HAZARDOUS DRUGS AND OCCUPATIONAL RISK:

The unknown siblings of antineoplastic drugs

With the endrsement of

SOCIETA' ITALIANA DI FARMACIA
OSPEDALIERA E DEI SERVIZI FARMACEUTICI
DELLE AZIENDE SANITARIE

HAZARDOUS DRUGS AND OCCUPATIONAL RISK:

The unknown siblings of antineoplastic drugs

EDRA S.p.A.
Via G. Spadolini 7
20141 Milan, Italy
Tel. 02 88184.1
Fax 02 88184.302

Ludovico Baldessin
Chief Business & Content Officer

Susanna Garofalo
Editorial manager

Published with the unconditional contribution of Becton Dickinson Italia SpA.

Edition reserved for Specialized Health Professionals

Not for resale

Printed in April 2021 by Jona s.r.l. – Paderno Dugnano (MI)

AUTHOR

FRANCESCA DE PLATO
SIFO National Contact Person for the "Chemical and Biological Risk" Scientific and Cultural Area
Pharmacy Unit Acting Director, Mazzini Hospital, Teramo

CONTENTS

KEY POINTS*

- The existence of the risk of long-term and short-term toxicity (onset of neoplasia, reproductive and developmental toxicity) for staff preparing and administering different classes of drugs.
- The exposure of healthcare operators may occur via inhalation, contact, absorption through the skin, ingestion or injection. It can be increased by handling operations such as the reconstitution of lyophilised drugs (when aerosols are often generated) or dilutions, and through contact with contaminated surfaces or vials.
- With regard to the risk of exposure described above, EU regulations on health and safety in the workplace implemented in Italian law require employers to assess the risk and to put into effect all the necessary safety measures.
- Considering their undisputed level of innovation, there is an ever increasing use of so-called CSTDs (Closed System Drug Transfer Devices) for the transfer of hazardous drugs in the preparation and administration phases. To these systems refers the recent definition of NIOSH, "drug transfer device that mechanically prohibits the transfer of environmental contaminants into a system and the escape of hazardous drug or vapour concentrations outside the system"
- The adoption of closed systems (CSTDs and equipment defined as "isolators") still seems dishomogeneous in Italy.
- This document of consent aims to highlight the added value (in terms of protection) that these devices offer to healthcare facilities in which hazardous drugs are handled.

* The consensus document "Gestione Del Rischio Di Esposizione del personale sanitario nella manipolazione dei farmaci antineoplastici iniettabili: gli aspetti di prevenzione e la caratterizzazione delle misure di sicurezza" (Management of the exposure risk of healthcare workers in the handling of injectable antineoplastic drugs: prevention aspects and characterisation of safety measures) was published in 2017.
This new document supplements the analysis by discussing all those drugs that are not classified as antineoplastic drugs.
An excerpt from the principles of the 2017 consensus document, identified in key points, which also apply to non-antineoplastic drugs, is provided here.

1. INTRODUCTION

The earliest evidence of the health risk to health professionals associated with the handling of drugs (antiblastics) dates back to the 1970s. Since then, scientific evidence documenting this risk has grown exponentially and led to the publication of numerous guidelines and recommendations on occupational health prevention and protection practices. Despite the good degree of awareness achieved, international studies show that the risk of occupational exposure to hazardous drugs has not yet been adequately reduced and that there are still organisational and cultural barriers to the adoption of appropriate protection measures [1]. Data published by the European Biosafety Network (EBN) in 2019 shows that safety protocols on the management of hazardous drugs are still implemented inconsistently in healthcare facilities in the European Community (EC) and that many hazardous practices take place outside hospital pharmacies, significantly exposing hospital wards to risk.

Thanks to the considerable technological progress made, today there are systems available that ensure the highest level of protection, but their adoption throughout Europe as well as in Italy is still rather slow [2].

Current Italian legislation, i.e., Legislative Decree 81/2008 as amended, implementing the European Union Directives on health and safety at work, requires a risk assessment and the implementation, by the employer, of all the resulting safety measures.

The occupational risk assessment on the handling of hazardous drugs is very complex and depends on several factors, the first of which is certainly the intrinsic toxicity of the substance.

While the intrinsic toxicity of antiblastic drugs has long been established and new knowledge is beginning to emerge on the long-term toxicity of new non-genotoxic antineoplastic drugs, for which an epigenetic toxiciy mechanism is assumed, for most drugs used in other specialist areas of medicine, and which may endanger the health of professionals exposed to these, there is still little literature available [1].

Data collected by the U.S. National Cancer Institute (NCI), referring to the years 1973–2000, indicate that cancer patients treated with antiblastic drugs that are able to bind and damage DNA, are 14% more likely to develop a second tumour than the general population [4]. For some of these, use is increasing, and they are used in a larger number of working environments, as they are increasingly indicated in the treatment of non-malignant immunological and rheumatological diseases. For instance, antineoplastic drugs such as cyclophosphamide and methotrexate have been shown to be effective in the treatment of rheumatoid arthritis and multiple sclerosis.

Some non-oncological drugs have toxic properties similar to those of antineoplastic drugs. Documents from the U.S. National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA), as well as numerous international studies indicate that, in addition to various antineoplastic drugs, some antiviral agents (e.g., ganciclovir), biotechnological drugs and antibiotics (e.g., chloramphenicol) may also interfere with the cell cycle or DNA synthesis. For some other drugs, toxic effects on reproduction are the main occupational hazard [5,6].

Hazardous non-oncological drugs are commonly used for a variety of clinical indications, from rheumatic diseases to the prevention of transplant rejection. An Australian prevalence study has shown that about 60% of hospitalised patients are prescribed drugs considered hazardous and that, often, the prescribed drug is not related to the reason for admission [7].

In accordance with the definition formulated by the American Society of Health-System Pharmacists (ASHP), and modified by NIOSH, a drug is considered hazardous if it has one or more of the following characteristics:

- *carcinogenicity* - i.e., the ability to cause or promote the development of cancer;
- *teratogenicity* - i.e., the ability to cause congenital foetal malformations;
- *toxicity to the reproductive system* - i.e., the ability to impair fertility (causing miscarriage, foetal death, infertility);
- *genotoxicity* - i.e., the ability to damage DNA, causing mutations;
- *organ toxicity* - i.e., the ability to cause significant toxic effects on organs at low doses;
- *chemical structure and toxicological profile* similar to those of a drug recognised as hazardous according to the above criteria [1,5].

Bearing in mind the conceptual distinction between the terms "antineoplastic" and "cytotoxic", the former being any agent used in cancer (e.g., cytotoxic drugs, hormones, immunomodulants, biotechnological drugs), and the latter, any agent capable of interrupting cell growth and function of both healthy and diseased cells [8], hazardous drugs were classified by NIOSH, for the first time in 2014, into three groups:

- antineoplastic drugs
- non-antineoplastic drugs that meet at least one hazard criterion
- drugs that pose a risk to reproductive health in men and women trying to conceive a child and in pregnant or breastfeeding women, but which pose no risk to the rest of the population [9].

In the new NIOSH list, which is currently being published, 16 drugs are likely to be added and 5 will be removed. The update has taken into account drugs that were recently approved, or received new FDA safety alerts, between January 2014 and December 2015.

NIOSH has also changed the classification of hazardous drugs, which are now divided into two groups:

- drugs that meet the NIOSH definition of a hazardous drug and contain instructions for safe handling in the package leaflet and/or are classified by the National Toxicology Program (NTP) as "known to be carcinogenic to humans" and/or classified by the International Agency for Research on Cancer (IARC) as "carcinogenic" or "probably carcinogenic";
- drugs that meet one or more NIOSH criteria, but do not contain instructions for safe handling in the package leaflet or are not classified by the NTP as "known to be carcinogenic to humans" or classified by the IARC as "carcinogenic" or "probably carcinogenic".

The concept of hazardous drug provided by NIOSH, however, is not intuitively transferable to the toxicity characteristics associated with some new-generation drugs, such as biotechnological drugs. New biologicals act at the molecular level and their interaction with cellular targets and the resulting consequences at the nuclear level are not clearly understood, so the effects of possible prolonged exposure are not fully predictable. However, in the absence of reliable scientific evidence allowing a thorough risk assessment, current Italian legislation (i.e., Legislative Decree 81/2008 as amended) requires the adoption of the precautionary principle by the employer, by virtue of the priority that is given to workers' health. Therefore, despite their increasing use, occupational exposure to biological drugs should be avoided, even in the absence of scientific evidence of the exact type of damage to health [3].

In any case, in the occupational risk assessment, the qualitative information relating to the intrinsic toxicity of the drug must be supplemented by the identification of the exposure risk, i.e., the quantitative estimate of exposure related to the activity performed by the professional.

Therefore, in order to characterise the exposure scenarios and stratify occupational risk, the following are to be taken into account:

- **the type of formulation and consequent method of handling** (tablets/capsules, oral solution, solution for injection, etc.)
- **administration route**
- **potential route of absorption**
- **frequency of exposure** (directly related to the extent of use)
- **safety measures** already in place and those to be implemented.

Oral formulations of hazardous drugs require additional precautions to be taken. These drugs may not pose a real risk of occupational exposure by virtue of their solid pharmaceutical form, as in the case of coated tablets or capsules, as long as it is not altered. For clinical needs, however, drugs are often handled, and the formulation is altered by crushing and solubilisation of the tablets or opening the capsules (e.g., in neurology, psychiatry, oncology departments). These practices can lead to the release of dust, which constitutes a real risk of exposure to the operator, either by contact or inhalation, and should be avoided, with liquid formulations being preferable where available [1,5]. Although outside the scope of this document, it should also be taken into account that oral formulations are widely used in the patient's home, posing a risk, often unknowningly, to family members, who should be given clear instructions and guidance.

Despite the efforts made in recent decades to ensure the safe handling of hazardous drugs, the recommendations of most guidelines are limited to antineoplastic drugs and there are currently no globally standardised prevention criteria [10]. In this regard, it is worth noting the chapter "*Hazardous Drugs Handling in Healthcare Settings*" of the US Pharmacopoeia [11], which requires health services to carry out a risk assessment for each drug in use.

Any healthcare organisation that fosters compliance with guidelines or recommendations aimed at drastically re-ducing occupational exposure to hazardous drugs, which is a legislative obligation for employers, is faced with the challenge of identifying a complete list of hazardous drugs that can be made available to healthcare professionals. Currently, also at European level, reference is made to the list of medicines drawn up and periodically updated by NIOSH. At the same time, however, NIOSH also suggests the adoption of personalised lists, which are better adapted to individual situations and which, thanks to greater flexibility, can more quickly include newly marketed medicines that should be a cause for concern in some way, until we have adequate information for their exclusion.

The periodic update of the NIOSH list is on average 4 years behind the marketing of new drugs, as the review process involves several steps, which take a long time.

