		Avoid eating, drinking and smoking in the drug preparation area
Administration and preparation area		Clean surfaces and hands according to SOPs
Waste identification and disposal		Used vials, ampoules, syringes, gloves, gauze, needle, IV sets marked as cytotoxic waste
		Disposal of sharps into labelled chemo sharps containers
		Expired drugs to be returned to manufacturer
		Approved chemotherapy waste bags according ASTM
		Treated patient's clothes and excreta, drug waste, used personal protective equipment to be disposed in appropriate containers designed for cytotoxic waste
Adherence to hygiene standard procedures		Proper dispose technique (donning and doffing gloves/PPE), washing hands after glove removal
		Waste disposal in separate waste area
Exposure and spill management		After exposure immediate washing-off of ANPDs, rinsing of eyes or exposed skin with isotonic water or in normal water for 15-20 minutes
		Identification of spill amount, liquid to be wiped off with wet absorbent gauze, spill area to be cleaned with detergents.
		Surfaces and equipment to be cleaned with alcohol or sodium hydroxide wipes
		Surveillance program and monitoring of affected or exposed patient to be established

Conclusions

The risks for HCWs being unnecessarily exposed to hazardous drugs are well known and have been more and more given investigative insight during the last four decades. It appears surprising that the related gaps in awareness of these risks' consequences are still existing in nowadays clinical practice.

The many surveys that have been conducted in a number of different countries reveal a lot of remaining tasks for many institutions worldwide in order to close gaps and increase occupational safety. Authoritative guidelines and related recommendations do exist and all of them summarize long standing elements of safe handling programs to be implemented in order to assure minimal risks to healthcare workers, following the "as low as reasonably achievable" - (ALARA-) principle of risk management[70] in the daily working procedures.

Additional awareness will be generated within the frame of the implementation for the "USP general Chapter <800> "titled "Hazardous Drugs-Handling in Healthcare Settings". This campaign will be accompanied by guidance for healthcare institutions "self assessment tools" in order to achieve preparedness to meet Chapter <800> standards.[66]

As already mentioned in preventive strategies tools and detailed information may be found on the website www.readyfor800.com – an educational resource provided by B. Braun.

The pivotal measures of risk reduction in ANPD handling are clearly targeted to personal protection, safety products, communication, proper education, supervision, control and surveillance.

The knowledge about the correct use of PPE including its surveillance and control is one of the most fundamental elements to minimize the impact of severe consequences to "burden-of-illness" and "burden-of-costs" in occupational health economy and patient safety.

HANDLING OF HAZARDOUS DRUGS

RISK PREVENTION

Vasco® Nitril long sterile

- Sterile nitrile examination gloves with long cuff suitable for cytotoxic drug preparation
- Tested for resistance to permeation by chemotherapy drugs according ASTM D 6978
- Detailed information on barrier properties: See technical data sheet

Vasco® OP surgical gloves

- High quality fully anatomical surgical gloves
- Made from natural rubber latex
- Powder-free
- Latex-free inner polymer coating
- Double-gloving indicator system: Vasco® OP Underglove plus Vasco® OP Sensitive/ Grip for a quick detection of perforations

Vasco® Nitril white/blue

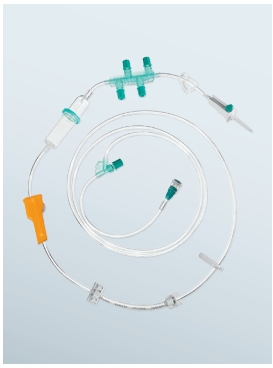
- Nitrile examination gloves suitable for cytotoxic drug application
- Tested for resistance to permeation by chemotherapy drugs according ASTM D 6978
- Detailed information on barrier properties: See technical data sheet

Cyto-Set® Mix

- Allows the needle-free admixture of cytotoxic drugs in the Ecoflac® plus IV container
- The needle-free connector made of tritan is tested with different kinds of cytostatic drugs

Cyto-Set® Infusomat Space

- Helps reducing the risks of chemical contamination and air embolism thanks to the creation of a closed system
- The risk of drug incompatibility is reduced through the flushing of the line
- The needle-free connectors made of tritan are tested with different kinds of cytotoxic drugs and have integrated back-check valves



Medibox®

- No-touch, twist-off and insertion inlets for all kinds of used luer and luer-lock needles as well as pen needles
- Large opening to ease the insertion of various medical sharps
- Easy to use temporary closure
- Irreversible final lock mechanism
- Overfill warning by maximum fill line

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NOTE:

The summarized scientific information in this document has been prepared for healthcare professionals.

It is based on an analysis of publicly available literature and guidelines. The intention is to give an introduction to the risks commonly associated with ANPDs to increase the awareness of healthcare workers to these kinds of problems. Due to its summary nature, this text is limited to an overview and does not take into account all types of local conditions. B. Braun does not assume responsibility for any consequences that may result from therapeutical interventions based on this overview.

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