Cleanroom garments for chemical and biological risks (PPE)

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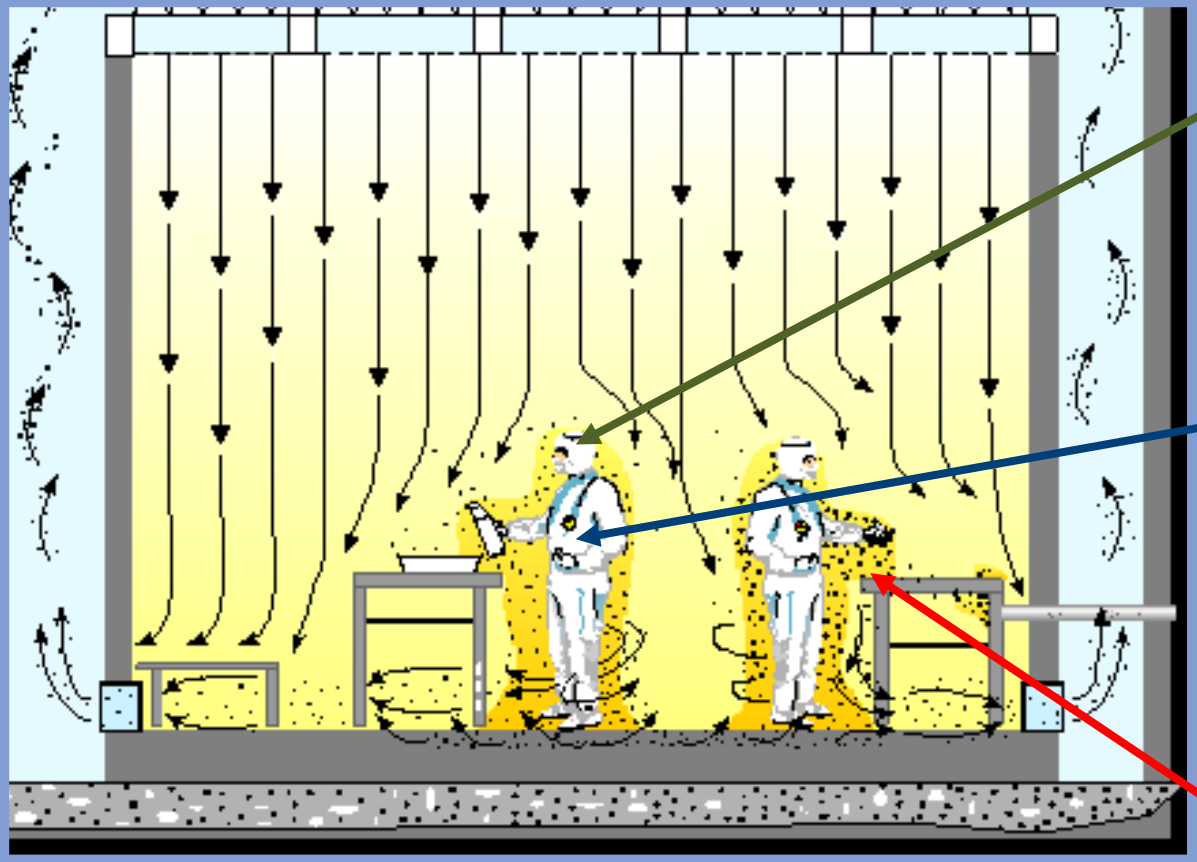
The draft revision of GMP Annex 1 from December 2017 has defined special requirements to minimize risks of microbiological, particulate and pyrogen contamination during the manufacturing of sterile products.

“Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM (Quality Risk Management) principles that provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality.”

For the future it will be essential to fully understand the risks to quality cleanroom garments can reduce or increase

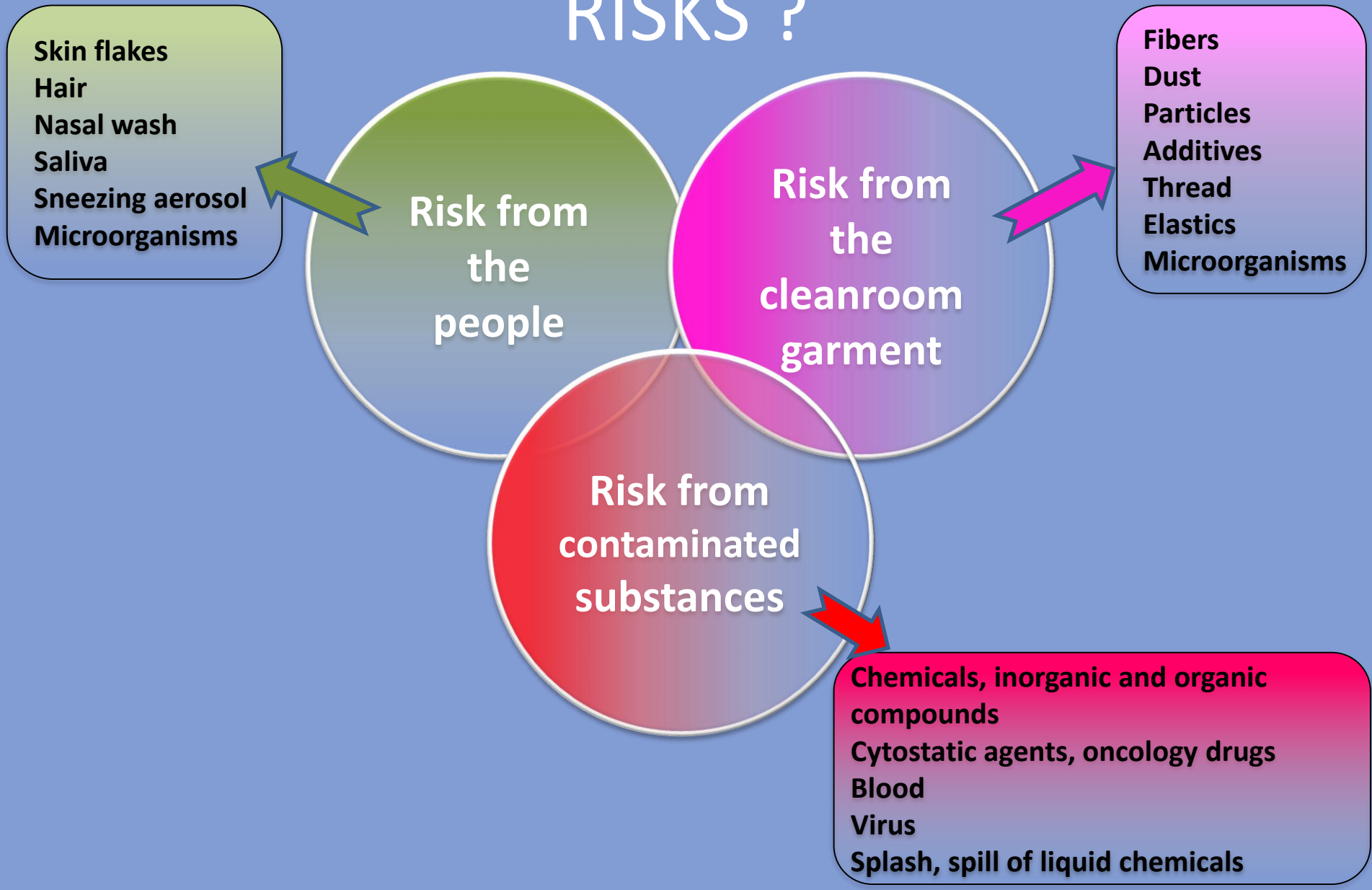
The contamination risks coming from operators wearing cleanroom garments can be divided into three categories