Thanks to the EBN initiative, in February 2019 the European Parliament unanimously approved some amendments aimed at including hazardous drugs in Directive 2004/37/EC on the protection of workers from the risks related to occupational exposure to carcinogens or mutagens.

This is an important step, as the availability of Community legislation with clear provisions on the subject could result in standardised prevention strategies based on recommendations better adapted to the operational reality of the EC, thanks to specific European guidelines and a European list of hazardous drugs [2].

An initial Italian Consensus Document on the management of the risk of exposure of healthcare personnel in hazardous drug handling was published in 2017, under the patronage of SIFO (Italian Society of Hospital Pharmacies and Healthcare System Pharmaceutical Services), regarding injectable antineoplastic drugs [3].

This new publication aims to improve the management of hazardous drugs used in specialist non-oncological areas as well, identifying occasions of risk, providing alerts for the

safety of health workers and recalling the aforementioned Consensus Document with regard to legislative aspects concerning prevention and protection strategies, as well as responsibility profiles.

The main objective of this document is to provide health professionals with a practical and easy-to-use tool for finding information on the hazard and toxicity properties of non-oncological drugs.

To this end, a final table is proposed here which comprises a list of hazardous drugs, obtained by cross-referencing several international databases, with the hope that it will be improved and adapted in the future thanks to the contribution of experts from the various Member States. For each active substance, reported in alphabetical order, the following is specified: pharmaceutical category, formulations currently available on the market, toxicity properties and the relevant bibliographical references. The list also includes drugs that expose to biological risk, regarding which protective measures are in any case mandatory. Anaesthetic gases (nitrous oxide, old and new halogenated gases such as halothane and enflurane, isoflurane, sevoflurane and desflurane), though toxic to bone marrow, the nervous system, the reproductive system, the liver and kidneys, are not considered here as they are subject to specific measures, both nationally and internationally.

To complete the work, a summary table is provided with recommendations for the use of personal protective equipment (PPE) and the application of engineering measures, depending on the pharmaceutical formulation and the activity carried out.

REFERENCES

1. Power LA, Coyne JW. ASHP Guidelines on Handling Hazardous Drugs. Am J Health Syst Pharm. 2018 Dec 15;75(24):1996-2031.
2. European Biosafety Network (EBN). Observatory on current biosafety practice in European Oncology. February 2019. https://www.europeanbiosafetynetwork.eu/wp-content/uploads/2019/03/Observatory-on-current-biosafety-practice-in-European-Oncology-1.pdf)
3. Lombardi R, Amari P, De Plato F et al.; Documento Italiano di Consenso SIFO (Società Italiana di Farmacia Ospedaliera e dei Servizi Farmaceutici delle Aziende Sanitarie). Gestione del rischio di esposizione del personale sanitario nella manipolazione dei farmaci antineoplastici iniettabili: gli aspetti di prevenzione e la caratterizzazione delle misure di sicurezza. Aprile 2017. https://www.sifoweb.it/images/pdf/attivita/attivita-scientifica/aree_scientifiche/area_oncologica/CONSENSUS_DOCUMENT_FINALE.pdf
4. Curtis RE, Freedman DM, Ron E, et al. (eds). New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000. National Cancer Institute. NIH Publ. No. 05-5302. Bethesda, MD, 2006 https://seer.cancer.gov/archive/publications/mpmono/MPMonograph_complete.pdf
5. NIOSH [2020]. Draft NIOSH List of Hazardous Drugs in Healthcare Settings, 2020 https://www.cdc.gov/niosh/docket/review/docket233c/pdfs/DRAFT-NIOSH-Hazardous-Drugs-List-2020.pdf
6. Occupational Safety and Health Administration (OSHA) 2016. Controlling Occupational Exposure to Hazardous Drugs. https://www.osha.gov/SLTC/hazardousdrugs/controlling_occex_hazardousdrugs.html
7. Bowen S. The new hazardous drugs lists: how hazardous is our hospital? Medicines Management 2015, Proceedings of the 41st SHPA National Conference; 2015 Dec 3-10; Melbourne
8. eviQ Cancer Treatments Online. Supporting Document – Safe Handling and Waste Management of Hazardous Drugs Cancer Institute NSW; 2016
9. NIOSH [2014]. Connor TH, MacKenzie BA, DeBord DG, Trout DB, O'Callaghan JP. National Institute for Occupational Safety and Health (NIOSH) list of antineoplastic and other hazardous drugs in healthcare settings 2014. Publication No. 2014-138 (Supersedes 2012-150) https://www.cdc.gov/niosh/docs/2014-138/pdfs/2014-138_v3.pdf?id=10.26616/NIOSHPUB2014138
10. Bernabeu-Martínez MA, Ramos Merino M, Santos Gago JM, et al. Guidelines for safe handling of hazardous drugs: A systematic review. PLoS One. 2018 May 11;13(5):e0197172
11. USP General Chapter <800> Hazardous Drugs – Handling in Healthcare Settings, November 2019 https://www.usp.org/sites/default/files/usp/document/our-work/compounding/usp-800-context-for-implementation-fs.pdf
12. Booth J et al. Hazardous non-cytotoxic medicines: uncertainty around safe handling? A new workplace guideline for hospital staff. Journal of Pharmacy Practice and Research (2019) 49, 62-68

2. SCENARIOS OF EXPOSURE TO HAZARDOUS NON-ONCOLOGICAL DRUGS

Since the legislative requirements (Legislative Decree 81/2008 as amended) that require the substitution, where possible, or use in the minimum possible quantities (ALARA, As Low As Reasonably Achievable) of the hazardous substance are not fully applicable in health settings, the prevention and protection measures adopted, which it would be desirable for them to be as uniform as possible at supranational level, play an even more crucial role. To this end, it is important to have up-to-date information on the consumption of hazardous drugs in Italian hospitals, in order to quantify the occupational exposure resulting from the volumes used and to focus on the areas that require the utmost attention and represent priorities for action.

The actual conditions of exposure to a hazardous drug, and therefore the potential occupational exposure, are the result of a combination of organisational methods and the volume of work with the drug.

An overview of the use of hazardous drugs in non-oncological settings in Italy will be provided below, with particular reference to public health facilities, reporting consumption data relating to the various therapeutic areas and the indications of the main hazardous drugs. The text will refer to the data collected by OsMed (Italian National Observatory on the Use of Medicines), contained in the latest version of the National Report on the Use of Medicines in Italy, published annually by AIFA (Italian Medicines Agency) and referring to 2018.

The analysis of the consumption of drugs purchased by healthcare facilities was conducted using the Drug Traceability Flow and the amount of drugs prescribed is expressed by the indicator DDD/1,000 inhabitants (inh.)/day, i.e., in terms of the average number of doses of drug consumed daily by 1,000 inhabitants, where DDD (Defined Daily Dose) is a standard reference unit representing the daily maintenance dose for an adult subject, relative to a substance's main therapeutic indication, and therefore does not mean the recommended dose for the individual patient.

2.1 Immunomodulatory Drugs

In 2018, immunomodulatory drugs, together with antineoplastic drugs, were the number one therapeutic category in terms of public expenditure, mainly determined by the purchase by public healthcare facilities, while the contribution related to pharmaceutical assistance under the agreement was much lower. The comparative analysis versus 2017 shows an increase in hospital spending (+9.7%) and consumption (equal to 9.5 DDD/1,000 inh./day in 2018; +4.1%) for these drugs.

The use of cytotoxic drugs in indications other than cancer diseases, such as autoimmune pathogenesis diseases and prevention of organ transplant rejection, has grown over time thanks to the recognition of the important immunosuppressive and immunomodulating properties that some of them have. Overall, consumption increases with age, with a marked increase in the prevalence of use among women compared to men aged 35 and over, in line with the higher gender prevalence of autoimmune diseases in this age group. Above the age of 75, on the other hand, there is once again an increase in prevalence of use in the male population (4.6% in men compared to 3.4% in women).

In recent years the prescription of drugs for multiple sclerosis (MS) has increased by 28% (from 2 in 2013 to 2.6 DDD/1,000 inh./day in 2018), with an increase in the use of immunosuppressants and, in particular, **methotrexate**, an antineoplastic drug with anti-inflammatory and immunosuppressive action, which alone accounts for more than half of the consumption of the entire category (from 0.7 DDD in 2013 to 1.3 DDD/1,000 inh./day in 2018). In addition to oncological indications (acute lymphatic leukemia, non-Hodgkin's lymphomas, choriocarcinoma in women), this drug is prescribed as a second-line therapy in rheumatoid arthritis (RA), adult psoriatic arthritis, active polyarticular juvenile rheumatoid arthritis in children, severe relapsing and disabling psoriasis and mild to moderate Crohn's disease.

Cyclophosphamide is a nitrogen mustard analogue and its cytotoxic action is based on the interaction between its alkylating metabolites and DNA. It is mainly an antineoplastic drug, indicated in the treatment of various solid and haematological tumors but due to its powerful immunosuppressive action it is also used in the treatment of autoimmune diseases such as MS, RA, systemic lupus erythematosus and some forms of vasculitis affecting the nervous system (Behçet's disease, isolated vasculitis of the central nervous system) or secondary to RA.

Among immunosuppressants, **cyclosporine** is a calcineurin inhibitor indicated in the prevention of solid organ transplant rejection, in the treatment of transplant cell rejection in non-responders to other immunosuppressive therapies, in the prevention of allogeneic bone marrow and stem cell transplant rejection and in the prophylaxis or treatment of Graft Versus Host Disease (GVHD). Indications other than transplantation include endogenous uveitis (of non-infectious origin) and Behçet's disease, some forms of nephrotic syndrome due to primary glomerulopathies, severe active phase RA, severe psoriasis refractory to conventional therapy and severe atopic dermatitis requiring systemic therapy.

The macrolide **tacrolimus** also belongs to the class of calcineurin inhibitors and has an action similar to that of cyclosporine. Administered orally or intravenously, it is indicated in the prophylaxis of allogeneic transplant rejection of the liver, kidney or heart and in the treatment of allogeneic transplant rejection resistant to treatment with other immunosuppressants.

Abatacept is a chimeric protein produced by recombinant DNA technology, consisting of the extracellular domain of the antigen 4 associated with the human cytotoxic T cell (CTLA-4) bound to the modified Fc portion of human immunoglobulin

G1 (IgG1). Abatacept selectively modulates a key co-stimulation signal necessary for the full activation of T cells expressing CD28, reducing their proliferation and the production of inflammatory cytokines. In combination with methotrexate, it is indicated for the treatment of moderate to severe non-responsive active RA and very active and progressive RA not previously treated with methotrexate. Abatacept is also used in the second line therapy of active psoriatic arthritis (PsA) and moderate to severe juvenile polyarticular idiopathic arthritis in pediatric patients aged 6 years and older.

