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RESISTANCE OF GLOVES AND PROTECTIVE CLOTHING MATERIALS TO PERMEATION OF CYTOSTATIC SOLUTIONS

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Abstract

Objectives: The objective of the work was to determine the resistance of selected protective clothing and glove materials to permeation of cytostatics such as docetaxel, fluorouracil, and doxorubicin. **Material and Methods:** The following glove materials were used: natural rubber latex (code A), acrylonitrile-butadiene rubber (code B) and chloroprene rubber (code C). In addition, we tested a layered material composed of a non-woven polyester (PES), a polypropylene (PP) film, and a non-woven PP used for protective coats (code D). The cytostatics were analyzed by liquid chromatography with diode array detection. The tested samples were placed in a purpose-built permeation cell modified to be different from that specified in the standard EN 6529:2001. **Results:** The tested materials were characterized by good resistance to solutions containing 2 out of the 3 selected cytostatics: doxorubicin and 5-fluorouracil, as indicated by a breakthrough time of over 480 min. Equally high resistance to permeation of the third cytostatic (docetaxel) was exhibited by natural rubber latex, acrylonitrile-butadiene rubber, and chloroprene rubber. However, docetaxel permeated much more readily through the clothing layered material, compromising its barrier properties. **Conclusions:** It was found that the presence of additional components in cytostatic preparations accelerated permeation through material samples, thus deteriorating their barrier properties. Int J Occup Med Environ Health 2018;31(3)

Key words:
Permeation, Cytostatic, Protective materials, Docetaxel, Fluorouracil, Doxorubicin

INTRODUCTION

The growing incidence of cancers leads to an increased use of cytostatics, thus raising the numbers of health care workers exposed to them during the performance of their duties. The professionals at greatest risk of exposure to cytostatics are nurses, physicians, and pharmacists working at oncological hospital wards and at pharmacies compounding such medications [1–5]. It is estimated that the worldwide population of health care and pharmaceutical workers exposed to cytostatics amounts to 5.5 million [6].

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Under typical workplace conditions, cytostatics are mostly absorbed through the skin and mucosae. The manipulation of medications, the opening of ampoules, the preparation of injection solutions, and the removal or air from the syringe may cause some of the medicine to be released into the air and absorbed through the respiratory system, while accidental contamination of the skin may lead to transdermal absorption. Furthermore, cytostatics may also enter the body through the skin in the process of cleaning objects and surfaces contaminated with urine or vomit by patients undergoing chemotherapy, as well as during direct contact with the patients.

Previous research has demonstrated the presence of airborne cytostatics in a number of hospital areas. These substances have also been found in the urine of nurses and pharmacists [4]. The presence of cytostatics has been detected in compounding rooms, examination rooms, nurses' lounges, and doctors' lounges. An airborne cytostatic (cyclophosphamide) has been found in laundries cleaning the clothes, towels, and bedding of patients treated with these medications [6]. A study conducted in Swedish oncological hospitals [7] reported a cytostatic (cisplatin) in the blood of nurses. In turn, an investigation of Canadian hospital pharmacies [8] showed that more than 60% of the tested surfaces were contaminated with a cytostatic (methotrexate – MTX). Methotrexate has also been found on the surface of tools [9] and on protective gloves used in oncological wards in British hospitals [10].

Research has shown that individuals who professionally deal with cytostatics are also exposed to their harmful activity. Therefore, medical personnel should wear appropriate protection devices preventing the absorption of those substances [11–13]. Thus, it is necessary to study the protective properties of materials used in the production of personal protective equipment (PPE) with a particular focus on protective gloves and clothing to ascertain that they meet the requirements. Personal protective equipment should be used whenever workers may be exposed to hazardous substances, also with a view upon preventing congenital defects in the case of children [14,15].

The objective of the work was to determine the resistance of selected glove and clothing materials to permeation of solutions of the tested cytostatics (docetaxel, fluorouracil, and doxorubicin).

MATERIAL AND METHODS

Materials

The study involved the determination of barrier properties of selected clothing and glove materials used for chemical protection: natural rubber latex, acrylonitrile-butadiene rubber and chloroprene rubber for gloves as well as a layered material composed of a non-woven polyester (PES), a polypropylene (PP) film, and a non-woven PP for protective coats. The glove materials were coded A, B, and C, respectively, and the clothing material was coded D.

