Dipl.-Phys.
Prof. Dr. Horst Weißsieker

Von der Industrie- und
Handelskammer zu Köln
öffentlich bestellter und
vereidigter Sachverständiger
für Reinraumtechnik

Training

Biosafety & Biosecurity

Prof. Dr. Horst Weißsieker

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AGENDA / SCHEDULE

Part I: „Basics / Installation / Construction

A)	
a.) Biosafety / Biosecurity	1 h
b.) Laws and Regulations	1 h
c.) Risk Analysis / Applications	1 h
B)	
a.) Construction and Design Criteria	1 h
b.) Documentation / SOPs / User Manuals	1 h
c.) Installations (HVAC and Media)	1 h
C)	
a.) Laboratory Equipment (Biosafety Bench, Autoclaves, Washing and Sterilization)	1 h
b.) Question / Answers / Control of Success	1 h

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AGENDA / SCHEDULE

Part II: Hook Up, Certification , Operation, Maintenance

D)

a.) Microbiological Working in a Laboratory	1 h
b.) Maintenance	1 h
c.) Qualification / Validation of Operation	1 h

E)

a.) Laboratory Operation	1 h
b.) Contamination Control	1 h
c.) Cleaning and Disinfection	1 h

F)

a.) Testing, Certification, Accreditation	1 h
b.) Question & Answers / Control of Success	1 h

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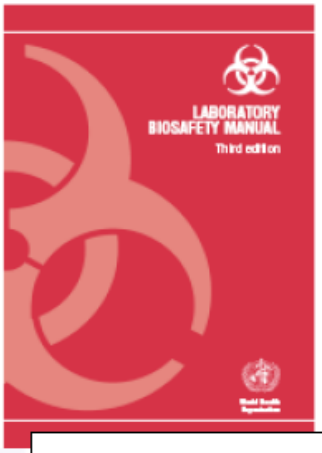
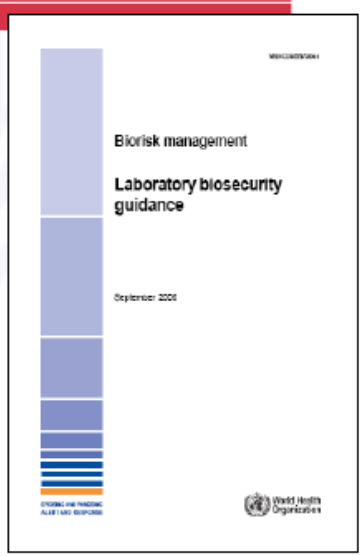
Definitions

- **Laboratory biosafety**[1]: containment principles, technologies, and practices implemented to prevent unintentional exposure to pathogens and toxins, or their unintentional release

- **Laboratory biosecurity**[2]: protection, control and accountability for valuable biological materials within laboratories, in order to prevent their unauthorized access, loss, theft, misuse, diversion, or intentional release





[1] *Laboratory biosafety manual, Third edition* (WHO, 2004)

[2] *Biorisk management Laboratory biosecurity guidance* (WHO, 2006)

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Hazard, Threat, and Risk

- A **hazard** is a source or object that can cause harm
- In security terms, a **threat** is associated with a person who has intent to cause harm to other people, animals, or the institution
- A **risk** can be based on either a hazard, or a hazard and a threat

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Risk, Likelihood, and Consequences

- **Risk** is the likelihood of an event with a hazard (or a hazard and threat) that has consequences
- **Likelihood** is the probability an event occurring
- **Consequences** is the severity of an event

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Mitigation Control Measures

- Engineering Controls: Physical changes to work stations, equipment, materials, production facilities, or any other relevant aspect of the work environment that reduce or prevent exposure to hazards
- Administrative Controls: Policies, standards and guidelines used to control risks
- Practices and Procedures: Processes and activities that have been shown in practice to be effective in reducing risks
- Personal Protective Equipment: Devices worn by the worker to protect against hazards in the laboratory

Mitigations Measures II

Advantages/Disadvantages

Control Measure	Advantages	Disadvantages
Engineering	Efficient, eliminates hazard	Cost, complexity
Administrative	Authority approach	Indirect approach, primarily addresses the human factor
Practices & Procedures	SOP based (standardized approach)	Training and supervision requirements
PPE	Ease of use, relative cost	Does not eliminate hazard, PPE fails exposure happens, uncomfortable, limits ability

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Performance

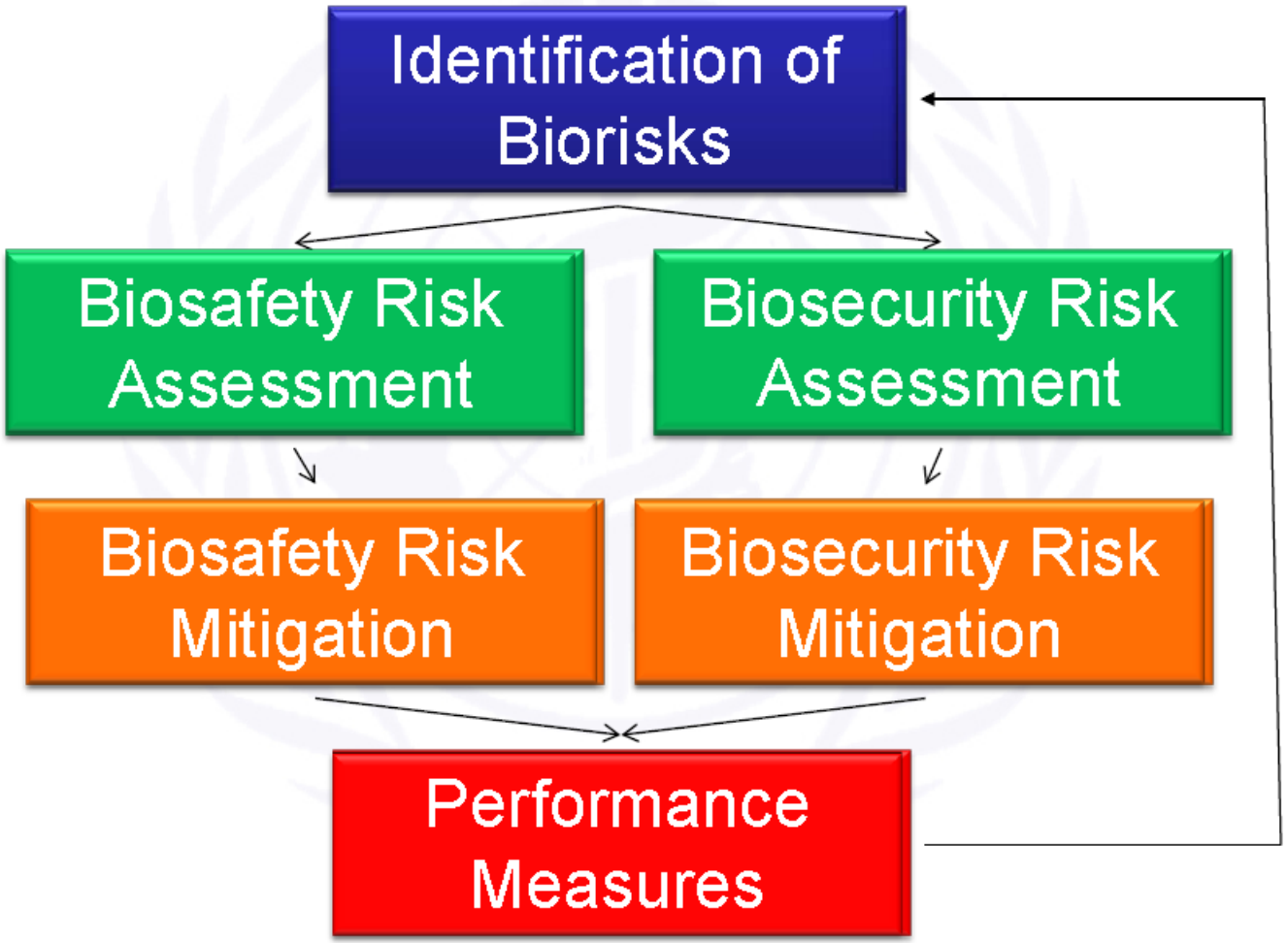
Performance is the way in which someone or something functions