1. Risk from the people
2. Risk from the cleanroom garment
3. Risk from chemical and biological substances

HOW TO CONTROL CONTAMINATION

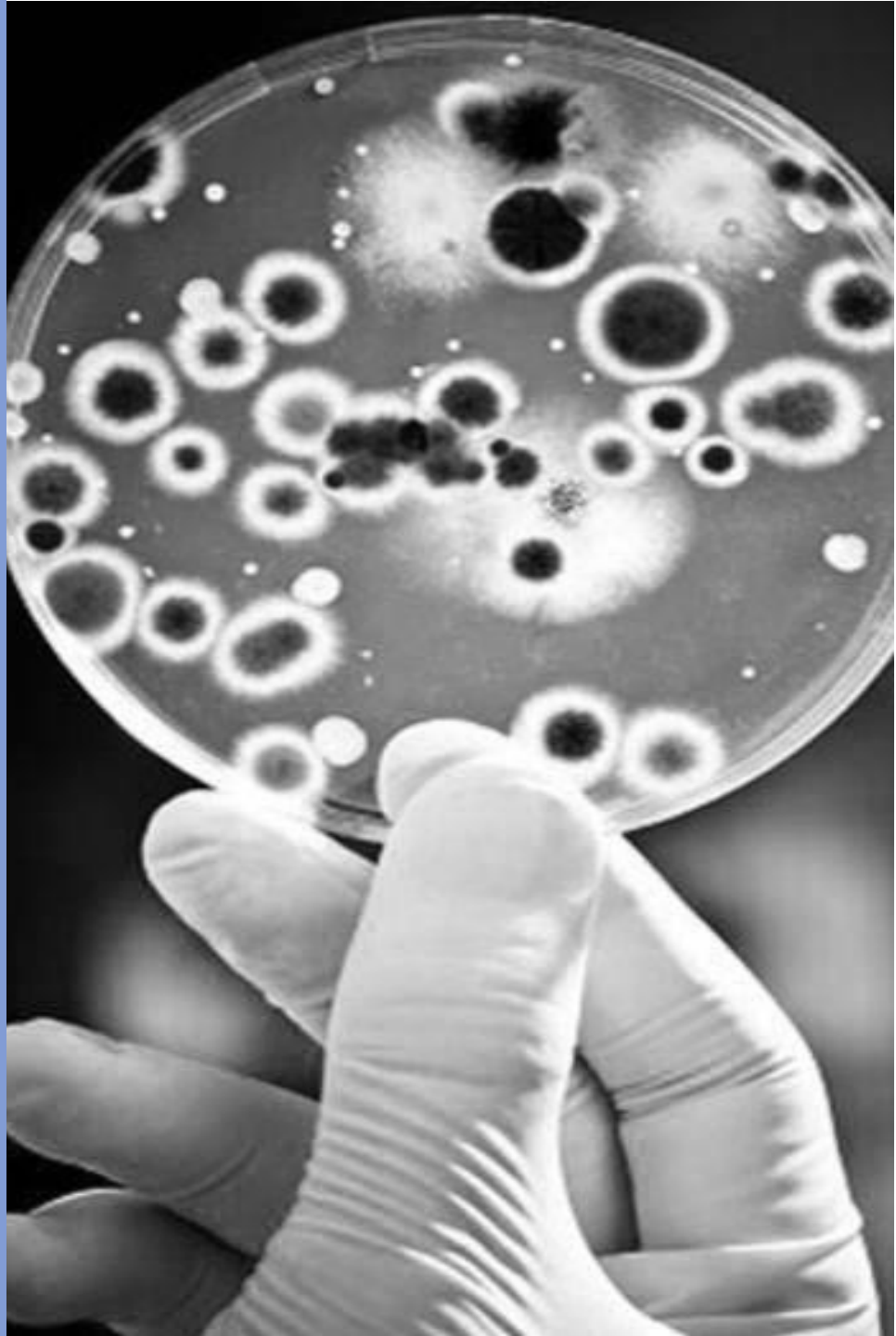
RISKS ?



Understanding the contamination risks

Human contamination

Risk from the people



PEOPLE REMAIN THE BIGGEST CONTAMINATION RISK IN A CLEANROOM ENVIRONMENT

CONTAMINATION SOURCES

People 75%

Ventilation 15%

Room Structure 5%

Equipment 5%

Source: http://www.climet.com/library/particle_sources.htm

HOW TO CONTROL CONTAMINATION RISK BY PEOPLE?

ORGANISATIONAL MEASUREMENTS

- Selection of personnel
- Education and training of personnel
- Safety aspects in cleanrooms
- Personnel practice and hygiene
- The medical condition of the personnel
- Which members or staff should enter the cleanroom
- Decisions on maximum occupancy
- Entry as well as exit procedures
- The passage in and out of a cleanroom
- ….

+ CLEANROOM CLOTHING

PERFORMANCE

PROTECTING THE ENVIRONMENT FROM HUMAN CONTAMINATION

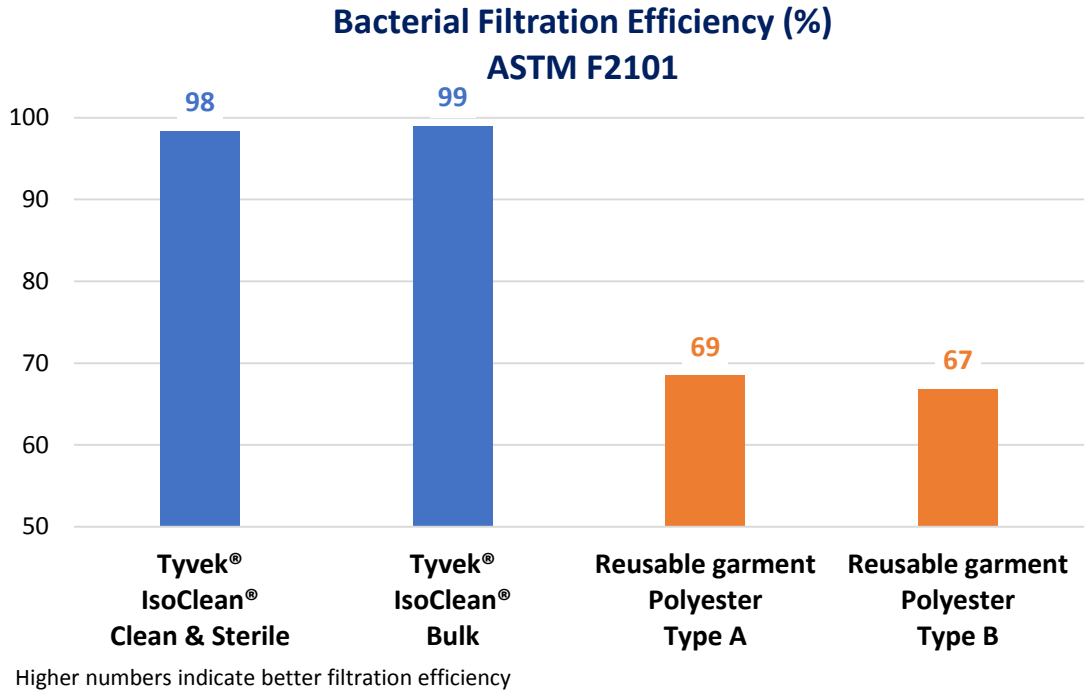
Garment fabric & garment design should act as a filter and keep the contamination inside the garment.

GARMENT FILTRATION EFFICIENCY

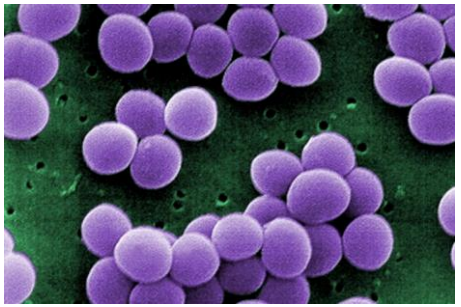
Filtration efficiency is depending on the following factors

- **Fabric: fibers, weaving pattern, pore size & finish**
- **Design: seams construction, closures, zipper**
- **Age: the number of times the garment has been washed, dried & sterilized**

RISK BY PEOPLE CONTAMINATION
BACTERIAL FILTRATION EFFICIENCY



Higher numbers indicate better filtration efficiency

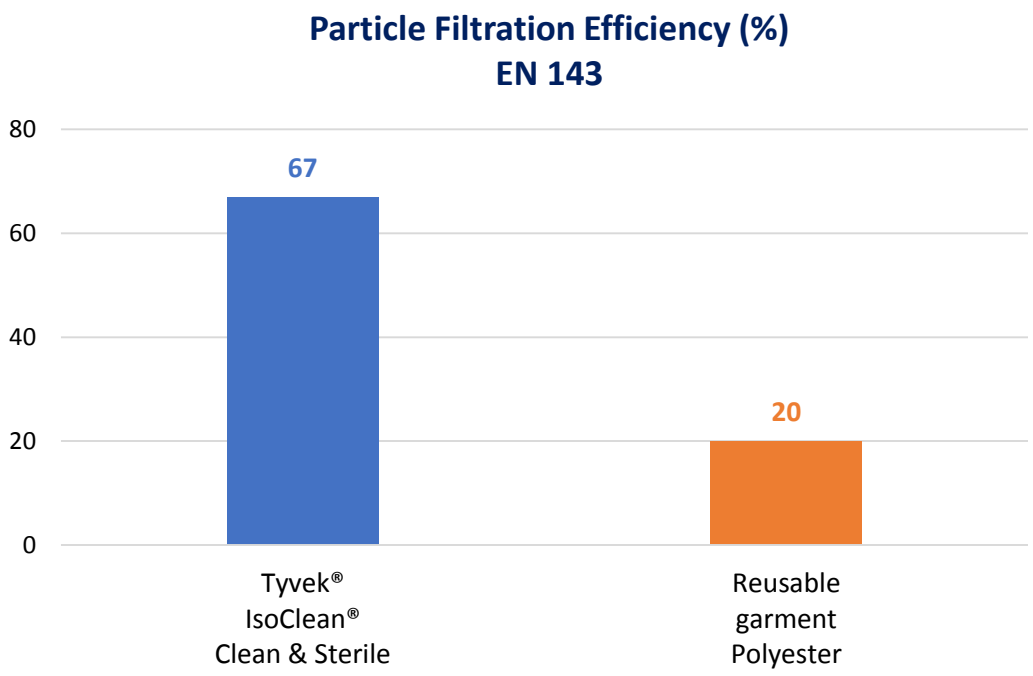


Bacterial Filtration Efficiency – ASTM F2101 measures the ability of the fabric to filter out bacteria (staphylococcus aureus) from a standard aerosol challenge. Particle size = 3.0 µm

The more operators move (e.g. during cleaning operations), the higher the risk of contamination with microorganisms, the better the bacterial filtration efficiency must be.

