S. Dugheri, N. Mucci, E. Mini, G. Cappelli, E. Bucaletti, D. Squillaci, L. Trevisani, G. Arcangeli*

AN UPDATE ON PERMEATION OF PROTECTIVE MEDICAL GLOVES BY ANTINEOPLASTIC DRUGS

UDK 615.262:615.478.4]:004.65
RECEIVED: 2021-05-24
ACCEPTED: 2022-08-23

SUMMARY: Occupational exposure to antineoplastic drugs (ADs) handling and administration is one of the main risks in the healthcare sector. Dermal absorption represents the primary route of exposure to ADs. Personal preventive equipment, especially medical gloves, is crucial to safeguard the workers health in ADs handling; thus, chemicals permeating through protective materials is an essential aspect to estimate and consider. Several studies on permeation through medical gloves reported that breakthrough time and permeation rate are the values that must be studied, observing that physical-chemical properties of drugs, PPE materials and thickness, and temperature are crucial features to estimate them. In the European Union, standardized permeation testing is not mandatory for gloves used in ADs manipulation, in contrast with the United States, that proposed stringent requirements in the American Society of Testing and Materials International standard D6978-05. This review would help identify the main characteristics of the best protective glove used by employees frequently exposed to ADs: the major aspects implicated in permeation, reported in the literature, are listed and discussed.

Key words: *antineoplastic drugs, medical gloves, occupational monitoring, permeation testing, surface contamination, occupational healthy*

INTRODUCTION

Occupational exposure to antineoplastic drugs (ADs) may occur in drug compounding and administration, and it is an unpredictable risk *(Harris, 1976, Falck et al., 1979, Anderson et al., 1982, Massoomi et al., 2008)*. Measurable concentrations of drug contamination have been documented, through environmental studies of ADs handling, even in facilities considered following the recommended handling guidelines *(Pethran et al., 2003)*. Over the life cycle of a drug - from manufacture to transport and distribution, to use in healthcare or homecare settings, to waste disposal - workers may be exposed. Over 5.5 million workers may be exposed to hazardous drugs *(Connor et al., 2016)*. The International Agency for Research on Cancer classified ADs as carcinogenic or probably carcinogenic in humans (group 1 or 2A) (Table 1) *(Connor et al., 2016)*. Therefore, the ideal situation for safely handling these drugs would be the absence of direct contact with them; thus, the permeation of these compounds through protective clothing must be minimized. Under these circumstances, the more the guidelines and/or international standards are restrictive, the more healthcare workers are safe. Nevertheless, only in the past three decades, guidelines and recommendations have been established to handle hazardous drugs safely.

*Prof. Stefano Dugheri, M.Sc. (Corresponding Author) (stefano.dugheri@unifi.it), Careggi University Hospital, Industrial Hygiene and Toxicology Laboratory, Florence, Italy, Prof. Nicola Mucci, M.D. Ph.d., University of Florence, Department of Experimental and Clinical Medicine, Florence, Prof. Enrico Mini, University of Florence, Department of Health Science, Florence, Italy, Giovanni Cappelli, M.Sc., Elisabetta Bucaletti, M.Sc., Donato Squillaci, M.Sc., Lucia Trevisani, M.Sc., Prof. Giulio Arcangeli, M.D., University of Florence, Department of Experimental and Clinical Medicine, Florence, Italy.

In 1981 was published one of the first articles addressing the safe handling of ADs *(Harrison, 1981)*. Only in 1985, the practitioners were provided with guidelines about the safe compounding and administration of hazardous drugs *(American Society of Hospital Pharmacists, 1985)*. In 2006, the American Society of Health-System Pharmacists revised these guidelines to raise awareness of risks associated with handling toxic agents, linked to the advent of new technologies to minimize occupational exposure *(American Society of Health-System Pharmacists, 2006)*. Meantime in 2004, the National Institute for Occupational Safety and Health (NIOSH) published an alert on antineoplastic and other hazardous drugs, indicating safe handling practices for all healthcare workers. In 2016, an update of this document reported new drugs approved by the Food and Drug Administration (FDA) *(Connor et al., 2016)*: slightly more than half of these new hazardous drugs are classified as antineoplastic/cytotoxic agents. In December 2019, to minimize risk to all healthcare workers, new regulations were released, forcing healthcare organizations to implement the United States Pharmacopeia General Chapter <800> Hazardous Drugs - Handling in Healthcare Settings safety standards *(United States Pharmacopeia, 2019)*. In this document, worker safety measures are reported, including wearing personal protective equipment, even in homecare settings.

Table 1. International Agency for Research on Cancer classification of Ads

Tablica 1. Međunarodna agencija za istraživanje klasifikacije raka AD-ova

International Agency for Research on Cancer classification group	Antineoplastic drug
1 (Carcinogenic to humans)	Arsenic trioxide, Busulfan, Chlorambucil, Cyclophosphamide, Etoposide, Melphalan, Tamoxifen, Thiotepa
2A (Probably carcinogenic to humans)	Azacitidine, Carmustine, Cisplatin, Doxorubicin, Lomustine, Procarbazine, Teniposide
2B (Possibly carcinogenic to humans)	Amsacrine, Bleomycin, Daunomycin, Mitomycin, Mitoxantrone, Streptozotocin

Since 2004, the European community has promoted the implementation of both administrative and engineering controls among the member states, to provide the highest protection to healthcare workers and to guarantee the use of appropriate and validated procedures for handling hazardous drugs. In February 2019, modifications to Directive 2004/37/CE on carcinogens and mutagens and their healthcare implications were approved by the European Parliament *(European Parliament and of the council, 2019)*. More recently, the European Biosafety Network has published an amendment where is recommended a surface threshold contamination for ADs of 0.1 ng/cm^2 *(European BioSafety Network, 2019)*. The dermal absorption is the primary route of exposure in ADs manipulation *(Connor, 2006)*. Therefore, the main routes of dermal exposure with drugs that should be considered are direct contact (manipulate vials producers and/or pharmacological solutions in intravenous bags) or indirect contact (as a result of touching contaminated surfaces). The potential risk for dermal contact can be monitored by wipe tests in the exposed area; the biological monitoring of workers (urine analysis) for ADs or their metabolites (alpha-fluoro-beta-alanine for 5-fluorouracil) *(Dugheri et al., 2017)* could provide valuable information only in critical exposure situations. In fact, already in 2016, the recommendations listed in "Preventing occupational exposure to cytotoxic and other hazardous drugs. European Policy Recommendations" put effort into the adoption of environmental monitoring procedures to identify the route of releasing and spreading of the drugs, to monitor and improve the protective measures and equipment's effectiveness *(European BioSafety Network, 2016)*. In addition, in January 2019, the American Conference of Governmental Industrial Hygienists introduced the Threshold Limit Value (TLV) – the Surface Level (SL), which is a new limit value for surface contamination.

Since the ADs handling is a high-risk process for occupational exposure, the proper use of safety cabinets, closed-circuit transfer devices and personal preventive equipment (PPE) are highly recommended to minimize risks. About the latter, medical gloves are the most important PPE, because they are a direct protection for the hands, which are at a higher risk of exposure to ADs *(Oriyama et al., 2020)*. When handling cytotoxic

drugs, they are the first line of protection, so the choice of safer gloves must be contextualized to the physical-chemical properties of the used ADs and the handling time. In Europe, the medical gloves are legally covered by the European Council Directive 93/42/EEC, the European Standard (EN) 455 *(European committee for standardization, CEN, 2002)*, and the UNI EN 16523-1:2019 *(UNI EN, 2019)*, which sustains the previous UNI EN ISO 374-1:2018 *(UNI EN, 2019)*. The EN 455 defines the minimum protective properties and the quality tests designed to ascertain physical properties and macroscopic material defects. The UNI EN 16523-1:2019 defines performance characteristics of gloves about protection against chemicals but do not require permeability tests for chemotherapy drugs. In the United States, gloves should be tested according to the American Society of Testing and Materials (ASTM) D 6978-05 *(ASTM International, 2005)*, which is, nowadays, the more stringent testing method for protective gloves used in ADs handling.