Performance is the result of all the efforts of a company or organization

Performance improves biorisk management: you know that your system works and is sustainable, and that the risk is acceptable

WHO Risk Identification

Identification of Biorisks



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BSL Laboratories

Regulatory Environment and User Requirement

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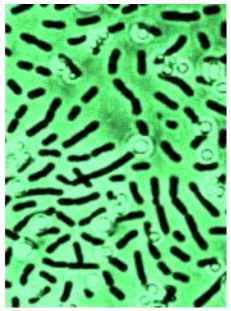
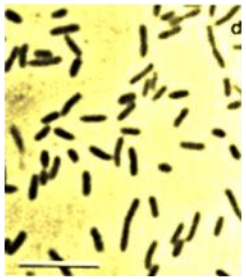
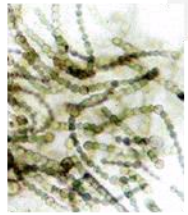
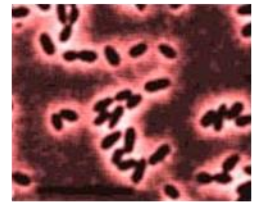
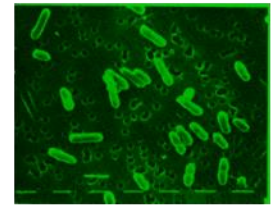
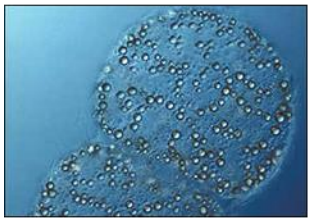