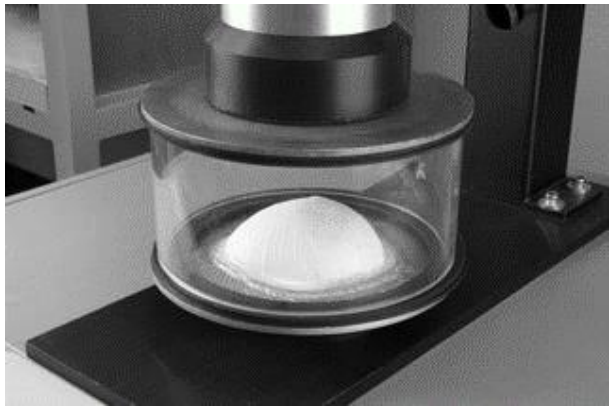
For single-use garments, the impact of gamma radiation on the polymer only occurs one time, so properties are consistent

RISK BY PEOPLE CONTAMINATION PARTICLE FILTRATION EFFICIENCY



Source: DuPont laboratory test

Higher numbers indicate better filtration efficiency



Picture source: Nelson Labs

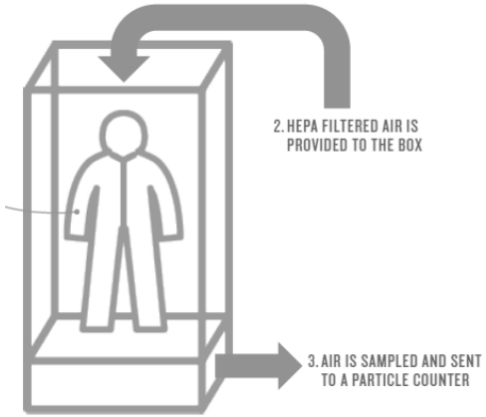
Particle Filtration Efficiency – evaluates the nonviable particle retention or filtration efficiency of filter media and other filtration devices at sub-micron levels.
Tester : TSI 8130
Particles : Sodium chloride (NaCl)
Flow rate : 2.3 l/min
Particle size = 0.3 µm

Higher percentages indicates higher particle barrier

RISK BY PEOPLE CONTAMINATION
BODY BOX TESTS

BODY BOX TESTS
IEST-RP-CC003.4

- simulates particle release under real wear conditions. A test person performs a series of defined movements in a cabin.
- Concentration of particles are counted by a particle counter



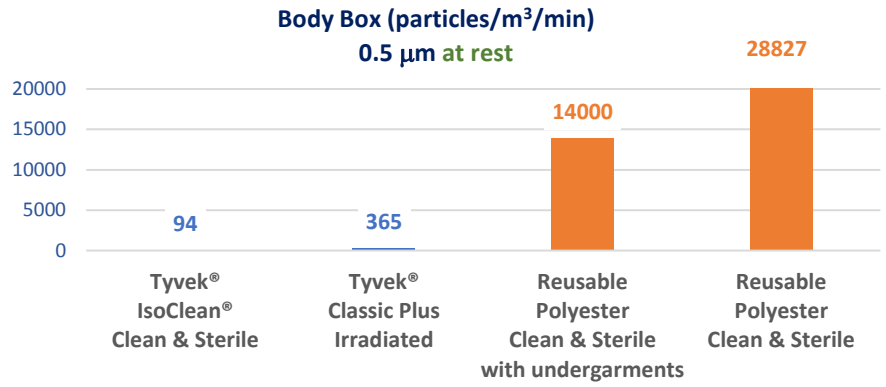
Limitation: due to the high variation in particle generation between individuals, one can only compare relative performance of garment systems **if the test person and the test parameters are identical**

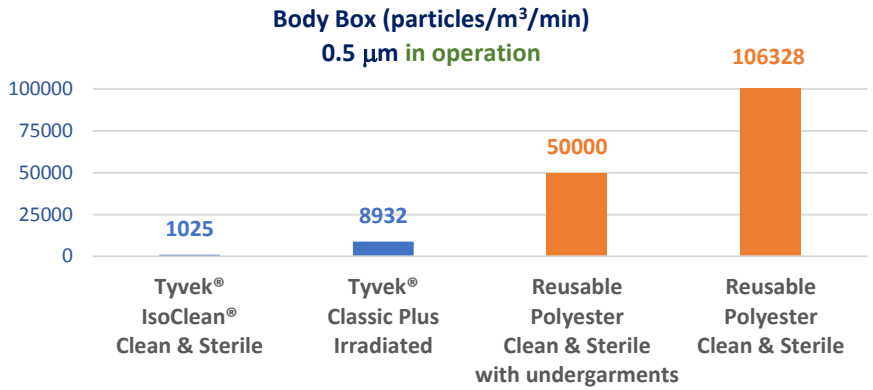
Picture source: C. Moschner, *Contamination Source "Human" or how efficient is Cleanroom Garment*

COMPARATIVE BODY BOX TESTS

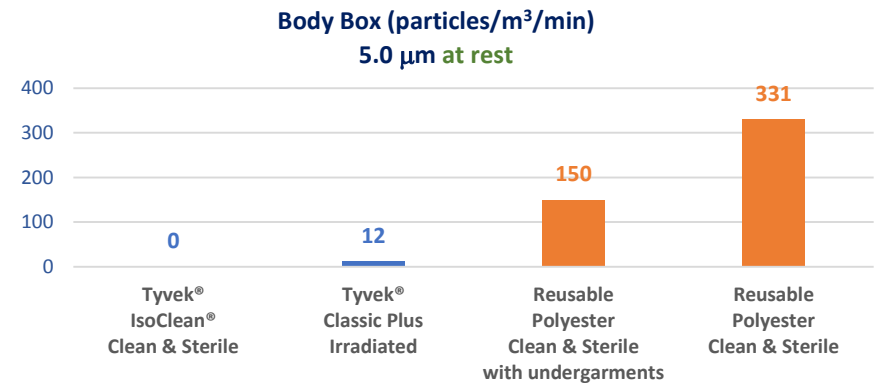
Differences in garment filtration efficiencies using different garment systems

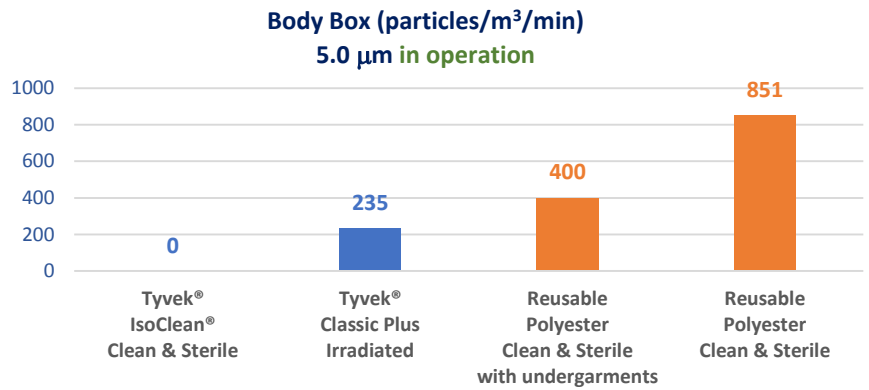
0.5 µm





5.0 µm





Sources: C. Moschner, *Contamination Source "Human" or how efficient is Cleanroom Garment*, 2017 & G. Maik, *Work With Cytotoxic Drugs In Pharmacies & Pharmaceutical Industry*, 2018

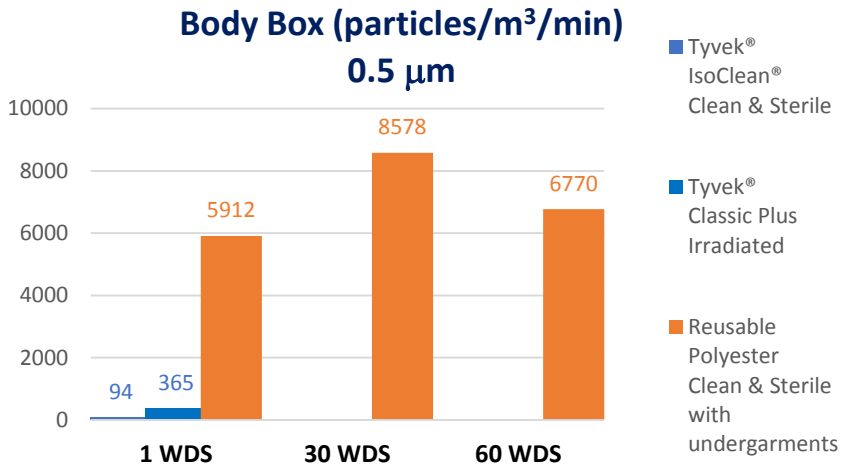
Clean & sterile single-use garments seem to offer the highest filtration efficiency