From 1975 to 1999, different studies about glove materials permeability to ADs are reported *(Thomsen, Mikklesen, 1975, Slevin et al., 1984, Colligan, Horstman, 1990, Singleton, Connor, 1999)*: one of the most complete was conducted by Connor in 1999, who carried out a permeability study of 18 ADs on various glove materials (nitrile rubber, latex, polyurethane, and neoprene), identifying in exposition times, ADs physical-chemical features and gloves thickness the crucial aspects in ADs safe handling *(Connor, 1999)*. This article focused on three major themes to describe the whole risk scenario related to ADs and their safe handling in healthcare facilities, underlining the significance of PPE, particularly medical gloves. The main themes are i) ADs manipulation and exposed population, ii) permeation and ADs physical-chemical properties, iii) permeation testing to ADs for medical gloves. The aims of the authors are to detail the contexts in which ADs are spreadly used, focusing on challenging ADs types, medical gloves features, and workplaces. Thus, a literature search has been conducted considering only sources from 2000 to provide a comprehensive view of the most recent information about medical gloves related to ADs manipulation. These information could represent a valuable tool to industrial hygienists and environmental professionals to assess occupational risk related to ADs manipulation and minimize it, starting from the right choice of gloves.

MATERIAL AND METHODS

Due to the newer agents for cancer treatment, new glove materials, current regulations, and technology evolution, a computer-based scientific and non-scientific source research was performed in March 2021 on the following databases: PubMed, Web of Science, and Google Scholar. This research has been integrated with non-scientific sources, such as manufacturer datasheets and application notes.

RESULTS AND DISCUSSION

ADs manipulation and exposed population

The chemotherapy market is expected to reach a valuation close to 56.5 billion USD by 2024 and exhibit a robust 11.5% Compound Annual Growth Rate over the forecast period from 2019 to 2024 *(Allied Market Research, 2019)*. More than 100 ADs are currently used in clinical practice, among which alkylating agents, alkaloids, anthracyclines, antimetabolites, topoisomerase inhibitors, and aromatase inhibitors *(National Cancer Institute at the National Institutes of Health, 2021)*. Moreover, the appropriate use of safety cabinets, closed-system transfer devices, and PPE is crucial to safeguard professionals from exposure to ADs in the manipulation setting.

The exposed population to ADs includes manufacturing, shipping, and receiving personnel, pharmacists, nursing and operating room personnel, home healthcare agencies, environmental services operators, physicians, research laboratories, and veterinary practices *(Hamscher et al., 2010)*, as listed by NIOSH *(Connor et al., 2016)*. The handling process of antineoplastic agents needs to be performed with care to avoid unintended exposure. For a safe workplace, it is crucial to evaluate the contamination of indoor and outdoor work and living environments as well as the external surface of the vial and/or the primary packaging containing the drugs. Routes of exposure for

professionals include contact with contaminated ampoules during manufacture, preparation, shipping, and administration (especially the manipulation of powdered or lyophilized ADs or concentrated liquid forms) *(Fransman et al., 2007)*, in intraoperative hyperthermic intraperitoneal chemotherapy in the operating room *(Stuart et al., 2002, Scaringi et al., 2010)*, decontaminating and cleaning drug preparation or clinical areas, transporting infectious, chemical, or hazardous waste containers, removing and disposing of PPE after handling hazardous drugs or waste. Moreover, the excretions of patients (urine, feces, vomit, and sweat) may contain chemotherapy drugs, leading to remarkable amounts of them in urine bags, clothes, and bedding *(Kromhout et al., 2000)*. Patients can carry ADs in domestic environments *(Böhlandt et al., 2017)*, contaminating even soil and superficial water *(Kümmerer et al., 2016, Dugheri et al., 2018, Mukherjee et al., 2020)*.

The ten most prescribed ADs among 111 pharmacies in Germany included 5-fluorouracil (5-FU), cyclophosphamide (CP), etoposide (ETP), cisplatin, gemcitabine (GEM), carboplatin, cytarabine, irinotecan, oxaliplatin, and doxorubicin (DXR) *(Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege (BGW), 2008)*. Nowadays, about 80% of 331 oncology wards used centralized preparation units in Italy, with a mean volume of activity of 20,000 doses per year, although some units administer over 40,000 (Il Sole 24 ORE, 2017).

External vial contamination has been previously reported *(Mason et al., 2003, Hedmer et al., 2005, Hilliquin, Bussières, 2020, Mucci et al., 2020)*, and it seems to be a significant factor both for direct - contact with the external surface of the vial and/or the primary packaging – and/or indirect - on surfaces where vials were placed and handled - contamination. ADs contamination can be present in preparation and administration units in a healthcare environment *(Crickman, Finnell, 2016, Dugheri et al., 2018)*. Several authors *(Sessink et al., 1997, Hedmer et al., 2005)* have demonstrated general contamination of the work environment of persons involved in the packaging of ADs, therefore, the contamination of the vials themselves. To our knowledge, only two articles reported the contamination of the outer wall of vials *(Sessink et al., 1994, Delporte et al., 1999)*, showing that one of nine CP vials was contaminated with 60 ng and one of fifteen methotrexate (MTX) vials was contaminated with 15 µg. As well, in 2003, Mason et al. *(2003)* monitoring 30 vials of cisplatin, carboplatin, CP, iphosphamide (IP), and MTX, found ADs levels of contamination up to 344 ng/vial. Furthermore, they revealed a relatively high level of CP contamination on a pair of gloves, used as PPE during sampling of vials containing IP, and that two wipes from CP vials showed IP contamination. These results suggested possible general CP or IP contamination on the pharmacy shelves or cross-contamination between vials, as supplied by the drug manufacturers. Recently, Mucci et al. *(2020)* carried out wipe tests from the surface of 25 drug vials, revealing up to 0.044 ng/cm^2.

Several combined industrial hygiene control methods in a specific hierarchy represent the basic occupational health approach to minimize exposure risks. Environmental monitoring is one of these methods, which enables the determination of contamination trends, identifying corrective measures, and increasing the awareness of workers. Monitoring ADs surface contamination usually involves wipe tests as an easy way to indirectly assess dermal occupational exposure *(Mucci et al., 2020)*. ADs, due to their carcinogenicity, must be handled following the As Low As Reasonably Achievable principle; however, environmental and equipment contamination are generally related to their massive use. Thus, to evaluate the minimal exposure or the reduction of contamination, quantitative proofs are needed. Many studies show a variety of contaminations involving both different ADs and healthcare occupational settings (Table 2).