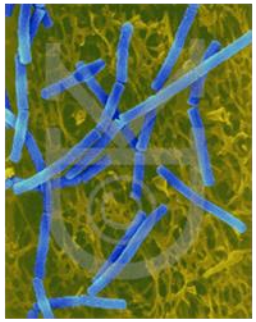


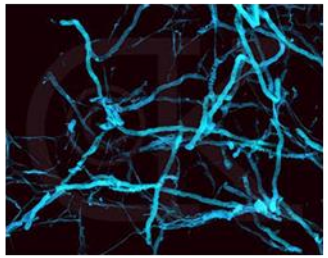


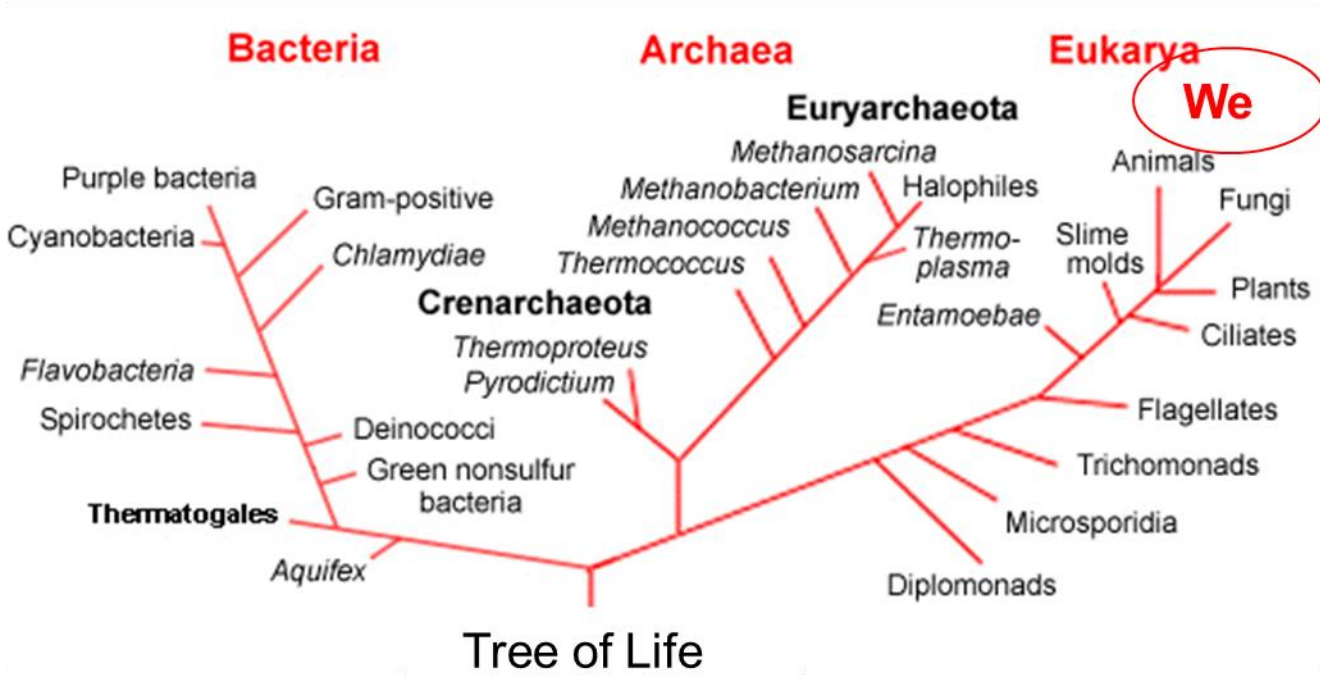


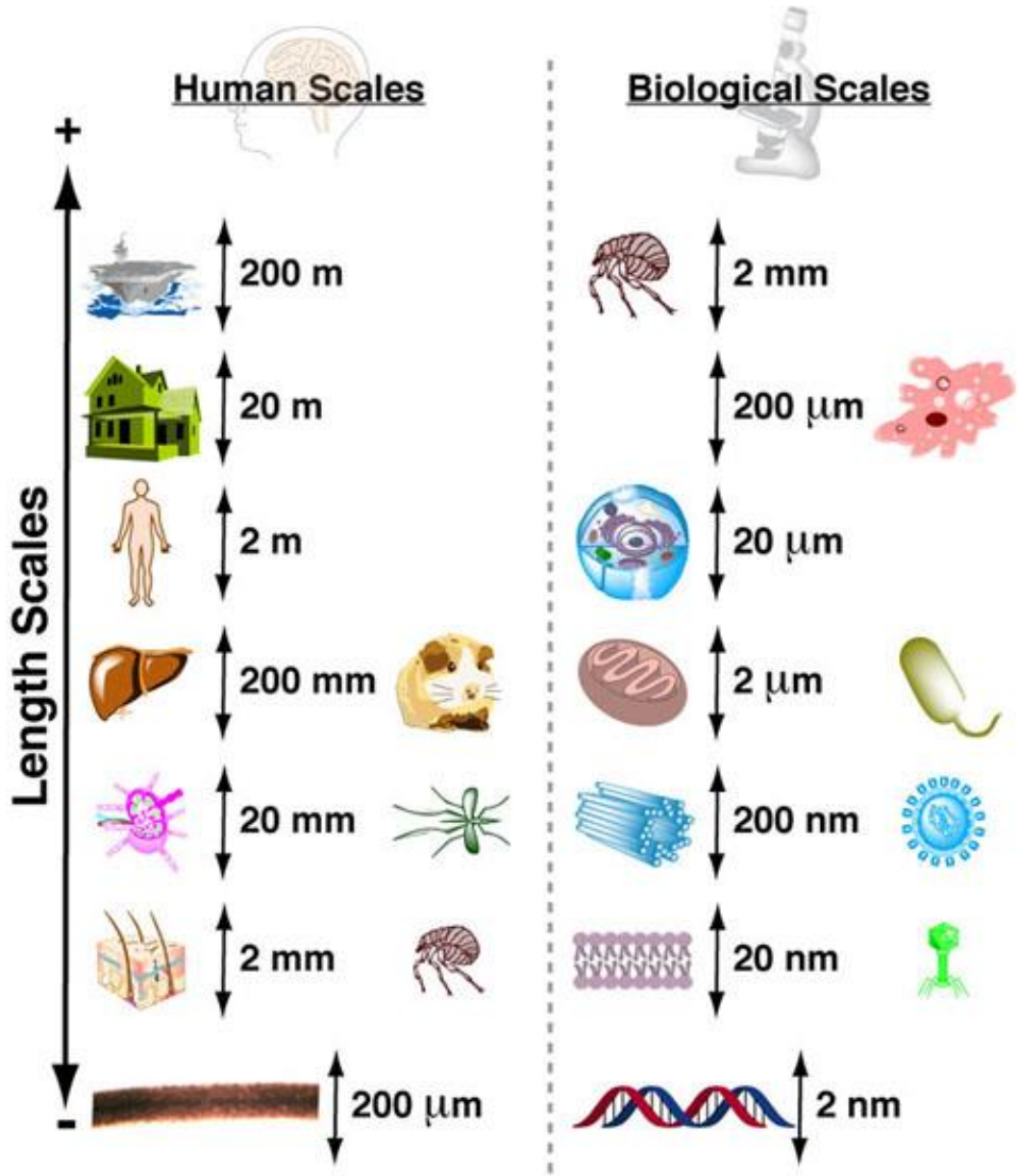




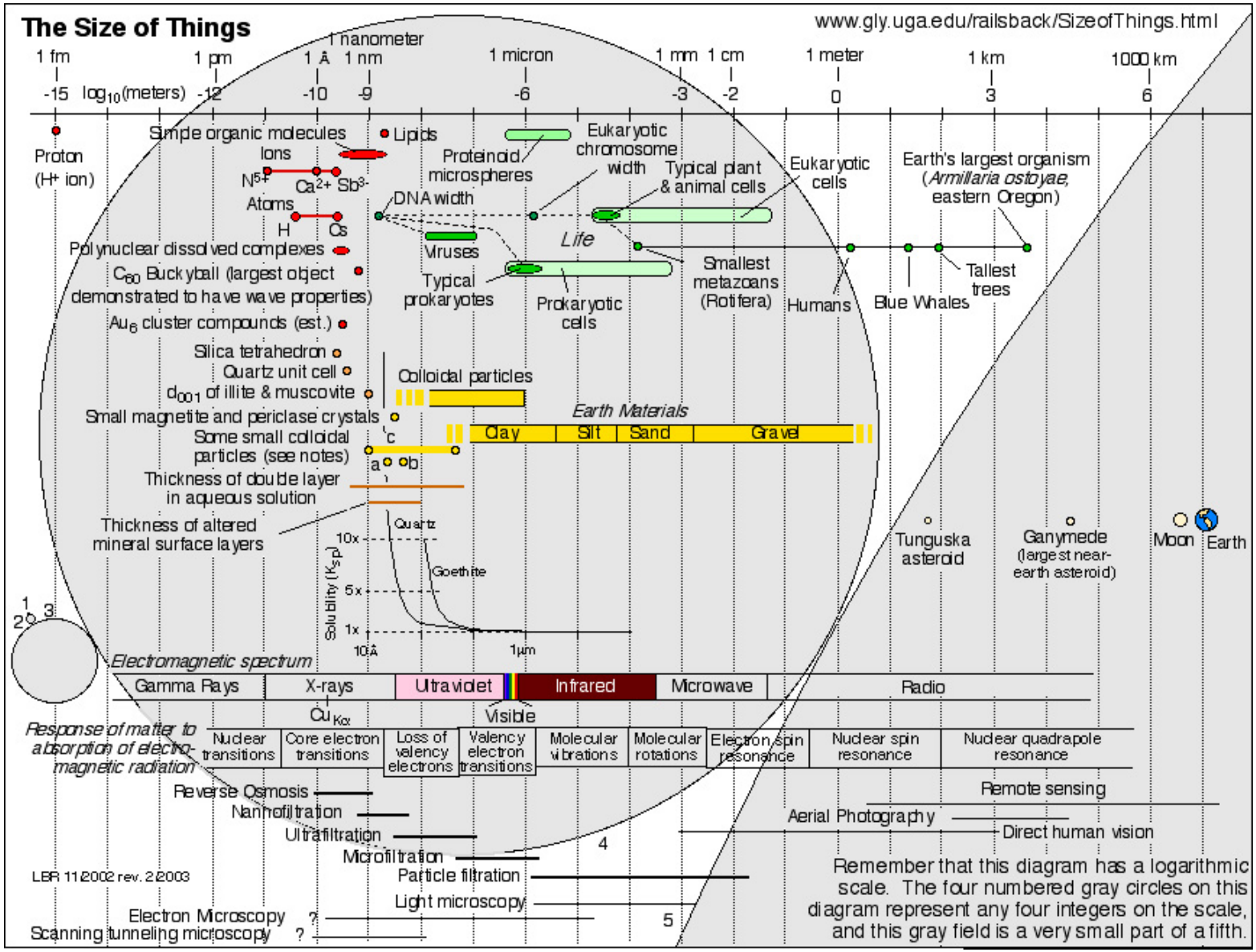








http://www.practicallyscience.com/category/physics/



http://www.gly.uga.edu/railsback/SizeofThings.jpeg

TABLE 1
Airborne Respiratory Pathogens—Sizes and Dimensions

AIRBORNE PATHOGEN	AVG DIA	DIA/WIDTH		LENGTH		AR	EQUIV DIA	LOGMEAN DIAMETER	LN STDEV
		MIN	MAX	MIN	MAX				
Parvovirus B19	0.022	0.018	0.026			1		0.022	0.074
Rhinovirus	0.023	0.018	0.028			1		0.022	0.088
Coxsackievirus	0.025	0.02	0.03			1		0.024	0.081
Echovirus	0.025	0.02	0.03			1		0.024	0.081
Hantavirus	0.06	0.05	0.07			1		0.059	0.067
Togavirus	0.063	0.05	0.075			1		0.061	0.081
Reovirus	0.073	0.07	0.075			1		0.072	0.014
Adenovirus	0.08	0.07	0.09			1		0.08	0.050
Orthomyxovirus	0.1	0.08	0.12			1		0.10	0.081
Coronavirus	0.11	0.08	0.13			1		0.10	0.097
Varicella-zoster	0.15	0.1	0.2			1		0.14	0.139
Arenavirus	0.18	0.05	0.3			1		0.12	0.358
Francisella tularensis	0.19	0.08	0.3	0.2	0.7	2.4	0.13	0.15	0.264
Morbillivirus	0.2	0.1	0.3			1		0.17	0.220
Respiratory Syncytial Virus	0.22	0.14	0.3			1		0.20	0.152
Parainfluenza	0.23	0.15	0.3			1		0.21	0.139
Poxvirus - Vaccinia	0.23	0.2	0.25	0.25	0.3	1.2	0.08	0.22	0.045
Mycoplasma pneumoniae	0.23	0.15	0.3			1		0.21	0.137
Paramyxovirus	0.23	0.15	0.31			1		0.22	0.145
Bordetella pertussis	0.25	0.2	0.3	0.5	1	3	0.21	0.24	0.081
Chlamydia pneumoniae	0.3	0.2	0.4			1		0.28	0.139
Chlamydia psittaci	0.3	0.2	0.4			1		0.28	0.139
Klebsiella pneumoniae	0.4	0.3	0.5			1		0.39	0.102
Haemophilus influenzae	0.43	0.2	0.3	1	1.5	5	0.43	0.35	0.081