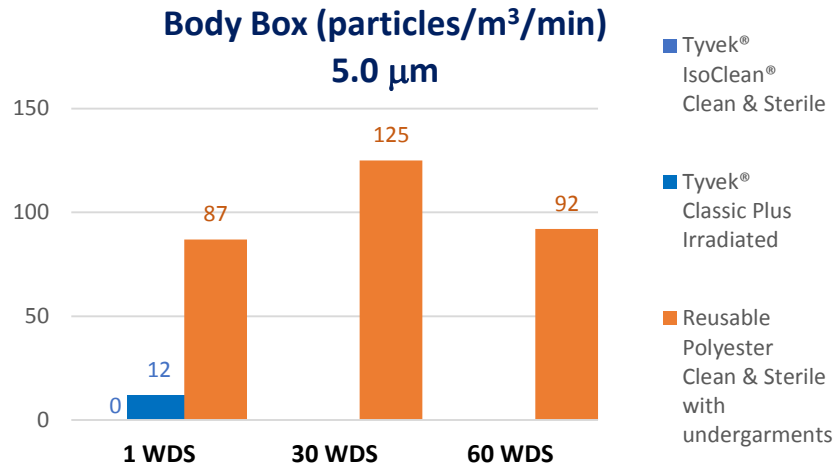
Irradiating industrial garments is not the best option

Cleanroom undergarments contribute significantly to the filtration efficiency of reusable cleanroom garments

COMPARATIVE BODY BOX TESTS

Effects of washing, drying & sterilizing on the garment filtration efficiencies using different garment systems



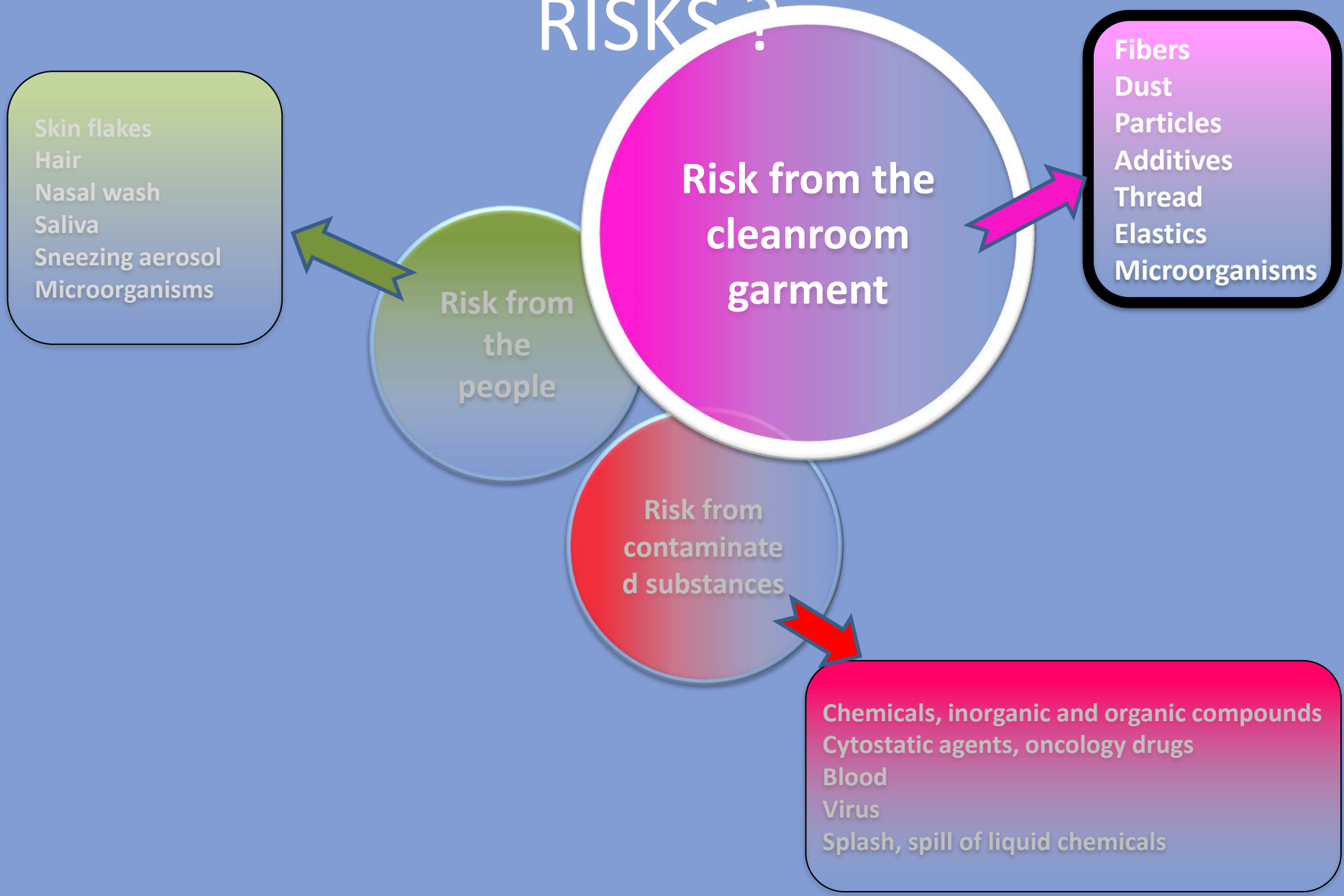


Sources: Romano F., Ljungqvist B., Reinmüller B., Gustén J. and Joppolo C.M., *Performance test of technical cleanroom clothing systems*, 2016 & G. Maik, *Work With Cytotoxic Drugs In Pharmacies & Pharmaceutical Industry*, 2018

For reusable garments undergarments the filtration efficiency fluctuates during their lifetime

Single use clean & sterile have a constant filtration efficiency and make the quality risk assessment easier

HOW TO CONTROL CONTAMINATION RISKS ?



Understanding the contamination risks

Garment contamination

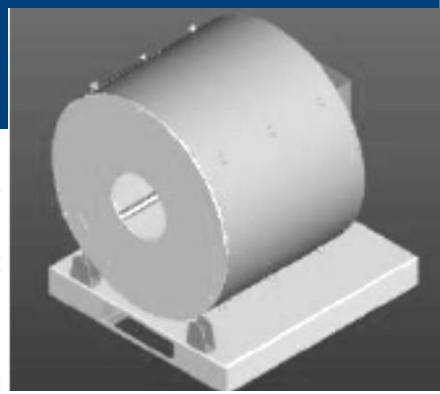
Risk from the cleanroom garment

GARMENTS AS A CONTAMINATION RISK

Particle shedding is depending on the following factors

- **Fabric: fibers, weaving pattern & finish**
- **Design: seams construction, closures, zipper**
- **Age: the number of times the garment has been washed, dried & sterilized**
- **Processing: supply chain, handling, washing, packaging & sterilization process**

RISK BY GARMENT CONTAMINATION PARTICLE RELEASE



HELMKE DRUM TESTS
IEST-RP-CC003.4

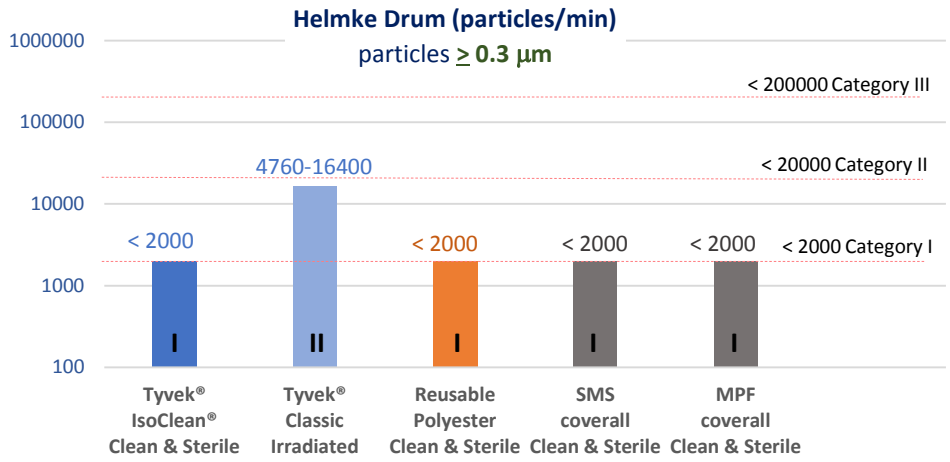
- A garment is tumbled in a rotating drum called Helmke Drum
- Concentration of particles are counted by a particle counter

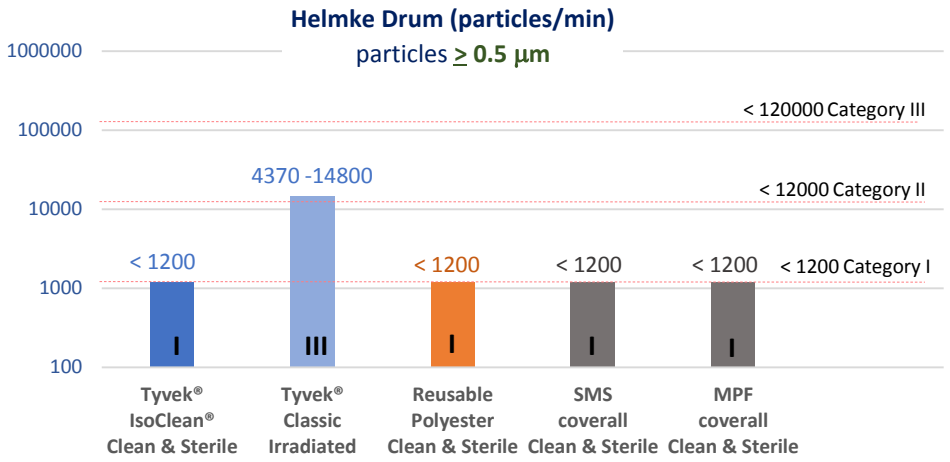
Category	Garment Type	Particle Emission Rate (particles/min)	
		0.3µm and larger	0.5 µm and larger
I	Coverall	< 2000	< 1200
II	Coverall	2000 - 20000	1200 - 12000
III	Coverall	20000 - 200000	12000 - 120000

Limitation: does not simulate real wear conditions, garments may not tumble properly due to stiffness, size or other factors.