Table 2. Occupational exposure studies on environmental ADs contaminations

Tablica 2. Studije profesionalne izloženosti onečišćenjima okoliša AD-ima

Reference	N° samples	ADs investigated	Outcome	Study findings
Kiffmeyer et al., 2013	1,269 wipe samples	CP, docetaxel, ETP, 5-FU, GEM, IP, MTX, and paclitaxel	61%	The four most frequently detected substances were CP, GEM, 5-FU, and IP, mainly on the floor in front of the safety cabinet, the worktop, and the refrigerator door.
Schierl et al., 2009	1,237 wipe samples	5-FU	74.4% (above 0.75 pg/cm^2)	In the 102 German hospital and retail pharmacies investigated, the highest levels were find on storage shelves and floors.
Böhlandt, Schierl, 2016	3,584 wipe samples - 2,955 samples	5-FU - Cis-, carbo- and oxaliplatin	56% (0.5 pg/cm^2) - 82% (0.1 pg/cm^2)	The highest concentration was located on a storage surface, but also the biological safety cabinets and the waste disposal systems were strongly contaminated.
Hedmer and Wohlfar, 2012	447 wipe samples	CP and IP	More than 70% (from 10 to 95 ng/cm^2)	The highest surface loads were found on the floors.
Sottani et al., 2017	349 wipe samples - 422 wipe samples	CP, GEM, 5-FU, platinum compounds, epirubicin, and DXR	85% of the pharmacies - 93 % of outpatient care units	The highest levels of CP, 5-FU, GEM, and Pt were specially found on floor surfaces.
Dugheri et al., 2018	3,749 wipe samples	CP, 5-FU, dacarbazine, GEM, MTX, irinotecan, vincristine, vinblastine, epirubicin, DXR, ETP, docetaxel, paclitaxel, topotecan, melphalan, idarubicine, fotemustine, citarabine, cis-, carbo- and oxaliplatin	3.9%	The highest levels were found on floor, biological safety cabinets and syringe pump surfaces and door handles.

The ubiquitous contaminations could lead to the improper exposure of workers who are not directly involved in ADs administration or preparation. Mucci et al. *(2020)* reported the study of 552 wipes on the spaces between the hospital exit and the preparation, administration, and pharmacy warehouse units to analyse the CP and IP contamination and to identify the possible migration routes of these substances: 22 were greater than or equal to the LOQs (0.6 and 0.5 pg/cm2 for CP and IP, respectively). Moreover, in recent years, the chemotherapy treatment has been moved from oncology wards to outpatient departments, leading to a presence of the patient of only few hours. So, patients and workers can carry ADs contamination by dragging contamination from hospitals to domestic environments *(Thornton et al., 2016, Huff, 2020)*. In addition, patients continued to excrete ADs at low levels for more than 4 days after treatment with urine, feces, and breathing patterns *(Yuki et al., 2013, Böhlandt et al., 2017)*: Yuki et al. *(2015)* detected CP in 8 of the 12 wipe samples obtained from the homes of the treated patients, founding higher concentration of CP in the toilets (7.34 ng/cm2), especially on the toilet seats.

Since 2006, the European legislation imposes an environmental risk assessment, according to the European Medicines Agency (EMEA) guide-

line on environmental risk assessment of human pharmaceuticals. In comparison, the US FDA guidelines came into force in 1998. Both recommendations reported that data on physical-chemical properties, fate, and effects of drug substances are required to evaluate the risk assessment.

Permeation and ADs physical-chemical properties

Penetration of any compound into the body is principally prevented by the corneal layer of the epidermis *(Boer et al., 2016)*. Due to its hydrophobicity, the stratum corneum barrier will allow lipid-soluble molecules to penetrate more readily than water-soluble ones. Hydrophilic molecules, instead, may penetrate through the openings of sweat glands and hair follicles *(Bos, Meinardi, 2000)*. Generally, drugs with a molecular weight (MW) lower than 500 Dalton *(Connor, 2006)* are the most inclined to dermal absorption. Some authors have suggested that the permeation of the compound would be increased by low MW and high lipophilia (defined by the high logarithm of octanol-water partition coefficient, Log P) *(Oriyama et al., 2020)*. However, the lipophilia of drugs could, in some case, mislead estimating their permeability: ADs with similar Log P, as carmustine (CAR) (Log P=1.5) and DXR (Log P=1.3) have notably different permeation rate, that is most likely due to their MW (214 and 543 Da, respectively) *(Wallemacq et al., 2006)*. Recently, Nalin et al. *(2020)* focused on four parameters): the MW, the Log P, the topological polar surface area and the hydrogen bond donor. These parameters are generally considered to have the most decisive impact on the extent to which drugs overcome the blood-brain barrier. They showed that a chemical is more likely to overcome the blood-brain barrier if its topological polar surface area is < 70 Å^2, its hydrogen bond donor is equal to 0 or 1, its Log P is between 2 and 4, and its MW is < 450 Da. Nowadays, considering the introduction on the market of new drugs, the chemical-physical constants' predictivity could represent valid support in permeation study and ADs' risk assessment.

Permeation testing to ADs for medical gloves

The penetration of drugs concerns not only biological barriers (skin or mucous membrane) but all kinds of material, such as the different polymers used in the manufacture of medical gloves. The MW and Log P represent crucial features for ADs permeation through gloves and PPE *(Pieri et al., 2013)*. Regarding the liposolubility, analysis of drugs Log P suggests a trend toward higher permeation rates for drugs with a high Log P (e.g., CAR, CP, and thiotepa). In contrast, drugs characterized by the lowest Log P values generally have the lowest mean permeation rates (e.g., MTX, cytarabine, cisplatin). Wallemacq et al. *(2006)* reported that ADs with Log P values > 0.5 tended to exhibit higher permeation rates through medical gloves than those with Log P values < 0.5. In 2020, Oriyama et al. *(2020)* tried to foresee the risk of permeation of the ADs through nitrile medical gloves based on their MW and Log P values by three zones: Zone A - high Log P/low MW (Log P ≥ -1 and MW ≤ 500), Zone B - high Log P/high MW (Log P ≥ -1 and MW > 500), and Zone C - low Log P (Log P <-1), where Zones A, B, and C corresponded to high, moderate, and low permeation risk, respectively.

Nowadays, the level of ADs personal protection of medical gloves by permeation testing could be evaluated according to the American Society of Testing and Materials (ASTM) D-6978-05 *(ASTM International, 2005)* or the European Standards EN 16523 (UNI EN, 2019), which propose a permeation breakthrough limit equal to 10 ng/(min cm^2) and 1,000 ng/(min cm^2), respectively. The American requirement is more stringent, reflecting the potential hazards presented by ADs; the permeation limit is set at 100th of the European one. The ASTM assesses the resistance of medical gloves to permeation by chemotherapy drugs - the tests are carried out with a minimum of 9 ADs, 7 of which are mandatory -, while the European Standards determines the material resistance to permeation by liquid chemicals (no chemotherapy drugs). Other significant differences lie in test temperature and the gloves sampling area: ASTM carries out the test at a temperature like the body one and, not only on the palm of the glove but even on the glove cuff, which is the thinnest part *(Cleanroom Technology, 2020)*. In 2019 has been approved the US ASTM D6978-05 guideline, which shows the experimental settings to be met for the static method but does not refer to test the material under stress, stretch, or flex.

Nowadays, newer agents for cancer treatment have replaced some used previously *(Guichard et al., 2017)*. Furthermore, new glove materials have emerged for handling ADs: in part because there was concern about allergic reactions to latex-based products *(Crepy et al., 2020)*, while other materials, as vinyl, are dismissed due to their high permeability *(Landeck et al., 2015)*. There are several classes of protective glove materials: the most common is nitrile (acrylonitrile-butadiene), but also natural rubber latex (NRL), neoprene, polyvinyl alcohol, polyethylene, polyurethane, and polyisoprene are used in ADs manipulation.

There are many types of protective gloves available on the market; the most widely used in handling ADs with their main characteristics are listed in Table 3.

In the absence of commercially available equipment, original "home-made" systems to test drugs permeation through PPE in static (*Dinter-Heidorn, Carstens, 1992, Connor, 1999, Boccellino et al., 2010)* and dynamic *(Klein et al., 2003, Wallemacq et al., 2006, Oriyama et al., 2017)* mode were conceived and designed.