Coxiella burnetii	0.5	0.45	0.55			1		0.50	0.040
Pseudomonas aeruginosa	0.57	0.3	0.8	1	3	3.6	0.57	0.51	0.209
Pseudomonas pseudomallei	0.57	0.3	0.8	1	3	3.6	0.57	0.51	0.209
Actinomyces israelii	0.6	0.2	1	2	5	5.8	1	0.90	0.183
Legionella pneumophila	0.6	0.3	0.9	2	2	3.3	0.57	0.72	0.091
Thermomonospora viridis	0.6	0.3	0.9	0.6	1.5	1.8	0.30	0.52	0.220
Cardiobacterium	0.63	0.5	0.75	1	3	3.2	0.57	0.65	0.107
Micropolyspora faeni	0.69	0.66	0.72			1		0.7	0.017
Thermoactinomyces sacchari	0.7	0.6	0.8	1	3	2.9	0.57	0.72	0.071
Mycobacterium kansasii	0.71	0.2	0.6	1	4	6.3	0.71	0.57	0.277
Alkaligenes	0.75	0.5	1	0.5	2.6	2.1	0.44	0.71	0.139
Yersinia pestis	0.75	0.5	1	1	2	2	0.43	0.71	0.139
Pseudomonas mallei	0.77	0.3	0.8	1.4	4	4.9	0.77	0.67	0.210
Neisseria meningitidis	0.8	0.6	1			1		0.77	0.102
Streptococcus pyogenes	0.8	0.6	1			1		0.77	0.102
Mycobacterium tuberculosis	0.86	0.2	0.6	1	5	7.5	0.86	0.64	0.322
Staphylococcus aureus	0.9	0.8	1			1		0.89	0.045
Streptococcus pneumoniae	0.9	0.8	1			1		0.89	0.045
Corynebacteria diphtheria	1	0.3	0.8	1	6	6.4	1.0	0.72	0.348
Haemophilus parainfluenzae	1	0.75	1.25			1		0.97	0.102

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Filtration of Airborne Microorganisms: Modeling and Prediction

W.J. Kowalski, M.S., P.E.
Student Member ASHRAE

William P. Bahnfleth, Ph.D., P.E.
Member ASHRAE

T. S. Whittam, Ph.D.

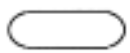
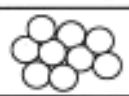
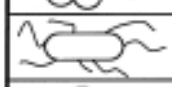
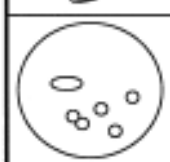
ASHRAE Transactions: Research

https://www.engr.psu.edu/ae/faculty/bahnfleth/filtration_of_airborne_microorg.pdf