Plerixafor, which belongs to the category of immunostimulants, is a derivative of bicyclam, a selective reversible receptor antagonist for CXCR4 chemokines, which is able to block the binding of its related ligand, stromal cell-derived factor 1a (SDF-1a), also called CXCL12, which has a leukocytotic effect and increases circulating levels of haematopoietic progenitor cells. Administered by subcutaneous injection, plerixafor is indicated in combination with granulocyte colony stimulating factor (G-CSF) to increase the mobilisation of hematopoietic stem cells to peripheral blood, for collection and subsequent autologous transplantation, in adult patients with lymphoma and multiple myeloma.

In the purchases of antineoplastic and immunomodulatory drugs made by public facilities in 2018, **monoclonal antibodies** are the number one category in terms of per capita expenditure, an increase of 18.4% compared to the previous year. Similarly, hospital consumption of these drugs, at 1.1 DDD/inh./day in 2018, increased by 6.8% compared to 2017. Tumour necrosis factor alpha (TNFα) antagonists are the category with the highest spending, with a consumption of 1.2 DDD/inh./day, up 6% compared to 2017.

Infliximab is a human monoclonal chimeric IgG1 antibody produced in murine hybridoma cells with recombinant DNA technology, which exerts an antagonistic action against TNFα, a proinflammatory cytokine with a key role in chronic inflammation processes and autoimmune reactions. Infliximab, in association with methotrexate, is indicated in adult patients with non-responsive active phase RA and naive patients with severe, active and progressive disease. Infliximab is also used in the treatment of adult patients with moderate to severe active Crohn's disease and paediatric patients with severe forms that are either intolerant or refractory to first-line therapy. Also as second line in conventional therapy, infliximab can be used in moderate to severe ulcerative colitis in the active phase, severe paediatric ulcerative colitis, severe ankylosing spondylitis in the active phase, active and progressive psoriatic arthritis and moderate to severe plaque psoriasis.

Rituximab is a murine-human monoclonal chimeric antibody consisting of a glycosylated immunoglobulin obtained by combining the constant IgG1 regions of human origin with the sequences of the variable region of the light and heavy chain of murine origin with genetic engineering techniques, using a culture of suspended mammalian cells. The mechanism of action involves selective binding to the CD20 surface transmembrane antigen on pre-B lymphocytes and mature B lymphocytes, present on normal B cells (but not on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues) and neoplastic B cells (on more than 95 % of all non-Hodgkin's B-cell lymphomas), causing cell death through three possible mechanisms such as complement-dependent cytotoxicity (CDC), C1q binding, cell-mediated antibody-dependent cellular cytotoxicity (ADCC) (Fcγ receptors on the surface of granulocytes, macrophages and NK cells) and apoptosis.

In addition to oncological indications such as non-Hodgkin's lymphoma and chronic lymphatic leukemia, rituximab is indicated for the treatment of adult patients with severe active RA not responsive or intolerant to other DMARDs, in association with methotrexate, those with granulomatosis with polyangitis (Wegener's) and severe active microscopic polyangitis in association with glucocorticoids, and those with moderate or severe pemphigus vulgaris.

An example of exposure to biological risk is the BCG vaccine, consisting of a lyophilised suspension of live Bacillus Calmette-Guérin bacteria with low infectious potential (attenuated) derived from *Mycobacterium bovis*, whose endovesical instillation has an immunostimulating action with anti-tumour effect in the treatment of non-invasive urothelial carcinoma. The BCG vaccine was recently removed from the NIOSH 2020 list because it was not classified as a drug by the FDA.

2.2 General Antimicrobials for Systemic Use

General antimicrobials for systemic use are the number three therapeutic category with highest public expenditure in 2018, after cardiovascular drugs, largely determined by purchases by public healthcare facilities.

The highest consumption of antimicrobials is found in the extreme age groups, i.e., in the first four years of life (17.9 in males and 16.2 DDD/1,000 inh./day in females) and after 75 years (27.7 DDD/1,000 inh./day), while in the intermediate age groups the highest use concerns females.

In 2018, the most significant share of consumption concerned the purchase of antivirals for the treatment of Human Immunodeficiency Virus (HIV) infection in association.

Zidovudine is a nucleoside analogue with antiviral action against retroviruses, including HIV, which acts as an inhibitor for viral reverse transcriptase after transformation to the active substance zidovudine triphosphate (TP), following three steps of kinase-dependent phosphorylation. Zidovudine for infusion is indicated, only when oral treatment is not possible, for the short-term treatment of severe clinical manifestations of HIV infection in patients with acquired immunodeficiency syndrome (AIDS), possibly in combination with other drugs, for the prevention of maternal-foetal transmission of HIV in HIV-positive pregnant women (over 14 weeks of pregnancy) and for the primary prophylaxis of HIV infection in infants. Among the drugs indicated in combination therapy for the treatment of HIV patients, **nevirapine** and

efavirenz are non-competitive inhibitors of HIV-1 reverse transcriptase. **Abacavir** is a selective inhibitor of HIV-1 and HIV-2, metabolised intracellularly in the active form carbovir 5'-triphosphate (TP).

Among antivirals for systemic use, **cidofovir** belongs to the nucleoside and nucleotide category; it is a cytidine analogue capable of suppressing the replication of the pathogenic cytomegalovirus in humans (HCMV) by selective inhibition of viral DNA synthesis. It is indicated for the treatment of cytomegalovirus (CMV) retinitis in adults with AIDS without renal dysfunction unsuitable for other therapies.

Ganciclovir is a synthetic analogue of 2'-deoxyguanosine, which inhibits the replication of several herpes viruses both in vitro and in vivo. Clinical studies have been limited to the evaluation of patients with CMV infection, which is its main indication, both for the treatment of the disease in immunocompromised adults and adolescents aged 12 years and older, and for prevention in patients with pharmacological immunosuppression (e.g., after organ transplantation or chemotherapy). In particular, ganciclovir inhibits the synthesis of cytomegalovirus DNA, blocking its growth and replication and is indicated for induction and maintenance treatment of cytomegalovirus (CMV) retinitis in adult patients with AIDS.

Valganciclovir is a ganciclovir prodrug.

Fluconazole is a triazole antifungal agent indicated for the treatment of cryptococcal meningitis (and for the prophylaxis of relapses in immunocompromised patients) in adulthood and paediatric age, coccidioidomycosis, chronic atrophic oral candidiasis, invasive candidiasis, mucosal candidiasis, including candiduria, chronic mucocutaneous candidiasis and oropharyngeal or oesophageal candidiasis (for which it is also used for prophylaxis of relapses in immunocompromised patients) in adulthood and paediatric age, and for prophylaxis of candidemias in patients with prolonged neutropenia.

Voriconazole is a broad-spectrum triazole antifungal agent indicated in adults and children 2 years of age and older for the treatment of invasive aspergillosis, candidaemia in non-neutropenic patients, severe and invasive Candida infections resistant to fluconazole (including *C. krusei*), severe fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. and for the prophylaxis of invasive fungal infections in high-risk patients undergoing allogeneic haematopoietic stem cell transplantation (HSCT).

Chloramphenicol is a broad-spectrum antibiotic, mainly bacteriostatic, but with bactericidal activity at high concentrations, and is able to inhibit the protein synthesis of bacteria. Chloramphenicol for intravenous use is indicated when oral administration is not possible due to vomiting, diarrhoea or severe septic states and when other less toxic drugs have been found to be ineffective or contraindicated. Chloramphenicol is indicated in the treatment of various infections such as typhoid fever and salmonellosis (*Salmonella typhi*), bacterial meningitis (*Haemophilus influenzae*, *Neisseria meningitidis*), rickettiosis (*Rickettsia*), brucellosis (*Brucella*), psittacosis (*Chlamydophila psittaci*), venereal lymphogranuloma (Lymphogranuloma-psittacosis), urinary infections by Gram-negative bacteria, infections by anaerobic bacteria (gram-positive cocci, *Clostridium*).

Pentamidine, aromatic diamidine, is an antiprotozoal agent that acts by interfering with DNA and folate transformation and inhibiting RNA and protein synthesis. It is indicated in the treatment of *Pneumocystis carinii* pneumonia in debilitated or immunodepressed patients, such as AIDS, leishmaniasis (visceral and cutaneous) including cases resistant to treatment with pentavalent compounds of antimony, and African trypanosomiasis (early-stage sleeping sickness due to Trypanosoma gambiense).

Entecavir is a chemical analogue of nucleoside guanosine. It is a virustatic of the nucleoside group of reverse transcriptase inhibitors (NRTI) and is used for the treatment of hepatitis B.

Ribavirin is a synthetic nucleoside analogue and is indicated for the treatment of chronic hepatitis C virus (HCV) infection.

2.3 Gastrointestinal Tract and Metabolism

The consumption of drugs of the gastrointestinal tract and metabolism shows an increasing trend with age in both genders, with the exception of a drop between 5 and 14 years of age and a more marked increase between 45 and 74 years of age.

This therapeutic category occupies fourth place among the items with highest public expenditure in 2018, mainly due to the provision of pharmaceutical care under specific agreements. The spending associated with the purchase of these drugs by public health facilities is lower. The most significant increases in spending were recorded for some subcategories, such as the latest diabetes treatments, including glucagon-like-peptide-1 (GLP-1) analogues (+17%), which also recorded a significant increase in consumption (+26%), equal to 1.6 DDD/1,000 inh./day in 2018.

Liraglutide is an agonist of the GLP-1 receptor, an endogenous incretin hormone that potentiates the secretion of glucose-dependent insulin by beta cells of the pancreas. Administered subcutaneously, it is indicated for the treatment of type 2 diabetes mellitus, as an alternative to metformin, in patients with intolerance or contraindications to it or in addition to other medicines.

Exenatide is another GLP-1 analogue that has shown in vitro a mechanism of action mediated by cyclic adenosine monophosphate (AMP) and/or other intracellular signaling pathways, with the effect of activating the human GLP-1 receptor. It is indicated in adult patients with type 2 diabetes mellitus in addition to other hypoglycemic drugs, including basal insulin, in the absence of adequate glycemic control.

2.4 Blood and Hematopoietic Organs

Drugs affecting blood and hematopoietic organ account for the fifth largest public spending therapeutic category in 2018, the largest share of which is determined by the purchase by public health facilities.

Icatibant is a selective and competitive bradykinin type 2 (B2) receptor antagonist, included in the pharmacotherapeutic subcategory "other haematological agents". Administered by subcutaneous injection, it is indicated for the symptomatic therapy of acute attacks of hereditary angioedema (HAE) in adults, adolescents and children from 2 years of age with deficiency of C1 esterase inhibitor.
The subcategory of antianaemic preparations recorded a consumption of 3.3 DDD/1,000 inh./day, up from 2017 (+3.8%).