The static ones consist of testing the whole glove external surface or specific part of it (as the middle finger) in permeation cell-like devices (Figure 1) *(Franz, 1978)*. In the upper chamber, there is an ADs solution and water in the lower chamber as receiving solution; the glove could be stirred and heated. The testing material is located with an o-ring between the two chambers, and the receiving solution is sampled and tested at an established time.

In the dynamic system, the permeation study is like the static one, but the tests are conducted with the gloves, or part of them, stretched or flexed to simulate the thinning of the materials during their use *(Colligan, Horstman, 1990)*.

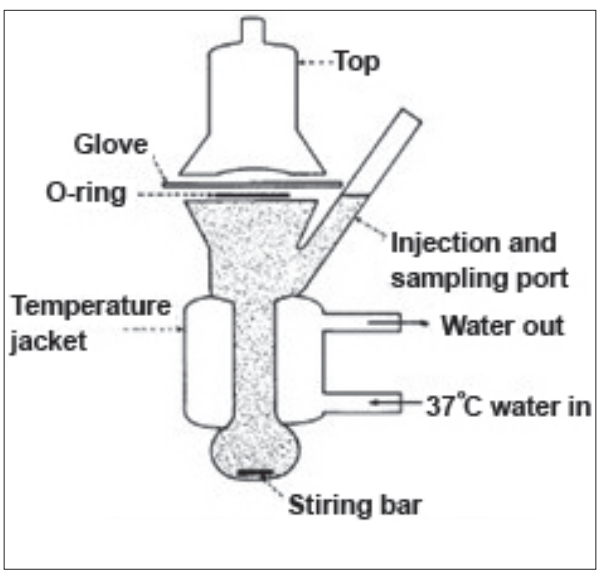

Figure 1. Permeation cell test
Slika 1. Test permeacijske stanice

Table 3. List of commercially available powder-free medical gloves to handle antineoplastic drugs

Tablica 3. Popis komercijalno dostupnih medicinskih rukavica bez pudera za rukovanje antineoplastičnim lijekovima

Product name	Producers	Material	Thickness [mm]		Permeability test	Sterile	Elongation at break	Tensile strength
			Palm	Finger				
Micro-touch Nitra-tex	Ansell *Richmond Australia*	Nitrile	0.10	0.12	ASTM D6978	No	595%	>14Mpa
ChemoPlus Gloves	Covidien Dublin Ireland	Latex or Nitrile	-	0.23	ASTM D6978	No	n.d.	n.d.
Kimtech Purple Nitrile	Kimberly Clarck Irving Texas	Nitrile	0.14	0.16	ASTM D6978	No	550%	21Mpa
Vasco Surgical Powder-free	B.Braun Melsungen Germany	Natural rubber latex	0.21	-	ASTM D6978	Yes	750%	29 Mpa
ESTEEM	Cardinal Health Dublin Ireland	Nitrile	-	0.18	ASTM D6978	Yes	533%	19 Mpa
Syntrile	Cypress Medical Wheeling Illinois	Nitrile	0.05	0.07	ASTM D6978	No	500%	>18MPa
Sterling Nitrile Exam	HALYARD health Alpharetta Georgia	Nitrile	0.07	0.09	ASTM D6978	No	580%	35MPa
Aurelia Robust Plus	Aurelia Aurora Illinois	Nitrile	0.10	0.13	ASTM D6978	No	500%	14MPa
Cranberry Evolve	Cranberry Int. Selangor Malaysia	Nitrile	0.05	0.05	ASTM D6978	No	540-580%	21-25 MPa
COATS	Hartalega Kuala Lumpur Malaysia	Nitrile	0.07	0.09	ASTM D6978	No	500%	18MPa
Biogel	Mölnlycke HC Norcross Georgia	Polyisopren	0.10	-	ASTM D6978	No	650%	>17MPa
StarMed Plus	Sempermed Clearwater Florida	Nitrile	-	0.07	ASTM D6978	No	550%	19.7MPa

As far as we know, only two studies have compared the difference in gloves' ADs permeation according to whether they were in static or dynamic conditions. Colligan and Horstman *(1990)* tested the permeation rate of 4 ADs (CP, DXR, MTX, 5-FU), revealing that CP had a double rate tested with the dynamic approach, while the other drugs did not show this trend. Furthermore, Nalin et al. *(2020)* revealed a permeation rate in dynamic mode for busulfan higher than the US norm than in static one.

Generally, the permeation rate (P) of the AD was determined by measuring its concentration in the acceptor medium as:

$$P=\frac{(C\times V)}{(t\times S)} \quad [1]$$

where, C is ADs concentration in the acceptor medium, V is volume of acceptor medium, t is duration of exposure, S is surface area of the glove exposed to the ADs *(Wallemacq et al., 2006)*. One of the first studies using the permeation test cell was carried out by Colligan and Horstman *(1990)*; they tested surgical latex, exam latex, and polyvinyl chloride gloves with CP, DXR, MTX, and 5-FU in static and dynamic condition. The latter was conducted thanks to special upper chamber tops fitted with a tube connected to a manifold to pump air on the surface of the gloves and stress it. In 1992, Dinter-Heidorn and Carstens *(1992)* tested in static mode latex and vinyl gloves without a permeation cell: they divided the middle finger of the gloves, filled with 3.3 mg/mL solution of CAR, in stirred distilled water at room temperature and they analysed this receiving solution at 5, 10, 15, 20, 30, 45, 60, 120, 180, 240, 300, 380 minutes. More recently, a static permeation study of Mitomycin through modern gloves materials was conducted in two devices, the permeation cell and a glass chamber *(Korinth et al., 2007)*. To better simulate a realistic condition, the test in the glass chamber was carried out with a receiving solution heated to 40 °C, to recreate the situation in which surgeons touch the patient's viscera treated with ADs solution at 40-41 °C. A new static approach for routine permeation analysis of ADs was adopted by Oriyama et al. *(2017)* and, more recently, by Krzeminska et al. *(2018)*: medical gloves were placed in a modified permeation cell (Figure 2) *(Krzemińska et al., 2018)*, in which the receptor solution was pumped continuously through the receptor chamber at a flow rate ranging from 0,01 mL/min to 175 mL/min. The tests carried out by Oriyama et al. *(2017)* in this device with five drugs (ETP, CP, DXR, paclitaxel, and 5-FU) at the highest concentrations employed in general clinical practice showed that for non-chlorinated gloves, the permeation of CP and 5-FU increased in a time-dependent manner, while the chlorinated one were less permeable to CP and 5FU. In contrast, for ETP, DXR, and paclitaxel no permeation was observed through both latex gloves within 240 minutes. For nitrile gloves, was not detected any permeation for any of the five ADs tested at any test-time point.

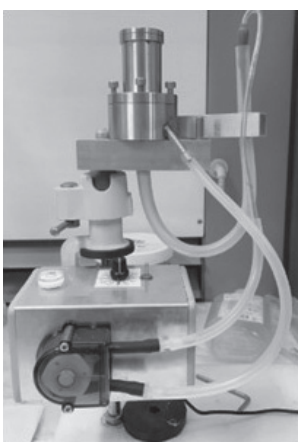

Figure 2. Modified permeation cell
Slika 2. Modificirana permeacijska stanica

Concerning the ADs permeation through protective gloves in dynamic conditions (stretching, tension and rubbing), Wallemacq et al. *(2006)* proposed a device equipped with a motor-driven plate with 20 drilled holes containing polyethylene tube, coated by the middle finger of a glove, with a cytotoxic solution in it. This tube coated with the gloves was pushed by brass shaft in a second larger tube containing a receptor solution; thus, the glove permeability could be tested under a tension of 350 g (Figure 3) *(Wallemacq et al., 2006)*.