TABLE 1 (CONTINUED)
Airborne Respiratory Pathogens—Sizes and Dimensions

AIRBORNE PATHOGEN	AVG DIA	DIA/WIDTH		LENGTH		AR	EQUIV DIA	LOGMEAN DIAMETER	LN STDEV
		MIN	MAX	MIN	MAX				
Moraxella lacunata	1	0.8	1.2	1.5	3	2.3	0.64	0.98	0.081
Micromonospora faeni	1	0.5	1.5			1		0.87	0.220
Thermoactinomyces vulgaris	1	0.5	1.5			1		0.87	0.220
Bacillus anthracis	1.13	1	1.25			1		1.12	0.045
Nocardia asteroides	1.14	1	1.25	3	5	3.6	1.14	1.19	0.071
Mycobacterium avium	1.2	1.075	1.325			1		1.19	0.042
Mycobacterium intracellulare	1.2	1.075	0.325			1		1.2	0.042
Acinetobacter	1.25	1	1.5	1.5	2.5	1.6	0.57	1.22	0.081
Moraxella catarrhalis	1.25	1	1.5	2	3	2	0.71	1.22	0.081
Serratia marcescens	1.25	1	1.5	2	6	3.2	1.14	1.31	0.107
Nocardia brasiliensis	1.5	1	2			1		1.41	0.139
Nocardia cavine	1.5	1	2			1		1.41	0.139
Phialophora spp.	1.5	1.20	1.8	3	4	2.3	1.0	1.5	0.081
Pneumocystis carinii	2	1	3			1		1.7	0.220
Acremonium spp.	2.5	2	3	4	6	2	1.43	2.4	0.081
Geomyces pannorum	3	2	4	2	5	1.2	1.0	2.8	0.139
Histoplasma capsulatum	3	1	5			1		2.2	0.322
Paecilomyces variotii	3	2	4	3	5	1.3	1.14	2.8	0.139
Wallemia sebi	3	2.5	3.5			1		3.0	0.067
Emericella nidulans	3.25	3	3.5			1		3.2	0.031
Phoma spp.	3.25	2.5	4	6	10	2.5	2.28	3.2	0.094
Penicillium spp.	3.3	2.8	3.8	3	4	1.1	1.0	3.3	0.061
Aspergillus spp.	3.5	2.5	4.5			1		3.4	0.118
Absidia corymbifera	3.75	2.5	5			1		3.5	0.139
Coccidioides immitis	4	2	6			1		3.5	0.220
Trichoderma spp.	4.1	3.6	4.5			1		4.0	0.045
Rhizomucor pusillus	4.25	3.5	5			1		4.2	0.071
Aureobasidium pullulans	5	4	6	8	12	2	2.85	4.9	0.081
Chaetomium globosum	5.5	4.8	6.2	5.9	6.8	1.2	1.81	5.5	0.051
Cryptococcus neoformans	5.5	5	6			1		5.5	0.036
Stachybotrys spp.	5.65	5.1	6.2			1		5.6	0.039
Eurotium spp.	5.75	4.5	7			1		5.6	0.088
Scopulariopsis spp.	6	5	7	5	8	1.1	1.85	5.9	0.067
Sporothrix schenckii	6.5	5	8	10	20	2.30	4.28	6.3	0.094
Botrytis cinera	7	5	9	7	14	1.5	2.99	6.7	0.118
Mucor plumbeus	7.5	5	10			1		7.1	0.139
Rhizopus stolonifer	8	4	12			1		6.9	0.220
Cladosporium spp.	9	5	13			1		8.1	0.191
Fusarium spp.	11.5	9	14			1		11.2	0.088
Helminthosporium	12.5	7.5	8.8	27.5	60	5.4	12.47	11.6	0.156
Blastomyces dermatitidis	14	8	20			1		12.6	0.183
Rhodotorula spp.	14	12	16			1		13.9	0.058
Alternaria alternata	14.4	7	18	18	83	4	14.39	12.9	0.244
Ulocladium spp.	15	10	20			1		14.1	0.139
Paracoccidioides brasiliensis	18.25	6.5	30			1		14.0	0.306

TABLE 3
Shape and Aspect Ratios of Microorganisms

Shape	Type	Description	AR
	Icosahedral Helical	All respiratory viruses, whether icosahedral or helical, are so much smaller than filter fibers that they can be considered spherical for filtration calculations.	1
	Spherical	Most bacteria and spores are approximately spherical.	1
	Ovoid	Some bacteria and spores are ovoid.	1-3
	Rods	Bacteria classed as bacilli are rod-shaped.	1-10
	Diplo-cocci	Certain bacteria normally occur in pairs.	1-3
	Strepto-cocci	Some bacteria occur in strings (i.e. strepto-coccus) but are likely to break up on impact with filter fibers.	NA
	Staphylo-cocci	Some bacteria occur in bunches (i.e. staphylo-coccus) but are likely to break up on impact with filter fibers.	NA
	Flagella	Some bacteria have flagella, enabling motility.	NA
	Capsule	Some bacteria have hydrophobic capsules that can be shed or regenerated depending on the environment.	1-3
	Slime layer	Some microbes produce slime layers in addition to capsules that can be shed at any time.	1-3
	Droplets & Droplet Nuclei	Aerosolized droplets, typically 20-100 microns, may contain numerous microbes and other particles. These evaporate to condensation nuclei that may contain several viable microbes and residue. These will break up upon impact with filter fibers.	1-3

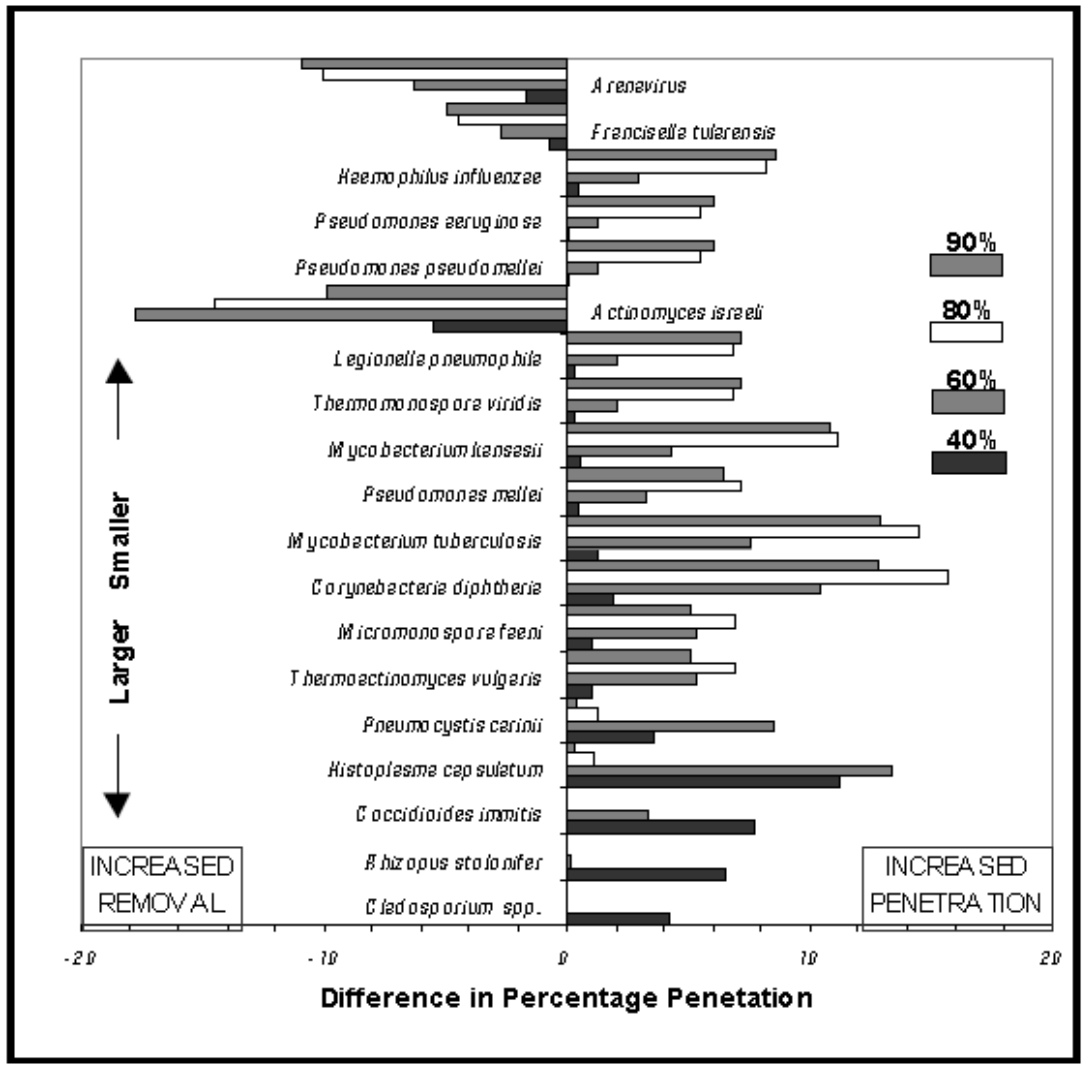


Figure 8 *Difference in predicted filter penetration by the size distribution method over predictions based on average diameter.*