RISK BY GARMENT CONTAMINATION
Helmke Drum test results

Results of different garments





Only clean processed & properly designed coveralls meet category I
Irradiated, non clean-processed industrial garments meet category II
Both reusable & single-use clean-processed garment meet category I

When selecting sterile garments think how they will perform

OVER THE ENTIRE LIFE CYCLE.

DETAILS OF DUPONT STUDY ON REUSABLE GARMENTS

Two types of polyester, woven garments typically worn in cleanrooms were purchased. They were laundered and exposed to gamma radiation at a target of 25 kGy – 40 kGy per cycle, through 30 cycles. Garments were designated as "A" and "B".

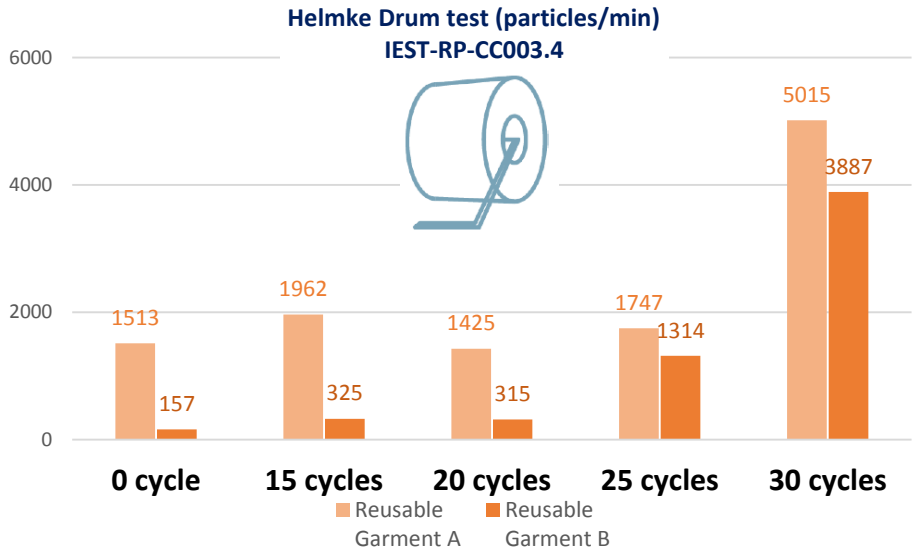
Garments were not subjected to wear, only to laundering and radiation exposure.

Garments were tested for physical properties in “as-received” condition or after one laundering and after set numbers of cycles.

Data shown as a function of “mid-received” radiation dose and number of cycles.

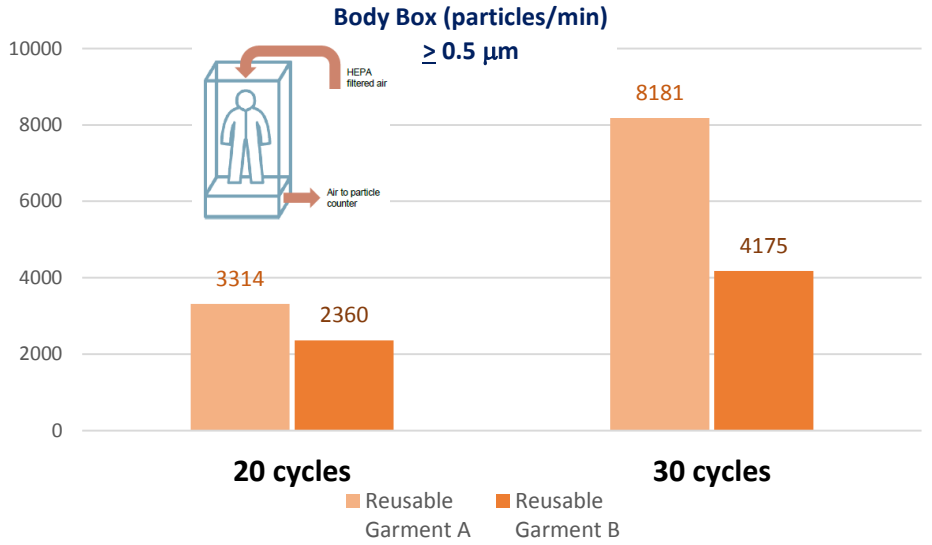
RISK BY GARMENT CONTAMINATION PARTICLE SHEDDING vs number of cycles

Helmke Drum Test – Particle Shedding (>0.5µm)



Helmke Drum particle shedding measured on 20 x 30 cm swatches, not full garments

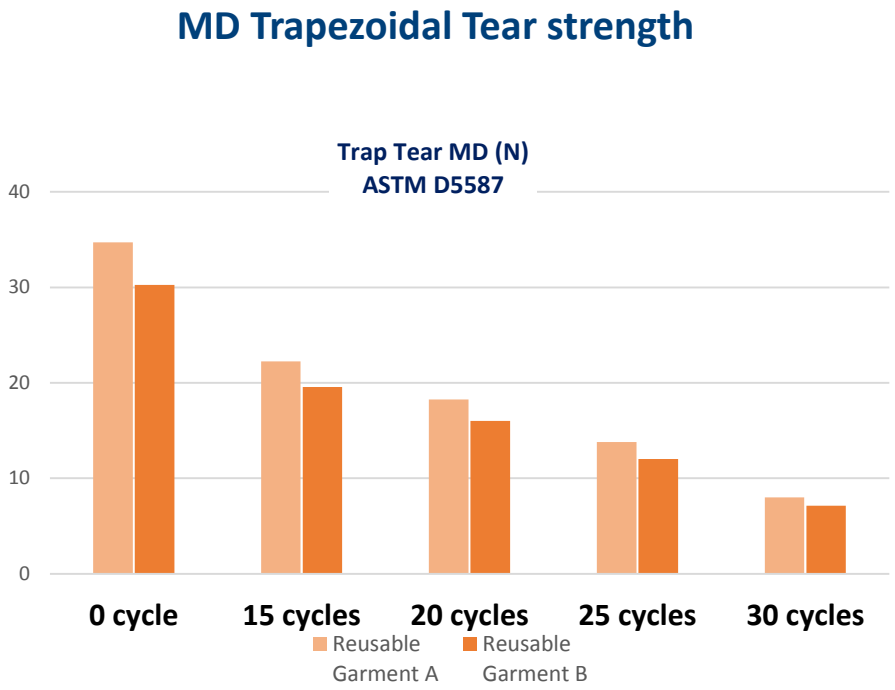
Body Box Test – Particle Shedding for all activities (>0.5µm)



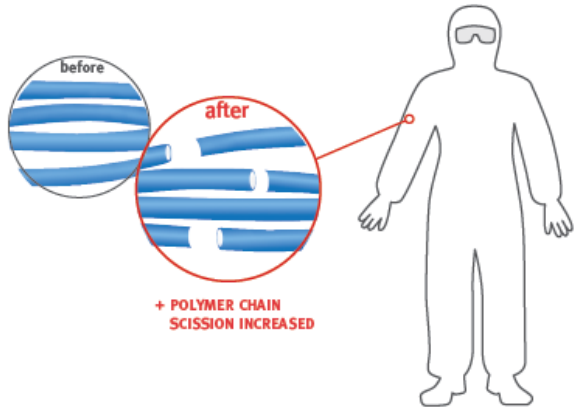
Body Box particle shedding measured for reusable garment for all activities

For both reusable garments, increases in particle generation occured with increased gamma exposure

RISK BY GARMENT CONTAMINATION TRAP TEAR vs number of cycles



Relevant Findings from DuPont Study
With Increased Radiation Exposure:



Impact of gamma radiation exposure seen in reduction in tear strength with increased nominal received dose

Damaged coverall represents a risk of tear during use and a risk of contamination of the environment.