The tested materials were subjected to the following preliminary tests to determine their characteristics:

- thickness according to the standard EN ISO 5084: 1996 [16],
- surface density according to the standard PN-EN 12127: 1997 [17],
- puncture resistance according to the standard EN 863 1995 [18],
- abrasion resistance according to the standard EN 388: 2003 [19].

The Table 1 shows the properties of the studied materials.

Chemicals

Taking into consideration the diverse types of cytostatics used in the treatment of cancers in Poland and the results of a questionnaire survey concerning health care units compounding chemotherapy medications for oncological wards [15], the following cytostatics were selected:

Table 1. Physical properties of the studied materials

Parameter	Material			
	A	B	C	D
Thickness [mm] (M±SD)	0.21±0.01	0.10±0.00	0.17±0.01	0.32±0.02
Surface density [g/m^2] (M±SD)	191.80±9.10	100.80±2.20	214.90±4.00	83.80±0.90
Puncture resistance [n] (M±SD)	6.95±0.37	11.30±1.20	14.07±2.09	6.62±0.90
Abrasion resistance [cycles] (M±SD)	48.00±3.00	20.00±0.00	8 000.00±0.00	1 250.00±290.00

M – mean; SD – standard deviation.
A – natural rubber latex; B – acrylonitrile-butadiene rubber; C – chloroprene rubber; D – layered clothing material composed of a non-woven polyester (PES), a polypropylene (PP) film, and a non-woven PP.

– 5-fluorouracil – a topoisomerase inhibitor,
– docetaxel – an inhibitor of the mitotic spindle,
– doxorubicin – an antimetabolite and a natural antibiotic.

The cytostatics were tested in the form of solutions. Commercially available cytostatic preparations were prepared by dilution in saline using the maximum cytostatic concentration that can be administered to the patient.

The test substances used in the permeation study were prepared using the following reagents:

– docetaxel: 10 mg×ml^{-1} in saline solution with the addition of ethanol, 10 ml vial (Ebewe Pharma),
– doxorubicin: 1 mg×ml^{-1} in saline solution, 25 ml (Ebewe Pharma),
– 5-fluorouracil: 50 mg×ml^{-1} in saline solution, 20 ml vial (Ebewe Pharma).
– 0.9% sodium chloride (NaCl) solution, 500 ml (saline solution) (Kaliclear).

The respective phases used in high-performance liquid chromatography (HPLC) were prepared with the following reagents:

– ammonium acetate (CH_3COONH_4) (Merck),
– disodium phosphate (Na_2HPO_4) (POCH S.A.),
– orthophosphoric acid (H_3PO_4) (POCH S.A.),
– triethylamine (TEA) (Sigma-Aldrich),
– acetonitrile (ACN) (Merck),
– methanol (CH_3OH) (Merck).

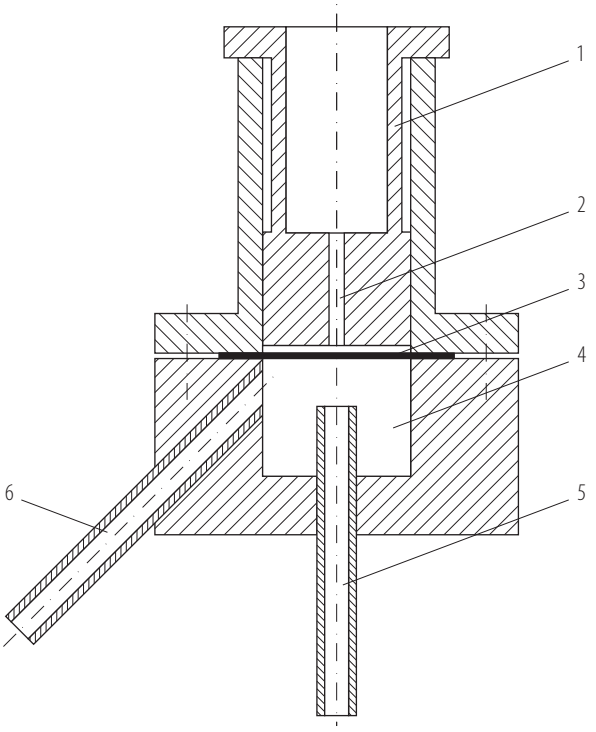
Experimental stand

The experimental stand consisted of:

– a Merck–Hitachi Elite LaChrom liquid chromatograph with an L2200 autosampler and a DAD L-2450 diode array detector,
– a C18 analytical column (RP-18 endcapped Purospher Star) with dimensions of 250×4.6 mm and a particle size of 5 μm with a guard column,
– a permeation cell in which the samples were placed (Figure 1),
– a peristaltic pump with a flow rate of 0–2100 ml×min^{-1},
– an analytical scale with an accuracy of 0.1 g,
– a disc micrometer with a disc diameter of 10 mm and a pressure of 4.9 Pa.