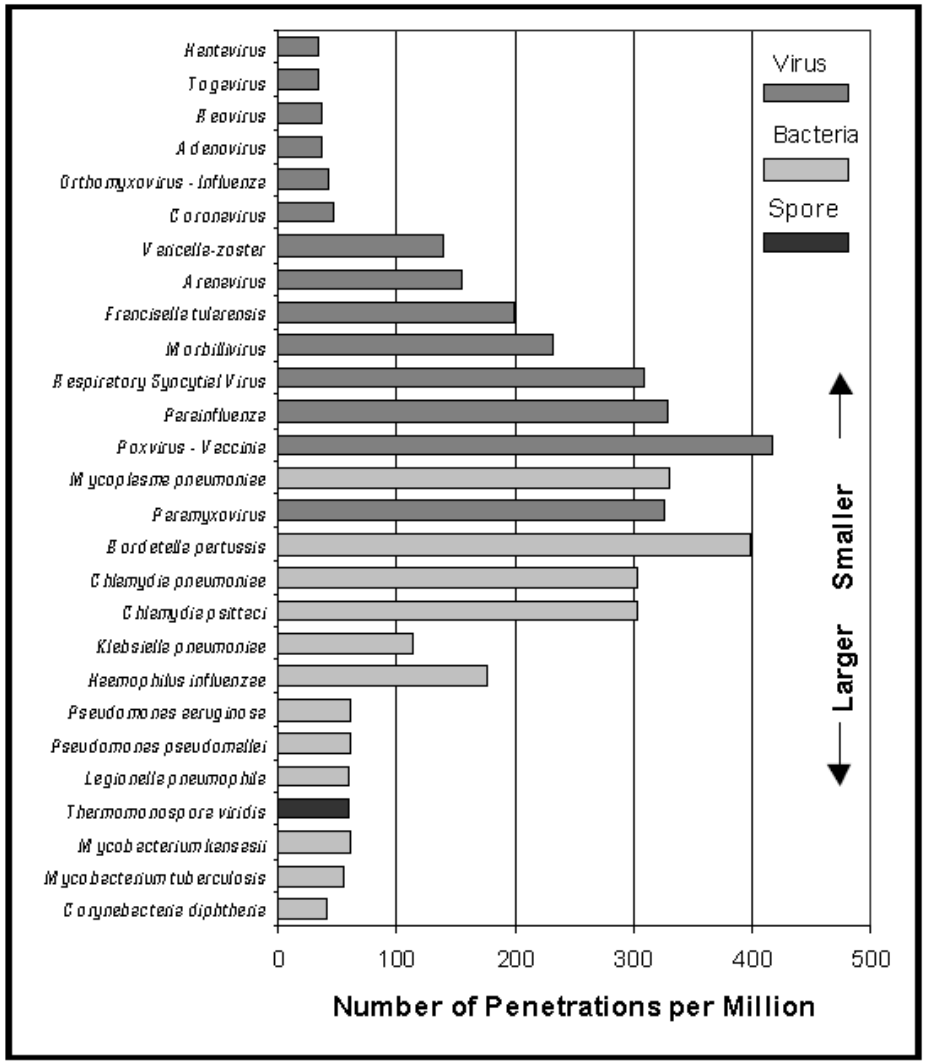
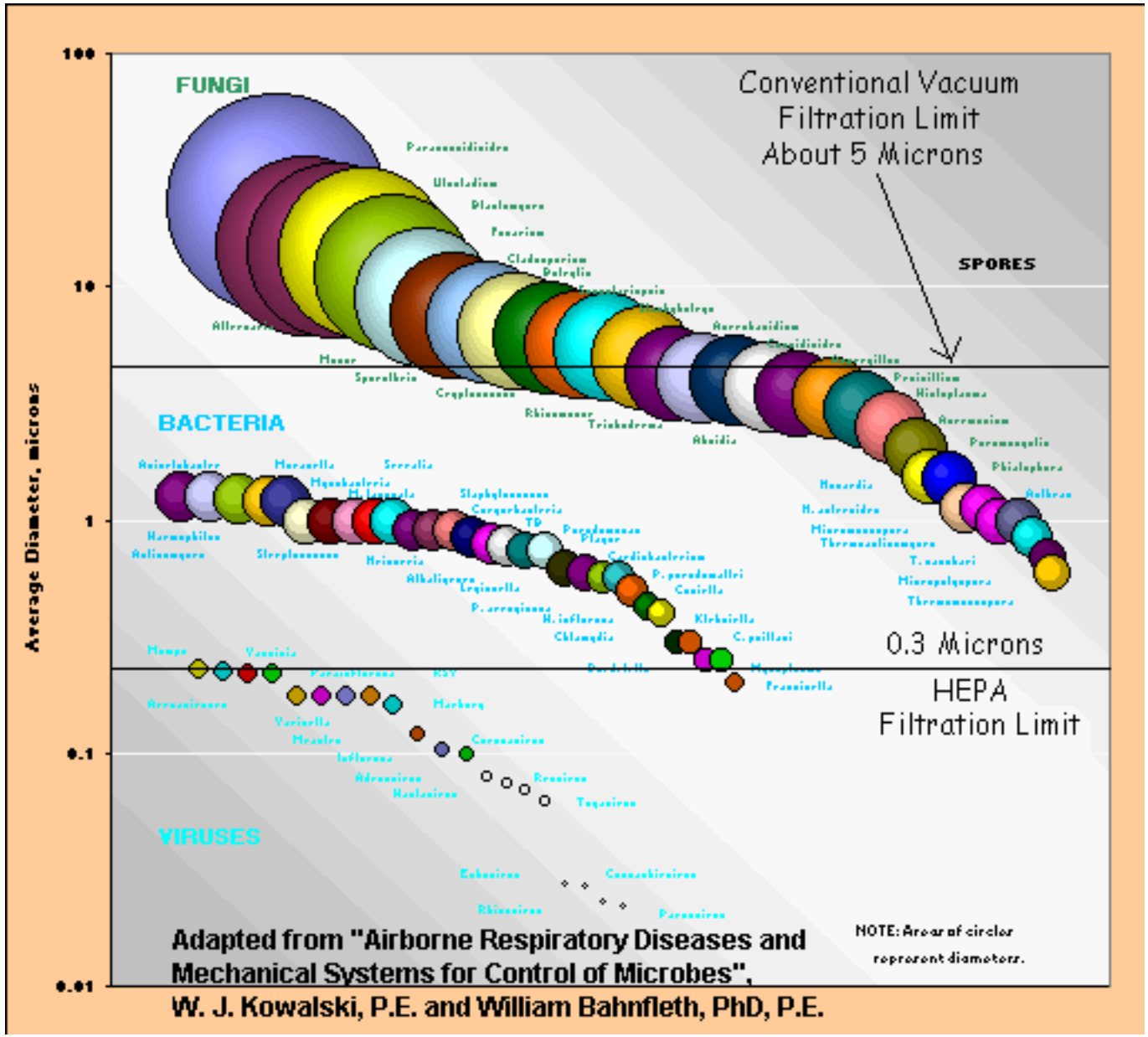
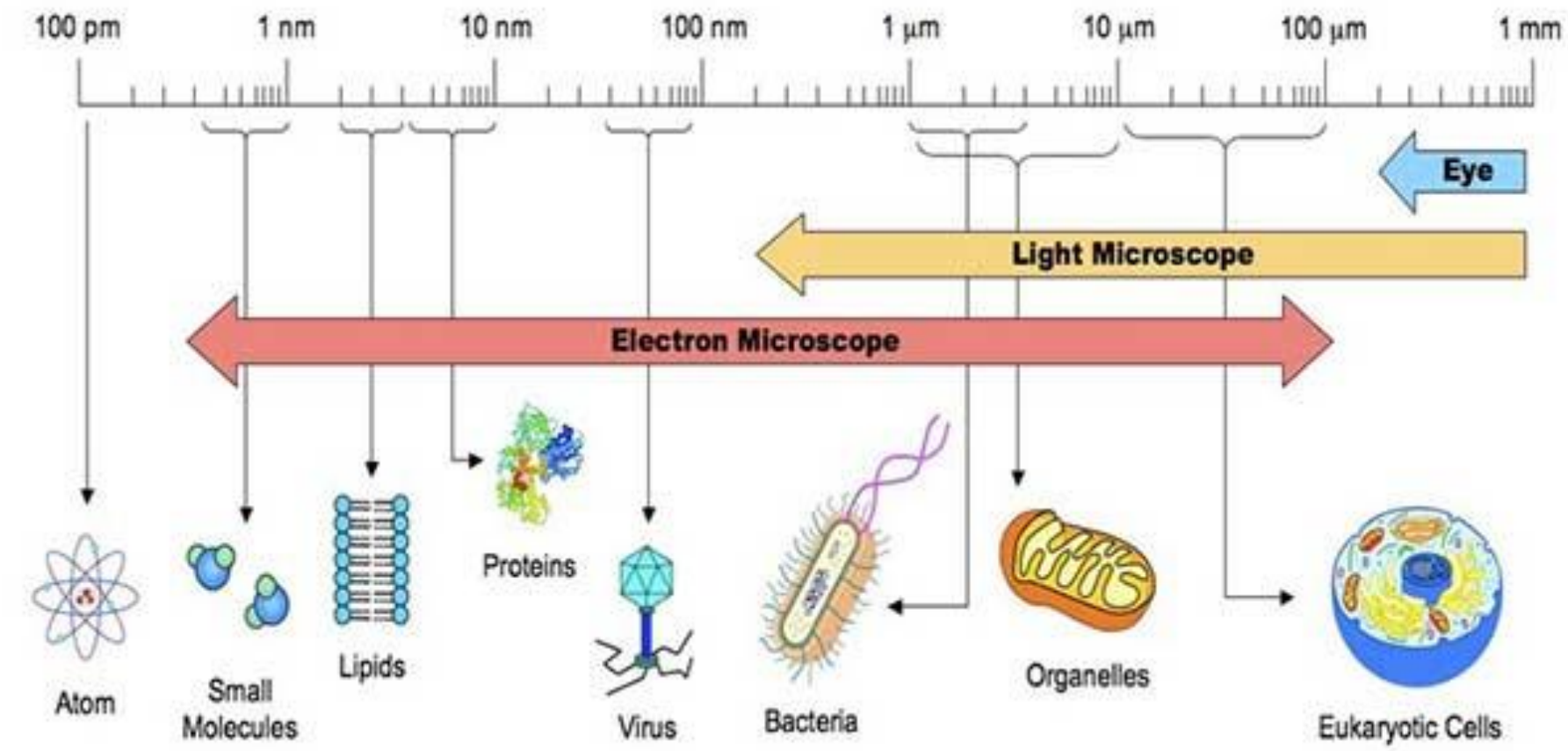