2.5 Central Nervous System

The category of central nervous system drugs ranked sixth among the highest public spending items in 2018. Although the largest share relates to the purchase of assistance under special agreements, consumption increased compared to 2017 (+5.2%), equal to 29.1 DDD/1,000 inh./day for the entire category.
The analysis of the drug utilisation profile reveals a constant increase in consumption with age in both genders, although there is a greater prevalence of use in women from the age of 35 years, in relation to the greater frequency of neuropsychiatric diseases in women than in men. Considering the drugs purchased by public healthcare facilities, antipsychotics are among those with the highest consumption (2.3 DDD/1,000 inh./day), an increase compared to 2017 (+5%). Paliperidone is the medicinal product with the highest per capita spending and shows the greatest increase in consumption compared to the previous year (+17.1%), equal to 0.7 DDD/1,000 inh./day in 2018, while risperidone is the active ingredient with the most significant reduction in consumption (-5%).
Paliperidone and **risperidone** are two selective monoaminergic antagonists with high affinity for serotonergic 5-HT2 and dopaminergic D2 eceptors. The formulation for injection of these drugs is indicated for maintenance therapy in schizophrenia in adult patients clinically stabilised with oral antipsychotics. Based on data from studies provided by manufacturers, NIOSH has determined that paliperidone and risperidone are unlikely to pose a carcinogenic, reproductive or developmental risk to healthcare workers and are therefore no longer on the NIOSH list of hazardous drugs.
With regard to epilepsy therapy, **valproic acid** is the most widely used substance in paediatric age (52.4 prescriptions per 1,000 children, prevalence of 0.3%), especially in the age group between 2 and 11 years, although slightly reduced (-1.0%) compared to 2017.
Valproic acid is a broad-spectrum antiepileptic, belonging to fatty acid derivatives, whose mechanism of action boosts the gabaergic pathway. It is indicated in the treatment of generalised epilepsy in the form of absences, myoclonic and tonic-clonic seizures, partial (focal) and secondary generalised seizures and specific syndromes (West, Lennox-Gastaut).
Phenytoin is an anticonvulsant drug derived from hydantoin. Parenteral phenytoin is indicated for the control of tonic-clonic seizures (grand mal) and for the prevention and treatment of seizures that appear during or after neurosurgery and/or severe head trauma. It is also used in the treatment of cardiac arrhythmias such as life-threatening ventricular arrhythmias or secondary arrhythmias caused by digoxin poisoning, in cases of non-response or intolerance to other anti-arrhythmic treatments.
The consumption of antiparkinson drugs has increased over the last six years on average (Compound Annual Growth Rate, CAGR) by around 2% a year, reaching 5.2 DDD/1,000 inh./day in 2018; dopa-derivative agonists, with a consumption of 2.3 DDD/1,000 inh./day, are among the most prescribed subcategories, up from 2017 (+1.1%).
Apomorphine is a potent synthetic D1 and D2 dopaminergic agonist, very similar to dopamine, administered subcutaneously by infusion in patients with advanced Parkinson's disease, for the treatment of severe motor fluctuations, occurring several times, and resistant to therapy with levodopa and oral dopamine agonists.
The benzodiazepines are widely used and have sedative, hypnotic, anxiolytic, anticonvulsant, myorelaxant and amnestic properties, which are useful in a variety of indications, such as alcohol addiction, convulsions, anxiety, insomnia and agitation.
Clonazepam is indicated for most clinical forms of epilepsy in infants and children. **Clobazam** is indicated in the treatment of anxiety, stress and other somatic or psychiatric manifestations associated with anxiety syndrome and in the treatment of insomnia.

2.6 Musculoskeletal System

In 2018, musculoskeletal system drugs ranked eighth among public spending items. Expenditure on purchases by public healthcare facilities is lower, but it is up sharply yoy (+103.7%), as is consumption (4.6 DDD/1,000 inh./day; +8% compared to 2017).
The consumption of drugs in this category increases with age in both genders, with the highest values in the over-75 age group, but with a higher per-capita expenditure in women (29.6 euros) versus men (15.9 euros) in relation to the increased use of bisphosphonates in women for the treatment of osteoporosis.
Zoledronic acid is a bisphosphonate and acts as an inhibitor of osteoclastic bone resorption. For intravenous use, it is indicated for the treatment of osteoporosis, osteoporosis associated with chronic systemic glucocorticoid therapy in post-menopausal women and adult men in the presence of increased risk of fractures, tumour-induced hypercalcemia (TIH) and prevention of skeletal damage (pathological fractures, vertebral compression fractures, etc.) in adult patients with advanced malignant tumors affecting bones.
Disodium pamidronate also belongs to bisphosphonates and is used by infusion in the treatment of tumour-induced hypercalcaemia (TIH) and osteolytic lesions in patients with bone metastases associated with breast cancer, in addition to specific tumour treatment, or with stage III multiple myeloma.

Biohazard are present also among myorelaxants.
An AIFA note of 14/03/2019 reported that the preclinical results showed a risk of genotoxicity associated with the systemic use of **thiocolchicoside**, a semi-synthetic sulphurous derivative of colchicoside with myorelaxant pharmacological activity and used in the treatment of painful muscle contractures in acute spinal diseases.

2.7 Systemic Hormonal Preparations, Excluding Sex Hormones

In 2018, this therapeutic category is the ninth largest public expenditure item, largely linked to purchases by public health facilities. Consumption of these drugs decreased by 4.3% compared to 2017 to 5.2 DDD/1,000 inh./day.
The subcategory with the highest impact on expenditure is that of somatostatin and its analogues, which account for 32.1% of the expenditure of the whole class.
This subcategory includes **pasireotide**, a cyclic hexapeptide that exerts its pharmacological action by binding to somatostatin receptors and is used for subcutaneous or intramuscular administration in the treatment of adult patients with acromegaly for whom surgery is not indicated or has not been resolved or adequately controlled with other therapies, and in that of adult patients with Cushing's disease for whom surgery is not indicated or has proven ineffective.
Among the hormones of the posterior lobe of the pituitary gland, **oxytocin** is a cyclic nonapeptide obtained by chemical synthesis and identical to the natural hormone produced by the hypothalamus and stored in the posterior pituitary gland, from where it is released into circulation in response to sucking and labour. Due to its action in stimulating the smooth muscles of the uterus, the drug is used in the medical induction of labour (in cases of pregnancy beyond term, premature rupture of membranes, pre-eclampsia), in selected cases of primary or secondary uterine inertia and in post-partum haemorrhages not responsive to methylergometrine.

2.8 Genito-urinary System and Sex Hormones

In 2018, drugs for the genito-urinary system and sex hormones are the tenth largest public expenditure item. The share referred to the purchase by public healthcare facilities is modest and has recorded a reduction in consumption (-2.2%) compared to 2017.
Consumption of this category is almost exclusive to women in the 15-to-54 age group, with a peak between 25 and 44 years of age in relation to the use of hormonal preparations, while there is a sharp shift in the use of these medicinal products towards men, from the age of 55, mainly for the treatment of prostatic hypertrophy, up to a prevalence of use of 40% in men over 75.
With regard to medicines purchased by public health facilities, gonadotropins for the treatment of infertility are the category with the highest incidence on expenditure, accounting for 7% of consumption of the entire category.
Human chorionic gonadotropin (hCG) is obtained from the urine of pregnant women, collected between 60 and 90 days of pregnancy, and subjected to a purification process. It has a biological action similar to that of the luteinising hormone (LH), secreted in the pituitary gland, which is expressed in men with the stimulation of Leydig cells (development of secondary sexual characteristics, descent of the testicles) and in women with the maturation of the ovarian follicle and the induction of ovulation. In males, it is used in paediatric age for the treatment of cryptorchidism, hypogonadism and hypogonadotropic eunuchoidism and in adults with azoospermia, oligoasthenospermia, or asthenospermia, when due to a condition of hypogonadotropic hypogonadism, in association with FSH. In women, it is indicated in cases of primary and secondary amenorrhea, ovarian hypoplasia, menometrorrhagia, recurrent abortion, threatened abortion, anovulatory infertility, or infertility from deficient oogenesis.
Alpha choriogonadotropin is recombinant human choriogonadotropin (r-hCG) produced using recombinant DNA technology in Chinese hamster ovarian cells (CHO) and, like physiological choriogonadotropin, simulates the action of LH. It is used in the treatment of adult women undergoing superovulation in preparation for medically assisted reproduction and anovulatory or oligo-ovulatory techniques.
Cetrorelix is an antagonist of the luteinising hormone release hormone (LHRH), which prevents it from binding to the membrane receptors of pituitary cells by controlling the secretion of gonadotropins (LH and FSH). The drug is used as part of assisted reproduction techniques to prevent premature ovulation in patients undergoing controlled ovarian stimulation for oocyte collection.
Ganirelix is a GnRH antagonist that modulates the hypothalamic-pituitary-gonadal axis by competitive bonding with GnRH receptors in the pituitary gland, causing a rapid and intense reversible suppression of endogenous gonadotropin release without the initial stimulation observed with GnRH agonists. It is used to prevent the early peak of LH in women undergoing controlled ovarian hyperstimulation (COH) in assisted reproduction techniques (ART).
Urofollitropin is a hormone with follicle-stimulating activity only (FSH), highly purified from post-menopausal human gonadotropin (hMG). The main effect of parenteral administration in women is the development of mature Graaf follicles and ovulation induction. It is indicated for the treatment of infertility, in combination with chorionic gonadotropin, in patients with polycystic ovary syndrome, amenorrhea or anovulatory states due to follicular phase failure, with an increased LH to FSH ratio. It is also used to stimulate multiple follicular development in women undergoing ovulation induction in assisted reproduction programmes. In male sterility, in association with hCG, it is indicated to induce spermatogenesis in the presence of hypogonadotropic hypogonadism.
Progesterone is a natural steroid secreted by the ovary, placenta and adrenal glands. In the presence of adequate oestrogen levels, progesterone transforms a proliferative endometrium into a secretory endometrium, increases

endometrial receptivity for the purpose of implanting an oembryo and, once this has occurred, promotes the maintenance of pregnancy. Administered by subcutaneous or intramuscular injection, it is indicated in women as a support for the lutein phase in assisted reproduction programmes, in the preparation for gynaecological and extra-gynaecological surgery to be performed during pregnancy, in case of threat of abortion, habitual abortion, threat of premature birth, hypermenorrhea, polymenorrhea, metrorrhagia, amenorrhea, hypomenorrhea, oligomenorrhea, premenstrual syndrome and for the prophylaxis of post-partum depression.

Cyproterone acetate is a peripheral androgen receptor antagonist steroid with progestin and antigonadotropic effects, which reduce testosterone synthesis in the testicles. It is indicated as an antiandrogen treatment in inoperable prostate cancer and in the therapy of sexual deviations in men. The use of cyproterone acetate is not indicated in women.