The permeability of 13 gloves (made of neoprene, NRL, nitrile, and vinyl) to 13 ADs was tested with this apparatus, showing that all materials presented permeability for at least one AD after one hour of contact. They observed a trend toward greater permeation over time, increasing by a mean of 5-fold factor between 15 and 60 minutes, with the more relevant increase after the first 15 minutes.

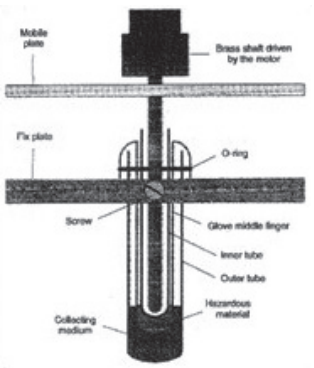

Figure 3. Wallemacq dynamic permeation test system
Slika 3. Wallemacq sustav za ispitivanje dinamičke propusnosti

In 2020, Nalin et al. *(2020)*, using a permeation system like Wallemacq, tested 27 ADs (including Busulfan) - prepared at the highest concentrations usually encountered by hospital personnel – on 15 gloves. They found that 35 of 495 tests did not meet the requirements of the ASTM D6978-05: the permeation of CAR, thiotepa, and busulfan exceed the 10 ng/(min cm^2) for several kinds of gloves (especially nitrile ones) but, in some cases, also docetaxel and ETP were revealed in the receiving medium. In addition to the previous dynamic studies, these experiments were carried out at 37 °C and 45 °C to mimic body temperature and peritoneal dialysis solution, respectively. However, despite the efforts of the scientific community to simulate a realistic situation, several parameters that may influence the permeation process in a non-assessable manner, such as higher skin temperatures and the lipophilic character of the skin surface, were difficult to replicate and, subsequently, to estimate their effect *(Nalin et al., 2020)*.

Other tested factors for permeation through gloves, apart from material, time of exposure, temperature, and drugs physical-chemical properties, are thickness and stress (stretching and rubbing) condition of the material and the possible interaction with solvents, as alcohols or acids. In fact, interactions between solvents and gloves could cause the degradation of their materials *(Landeck et al., 2015)*. Polar materials (polyvinyl alcohol, nitrile) may be degraded by polar chemicals, while non-polar substances degrade non-polar ones (NLR, neoprene). Considering the chemicals' pH, Boccellino et al. *(2010)* showed that DXR could penetrate nitrile gloves treated with an acid solution, while neither NLR nor nitrile are permeable to neutral ones. In 2007, Mäkelä et al. *(2007)* indicated that 5-minutes alcohol wash did not significantly increase the permeation of CP or CAR through vinyl, nitrile, NLR, and chloroprene gloves, respect to their breakthrough times. Differently, Capron et al. *(2012)* reported increased permeation of 17 ADs through 6 kinds of gloves (neoprene, NRL, nitrile, and polyisoprene), previously treated with an alcohol solution for 15 minutes, tested in dynamic condition. About the thickness of the material, already in the first half of the 1980s, several authors have suggested that thinner gloves were characterized by a higher compound permeation *(Slevin et al., 1984)*. Moreover, stress the glove material by stretching or rubbing can change the materials' properties, causing thinning and defection *(Klein et al., 2003)*. In early 2000, Wallemacq et al. *(2006)* observed the highest resistance to permeation in gloves with a thickness of 0.24 mm for NRL and 0.16 for nitrile, while the neoprene one offered the higher level of protection to permeation. However, as indicated above, the permeation does not solely depend on material thickness: indeed, recently, Capron et al. *(2012)* reported different permeation rates for NRL gloves of similar thickness (0.22 mm).

The permeation of ADs can be limited using double gloves. Of great interest is the experiment of Oriyama et al. *(2017)*: even though the total thickness was equal in both conditions, the use of double glove (0.1 mm × 2) blocked the permeation of CP more effectively compared to a single glove 0.2 mm thick. Moreover, double gloves are recommended as safer practice in handling hazardous drugs *(American Society of Health System Pharmacists, 2014, United States Pharmacopeia, 2019)*: wearing two pairs of gloves allows the removal of the outer one maintaining covered the skin of the hand and wrist. Hence, the change of the outer glove and the retaining of the inner glove during any AD handling is a work practice that consent to obtain an added protection against skin contacts with ADs. The work phases for which NIOSH recommends double gloves are: spill control, cleaning, and disposal of AD waste and patient waste. It also allows single gloves use to receive, unpack, and place ADs in storage; however, any package that does not appear intact should be handled with 2 pairs of chemotherapy gloves *(Power, Coyne, 2018)*.

To detect smaller quantities of ADs in the acceptor medium, the analytical part arouses no less interest in the scientific community. The analytical techniques to reveal the ADs in the receiving solution are various, with different sensitivity and selectivity: mutation tests (bacterial mutation assay), conductivity, radioactivity, Liquid Chromatography (LC), and fluorescence *(Nalin et al., 2020)*. Because most ADs are mutagenic *(Sasaki et al., 2008)*, their presence in receptor solution had been detected observing their activities on strains of *Salmonella typhimurium*. The mutagenicity assays spot test *(Connor et al., 1984, Connor, 1999, Singleton, Connor, 1999)* employed from up to 1999, is the one introduced by Maron and Ames *(Maron, Ames, 1983, Levin et al., 1985)* with slight modifications: a paper disc wetted in receiving solution of permeation test is placed into a plate with Vogel-Bonner minimal medium, then 2.5 mL of soft agar at 47 °C, containing 0.1 mL of a 16-hour culture of *Salmonella typhimurium*, is poured over the surface of the plate; after the solidification, the plates were inverted and incubated (in the dark at 37 °C for 48 hours), then the colonies on each plate are manually counted. A dose-response curve for AD was generated similarly for each assay, by adding an appropriate dilution of the drug directly to the paper. The amount of AD on each exposed paper disc was calculated from the number of colonies per plate by applying linear regression analysis to the dose-response curve. This spot test allows detecting ADs in the order of micrograms *(Matney et al., 1985)*.

Nowadays, LC represents an essential analytical technique to investigate traces of ADs contamination of work environments *(Dugheri et al., 2018)*. Moreover, the development of new analytical columns based on different types of particles, sizes, and stationary phase chemistry has played a key role in expanding the LC use, especially coupled with mass spectrometry (MS), in discerning and quantify ADs in concentrations equal to ng/mL *(Colombo et al., 2017, Dugheri et al., 2018, Mucci et al., 2020, Dugheri et al., 2021)*. Thanks to this technology, the quantification of ADs to calculate the permeation rate reach limits of detection extremely low, allowing the measurement of permeation rates 90 to 10,000 times lower than the threshold set by the US standard ASTM D-6978-05. Thus, LC-MS could represent an optimal technique to conduct permeation study, in line with the future tighter regulation about PPE safety *(Nalin et al., 2020, Oriyama et al., 2020)*.

CONCLUSIONS

In the 21st century, the healthcare sector has been one of the most significant areas to develop the theme of chemicals permeation through PPE, particularly ADs through protective gloves. Among the various PPEs, the medical gloves are the ones that come across the highest risk of exposure to ADs during the handling process. Therefore, the choice of appropriate gloves is of outstanding importance: medical gloves characterized by low permeability to chemicals are recommended to prevent healthcare professionals from unintended exposure. Considering the results of permeation studies, nitrile and chloroprene rubber are protective materials more effective than vinyl and NLR. Moreover, noticeable is that the breakthrough times of each material are affected by possible abrasion and flexing, time of contact, and temperature, resulting in an increase of permeation. In the European Union, the permeation test is not required for gloves used in ADs handling, which constitutes a severe deficiency, while in the US, medical gloves must fulfill the ASTM standard D 6978-05. Thus, to facilitate safer chemicals handling and avoid potential hazards and late sequelae, general guidelines to evaluate appropriate materials and define quality standards for PPE must be introduced and standardized, continuously updating them with the newest chemicals and PPE materials.