GARMENTS AS A CONTAMINATION RISK

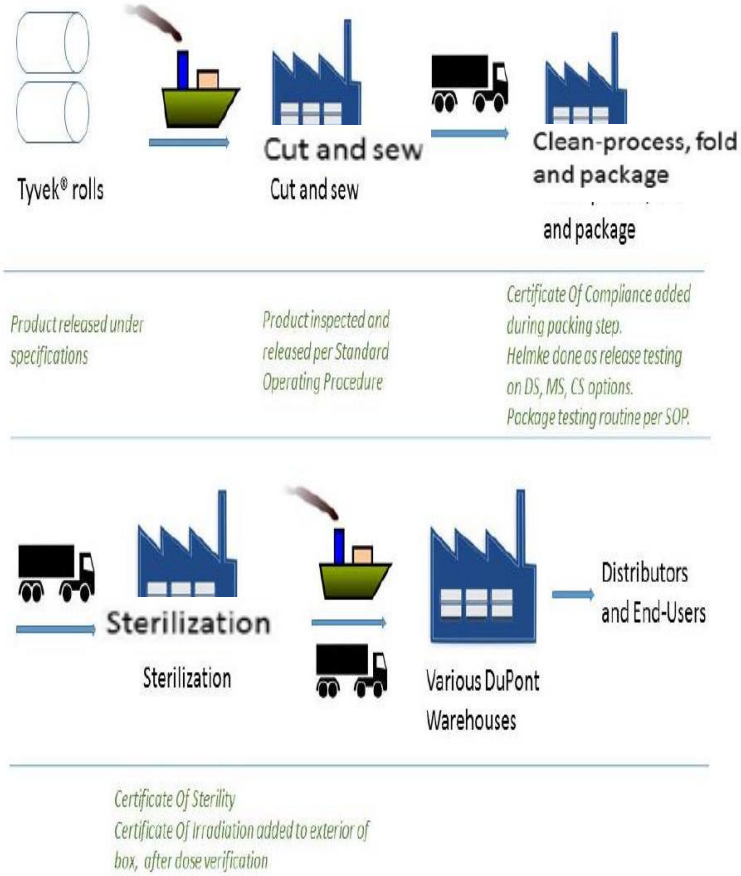
Processing risks:

- **Sterilization process**
- **Handling**
- **Folding**
- **Packaging**

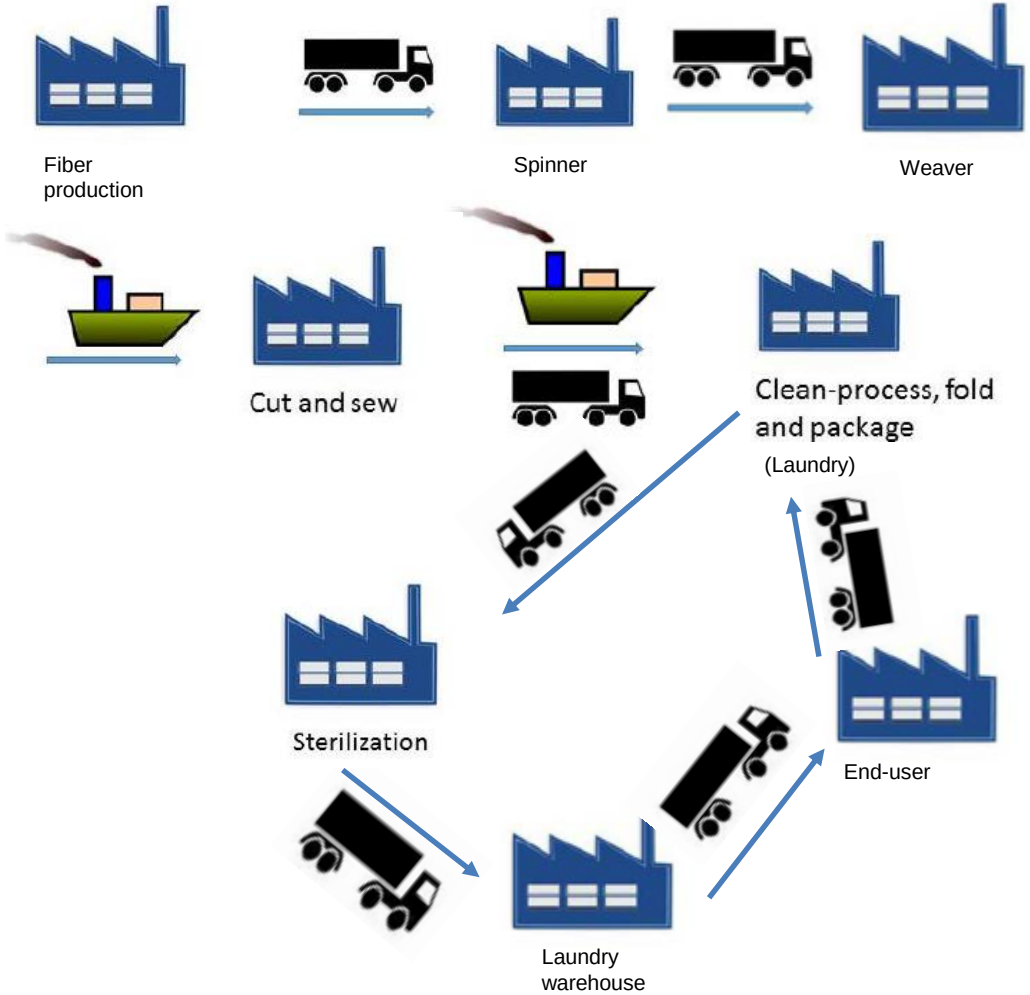
HANDLING RISKS

- Are the garments washed, folded and packed in a cleanroom (ISO 4/5) or not?
- How is the cleanroom monitored?
- How are the labels and patches put on the garments?
- Are the repairs done with the same fabric or sewing thread?
- Are the garments checked for integrity and cleanliness before the packing?
- How is the bioburden monitored before the sterilization?
- How are garments packed, transported and handled during the transit laundry-sterilizer-warehouse-customer?

RISK BY GARMENT CONTAMINATION
Risk of the value-chain



Example for the value chain of a disposable garment (Tyvek® IsoClean®): from polymer to finished product.



Example for the value chain of reusable cleanroom garments: from fiber to finished product

ASEPTIC FOLDING PROCEDURES

Operators must know how to properly gown the coverall in order to minimize the contamination risk and not transfer contamination into clean areas.

The suppliers should be able to provide an easy to follow documented guidance that could serve as training for operators e.g. video instruction when entering specific grades of cleanrooms.

RISK BY GARMENT CONTAMINATION Packaging

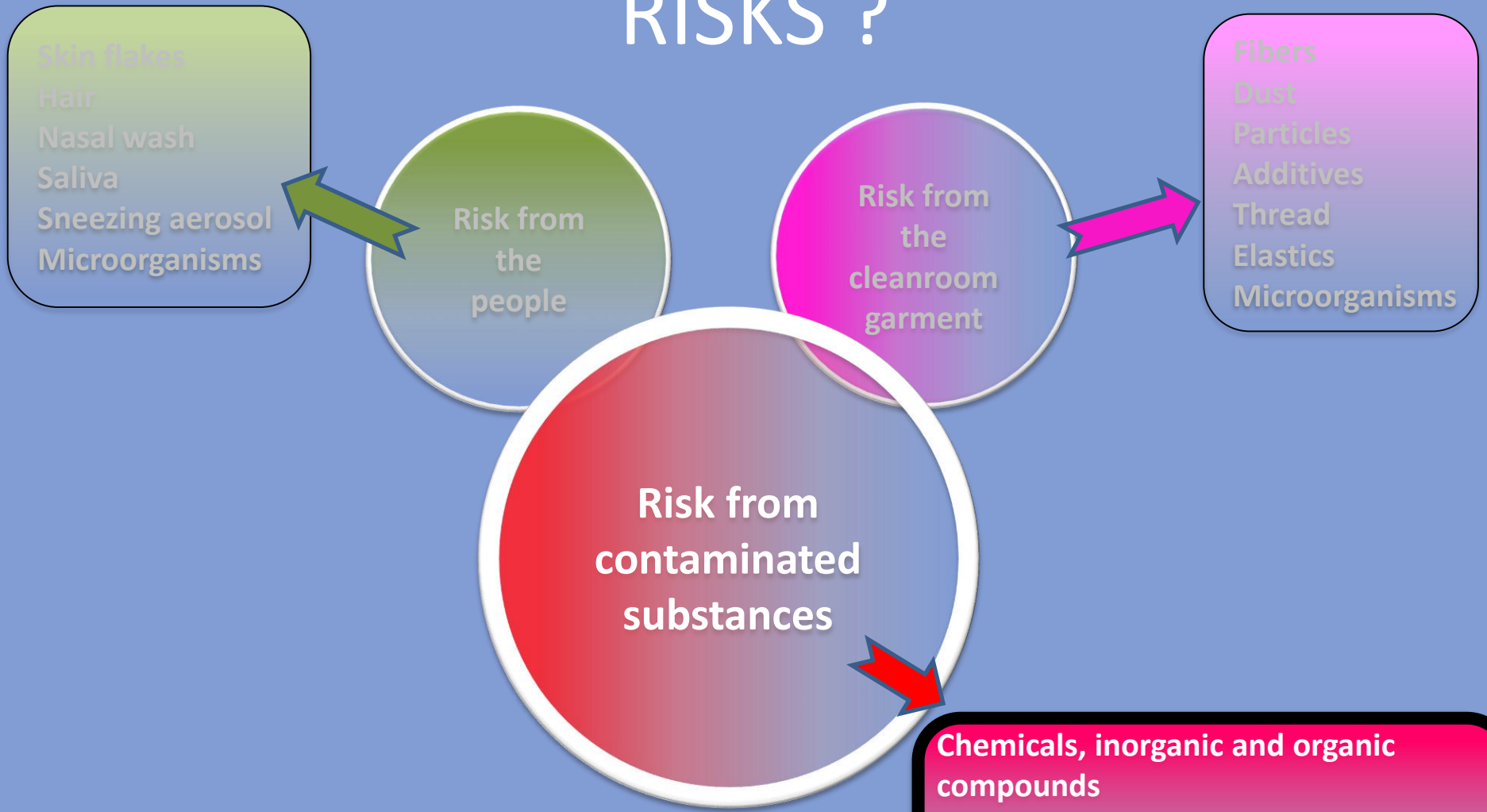
- Double bagging with validated, cleanroom bags is a key element for contamination risk reduction when transferring apparel into clean areas.