Testosterone (**undecanoate, enanthate, propionate**) is a derivative of the male sex hormone normally present in nature, synthesised in the testicles and, to a lesser extent, in the adrenal cortex. For intramuscular use, it is indicated in replacement therapy for male hypogonadism. In women it is used in cases of haemorrhages due to fibromyoma and in certain forms of breast cancer, as an adjuvant.

2.9 Miscellaneous

This therapeutic category comprises drugs that cannot be classified in the categories above, such as antidotes, diagnostic radiopharmaceuticals, drugs for the treatment of hyperkalaemia and hyperphosphataemia, which, taken as a whole, constitute the twelfth item of public expenditure, almost entirely determined by purchases by public health facilities.

The use of these drugs appears to be marginal up to the age of 55 in both genders, while subsequently there is a progressive increase with age, greater in men, up to a prevalence of use of 3.2% in men and 2.7% in women after the age of 75.

The subcategory with the greatest impact on hospital spending is iron-chelating substances, which account for 27.5% of the expenditure of the entire class.

Dexrazoxane is an analogue of EDTA (ethylendiammine tetracetic acid) used as an antidote to anthracyclines, as it is able to chelate metal ions, including iron, reducing the iron-dependent oxidative stress that causes the cumulative chronic cardiotoxicity induced by anthracyclines. Another mechanism of action would involve type II topoisomerase inhibition. **Dexrazoxane** is indicated for the prevention of cardiotoxicity in adults with advanced and/or metastatic breast cancer treated with anthracyclines.

Among diagnostic radiopharmaceuticals, **calcium trisodium pentetate** has only recently received marketing authorisation in Italy (Official Gazette General Series no.134 of 12/06/2018). The solution obtained from radiolabelling with sodium pertechnetate (99m Tc) can be used intravenously in dynamic renal perfusion scintigraphy (functional and urinary tract studies), brain angiography and brain scintigraphy.

Among the endothelin receptor antagonists, **bosentan** and **macitentan** are indicated in the treatment of pulmonary arterial hypertension.

Dronedarone is an antiarrhythmic agent indicated for the maintenance of sinus rhythm following cardioversion with satisfactory outcome in clinically stable adult patients with paroxysmal or persistent atrial fibrillation (AF).

In the treatment of symptoms of benign prostatic hyperplasia, a condition with high prevalence and social impact, **dutasteride** and **finasteride** are both competitive inhibitors of 5-α-reductase.

REFERENCES

1. Osservatorio Nazionale sull'impiego dei Medicinali. L'uso dei farmaci in Italia. Rapporto Nazionale Anno 2018. Roma: Agenzia Italiana del Farmaco, 2019. www.aifa.gov.it
2. Banca dati AIFA. https://farmaci.agenziafarmaco.gov.it/bancadatifarmaci/home

3.CONCLUSIONS

Despite the great efforts made around the world, defining shared standards on the safe handling of hazardous non-oncological drugs is still an unresolved issue.

The United States of America has drawn up useful technical guidance documents and the official publication of Chapter 800 of the US Pharmacopoeia is expected soon (*USP General Chapter <800> Hazardous Drugs-Handling in Healthcare Settings*), while Europe has generated the largest scientific output in this area. Although the work on both continents has the same scientific validity, it should be noted that the recommendations in US documents do not always lend themselves to be applied as they are to European countries, mainly due to regulatory differences between the various countries.

As a result of the lack of consistent data on the possible harmful effects associated with occupational exposure to hazardous non-cytotoxic drugs, the few standards issued so far have been consensus documents rather than evidence-based guidelines and often use heterogeneous terminologies.

There is no denying that there is no clear evidence of benefit in the application of additional procedures (such as CSTD controlled environmental systems, systems increasingly used in the handling of antiblastic drugs), but neither can it be ignored that these interventions are not harmful to exposed workers and produce minimal discomfort (implementation of uncertain and apparently unnecessary procedures or technologies, anxiety, physical and economic constraints) compared with the potential benefit of avoiding or mitigating harmful effects on the health of exposed workers.

Though not the subject of this publication, the exposure risk at the home of the patient treated with hazardous drugs should also be mentioned. With the increasing number of approved oral drugs, and not only in oncology, exposure risk for relatives and caregivers, in addition to healthcare workers engaged in home care. This can be done through direct contact with the drug or indirectly through the patient's excreta, and in this context, precautions are certainly less stringent.

Given the importance of the issue of health and safety in the workplace, more initiatives should be adopted at international level, with the aim of issuing appropriate procedures and standardising specific legislation as much as possible. A first step in this direction is certainly the creation of a list of "hazardous" drugs, a list inevitably characterised by accentuated dynamism, as new information becomes available and more accurate recommendations are made available.

This first list aims to provide a canvas on which to work with several hands, in order to provide a European programme for the management of exposure risk to hazardous drugs.

TABLE 1 - HAZARDOUS NON-ANTINEOPLASTIC DRUGS

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH 2020	abacavir	Antiretrovirals	film-coated tablets film-coated tablet suspension		H317 (13.33%): May cause an allergic skin reaction [Warning Sensitization, Skin] H318 (16.67%): Causes serious eye damage [Danger Serious eye damage/eye irritation] H341 (16.67%): Suspected of causing genetic defects [Warning Germ cell mutagenicity] H351 (86.67%): Suspected of causing cancer [Warning Carcinogenicity] H361 (83.33%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]
Alberta 2019	abatacept	Immunosuppressive drugs	preparation for injection solution (internal use) powder		no data available
NIOSH 2020	acitretin	Antipsoriatics	capsule		H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H360 (100%): May damage fertility or the unborn child [Danger Reproductive toxicity] H400 (100%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H410 (100%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	alitretinoin	Dermatologic drugs	soft capsule		H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (96.15%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H360 (96.15%): May damage fertility or the unborn child [Danger Reproductive toxicity]
NIOSH 2020	ambrisentan	Cardiovascular drugs: hypotensive (antihypertension) drugs	film-coated tablet		H351 (50%): Suspected of causing cancer [Warning Carcinogenicity] H360 (50%): May damage fertility or the unborn child [Danger Reproductive toxicity] H361 (50%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]
Alberta 2019	anagrelide	Antineoplastic drugs	capsule		no data available
NIOSH 2020	apomorphine	Antiparkinsonian drugs dopaminergics	solution (internal use)		H301 (50%): Toxic if swallowed [Danger Acute toxicity, oral] H302 (50%): Harmful if swallowed [Warning Acute toxicity, oral] H312 (100%): Harmful in contact with skin [Warning Acute toxicity, dermal] H317 (100%): May cause an allergic skin reaction [Warning Sensitization, Skin] H332 (100%): Harmful if inhaled [Warning Acute toxicity, inhalation] H334 (100%): May cause allergy or asthma symptoms or breathing difficulties if inhaled [Danger Sensitization, respiratory] https://pubchem.ncbi.nlm.nih.gov/compound/Apomorphine-hydrochloride#section=GHS-Classification&fullscreen=true
NIOSH 2020	azathioprine	Immunosuppressive drugs	film-coated tablets		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H315 (88.73%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (88.73%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (87.32%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H340 (64.79%): May cause genetic defects [Danger Germ cell mutagenicity] H350 (100%): May cause cancer [Danger Carcinogenicity] H360 (59.15%): May damage fertility or the unborn child [Danger Reproductive toxicity]

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
VDB 2019	baricitinib	Drugs for the treatment of rheumatoid arthritis	film-coated tablets		H302 (33.33%): Harmful if swallowed [Warning Acute toxicity, oral] H360 (66.67%): May damage fertility or the unborn child [Danger Reproductive toxicity] H373 (66.67%): Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure] H411 (66.67%): Toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	bosentan	Antihypertensives	film-coated tablets film-coated tablet		H302 (33.33%): Harmful if swallowed [Warning Acute toxicity, oral] H360 (33.33%): May damage fertility or the unborn child [Danger Reproductive toxicity] H361 (66.67%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H412 (66.67%): Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	cabergoline	Antiparkinsonian drugs Prolactin inhibitors	tablet		H302 (96.67%): Harmful if swallowed [Warning Acute toxicity, oral] H315 (80%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (76.67%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H332 (13.33%): Harmful if inhaled [Warning Acute toxicity, inhalation] H335 (76.67%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation]
NIOSH 2020	carbamazepine	Antiepileptic drugs	tablet modified-release tablet syrup		H302 (94.7%): Harmful if swallowed [Warning Acute toxicity, oral] H317 (91.67%): May cause an allergic skin reaction [Warning Sensitization, Skin] H334 (87.88%): May cause allergy or asthma symptoms or breathing difficulties if inhaled [Danger Sensitization, respiratory] H361 (15.15%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]
NIOSH 2020	cetrorelix	Anti-gonadotropin-releasing hormones	powder		H360 (100%): May damage fertility or the unborn child [Danger Reproductive toxicity] National Center for Biotechnology Information. PubChem Database. Cetrorelix, CID=25074887, https://pubchem.ncbi.nlm.nih.gov/compound/Cetrorelix (accessed on Oct. 2, 2019)
Alberta 2019	cetrorelix acetate	Anti-gonadotropin-releasing hormones	powder		H360 (100%): May damage fertility or the unborn child [Danger Reproductive toxicity] National Center for Biotechnology Information. PubChem Database. Cetrorelix acetate, CID=25078429, https://pubchem.ncbi.nlm.nih.gov/compound/Cetrorelix-acetate (accessed on Oct. 2, 2019)
NIOSH 2020	chloramphenicol	Antibacterial drugs Antibacterial drugs, chloramphenicol Corticosteroids + antibacterial drugs Proteolytic enzymes	eye drops suppository ointment gel powder		H350 (93.1%): May cause cancer [Danger Carcinogenicity] H361 (30.17%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]
NIOSH 2020	choriogonadotropin	Gonadotrophic hormones	solution (internal use)		no data available
NIOSH 2020	cidofovir	Antiviral drugs	solution (internal use)		no data available