LITERATURE

Allied Market Research - Global Chemotherapy Market: Global Forecast till 2024, May 2019, accessible at: https://www.marketresearchfuture.com/reports/chemotherapy-market-5791, accessed: 16.December.2020.

American Society of Health System Pharmacists: ASHP guidelines on compounding sterile preparations, *Am J Health Syst Pharm*, 71, 2014, 2, 145-66.

American Society of Health-System Pharmacists: ASHP guidelines on handling hazardous drugs, *Am J Health-Syst Pharm*, 63, 2006, 1172-93.

American Society of Hospital Pharmacists: ASHP technical assistance bulletin on handling cytotoxic drugs in hospitals, *Am J Hosp Pharm*, 42, 1985, 131-7.

Anderson, R. W., Puckett, W. H. Jr., Dana, W. J., Nguyen, T. V., Theiss, J. C., Matney, T. S.: Risk of handling injectable antineoplastic agents, *Am J Hosp Pharm*, 39, 1982, 1881-7.

ASTM International|Editor:3: Standard practice for assessment of resistance of medical gloves to permeation by chemotherapy drugs. D6978-05, ASTM International, West Conshohocken, 2005.

Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege (BGW) - Monitoring-Effekt-Studie für Wischproben in Apotheken, 2008, accessible at: http://www.pharma-monitor.de/download_mewip/MEWIP-Abschlussbericht_Sept_2008.pdf, accessed: 18.12.2020.

Boccellino, M., Pedata, P., Castiglia, L., La Porta, R., Pieri, M., Quagliuolo, L. et al.: Doxorubicin can penetrate nitrile gloves and induces apoptosis in keratinocytes cell line, *Toxicol Lett*, 197, 2010, 2, 61-68.

Boer, M., Duchnik, E., Maleszka, R., Marchlewicz, M.: Structural and biophysical characteristics of human skin in maintaining proper epidermal barrier function, *Postepy Dermatol Alergol*, 33, 2016, 1, 1-5.

Böhlandt, A., Schierl, R.: Benefits of Wipe Sampling: Evaluation of Long-Term 5-Fluorouracil and Platinum Monitoring Data, *Pharml Tech Hosp Pharm*, 1, 2016, 3, 139-150.

Böhlandt, A., Sverdel, Y., Schierl, R.: Antineoplastic drug residues inside homes of chemotherapy patients, *Int J Hyg Environ Health*, 220, 2017, 4, 757-65.

Bos, J. D., Meinardi, M. M.: The 500 Dalton rule for the skin penetration of chemical compounds and drugs, *Exp Dermatol*, 9, 2000, 3, 165-9.

Capron, A., Destree, J., Jacobs, P., Wallemacq, P.: Permeability of gloves to selected chemotherapeutic agents after treatment with alcohol or isopropyl alcohol, *Am J Health-System Pharm*, 69, 2012, 19, 1665-70.

Cleanroom Technology - PPE focus: Hand protection for working with chemotherapy drugs, 25 Febbraury 2020, accessible at: https://cleanroomtechnology.com/news/article_page/PPE_focus_Hand_protection_for_working_with_chemotherapy_drugs/162719, accessed: 23.1.2021.

Colligan, S. A., Horstman, S. W.: Permeation of Cancer Chemotherapeutic Drugs Through Glove Materials under Static and Flexed Conditions, *Appl Occup Environ Hyg*, 5, 1990, 12, 848-52.

Colombo, M., Jeronimo, M., Astrakianakis, G., Apte, C., Hon, C. Y.: Wipe sampling method and evaluation of environmental variables for assessing surface contamination of 10 antineoplastic drugs by liquid chromatography/tandem mass spectrometry, *Ann Work Expos Heal*, 61, 2017, 8, 1003-14.

Connor, T. H.: Permeability of nitrile rubber, latex, polyurethane, and neoprene gloves to 18 antineoplastic drugs, *Am J Health-Syst Pharm*, 56, 1999, 23, 2450-2453.

Connor, T. H.: Hazardous anticancer drugs in health care: environmental exposure assessment, *Ann N Y Acad Sci*, 1076, 2006, 615-623.

Connor, T. H., Laidlaw, J. L.,Theiss, J. C., Anderson, R. W., Matney, T. S.: Permeability of latex and polyvinyl chloride gloves to carmustine, *Am J Hosp Pharm*, 41, 1984, 4, 676-9.

Connor, T. H., MacKenzie, B. A., DeBord, D. G., Trout, D. B., O'Callaghan, J. P.: *NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings*, 2016, accessible at: https://www.cdc.gov/niosh/docs/2016-161/pdfs/2016-161.pdf, accessed: 15.1.2021.

Crepy, M. N., Boman, A., Zimmermann, F.: *Protective Gloves*, Springers Eds., London, 2020.

Crickman, R., Finnell, D.: Systematic review of control measures to reduce hazardous drug exposure for healthcare workers, *J Nurs Care Qual*, 31, 2016, 2, 183-90.

Delporte, J. P., Chenoix, P., Hubert, P. H.: Chemical contamination of the primary packaging of 5-Fluorouracil RTU solutions commercially available on the Belgian market, *Eur Hospital Pharm*, 5, 1999, 119-21.

Dinter-Heidorn, H., Carstens, G.: Comparitive study on protective gloves for handling cytotoxic medicines: a model study with carmustine, *Pharm Weekbl Sci*, 14, 1992, 4, 180-84.

Dugheri, S., Bonari, A., Pompilio, I., Boccalon, P., Mucci, N., Arcangeli, G.: A new approach to assessing occupational exposure to antineoplastic drugs in hospital environments, *Arh Hig Rada Toksikol*, 69, 2018, 3, 226-37.

Dugheri, S., Bonari, A., Pompilio, I., Boccalon, P., Tognoni, D., Cecchi, M. et al.: Analytical strategies for assessing occupational exposure to antineoplastic drugs in healthcare workplaces, *Med Pr*, 69, 2018, 6, 589-604.

Dugheri, S., Bonari, A., Pompilio, I., Gentili, M., Montalti, M., Mucci, M. et al.: A new automated gas chromatography/solid phase microextraction procedure for determining α-fluoro-β-alanine in urine, *Malaysian J Anal Sci*, 5, 2017, 1091-1100.

Dugheri, S., Mucci, N., Mini, E., Squillaci, D., Marrubini, G., Bartolucci, G. et al.: Characterization and separation of platinum-based antineoplastic drugs by zwitterionic hydrophilic interaction liquid chromatography (HILIC)- tandem mass spectrometry, and its application in surface wipe sampling, *Separation, 2021: In press*.

Dugheri, S., Palli, L., Bossi, C., Bonari, A., Mucci, N., Santianni, D. et al.: Development of an automated LC-MS/MS method for the determination of eight pharmaceutical compounds in wastewater, *Fresenius J Anal Chem*, 27, 2018, 9, 6394-6402.

European BioSafety Network - Preventing occupational exposure to cytotoxic and other hazardous drugs European Policy Recommendations, 2016, accessible at: https://www.europeanbiosafetynetwork.eu/wp-content/uploads/2016/05/Exposure-to-Cytotoxic-Drugs_Recommendation_DINA4_10-03-16.pdf, accessed: 13.12.2020.