Test method

The tested sample constituted a barrier between the upper and lower chambers of the permeation cell (Figure 1). A cytostatic solution was placed in the upper chamber, while a collection medium was circulated through the bottom chamber, sweeping the underside of the tested sample and collecting permeated cytostatic particles for chromatographic analysis. The presented method was developed based on the guidelines specified in the standard EN ISO 6529:2001 [20]. The tests were conducted pursuant to the Method A concerning liquid chemical substances in continuous contact.



1 – piston; 2 – chamber containing the chemical substance; 3 – tested material sample; 4 – chamber with collection medium; 5 – outlet of collection medium; 6 – inlet of collection medium.

Fig. 1. Permeation cell for testing the resistance of materials to permeation of cytostatic solutions

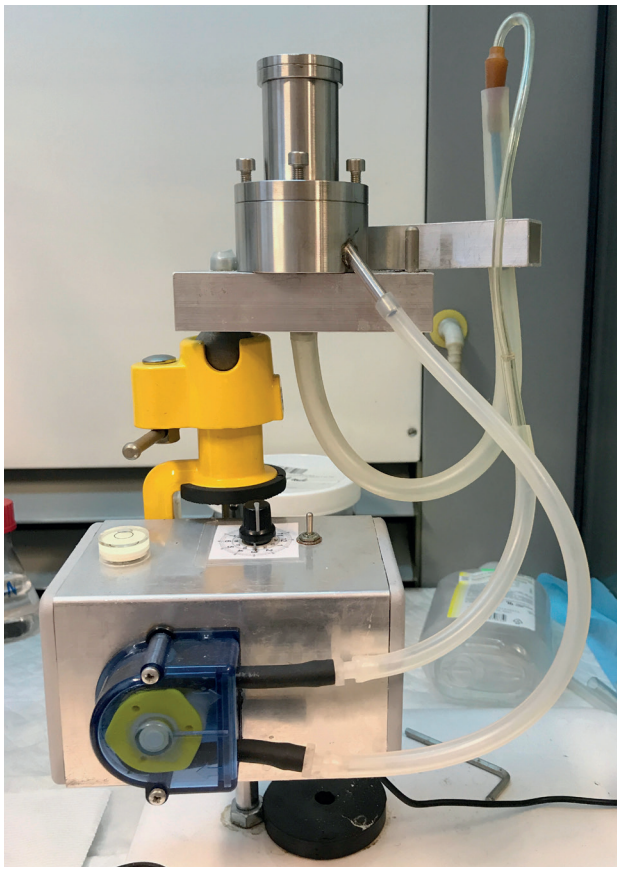


Photo 1. Permeation cell with a peristaltic pump used in testing material resistance to cytostatic permeation

Taking into consideration the toxicity of cytostatics, it was very important to minimize the amounts of those compounds used during the tests and left over after their completion. Consequently, the permeation cell presented in the standard EN ISO 6529:2001 [20] was modified to reduce the volume of cytostatic solutions used in the test (from 10 ml to 1.5 ml) and to decrease the flow of the collection medium (from 600 ml×min^{-1} to 175 ml×min^{-1}).

In the first step, the tested sample was placed between the upper and lower chambers of the permeation cell. Then, 1.5 ml of docetaxel solution at a concentration of 10 mg×ml^{-1} was placed in the upper chamber, which marked the beginning of the test. A liquid collection medium was circulated through the bottom chamber at a flow rate of 175 ml×min^{-1}. The bottom chamber with the inlet and outlet of the collection medium formed a closed circuit. The flow of the medium was forced by a peristaltic pump. The Photo 1 presents the permeation cell with a peristaltic pump as used in testing material resistance to cytostatic permeation [21].

At predetermined time intervals, 200 µl of the collection medium was taken for chromatographic analysis. Those intervals ranged from 10 min to 480 min and coincided with the intervals defined in the standards EN 14605+A1:2009 [22] and EN 374-1:2003 [23] (10 min, 30 min, 60 min, 120 min, 240 min, 480 min), defining performance levels for gloves and clothes protecting against chemical substances. The test continued for 8 h.