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH 2020	clobazam	Anxiolytics, benzodiazepines	capsule		H302 (75%): Harmful if swallowed [Warning Acute toxicity, oral] H336 (100%): May cause drowsiness or dizziness [Warning Specific target organ toxicity, single exposure; Narcotic effects] H361 (25%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H362 (25%): May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation] H412 (75%): Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	clomiphene	Gonadotrophic hormones	capsule		no data available
NIOSH 2020	clonazepam	Antiepileptic drugs	tablet drops		no data available
NIOSH 2020	colchicine	Antigout drugs	divisible tablet		H300: Fatal if swallowed [Danger Acute toxicity, oral] H340: May cause genetic defects [Danger Germ cell mutagenicity]
NIOSH 2020	cyclosporine	Immunosuppressive drugs Ophthalmic agents	eye drops soft capsule solution (internal use) solution		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H350 (98.61%): May cause cancer [Danger Carcinogenicity] H360 (94.91%): May damage fertility or the unborn child [Danger Reproductive toxicity] H372 (16.2%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure]
Alberta 2019	danazol	Androgens	capsule		H312 (92.31%): Harmful in contact with skin [Warning Acute toxicity, dermal] H332 (92.31%): Harmful if inhaled [Warning Acute toxicity, inhalation] H351 (28.21%): Suspected of causing cancer [Warning Carcinogenicity] H360 (35.9%): May damage fertility or the unborn child [Danger Reproductive toxicity] H361 (64.1%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]
NIOSH 2020	deferiprone	Antidotes	film-coated tablet solution		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (96.15%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation]
NIOSH 2020	dexrazoxane	Antidotes	powder		H315 (96.43%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (96.43%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (92.86%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation]
NIOSH 2020	diethylstilbestrol	Hormone therapy	tablets		H301 (10.34%): Toxic if swallowed [Danger Acute toxicity, oral] H315 (82.76%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (82.76%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H330 (10.34%): Fatal if inhaled [Danger Acute toxicity, inhalation] H335 (82.76%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H350 (82.76%): May cause cancer [Danger Carcinogenicity] H360 (89.66%): May damage fertility or the unborn child [Danger Reproductive toxicity] H410 (82.76%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] 410 (82.76%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH 2020	Dihydroergotamine	Ergot alkaloids	modified-release capsule solution		H302 (66.67%): Harmful if swallowed [Warning Acute toxicity, oral] H312 (33.33%): Harmful in contact with skin [Warning Acute toxicity, dermal] H332 (66.67%): Harmful if inhaled [Warning Acute toxicity, inhalation]
NIOSH 2020	dinoprostone	Oxytocic hormones	gel solution (internal use) intrauterine device		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H360 (95.83%): May damage fertility or the unborn child [Danger Reproductive t
NIOSH 2020	divalproex				H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H315 (94.44%): Causes skin irritation [Warning Skin corrosion/irritation] H318 (40.97%): Causes serious eye damage [Danger Serious eye damage/eye irritation] H319 (53.47%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (15.97%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H360 (80.56%): May damage fertility or the unborn child [Danger Reproductive toxicity]
NIOSH 2020	dronedarone	Antiarrhythmics	film-coated tablet		H360 (40%): May damage fertility or the unborn child [Danger Reproductive toxicity] H373 (40%): Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure] H400 (40%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H410 (60%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	dutasteride	Benign prostatic hypertrophy	capsule soft capsule		H360 (91.67%): May damage fertility or the unborn child [Danger Reproductive toxicity] H410 (41.67%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard] H412 (50%): Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]
VDB 2019	efavirenz	Antiretrovirals	film-coated tablets film-coated tablet capsule solution		H302 (61.97%): Harmful if swallowed [Warning Acute toxicity, oral] H319 (57.75%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H360 (57.75%): May damage fertility or the unborn child [Danger Reproductive toxicity] H372 (50.7%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure] H400 (90.14%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H410 (92.96%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	entecavir	Antiretrovirals	film-coated tablet		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H351 (80%): Suspected of causing cancer [Warning Carcinogenicity] H360 (40%): May damage fertility or the unborn child [Danger Reproductive toxicity] H361 (40%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H362 (40%): May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation] H372 (80%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure]

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
	ergonovine/ methylergonovine	Ergot alkaloids	film-coated tablet solution (internal use)	Off the market	H301 (100%): Toxic if swallowed [Danger Acute toxicity, oral] H311 (100%): Toxic in contact with skin [Danger Acute toxicity, dermal] H331 (100%): Toxic if inhaled [Danger Acute toxicity, inhalation]
NIOSH 2020	eslicarbazepine	Antiepileptic drugs	tablet		no data available
NIOSH 2020	estradiol	Systemic hormonal contraceptives Oestrogens + progestins Oestrogens	plasters film-coated tablets vaginal release system spray tablet film-coated tablet gel		H350 (42.28%): May cause cancer [Danger Carcinogenicity] H351 (54.47%): Suspected of causing cancer [Warning Carcinogenicity] H360 (93.5%): May damage fertility or the unborn child [Danger Reproductive toxicity] H362 (26.02%): May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation] H372 (37.4%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure] H400 (32.52%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H410 (38.21%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	estrogens, conjugated	Oestrogens Oestrogens + progestins	film-coated tablets modified-release tablet		H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (100%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H350 (100%): May cause cancer [Danger Carcinogenicity] H360 (100%): May damage fertility or the unborn child [Danger Reproductive toxicity]
	estrogens, esterified				H350 (42.28%): May cause cancer [Danger Carcinogenicity] H351 (54.47%): Suspected of causing cancer [Warning Carcinogenicity] H360 (93.5%): May damage fertility or the unborn child [Danger Reproductive toxicity] H362 (26.02%): May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation] H372 (37.4%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure] H400 (32.52%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H410 (38.21%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	estropipate				H302 (58.97%): Harmful if swallowed [Warning Acute toxicity, oral] H350 (58.97%): May cause cancer [Danger Carcinogenicity] H351 (41.03%): Suspected of causing cancer [Warning Carcinogenicity] H360 (41.03%): May damage fertility or the unborn child [Danger Reproductive toxicity] H362 (41.03%): May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation]
Duke 2019	etonogestrel implant	Oestrogens + progestins Progestins	vaginal release system implantable device		no data available
NIOSH 2020	exenatide	Hypoglycaemic drugs	vials/bottles + solvent solution (internal use) powder		H302 (33.33%): Harmful if swallowed [Warning Acute toxicity, oral] H351 (66.67%): Suspected of causing cancer [Warning Carcinogenicity] H361 (100%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH 2020	finasteride	Benign prostatic hypertrophy, alopecia	tablet film-coated tablets film-coated tablet		H302 (98.67%): Harmful if swallowed [Warning Acute toxicity, oral] H360 (50.67%): May damage fertility or the unborn child [Danger Reproductive toxicity] H361 (13.33%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H372 (45.33%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure] H410 (46.67%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	fingolimod	Immunosuppressive drugs	capsule		no data available
NIOSH 2020	fluconazole	Antifungals	capsule powder solution (internal use) solution		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H315 (72.86%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (62.14%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (27.14%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H360 (57.14%): May damage fertility or the unborn child [Danger Reproductive toxicity] H362 (18.57%): May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation] H371 (36.43%): May cause damage to organs [Warning Specific target organ toxicity, single exposure] H372 (32.86%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure] H412 (16.43%): Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	fluoxymesterone	Anabolic steroids	tablets		H361 (96.15%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]
NIOSH 2020	fosphenytoin			not available in the EU	no data available
NIOSH 2020	ganciclovir	Antiretrovirals Antiviral drugs	gel powder		H340 (10.34%): May cause genetic defects [Danger Germ cell mutagenicity] H360 (96.55%): May damage fertility or the unborn child [Danger Reproductive toxicity] H362 (10.34%): May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation]
NIOSH 2020	ganirelix	Gonadotropin-releasing hormones	solution (internal use) solution		H360 (100%): May damage fertility or the unborn child [Danger Reproductive toxicity] H372 (100%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure]
NIOSH 2020	gonadotropin, chorionic	Gonadotrophic hormones	powder		no data available
NIOSH 2020	icatibant	Antiangioedema drug	solution (internal use)		no data available
VDB 2019	idelalisib	Antineoplastic drugs	film-coated tablets		H360 (33.33%): May damage fertility or the unborn child [Danger Reproductive toxicity] H372 (66.67%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure]

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH 2020	isotretinoin	Antiacne antibacterial Antiacne retinoids	capsule cream soft capsule gel		H315 (31.31%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (32.32%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (30.3%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H360 (100%): May damage fertility or the unborn child [Danger Reproductive toxicity] H400 (71.72%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H410 (72.73%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	ivabradine	Antianginal drugs	film-coated tablets film-coated tablet		no data available
NIOSH 2020	leflunomide	Immunosuppressive drugs	film-coated tablets film-coated tablet		H301 (99.14%): Toxic if swallowed [Danger Acute toxicity, oral] H315 (95.69%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (95.69%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (95.69%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation]
NIOSH 2020	lenalidomide	Immunosuppressive drugs	capsule		H301 (18.18%): Toxic if swallowed [Danger Acute toxicity, oral] H302 (18.18%): Harmful if swallowed [Warning Acute toxicity, oral] H312 (27.27%): Harmful in contact with skin [Warning Acute toxicity, dermal] H360 (90.91%): May damage fertility or the unborn child [Danger Reproductive toxicity] H372 (72.73%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure]
NIOSH 2020	liraglutide recombinant	Hypoglycaemic drugs Oral hypoglycaemic drugs	solution (internal use) solution		no data available
NIOSH 2020	lomitapide	Hypolipidaemic drugs	capsule		no data available
NIOSH 2020	macitentan	Antihypertensives	film-coated tablets		no data available
NIOSH 2020	medroxyprogester-one acetate	Oestrogens + progestins Progestins	tablet solution (internal use) suspension		H302 (17.16%): Harmful if swallowed [Warning Acute toxicity, oral] H312 (16.42%): Harmful in contact with skin [Warning Acute toxicity, dermal] H332 (15.67%): Harmful if inhaled [Warning Acute toxicity, inhalation] H351 (99.25%): Suspected of causing cancer [Warning Carcinogenicity] H360 (44.78%): May damage fertility or the unborn child [Danger Reproductive toxicity] H362 (13.43%): May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation] H413 (14.93%): May cause long lasting harmful effects to aquatic life [Hazardous to the aquatic environ-ment, long-term hazard]
NIOSH 2020	menotropins	Gonadotrophic hormones	powder for solution powder		no data available
NIOSH 2020	methimazole	Antithyroid agents	tablet		no data available