European BioSafety Network - Amendments to the Carcinogens and Mutagens Directive (CMD), 2019, accessible at: https://www.europeanbiosafetynetwork.eu/wp-content/uploads/2019/03/Amendments-to-CMD3-and-implications.pdf, accessed: 30.11.2020.

European committee for standardization, CEN|Editor: 3: *European standard EN 455 I-III Medical gloves for single use*, European committee for standardization, Brussel, 2002.

European Parliament and of the council - *Directive 2004/37/ec of the European Parliament and of the council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work*, April 2019 accessible at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:229:0023:0034:EN:PDF, accessed: 3.12.2020.

Falck, K., Grohn, P., Sorsa, M., Vainio, H., Heinonen, E., Holsti, R. L.: Mutagenicity in urine of nurses handling cytostatic drugs, *Lancet*, 1, 1979, 1250-1.

Fransman, W., Roeleveld, N., Peelen, S., de Kort, W., Kromhout, H., Heederik, D.: Nurses With Dermal Exposure to Antineoplastic Drugs, *Epidemiol*, 18, 2007, 1, 112-9.

Franz, T. J.: The finite dose technique as a valid in vitro model for study of percoutaneous absorption in man, *Curr Probl dermatolo*, 7, 1978, 58.

Guichard, N., Guillarme, D., Bonnabry, P., Fleury-Souverain, S.: Antineoplastic drugs and their analysis: a state of the art review, *Analyst*, 142, 2017, 13, 2273-2321.

Hamscher, G., Mohring, S. A., Knobloch, A., Eberle, N., Nau, H., Nolte, I. et al.: Determination of drug residues in urine of dogs receiving anti-cancer chemotherapy by liquid chromatography-electrospray ionization- tandem mass spectrometry: is there an environmental or occupational risk?, *J Anal Toxicol*, 34, 2010, 3, 142-8.

Harris, C. C.: The carcinogenicity of anticancer drugs: a hazard in man, *Cancer*, 37, 1976, 1014-23.

Harrison, B. R.: Developing guidelines for working with antineoplastic drugs, *Am J Hosp Pharm*, 38, 1981, 1686-933.

Hedmer, M., Georgiadi, A., Bremberg, E. R., Jönsson, B. A., Eksborg, S.: Surface contamination of cyclophosphamide packaging and surface contamination with antineoplastic drugs in a hospital pharmacy in Sweden, *Ann Occup Hyg*, 49, 2005, 7, 629-37.

Hedmer, M.,Wohlfart, G.: Hygienic guidance values for wipe sampling of antineoplastic drugs in Swedish hospitals, *J Environ Monit*, 14, 2012, 7, 1968-75.

Hilliquin, D., Bussières, J. F.: External contamination of antineoplastic drug containers from a Canadian wholesaler, *J Oncol Pharm Pract*, 26, 2020, 2, 423-27.

Huff, C.: Hazardous Drug Residues in the Home Setting: Worker Safety Concerns, *J Infus Nurs*, 43, 2020, 1, 15-18.

Il Sole 24 ORE - Sanità 24-Superfarmaci, quali rischi per gli operatori che li "maneggiano"? Arriva la consensus Sifo-Aiiao, Giugno 2017, accessible at: https://www.sanita24.ilsole24ore.com/art/lavoro-eprofessione/2017-06-07/superfarmaci-quali-rischi-gli-operatori-che-li-maneggiano-arriva-consensus-sifo-aiiao-172822.php?uuid=AEunFPaB&refresh_ce=1, accessed: 20.12.2020.

Kiffmeyer, T. K., Tuerk, J., Hahn, M., Stuetzer, H., Hadtstein, C., Heinemann, A. et al.: Application and assessment of a regular environmental monitoring of the antineoplastic drug contamination level in pharmacies - the MEWIP project, *Ann Occup Hyg*, 57, 2013, 4, 444-55.

Klein, M., Lambov, N., Samev, N., Carstens, G.: Permeation of cytotoxic formulations through swatches from selected medical gloves, *Am J Health Syst Pharm*, 60, 2003, 10, 1006-11.

Korinth, G., Schmid, K., Midasch, O., Boettcher, M. I., Anger, J., Drexler, H.: Investingation on permeation of mytomycin C through double layers of natural rubber gloves, *Ann Occup Hyg*, 51, 2007, 7, 593-600.

Kromhout, H., Hoek, F.,Uitterhoeve, R., Huijbers, R., Overmars, R. F., Anzion, R. et al.: Postulating a dermal pathway for exposure to anti-neoplastic drugs among hospital workers. Applying a conceptual model to the results of three workplace surveys, *Ann Occup Hyg*, 44, 2000, 7, 551-60.

Krzemińska, S., Pośniak, M., Szewczyńska, M.: Resistance of gloves and protective clothing materials to permeation of cytostatic solutions, *Int J Occup Med Environ Health*, 31, 2018, 3, 341-50.

Kümmerer, K., Haiß, A., Schuster, A., Hein, A., Ebert, I.: Antineoplastic compounds in the environment—substances of special concern, *Environ Sci Pollut Res*, 23, 2016, 14791-804.

Landeck, L., Gonzalez, E., Koch, O. M.: Handling chemotherapy drugs - Do medical gloves really protect?, *Int J Canc*, 137, 2015, 8, 1800-5.

Levin, D. E., Hollstein, M., Christman, M. F., Schwiers, E. A., Ames, B. N.: A new Salmonella tester strain (TA102) with A X T base pairs at the site of mutation detects oxidative mutagens, *Proc Natl Acad Sci USA*, 79, 1985, 23, 7445-9.

Mäkelä, E., Tornaeus, J., Nieminen, K., Ilmarinen, R., Hesso, A., Rosenberg, C. et al.: Permeation of five antineoplastic drugs through four glove materials, *Third International Conference on Occupational and Environmental Exposure of Skin to Chemicals*, 2007.

Maron, D. M., Ames, B. N.: Revised method for the Salmonella mutagenicity test, *Mutat Res*, 113, 1983, 173-215.

Mason, H. J., Morton, J., Garfitt, S. J., Iqbal, S., Jones, K.: Cytotoxic drug contamination on the outside of vials delivered to a hospital pharmacy, *Ann Occup Hyg*, 47, 2003, 8, 681-5.

Massoomi, F., Neff, B., Pick, A., Danekas, P.: Implementation of a safety program for handling hazardous drugs in a community hospital, *Am J Health-Syst Pharm*, 65, 2008, 9, 861–865.

Matney, T. S., Nguyen, T. V., Connor, T. H., Theiss, J. C., Dana, W. J.: Genotoxic classification of anticancer drugs, *Teratog Carcinog Mutagen*, 5, 1985, 5, 319-28.

Mucci, N., Dugheri, S., Farioli, A., Garzaro, G., Rapisarda, V., Campagna, M. et al.: Occupational exposure to antineoplastic drugs in hospital environments: potential risk associated with contact with cyclophosphamide- and ifosfamide-contaminated surfaces, *Med Lav*, 71, 2020, 5, 519-529.

Mukherjee, S., Mehta, D., Dhangar, K., Kumar, M.: Environmental fate, distribution and state-of-the-art removal of antineoplastic drugs: a comprehensive insight, *Chem Eng J*, 2020, 127184.

Nalin, M., Hug, G., Boeckmans, E., Machon, C., Favier, B., Guitton, J.: Permeation measurement of 27 chemotherapy drugs after simulated dynamic testing on 15 surgical and examination gloves: A knowledge update, *J Oncol Pharm Pract*, 2020, 1-4.