The test results were expressed as the time to cytostatic breakthrough calculated as an arithmetic mean for 3 samples of a given type of material. Pursuant to

the standard EN 6529:2001 [20], breakthrough time was defined as the moment when the amount of the chemical substance penetrating though the sample reached 2.5 μg×cm^{-2}.

Analytical determination of cytostatics

The cytostatics were determined in 200 μl of collection medium by means of high performance liquid chromatography (HPLC) using a Merck–Hitachi Elite LaChrom liquid chromatograph with a L2200 autosampler, a DAD L-2450 diode array detector, and a C18 analytical column (RP-18 endcapped Purospher Star) with dimensions of 250×4.6 mm and a particle size of 5 μm with a guard column.

The Table 2 gives the parameters of the chromatographic analysis for the studied cytostatics. The basic validation parameters are given in the Table 3.

Statistics

The barrier properties of the materials were analyzed based on the breakthrough times determined individually for each material–cytostatic solution system.

The statistical analysis shows highly significant differences between groups ($H = 28.93$, $df = 9$, $p = 0.0007$). However, only the results for the breakthrough of material D by docetaxel solution are significantly ($p = 0.0027$) lower than the other results, which did not differ from one another ($p = 1.0000$).

Table 2. Parameters of chromatographic analysis of the studied cytostatics

Parameter	Cytostatic		
	fluorouracil	doxorubicin	docetaxel
Mobile phase	0.05 M disodium phosphate (Na_2HPO_4) : acetonitrile (ACN) (v/v 65:35) with the addition of 0.5 ml × l^{-1} triethylamine (TEA) pH = 3.7 (orthophosphoric acid)	0.05 M disodium phosphate (NA_2HPO_4) : acetonitrile (ACN) (v/v 65:35) with the addition of 0.5 ml × l^{-1} triethylamine (TEA) pH = 3.7 (orthophosphoric acid)	acetonitrile (ACN) : 0.01 M ammonium acetate (CH_3COONH_4) (v/v 45:55) pH = 4.5 (orthophosphoric acid)
Phase flow [ml×min^{-1}]	0.65	0.65	1.50
Injection volume [μl]	20.00	20.00	20.00
Detector wavelength [nm]	266.00	266.00	230.00

v/v – volume/volume.

Table 3. Validation parameters for chromatographic analysis of the studied cytostatics

Parameter	Fluorouracil	Doxorubicin	Docetaxel
Concentration [μg×ml^{-1}] (range)	0.03–16.00	0.09–50.00	0.20–200.00
Limit of detection [μg×ml^{-1}]	0.0007	0.0005	0.0065
Limit of quantification [μg×ml^{-1}]	0.0021	0.0015	0.0195
Correlation coefficient	0.9998	0.9976	0.9993
Overall measurement precision	1.1900	1.8900	1.8700
Total uncertainty of the method [%]	3.3800	4.7810	4.7600
Expanded uncertainty [%]	6.7700	9.5620	9.5200

The analysis of results was conducted using the package PQStat v. 1.6.

Distributions of results were evaluated using the Kruskal-Wallis test and the *post hoc* Dunn test. Test probability of $p < 0.05$ was considered significant, and $p < 0.01$ was deemed highly significant.

RESULTS

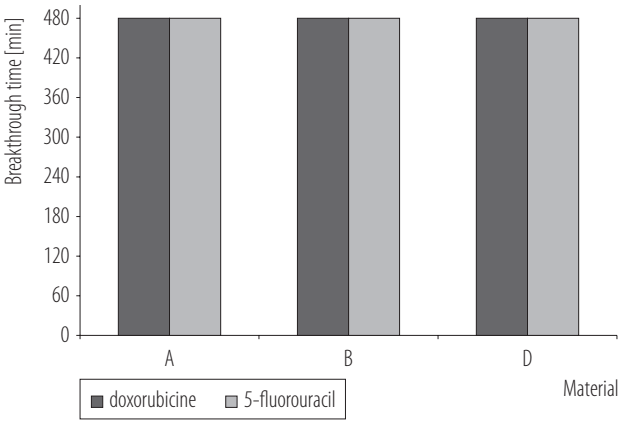
The barrier properties of materials were analyzed based on the breakthrough times determined individually for each material–cytostatic solution system. The results concerning the resistance of glove and protective clothing materials to permeation of cytostatic solutions are given in the Figures 2–4. In the case of the layered material in the D–docetaxel solution system, in which cytostatic permeation was detected, the cumulative quantity of the permeated cytostatic was measured (Figure 4).