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH 2020	methyltestosterone				H302 (26.32%): Harmful if swallowed [Warning Acute toxicity, oral] H317 (78.95%): May cause an allergic skin reaction [Warning Sensitization, Skin] H361 (76.32%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]
NIOSH 2020	mifepristone	Pharmacological abortifacients	tablet		H302 (30.77%): Harmful if swallowed [Warning Acute toxicity, oral] H312 (30.77%): Harmful in contact with skin [Warning Acute toxicity, dermal] H332 (30.77%): Harmful if inhaled [Warning Acute toxicity, inhalation] H360 (97.44%): May damage fertility or the unborn child [Danger Reproductive toxicity] H362 (28.21%): May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation]
NIOSH 2020	miltefosine	Antiprotozoal agents	granules		H301 (100%): Toxic if swallowed [Danger Acute toxicity, oral] H319 (16.67%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H334 (80%): May cause allergy or asthma symptoms or breathing difficulties if inhaled [Danger Sensitization, respiratory] H361 (20%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H372 (16.67%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure]
NIOSH 2020	mipomersen			not available in the EU	no data available
NIOSH 2020	misoprostol	NSAID analgesics Pharmacological abortifacients	gastro-resistant tablets/ capsules tablet modified-release tablet intrauterine device		H301 (100%): Toxic if swallowed [Danger Acute toxicity, oral] H360 (100%): May damage fertility or the unborn child [Danger Reproductive toxicity]
NIOSH 2020	mycophenolate mofetil	Immunosuppressive drugs	capsule		H302 (97.22%): Harmful if swallowed [Warning Acute toxicity, oral] H341 (16.67%): Suspected of causing genetic defects [Warning Germ cell mutagenicity] H360 (27.78%): May damage fertility or the unborn child [Danger Reproductive toxicity] H372 (13.89%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure] H400 (86.11%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H410 (19.44%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	mycophenolic acid	Immunosuppressive drugs	tablet gastro-resistant tablet film-coated tablet capsule		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H341 (94.38%): Suspected of causing genetic defects [Warning Germ cell mutagenicity] H360 (95.51%): May damage fertility or the unborn child [Danger Reproductive toxicity] H372 (93.26%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure] H400 (93.26%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H410 (93.26%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	nafarelin				H360 (100%): May damage fertility or the unborn child [Danger Reproductive toxicity

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH 2020	nevirapine	Antiretrovirals	tablet modified-release tablet extended-release tablet suspension		H302 (28.57%): Harmful if swallowed [Warning Acute toxicity, oral] H412 (92.86%): Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]
VDB 2019	nintedanib	Antineoplastic drugs, protease inhibitors Drugs for the treatment of idiopathic pulmonary fibrosis	soft capsule		H360 (100%): May damage fertility or the unborn child [Danger Reproductive toxicity] H373 (100%): Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure]
NIOSH 2020	oestrogen/progesterone combinations		soft capsule cream gel suppository solution (internal use)		no data available
NIOSH 2020	ospemifene	Selective oestrogen receptor modulators	film-coated tablets		H351 (38.64%): Suspected of causing cancer [Warning Carcinogenicity] H361 (40.91%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H400 (52.27%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H410 (52.27%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
Alberta 2019	oxandrolone				H312 (97.3%): Harmful in contact with skin [Warning Acute toxicity, dermal] H332 (97.3%): Harmful if inhaled [Warning Acute toxicity, inhalation] H351 (32.43%): Suspected of causing cancer [Warning Carcinogenicity] H360 (94.59%): May damage fertility or the unborn child [Danger Reproductive toxicity]
NIOSH 2020	oxcarbamazepine		tablet oral suspension		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H312 (58.06%): Harmful in contact with skin [Warning Acute toxicity, dermal] H332 (58.06%): Harmful if inhaled [Warning Acute toxicity, inhalation]
Duke 2019	oxcarbazepine	Antiepileptic drugs	divisible tablet film-coated tablets		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H312 (58.06%): Harmful in contact with skin [Warning Acute toxicity, dermal] H332 (58.06%): Harmful if inhaled [Warning Acute toxicity, inhalation]
NIOSH 2020	oxytocin	Oxytocic hormones	solution		H300 (40%): Fatal if swallowed [Danger Acute toxicity, oral] H301 (20%): Toxic if swallowed [Danger Acute toxicity, oral] H302 (50%): Harmful if swallowed [Warning Acute toxicity, oral] H312 (40%): Harmful in contact with skin [Warning Acute toxicity, dermal] H315 (30%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (30%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H332 (40%): Harmful if inhaled [Warning Acute toxicity, inhalation] H335 (20%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H361 (80%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH 2020	palifermin			not available in the EU	no data available
NIOSH 2020	pamidronate	Osteomodulating drugs	preparation for injection solution (internal use)		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H315 (20%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (20%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (20%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H371 (40%): May cause damage to organs [Warning Specific target organ toxicity, single exposure]
NIOSH 2020	paroxetine	SSRI antidepressants	tablet film-coated tablet suspension film-coated tablets drops		H302 (80%): Harmful if swallowed [Warning Acute toxicity, oral] H360 (60%): May damage fertility or the unborn child [Danger Reproductive toxicity] H361 (20%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H400 (20%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H410 (60%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	pasireotide	Antigrowth hormones	solution (internal use)		H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H361 (100%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H400 (100%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H410 (100%): Very toxic to aquatic life with long lasting effects [Warning Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	peginesatide			not available in the EU	no data available
Alberta 2019	pentamidine	Antileishmaniasis and antitripanoso-miasis drugs	powder		H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (96%): May cause an allergic skin reaction [Warning Sensitization, Skin] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (100%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation]
NIOSH 2020	pentetate calcium trisodium			not available in the EU	no data available
VDB 2019	phenol	Antifungals Antiseptics	cream drops dermatological powder solution		H301: Toxic if swallowed [Danger Acute toxicity, oral] H311: Toxic in contact with skin [Danger Acute toxicity, dermal] H314: Causes severe skin burns and eye damage [Danger Skin corrosion/irritation] H331: Toxic if inhaled [Danger Acute toxicity, inhalation] H341: Suspected of causing genetic defects [Warning Germ cell mutagenicity] H373: Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure]
NIOSH 2020	phenoxybenzamine			not available in the EU	no data available

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH 2020	phenytoin	Antiepileptic drugs	tablet solution (internal use) film-coated tablet		H302 (99.22%): Harmful if swallowed [Warning Acute toxicity, oral] H317 (85.27%): May cause an allergic skin reaction [Warning Sensitization, Skin] H351 (79.07%): Suspected of causing cancer [Warning Carcinogenicity] H360 (12.4%): May damage fertility or the unborn child [Danger Reproductive toxicity] H361 (86.05%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]
NIOSH 2020	plerixafor	Immunostimulants	solution (internal use)		no data available
NIOSH 2020	progesterone	Progestins	soft capsule cream gel suppository solution (internal use)		H350 (12.67%): May cause cancer [Danger Carcinogenicity] H351 (85.33%): Suspected of causing cancer [Warning Carcinogenicity] H360 (78.67%): May damage fertility or the unborn child [Danger Reproductive toxicity] H361 (18.67%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]
NIOSH 2020	progestins	Progestins Oestrogens + progestins	plasters tablet film-coated tablets film-coated tablet soft capsule cream vaginal release system gel implantable device suppository solution (internal use) suspension		H350 (12.67%): May cause cancer [Danger Carcinogenicity] H351 (85.33%): Suspected of causing cancer [Warning Carcinogenicity] H360 (78.67%): May damage fertility or the unborn child [Danger Reproductive toxicity] H361 (18.67%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]
NIOSH 2020	propylthiouracil	Antithyroid agents	film-coated tablet		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H351 (90.62%): Suspected of causing cancer [Warning Carcinogenicity]
NIOSH 2020	raloxifene	Oestrogens	tablet film-coated tablet		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H332 (100%): Harmful if inhaled [Warning Acute toxicity, inhalation] H335 (100%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation]
NIOSH 2020	rasagiline	Antiparkinsonian drugs dopaminergics	tablet		no data available

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH 2020	ribavirin	Antiretrovirals	film-coated tablets film-coated tablet capsule solution		H302 (10.53%): Harmful if swallowed [Warning Acute toxicity, oral] H317 (47.37%): May cause an allergic skin reaction [Warning Sensitization, Skin] H319 (48.68%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (57.89%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H341 (57.89%): Suspected of causing genetic defects [Warning Germ cell mutagenicity] H360 (48.68%): May damage fertility or the unborn child [Danger Reproductive toxicity] H361 (50%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H372 (10.53%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure] H373 (47.37%): Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure] H412 (47.37%): Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	riociguat	Antihypertensives	film-coated tablets		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral]
NIOSH 2020	sirolimus	Immunosuppressive drugs	film-coated tablet solution		no data available
NIOSH 2020	spironolactone	Diuretics, aldoste-rone antagonists	tablet film-coated tablet capsule		H302 (36.52%): Harmful if swallowed [Warning Acute toxicity, oral] H312 (31.3%): Harmful in contact with skin [Warning Acute toxicity, dermal] H332 (31.3%): Harmful if inhaled [Warning Acute toxicity, inhalation] H351 (62.61%): Suspected of causing cancer [Warning Carcinogenicity] H360 (53.91%): May damage fertility or the unborn child [Danger Reproductive toxicity] H373 (24.35%): Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure]
NIOSH 2020	tacrolimus	Immunosuppressive drugs	modified-release tablet capsule modified-release capsule solution (internal use) ointment		H301 (100%): Toxic if swallowed [Danger Acute toxicity, oral] H361 (100%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H372 (100%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure]
NIOSH 2020	temazepam	Benzodiazepine	soft capsules	Not for sale	H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral]
NIOSH 2020	teriflunomide	Inotropes, Sympathomimetic drugs + antiallergic drugs	film-coated tablet		H302 (93.55%): Harmful if swallowed [Warning Acute toxicity, oral]

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH 2020	testosterone	Androgens	soft capsule gel solution (internal use)		H302 (65.52%): Harmful if swallowed [Warning Acute toxicity, oral] H312 (13.79%): Harmful in contact with skin [Warning Acute toxicity, dermal] H332 (13.79%): Harmful if inhaled [Warning Acute toxicity, inhalation] H350 (32.18%): May cause cancer [Danger Carcinogenicity] H351 (68.97%): Suspected of causing cancer [Warning Carcinogenicity] H360 (66.67%): May damage fertility or the unborn child [Danger Reproductive toxicity] H361 (33.33%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H362 (49.43%): May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation] H400 (65.52%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard]
NIOSH 2020	thalidomide	Immunosuppressive drugs	capsule		H302 (92.11%): Harmful if swallowed [Warning Acute toxicity, oral] H360 (96.05%): May damage fertility or the unborn child [Danger Reproductive toxicity]
AIFA note 14/03/2019	thiocolchicoside	Anti-inflammatory drugs Myorelaxants			
NIOSH 2020	tofacitinib	Drugs for the treatment of rheumatoid arthritis	film-coated tablet		H301 (33.33%): Toxic if swallowed [Danger Acute toxicity, oral] H302 (33.33%): Harmful if swallowed [Warning Acute toxicity, oral] H311 (33.33%): Toxic in contact with skin [Danger Acute toxicity, dermal] H315 (33.33%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (33.33%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H331 (33.33%): Toxic if inhaled [Danger Acute toxicity, inhalation] H335 (33.33%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H360 (66.67%): May damage fertility or the unborn child [Danger Reproductive toxicity]
NIOSH 2020	topiramate	Antiepileptic drugs	film-coated tablets film-coated tablet capsule		H315 (81.01%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (82.28%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (81.01%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H361 (17.72%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity]
NIOSH 2020	tretinoin	Antiacne disinfectants Antineoplastics, antiacne retinoids	capsule cream gel solution		H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (96.15%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H360 (96.15%): May damage fertility or the unborn child [Danger Reproductive toxicity]
NIOSH 2020	ulipristal	Emergency contraceptives Antiprogestins	tablet film-coated tablet		H361 (100%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H413 (100%): May cause long-lasting harmful effects to aquatic life [Hazardous to the aquatic environment, long-term hazard]
NIOSH 2020	uracil mustard	Antithyroid agents	film-coated tablet		H300 (100%): Fatal if swallowed [Danger Acute toxicity, oral] H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H318 (100%): Causes serious eye damage [Danger Serious eye damage/eye irritation] H335 (100%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H351 (100%): Suspected of causing cancer [Warning Carcinogenicity]