National Cancer Institute at the National Institutes of Health - A to Z List of Cancer Drugs, 2021 accessible at: http://www.cancer.gov/cancertopics/druginfo/alphalist, accessed: 12.1.2021.

Oriyama, T., Yamamoto, T., Nara, K., Kawano, Y., Nakajima, K., Suzuki, H. et al.: Prediction of the permeability of antineoplastic agents through nitrile medical gloves by zone classification based on their physicochemical properties, *J Pharm Health Care Sci*, 6, 2020, 1, 23.

Oriyama, T., Yamamoto, T., Yanagihara, Y., Nara, K., Abe, T., Nakajima, K. et al.: Evaluation of the permeation of antineoplastic agents through medical gloves of varying materials and thicknesses and with varying surface treatments, *J Pharm Health Care Sci*, 3, 2017, 1, 13.

Pethran, A., Schierl, R., Hauff, K., Grimm, C. H., Boos, K. S., Nowak, D.: Uptake of antineoplastic agents in pharmacy and hospital personnel. Part I: monitoring of urinary concentrations, *Int Arch Occup Environ Health*, 76, 2003, 1, 5-10.

Pieri, M., Quagliuolo, L., La Porta, R., Silvestre, A., Miraglia, N., Pedata, P. et al.: Epirubicin permeation of personal protective equipment can induce apoptosis in keratinocytes, *J Expo Sci Environ Epidemiol*, 2013.

Power, L. A., Coyne, C. P.: ASHP Guidelines on Handling Hazardous Drugs, *Am J Health-Syst Pharm*, 75, 2018, 1996-2031.

Sasaki, M., Dakeishi, M., Hoshi, S., Ishii, N., Murata, K.: Assessment of DNA damage in Japanese nurses handling antineoplastic drugs by the comet assay, *J Occup Heal*, 50, 2008, 1, 7-12.

Scaringi, S., Liscia, G., Tognoni, D., Dugheri, S.: Risk of exposure to mitomycin C during hyperthermic intraperitoneal chemotherapy (HIPEC) with an open abdomen technique. Guidelines for safety in the operating room, *Eur J Surg Oncol*, 36, 2010, 10, 1028-9.

Schierl, R., Böhlandt, A., Nowak, D.: Guidance values for surface monitoring of antineoplastic drugs in German pharmacies, *Ann Occup Hyg*, 53, 2009, 7, 703-11.

Sessink, P. J., Timmersmans, J. L., Anzion, R. B., Bos, R. P.: Assessment of occupational exposure of pharmaceutical plant workers to 5-Fluorouracil, *J Occup Med*, 36, 1994, 79-83.

Sessink, P. J., Wittenhorst, B. C., Anzion, R. B., Bos, R. P.: Exposure of pharmacy technicians to antineoplastic agents: reevaluation after additional protective measures, *Arch Environ Health*, 52, 1997, 240-4.

Singleton, L. C., Connor, T. H.: An evaluation of the permeability of chemotherapy gloves to three cancer chemotherapy drugs, *Oncol Nurs Forum*, 26, 1999, 9, 1491-6.

Slevin, M. L., Ang, L. M., Johnston, A.,Turner, P.: The efficiency of protective gloves used in the handling of cytotoxic drugs, *Cancer Chemother Pharmacol*, 12, 1984, 3, 151-3.

Sottani, C., Grignani, E., Oddone, E., Dezza, B., Negri, S.,Villani, S. et al.: Monitoring Surface Contamination by Antineoplastic Drugs in Italian Hospitals: Performance-Based Hygienic Guidance Values (HGVs) Project, *Ann Work Expo Health*, 61, 2017, 8, 994-1.

Stuart, O. A., Stephens, A. D., Welch, L., Sugarbaker, P. H.: Safety monitoring of the coliseum technique for heated intraoperative intraperitoneal chemotherapy with mitomycin, *C. Ann Surg Oncol*, 9, 2002, 2, 186-91.

Thomsen, K., Mikklesen, H. I.: Protective capacity of gloves usedfor handling nitrogen mustard, *Contact Dermatitis*, 1, 1975, 268-269.

Thornton, S. L., Liu, J., Soleymani, K., Romasco, R. L., Farid, H., Clark, R. F. et al.: Review of Experience of a Statewide Poison Control Center With Pediatric Exposures to Oral Antineoplastic Drugs in the Nonmedical Setting, *Am J Ther*, 23, 2016, 2, 377-81.

UNI EN|Editor:3: *UNI EN 16523-1:2019*. Determination of material resistance to permeation by chemicals - Part 1: Permeation by potentially hazardous liquid chemicals under conditions of continuous contact, UNI EN, 2019.

UNI EN|Editor:3: *UNI EN ISO 374-1:2018*. Protective gloves against dangerous chemicals and micro-organisms - Part 1: Terminology and performance requirements for chemical risks, UNI EN, 2019.

United States Pharmacopeia - USP General Chapter Hazardous Drugs—Handling in Healthcare Settings, 2019 accessible at: https://www.usp.org/compounding/general-chapter-hazardous-drugs-handling-healthcare, accessed: 16.1.2021.

Wallemacq, P. E., Capron, A.,Vanbinst, R., Boeckmans, R. J. G., Favier, B.: Permeability of 13 different gloves to 13 cytotoxic agents under controlled dynamic conditions, *Am J Health Syst Pharm*, 63, 2006, 6, 547-56.

Yuki, M., Ishida, T., Sekine, S.: Secondary Exposure of Family Members to Cyclophosphamide After Chemotherapy of Outpatients With Cancer: A Pilot Study, *Oncol Nurs Forum*, 42, 2015, 6, 665-71.

Yuki, M., Sekine, S., Takase, K., Ishida, T., Sessink, P. J.: Exposure of family members to antineoplastic drugs via excreta of treated cancer patientsm, *J Oncol Pharm Pract*, 19, 2013, 3, 208-17.

AŽURIRANJE PODATAKA O PROŽIMANJU ZAŠTITNIH MEDICINSKIH RUKAVICA ANTINEOPLASTIČNIM LIJEKOVIMA

SAŽETAK: Radna izloženost rukovanju i primjeni antineoplastičnih lijekova (AD) jedan je od glavnih rizika u zdravstvenom sektoru. Kožna apsorpcija predstavlja primarni put izlaganju AD-ima. Osobna preventivna oprema, posebno medicinske rukavice, presudna je za zaštitu zdravlja radnika u radu s AD-ima; prema tome, kemikalije koje prodiru kroz zaštitne materijale bitan su aspekt za procjenu i razmatranje. Nekoliko studija o prožimanju kroz medicinske rukavice izvijestilo je da su vrijeme proboja i brzina prodiranja vrijednosti koje se moraju proučavati, primjećujući da su fizičko-kemijska svojstva lijekova, OZO materijali i debljina i temperatura ključne značajke za njihovu procjenu. U Europskoj uniji, standardizirano ispitivanje prožimanja nije obvezno za rukavice koje se koriste u manipulaciji ADs, za razliku od Sjedinjenih Država koje su predložile stroge zahtjeve u međunarodnom standardu D6978-05 Američkog društva za ispitivanje i materijale. Ovaj pregled pomogao bi identificirati glavne karakteristike najbolje zaštitne rukavice koju koriste zaposlenici često izloženi AD-ima: glavni aspekti uključeni u prožimanje, priopćeni u literaturi, navedeni su i raspravljeni.

Ključne riječi: *antineoplastični lijekovi, medicinske rukavice, nadzor rada, ispitivanje prožimanja, površinska kontaminacija, zdravlje na radu*

Pregledni rad
Primljeno: 24.5.2021.
Prihvaćeno: 23.8.2022.