DISCUSSION

The tested materials made of natural rubber latex (code A), acrylonitrile-butadiene rubber (code B) chloroprene rubber (code C) as well as the layered clothing material composed of a non-woven PES, a PP film, and a non-woven PP (code D) were found to exhibit very good resistance to solutions containing 2 of the 3 selected cytostatics: doxorubicin and 5-fluorouracil (Figure 2). The applied concentrations of the studied cytostatics were equivalent to their maximum concentrations in preparations administered to patients. Throughout the time of the experiment, neither doxorubicin nor 5-fluorouracil penetrated the glove or clothing material samples (Figure 2), which implies a breakthrough time of more than 480 min. Pursuant to the relevant standards, EN 14605+A1:2009 [22] and EN 374-1:2003 [23], these results indicate the highest (sixth) performance level of PPE protecting against chemical substances.

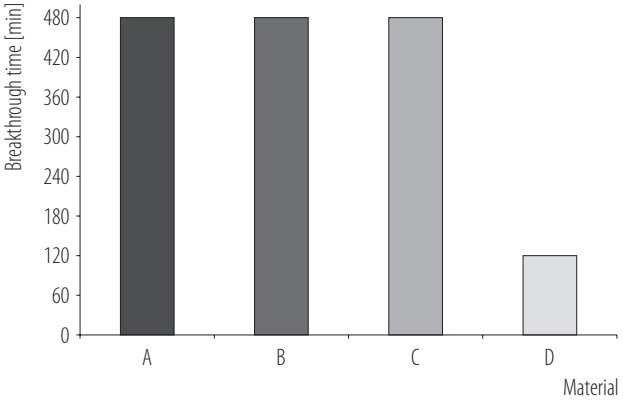
Equally high resistance to permeation of docetaxel solution was found for materials A, B, and C, with a breakthrough time longer than 480 min. This means that in respect of docetaxel these materials also met the requirements of the highest performance level (Figure 3).

However, it was found that docetaxel penetrated the layered clothing material (D) much more readily than the glove material samples as the breakthrough time for material D was only 120 min (Figure 3). It may be assumed that this result is attributable both to the properties of the material and those of the cytostatic solution. Material D is quite thick (0.32 mm) and contains 2 non-woven layers creating a complex structure that may facilitate the accumulation of cytostatics. While the other materials are



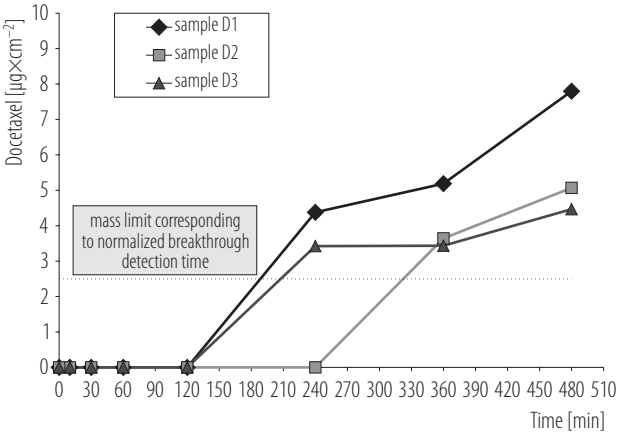
Abbreviations as in Table 1.

Fig. 2. Doxorubicin and 5-fluorouracil breakthrough time for the tested materials



Abbreviations as in Table 1.

Fig. 3. Docetaxel breakthrough time for the tested materials



D – layered clothing material composed of a non-woven polyester (PES), a polypropylene (PP) film, and a non-woven PP.

Fig. 4. Cumulative amount of cytostatic (docetaxel) permeated through the material D over time

smooth membranes, it should be noted that material D is composed of 3 layers, out of which only one constitutes a polymer barrier to permeation. The thickness of this membrane alone may in fact be smaller than the thickness of the other tested materials (0.10–0.21 mm).

Furthermore, of importance is the composition of the docetaxel preparation, which contains some ethyl alcohol (in contrast to the other 2 solutions). Due to this, we conducted an additional test investigating the resistance of material D to ethyl alcohol permeation and found that in this case the breakthrough time was only 65 min. Thus, it may be expected that the content of ethyl alcohol in the amount of 25.1% (weight to weight ratio – w/w) in the commercially available docetaxel preparation (and also in the tested solution) facilitated the diffusion of the cytostatic through the material structure.