- The validated dual barrier packaging system serves both as an additional sterility risk management component.

Example of dual barrier validated packaging system Tyvek® IsoClean ® garment model 183 B option DS.
The garment is individually packed in a dual barrier validated packaging system, consisting of an inner and outer easy tear, validated, cleanroom bag. The box quantities are packed in a cardboard box with two polyethylene liners.

HOW TO CONTROL CONTAMINATION

RISKS ?



Understanding the contamination risks

For cleanroom & operators

Risk from contaminated substances

PROTECTING THE OPERATOR

from on the job hazards like chemical risks (e.g. HPAPI).

It is mandatory to equip the employees with the appropriate PPE whenever there is potential risk of contamination.

The cleanroom garments must also be a chemical / biological protective garment

LEGISLATIVE CLOTHING REQUIREMENTS

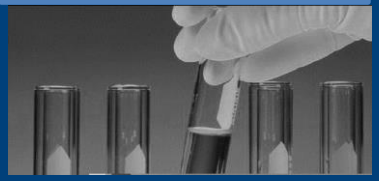
Directive 89/391/EEC
Introduction of measures to encourage improvements in safety and health of workers at work

Directive 89/656/EEC
Minimum health and safety requirements for the use by workers of personal protective equipment at the workplace

PEOPLE PROTECTION

GMP and IEST provide guidance on garment usage to maintain product quality and cleanroom environment.

PRODUCT PROTECTION



CORRECT PROTECTIVE SOLUTIONS SHOULD BE SELECTED AS A RESULT OF A RISK ASSESSMENT AND MUST BE PART OF THE CONTAMINATION CONTROL STATEGY

specific for individual end-user and cleanroom application,
to protect the products/processes and the operators and avoid cross-contamination.

RISK OF CHEMICAL SUBSTANCES

In order to provide appropriate protection against a specific chemical, performance properties of the fabric such as **PENETRATION** & **PERMEATION DATA** need to be consulted. Knowing the toxicity and consequences of short- or long-term exposure to a hazard is essential.

RISK OF CYTOSTATIC DRUGS HANDLING

The greatest hazard arise by contact with cytostatic dusts, liquids or through aerosol formation.

"The directives, regulations and guidelines currently in use stipulate the use of protective equipment by every employee of a cytostatic department deriving from evaluation of the hazard involved.
The PPE must carry the CE mark and must be specified in writing in the hazard evaluation."

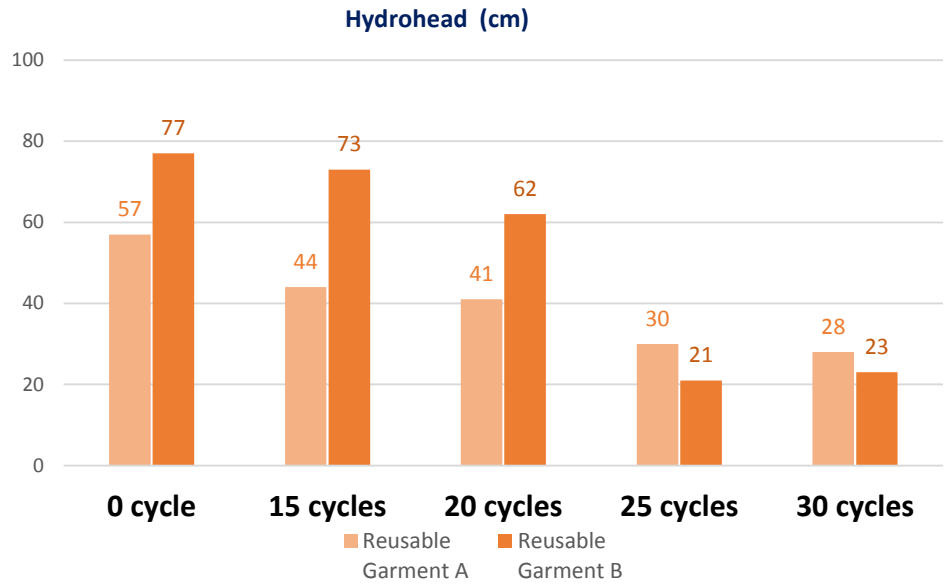
Quality Standard for the Oncology Pharmacy Service, European Society of Oncological Pharmacy, Hamburg 2014.

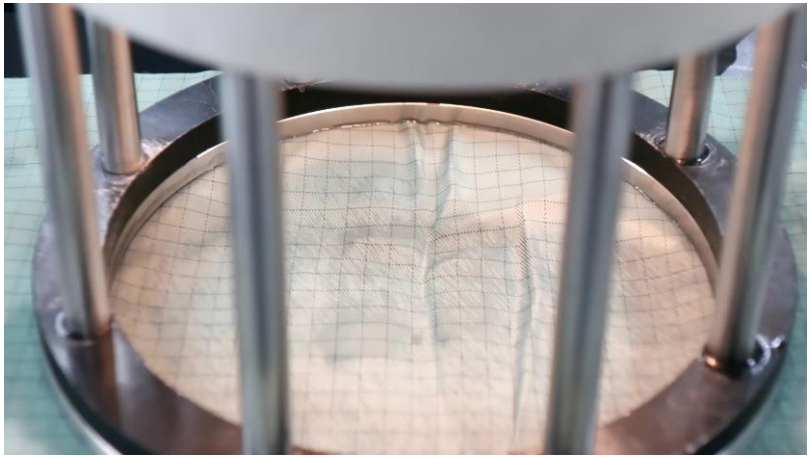
Permeation is measured on fabrics used in PPE to assist with the selection of a protective cleanroom garment.
Breakthrough times in minutes of critical cytostatics agents are provided on Tyvek® IsoClean ® materials.

Permeation data by hazard			Tyvek® IsoClean® 0B (non sterile, bulk)			Tyvek® IsoClean® CS Clean-processed&sterile		
Hazard name	Concentration	CAS number	BT 0.01	BT 0.1	BT 1.0	BT 0.01	BT 0.1	BT 1.0
Carmustine	3.3 mg/ml, 10 % Ethanol	154-93-8	<10	<10	>240	<10	<10	>240
Cyclophosphamide	20 mg/ml	50-18-0	>240	>240	>240	>240	>240	>240
Doxorubicin HCl	2 mg/ml	25136-40-9	>240	>240	>240	>240	>240	>240
Etoposide (Toposar®, Teva)	20 mg/ml, 33.2 % (v/v) Ethanol	33419-42-0	>240	>240	>240	>240	>240	>240
Paclitaxel (Hospira)	6 mg/ml, 49.7 % (v/v) Ethanol	33069-62-4	>240	>240	>240	>240	>240	>240
Thiotepa	10 mg/ml	52-24-4	<10	<10	<10	<10	<10	<10
Fluorouracil, 5-	50 mg/ml	51-21-8	<10	<10	>240	<10	<10	<10