Figure 9 *The most penetrating microorganisms: HEPA 99.9% filter, single pass.*

https://www.engr.psu.edu/ae/faculty/bahnfleth/filtration_of_airborne_microorg.pdf


FUNGI
BACTERIA
VIRUSES
SPORES
Conventional Vacuum
Filtration Limit
About 5 Microns
0.3 Microns
HEPA
Filtration Limit
Average Diameter, microns
100
10
1
0.1
0.01
Adapted from "Airborne Respiratory Diseases and
Mechanical Systems for Control of Microbes",
W. J. Kowalski, P.E. and William Bahnfleth, PhD, P.E.
NOTE: Area of circles
represent diameters.


100 pm
1 nm
10 nm
100 nm
1 µm
10 µm
100 µm
1 mm
Eye
Light Microscope
Electron Microscope
Atom
Small Molecules
Lipids
Proteins
Virus
Bacteria
Organelles
Eukaryotic Cells

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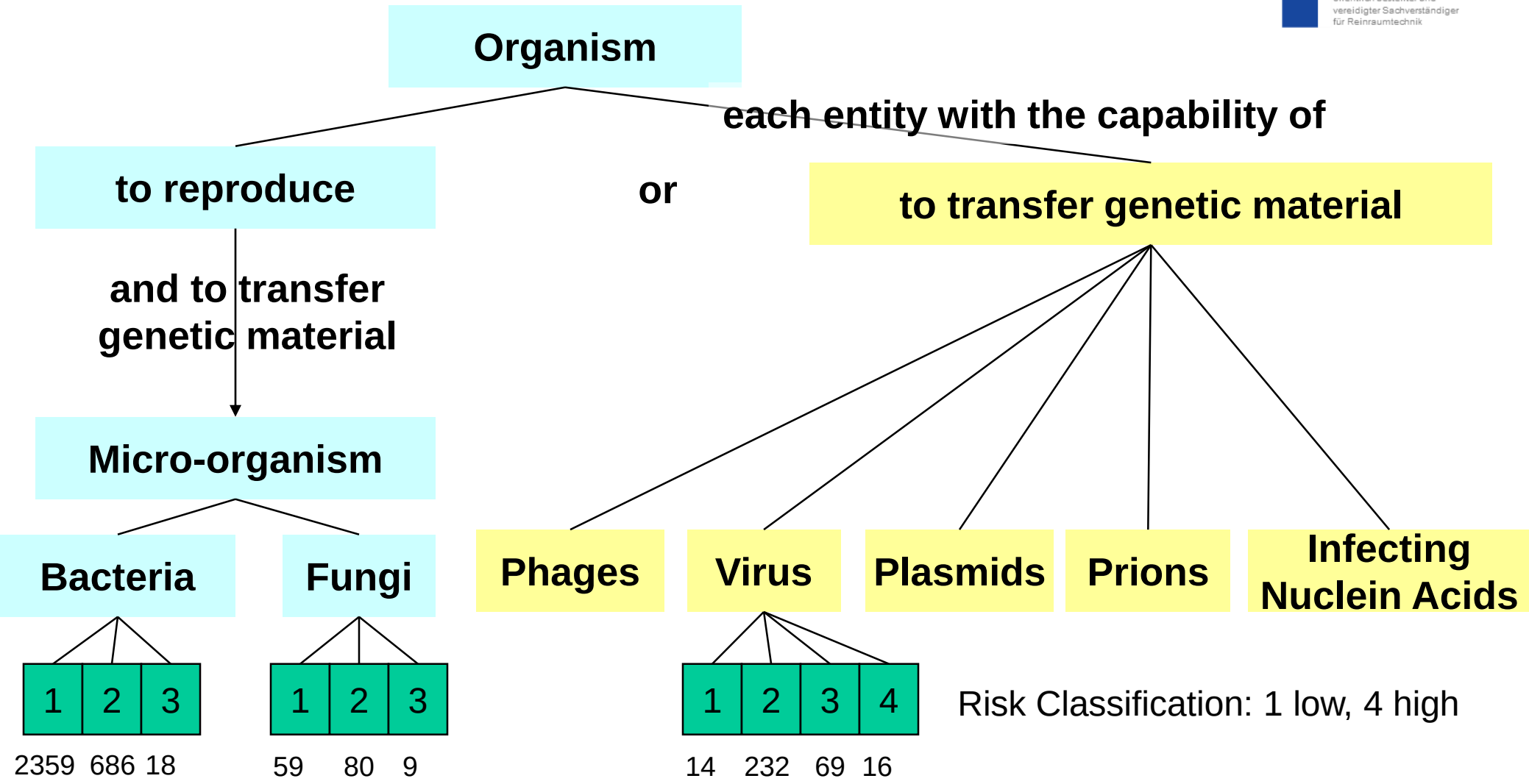