Indeed, according to the dissolution-diffusion model of permeation of chemical substances through polymer barrier materials, the presence of more readily permeable components may boost the penetration of other components [24,25]. In this case, the permeation of both components (docetaxel and ethyl alcohol) may proceed at a much higher rate than for each component separately. Furthermore, this may be linked to the solubility of the chemical solution – tested material system, as the number of liquid substances that may permeate through the polymer is limited. Therefore, it has been observed that increased permeation of one component of a mixture may be accompanied by lower permeation of another component [26].

In addition, the cumulative quantity of the permeated cytostatic was determined for the docetaxel–material D system. The results show that docetaxel solution started to penetrate through 2 samples of the layered material (D1 and D2) after 120 min (Figure 4), while the third sample of this material (D3) was not penetrated until 240 min of exposure to the cytostatic). Due to the fact that the collection medium was analyzed at intervals, it was not possible to precisely determine normalized breakthrough time. The data shows that upon sampling at 240 min and 360 min the cumulative quantity of the permeated cytostatic was between 4.5–7.8 $\mu g \times cm^{-2}$, exceeding the breakthrough amount defined in the standard (2.5 $\mu g \times cm^{-2}$). Given the above, under conditions of exposure to docetaxel, the safe use time for material D should be that during which permeation was not detected for all 3 samples, which is 120 min.

The results of the conducted tests show a slow permeation rate of the selected cytostatics through the tested materials as, except for 1 case, the maximum permissible volume of permeate (2.5 $\mu g \times cm^{-2}$) was not reached throughout the long experimental time (8 h). Such a long test time reflected a rigorous scenario according to the questionnaire survey in which medical or pharmaceutical personnel was exposed to cytostatics for several hours at a time. The obtained results indicate very good barrier properties of the tested materials as the breakthrough times (> 480 min) correspond to high performance levels.

Similar results were reported by Klein et al. [27], who studied the permeation of cytostatics (bleomycin, dacarbazine, daunorubicin, etoposide, etoposide phosphate, ifosfamide, idarubicin, irinotecan, mitomycin, mitoxantrone, oxalipla-

tin, teniposide, topotecan, and vinorelbine) through natural rubber latex and chloroprene rubber using HPLC with a ultraviolet-visible (UV-VIS) detector. For most cytostatics, the mean permeation rate obtained by Klein et al. was lower than 0.2 $nmol \times min^{-1} \times cm^{-2}$ or permeation was not observed at all (at the adopted limit of detection (LOD) level and sensitivity of the apparatus). Permeation below the threshold value indicated that breakthrough time was longer than the duration of the experiment (3 h). A much higher permeation rate (10-fold increase) was only found for carmustine, which was attributed by Klein et al. to the fact that the chemical compound was characterized by small, partially lyophilic particles, as it was previously noted by other researchers [28,29].

Moreover, Klein et al. reported that permeation rate was determined by glove thickness [27], which was not corroborated by the presented study. While the thickness of polymer materials in the form of smooth membranes differed by approx. a factor of 2 (0.10–0.21 mm), that did not lead to differences in the detected amounts of permeated cytostatics.

CONCLUSIONS

Most of the materials tested in the presented study, and in particular those made of natural rubber latex (code A), acrylonitrile-butadiene rubber (code B), and chloroprene rubber (code C), provide good protection against permeation of solutions of all selected cytostatics (docetaxel, 5-fluorouracil, and doxorubicin). Indeed, no cytostatic breakthrough was observed throughout the experiment despite its long duration (480 min), which indicates very high barrier properties of the materials.

Lower barrier properties were exhibited by the layered clothing material composed of a non-woven PES, a PP membrane, and a non-woven PP (code D), in particular with respect to one cytostatic (docetaxel). The results showed that docetaxel solution permeated through the layered material at a faster rate than through the other materials, which were smooth membranes sampled from protective gloves. Breakthrough time for material D was established at 120 min. It was found that the content of ethyl alcohol in the commercially available docetaxel preparation (and in the test solution) facilitated cytostatic diffusion through the sample of the layered material, compromising its barrier properties.

The tests have demonstrated that cytostatics may faster permeate through clothing materials, which often combine non-wovens and polymer films, than through the smooth membranes of glove materials. This may be due to the structure of material B, which facilitates wetting and cytostatic penetration. Therefore, personnel exposed to cytostatics should pay greater attention to the possibility of accidental contamination with those substances because they may affect not only gloves, but also other PPE products, which are under lower scrutiny than gloves. Naturally, individuals working with cytostatics stress that it is their hands which are at greatest risk of contamination, but it must be kept in mind that those substances may also contaminate other parts of the body.

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