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH2020	urofollitropin	Gonadotrophic hormones	powder		H317 (100%): May cause an allergic skin reaction [Warning Sensitization, Skin] H332 (100%): Harmful if inhaled [Warning Acute toxicity, inhalation] H334 (100%): May cause allergy or asthma symptoms or breathing difficulties if inhaled [Danger Sensitization, respiratory]
NIOSH2020	valganciclovir	Antiretrovirals	film-coated tablets film-coated tablet powder		H340 (100%): May cause genetic defects [Danger Germ cell mutagenicity] H350 (85.71%): May cause cancer [Danger Carcinogenicity] H351 (14.29%): Suspected of causing cancer [Warning Carcinogenicity] H360 (100%): May damage fertility or the unborn child [Danger Reproductive toxicity] H372 (85.71%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure]
NIOSH2020	valproate/valproic acid	Antiepileptic drugs Antimanic, antiepileptic drugs	gastro-resistant tablet modified-release tablet extended-release tablet modified-release granules powder solution		H302 (100%): Harmful if swallowed [Warning Acute toxicity, oral] H315 (94.44%): Causes skin irritation [Warning Skin corrosion/irritation] H318 (40.97%): Causes serious eye damage [Danger Serious eye damage/eye irritation] H319 (53.47%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (15.97%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation] H360 (80.56%): May damage fertility or the unborn child [Danger Reproductive toxicity]
NIOSH2020	vigabatrin	Antiepileptic drugs	film-coated tablet granules		H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (100%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation]
NIOSH2020	voriconazole	Antifungals	tablet film-coated tablets film-coated tablet powder solution (internal use)		H301 (99.02%): Toxic if swallowed [Danger Acute toxicity, oral] H351 (94.12%): Suspected of causing cancer [Warning Carcinogenicity] H360 (21.57%): May damage fertility or the unborn child [Danger Reproductive toxicity] H361 (77.45%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H373 (97.06%): Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure] H400 (45.1%): Very toxic to aquatic life [Warning Hazardous to the aquatic environment, acute hazard] H412 (96.08%): Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]
NIOSH2020	warfarin	Indirect anticoagulants	tablet		H300 (94.23%): Fatal if swallowed [Danger Acute toxicity, oral] H310 (72.12%): Fatal in contact with skin [Danger Acute toxicity, dermal] H312 (22.12%): Harmful in contact with skin [Warning Acute toxicity, dermal] H330 (72.12%): Fatal if inhaled [Danger Acute toxicity, inhalation] H360 (100%): May damage fertility or the unborn child [Danger Reproductive toxicity] H372 (100%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure] H411 (68.27%): Toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard] H412 (31.73%): Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM FINAL	NOTES	SAFETY AND HAZARDS (DA HTTPS://PUBCHEM.NCBI.NLM.NIH.GOV)
NIOSH 2020	zidovudine	Antiretrovirals	tablet film-coated tablets capsule syrup solution (internal use)		H341 (63.16%): Suspected of causing genetic defects [Warning Germ cell mutagenicity] H350 (61.84%): May cause cancer [Danger Carcinogenicity] H351 (36.84%): Suspected of causing cancer [Warning Carcinogenicity] H361 (63.16%): Suspected of damaging fertility or the unborn child [Warning Reproductive toxicity] H372 (60.53%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure]
NIOSH 2020	ziprasidone	Antipsychotics	capsule		H336 (100%): May cause drowsiness or dizziness [Warning Specific target organ toxicity, single exposure; Narcotic effects] H341 (100%): Suspected of causing genetic defects [Warning Germ cell mutagenicity]
NIOSH 2020	zoledronic acid	Osteomodulating drugs	preparation for injection powder solution (internal use) solution		no data available
NIOSH 2020	zonisamide	Antiepileptic drugs	capsule		no data available

SOURCE:

- NIOSH [2020]. Draft NIOSH List of Hazardous Drugs in Healthcare Settings, 2020 https://www.cdc.gov/niosh/docket/review/docket233c/pdfs/DRAFT-NIOSH-Hazardous-Drugs-List-2020.pdf
- NOTA AIFA 14/03/2019. Nota Informativa Importante su medicinali contenenti tiocolchicoside http://www.agenziafarmaco.gov.it/content/nota-informativa-importante-su-medicinali-contenenti-tiocolchicoside-14032019
- Alberta Health Services (Pharmacy Services, Health Professions Strategy and Practice and Workplace Health and Safety) and Covenant Health (Pharmacy Services) Hazardous Medication Personal Protective Equipment (PPE) Guide and List REDUCING OCCUPATIONAL EXPOSURE TO HAZARDOUS MEDICATION FOR ALL STAFF (2019)
- DUKE UNIVERSITY HOSPITAL Department of Pharmacy Center for Medication Policy SAFE HANDLING OF HAZARDOUS DRUGS (Updated 12/11/2019)
- Vanderbilt University Medical Center VUMC Hazardous Medication List January 2020
- PubChem® https://pubchem.ncbi.nlm.nih.gov/

TABLE 2 - SUGGESTED NOT INCLUDED OR DRUGS EXCLUDED FROM THE NIOSH 2020 LIST

SOURCE	DRUG	THERAPEUTIC GROUP	PHARMACEUTICAL FORM	SAFETY AND HAZARDS (da https://pubchem.ncbi.nlm.nih.gov)
New proposal not included	botulinum toxins, all forms, including abobotulinum toxin A and onabotulinum toxin A	Myorelaxants	powder solution (internal use)	no data available
New proposal not included	darbepoetin alfa	Antianemic drugs, erythropoietin	solution (internal use)	no data available
New proposal not included	interferon beta-1b	Antivirals, immunostimulants, interferons	powder	no data available
Supressed	paliperidone	Antipsychotics	modified-release tablet extended-release tablet pre-filled syringes/vial + syringe extended-release suspension	H301 (100%): Toxic if swallowed [Danger Acute toxicity, oral]
	podofilox topical solution/gel	antimitotic agents	gel	H301 (96.55%): Toxic if swallowed [Danger Acute toxicity, oral] H310 (100%): Fatal in contact with skin [Danger Acute toxicity, dermal] H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation] H319 (100%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] H335 (96.55%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation]
	podophyllum topical	antimitotic agents	cream	no data available
Supressed	risperidone	Antipsychotics	film-coated tablet drops powder solution	H301 (99.02%): Toxic if swallowed [Danger Acute toxicity, oral] H331 (13.73%): Toxic if inhaled [Danger Acute toxicity, inhalation] H351 (12.75%): Suspected of causing cancer [Warning Carcinogenicity] H411 (23.53%): Toxic to aquatic life with long lasting effects [Hazardous to the aquatic environment, long-term hazard]
Supressed	telavancin		solution for infusion	no data available
New proposal not included	triazolam	Hypnotics and sedatives benzodiazepines	tablet capsule drops	H360 (98.41%): May damage fertility or the unborn child [Danger Reproductive toxicity] H362 (100%): May cause harm to breast-fed children [Reproductive toxicity, effects on or via lactation]

SOURCE:

- NIOSH [2020]. Draft NIOSH List of Hazardous Drugs in Healthcare Settings, 2020 https://www.cdc.gov/niosh/docket/review/docket233c/pdfs/DRAFT-NIOSH-Hazardous-Drugs-List-2020.pdf

TABLE 3 - RECOMMENDATIONS FOR THE USE OF PPE AND ENGINEERING MEASURES

FORMULATION	ACTIVITY	GLOVES	LAB COAT/ OVERALLS	EYE/FACE PROTECTION	RESPIRATORY PROTECTION (FFP3)	CONTROLLED ENVIRON-MENT SYSTEM
All	Material receipt, Unpacking and Storage	Yes	Yes, in case of spills or leaks	No	Yes, in case of spills or leakages	No
Intact Tablets or Capsules	Administration	Yes	No	Yes, in case of vomiting or spitting	No	not applicable
Tablets or Capsules	Cutting, crushing or other handling of tablets or capsules; handling of uncoated tablets	Yes	Yes	No	Yes, if not carried out in an airtight device	Yes
Oral or infusion solutions	Preparation	Yes	Yes	Yes, if not carried out in an airtight device	Yes, if not carried out in an airtight device	Yes
	Administration	Yes	Yes	Yes, in case of vomiting or spitting	Yes, preferable	not applicable CSTD recommended
Topical formulations	Preparation	Yes	Yes	Yes, if not carried out in an airtight device	Yes, if not carried out in an airtight device	Yes
	Administration	Yes	Yes	Yes, if the liquid can splash	Yes, in case of potential inhalation	not applicable
Liquid solutions for subcutaneous/ intramuscular/ intravenous use	Preparation (vial suction/mixing)	Yes	Yes	Yes, if not carried out in an airtight device	Yes, if not carried out in an airtight device	Yes CSTD recommended
	Administration	Yes	Yes	Yes, if the liquid can splash	Yes, preferable	not applicable CSTD recommended
Irrigation solutions	Preparation	Yes	Yes	Yes, if not carried out in an airtight device	Yes, if not carried out in an airtight device	Yes
	Administration	Yes	Yes	Yes, if not carried out in an airtight device	Yes, if not carried out in an airtight device	not applicable CSTD recommended
Powder/Inhalation Solution (aerosol)	Preparation	Yes	Yes	Yes, if not carried out in an airtight device	Yes, if not carried out in an airtight device	Yes
	Administration	Yes	Yes	Yes, if the liquid can splash	Yes, in case of potential inhalation	not applicable
Drugs and Metabolites in Body Fluids	Disposal and Cleaning	Yes	Yes	Yes, if the liquid can splash	Yes, in case of potential inhalation	not applicable
Contaminated waste	Disposal and Cleaning	Yes	Yes	Yes, if the liquid can splash	Yes, in case of potential inhalation	not applicable
Spills	Cleaning	Yes	Yes	Yes	Yes	not applicable

CSTD: *closed system transfer device*

GENERAL TIPS

- **Oral/enteral formulations**: do not touch the tablets/capsules directly, but place the drug to be administered in a small glass/cup
- **Formulations for injection**: when preparing the drug, work at waist height and not face height, and use, only if a CSTD is not available, a large gauge needle to reduce the risk of vaporisation of the solution