ASTM 6978, Table 1

RISK OF LIQUID EXPOSURE HYDROHEAD



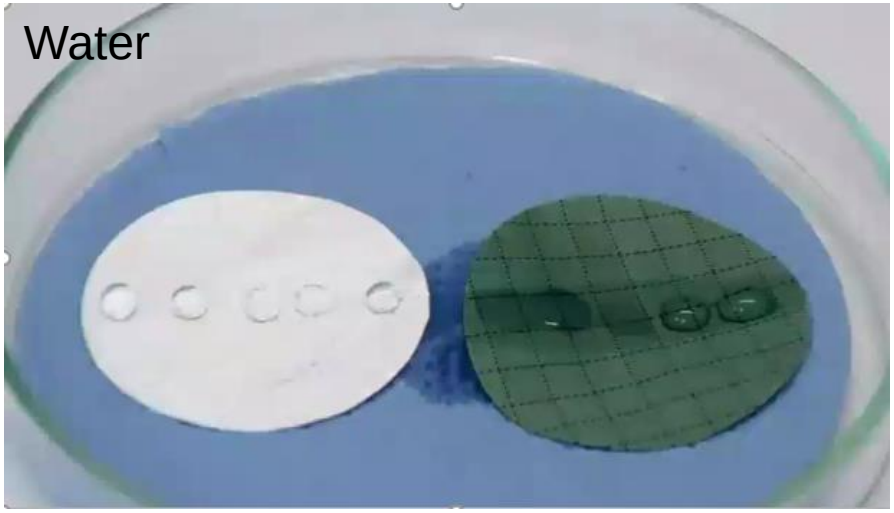


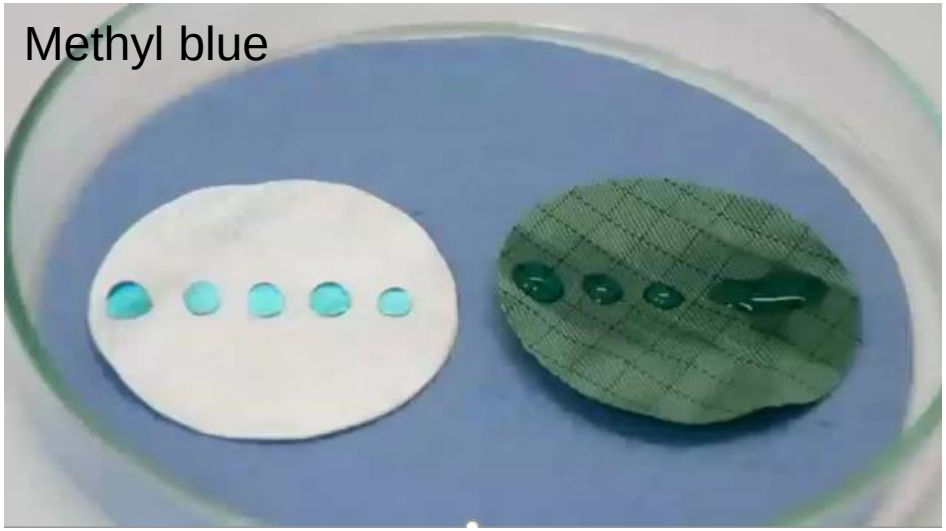
Resistance to water penetration measures the water pressure the fabric can withstand before leakage occurs.
Higher numbers indicate better penetration resistance

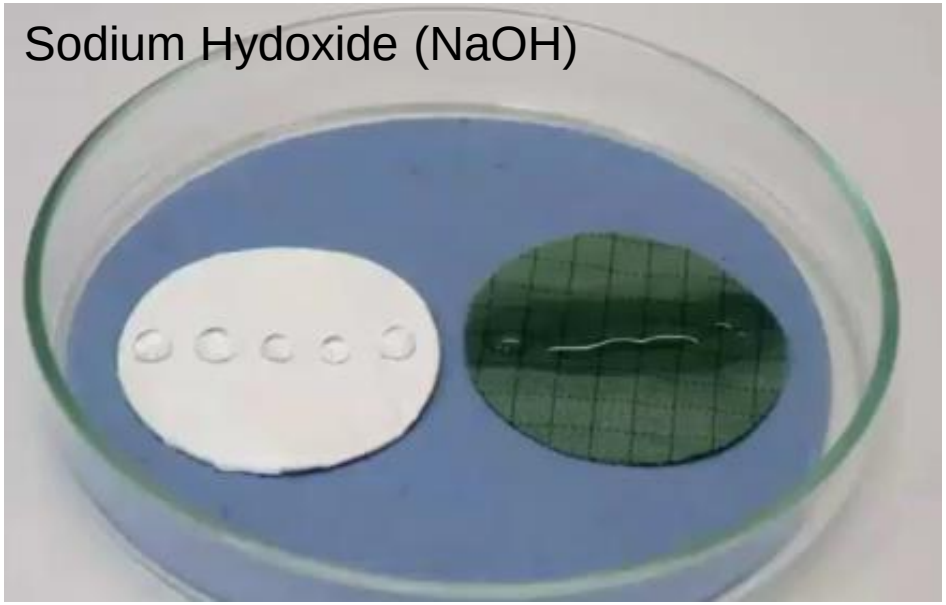
Hydrohead on reusable garments decreases with gamma radiation exposure

Protection of the operators is reduced when the cleanroom garment has been subjected to multiple cycles of laundering and sterilization

RISK OF CONTAMINATION BY LIQUIDS DROPLET TEST







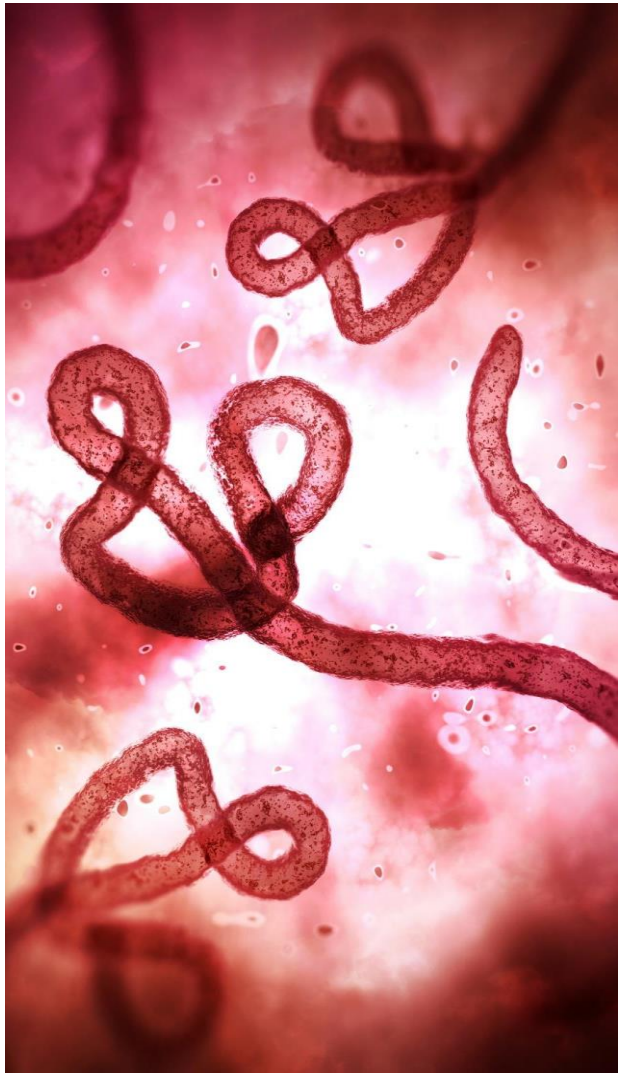
Single-use garments repel water-based liquids when reusable garments show liquid penetration

RISK BY CONTAMINATION BY INFECTIVE AGENTS

Biological agents could cause sickness in humans and represent a danger to employees

RISKS FROM

- Viruses (H1N1, HIV, ebola)
- Bacteria (anthrax, salmonella)
- Microorgnisms
- Fungi (mold)
- Parasites
- Prions (BSE)



Resistance to following biological contaminants is evaluated :

- Synthetic blood
- Virus
- Biologically contaminated liquids
- Biologically contaminated aerosols
- Biologically contaminated dust

To claim protection against hazardous biological substances, the material used in the cleanroom garment shall be compliant with EN

INFECTION PROTECTION

Test results for Tyvek® IsoClean® Clean & Sterile :

	TEST	TESTING METHOD	CLASSIFICATION acc. to **EN 14126**:2003
	Resistance to penetration of blood and body fluids using synthetic blood	ISO 16603	Class 3 of 6
	Resistance to penetration by blood-borne pathogens using bacteriophage Phi-X174	ISO 16604 Method D	No classification
	Resistance to penetration by infective agents due to mechanical contact with substances containing contaminated liquids	EN ISO 22610	Class 1 of 6
	Resistance to penetration against biologically contaminated aerosols	ISO/DIS 22611	Class 1 of 3
	Resistance to penetration against biologically contaminated dust	ISO 22612	Class 1 of 3

Tyvek® IsoClean® provides a limited barrier to infective agents

LIFE CYCLE CONSIDERATIONS

EVIDENCE OF DAMAGE IS OFTEN INVISIBLE TO THE NAKED EYE

- Multiple washing & sterilization cycles deteriorate garments
- Performance properties should not be assessed on new garment performances only
- Garment performance should be assessed over entire life-cycle
- Cleanroom operators should have their “eyes open” when making decisions about their garment systems.

When selecting garments for cleanroom use, it is important to understand how they will perform over their entire life cycle

CONCLUSIONS

- ✓ Cleanroom garments play a crucial role in reducing the risk of cleanroom contamination
- ✓ Assess, validate and audit the entire value-chain & life-cycle of the garments: from the fabric manufacturing, garment conversion, to packaging & sterilization and, if applicable, to the laundry process as well.
- ✓ As part of risk assessment, put in place testing protocols to evaluate cleanroom garments as they age
- ✓ It is of the utmost importance to evaluate their benefits and to understand their limitations in order to protect the following :
    1. The cleanroom from the people contamination
    2. The cleanroom from the garment contamination
    3. The operator from chemical and biological contamination

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Thank you !

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DISCLAIMER

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It is the user's responsibility to determine the level of toxicity and the proper personal protective equipment needed. This information is intended for use by persons having the technical expertise to undertake evaluation under their own specific end-use conditions, at their own discretion and risk.

Anyone intending to use this information should first check that the garment selected is suitable for the intended use. The end-user should discontinue use of garment if fabric becomes torn, worn or punctured, to avoid potential chemical exposure. Since conditions of use are beyond our control, we make no warranties, expressed or implied, including but not limited to warranties of merchantability or fitness for a particular purpose and assume no liability in connection with any use of this information.

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