Risk Classification: 1 low, 4 high

Numbers of Species for the Individual Groups of Risk (partially 3 to 10 CFUs are sufficient for an infection!)

Gentechnikgesetz

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Cleanliness Classes ISO 1 - 9

Grade A – D (E, F)

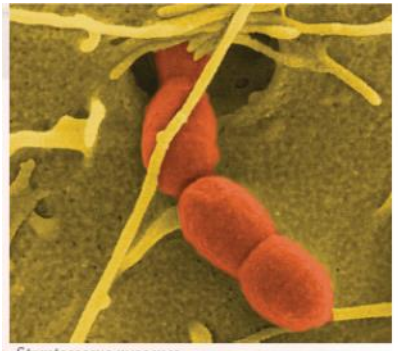
S 1 – S 4, L 1 – L 4

<u>Containment,</u> by definition, is the action of preventing a hostile force from expanding into other areas.

Ian Pearson

HIGH CONTAINMENT:

- **Containment Classification**
- **Containment Concepts**
- **Integration of the Technical Solution**



Streptococcus pyogenes

Planning of Measures

Hazard & Risk Analysis

Cause-Consequence-Analysis

Risk Evaluation

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High Containment Classification:

- **Particle / Aerosols – Cleanliness Classes as Number and Mass Concentrations**
- **Physical / Chemical – Airborne Molecular Contamination as Mass Concentrations**
- **Protection of Personnel – NOEL / Personnel Protection Factor**
- **Protection of Product – Product Protection Factor**

- GMP Good Manufacturing Practice
- GCP Good Clinical Practice
- GLP Good Laboratory Practice
- GDP Good Distribution Practice
- GSP Good Storage Practice
- GEP Good Engineering Practice

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Laboratory Biorisk Management Standard

- CWA 15793:2008
- Management system
- Consistent with other international standards such as ISO 9001/14001 and OHSAS 18001
- Performance based
- Voluntary
- PDCA based

Regulatory Environment

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- European Good Laboratory Practice GLP 88/320/EWG
- ENV/JM/MONO(2005)5, AN INTRODUCTION TO THE BIOSAFETY CONSENSUS DOCUMENTS OF OECD'S WORKING GROUP FOR HARMONISATION IN BIOTECHNOLOGY (ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT) and related OECD GLP documents
- **WHO** Laboratory biosafety manual,Third edition, 2004
- Primary Containment for Biohazards: Selection, Installation and Use of Biological Safety Cabinets, 2nd Edition, U.S. Department of Health and Human Services, Public Health Service Centers for Disease Control and Prevention *and* National Institutes of Health, September 2000 !
- Biosafety in Microbiological and Biomedical Laboratories,U.S. Department of Health and Human Services Public Health Service Centers for Disease Control and Prevention *and* National Institutes of Health, Fourth Edition April 1999
- Antimicrobial Resistance Surveillance - Assessment Tool for National Networks – DRAFT, WHO 2001
- CWA 15793
- CWA 16393 !

Regulatory Environment Part II:

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- *Aide mémoire Bio- und Gentechnologie, Aide mémoire 071210BN, 2004 ZLG, Germany*
- Verordnung über Sicherheit und Gesundheitsschutz bei Tätigkeiten mit biologischen Arbeitsstoffen (Biostoffverordnung - BioStoffV)*, 2003
- TRBA 100, Schutzmaßnahmen für gezielte und nicht gezielte Tätigkeiten mit biologischen Arbeitsstoffen in Laboratorien, 2002
- TRBA 105, Sicherheitsmaßnahmen bei Tätigkeiten mit biologischen Arbeitsstoffen Risikogruppe 3**, 2000, see also Anhang III der Richtlinie 90/679/EWG !
- VDI 6300, Draft, 2006, Gentechnische Arbeiten in geschlossenen Systemen; Leitfaden zum sicheren Betrieb gentechnischer Anlagen
- DIN EN 12128, Laboratorien für Forschung, Entwicklung und Analyse, Sicherheitsstufen ..., 1998
- BG-Chemie Merkblatt B 002: "Ausstattung und organisatorische Maßnahmen: Laboratorien"

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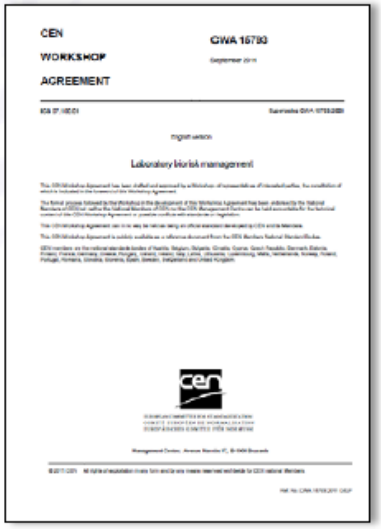
Regulatory Environment Part III:

CWA 15793:2008

Examples of topics covered:

- Biorisk Management Policy
- Hazard identification, risk assessment and risk control
- Roles, responsibilities and authorities
- Training, awareness and competence
- Operational control
- Emergency response and contingency plans
- Inventory monitoring and control
- Accident and incident investigation
- Inspection and audit
- Biorisk management review

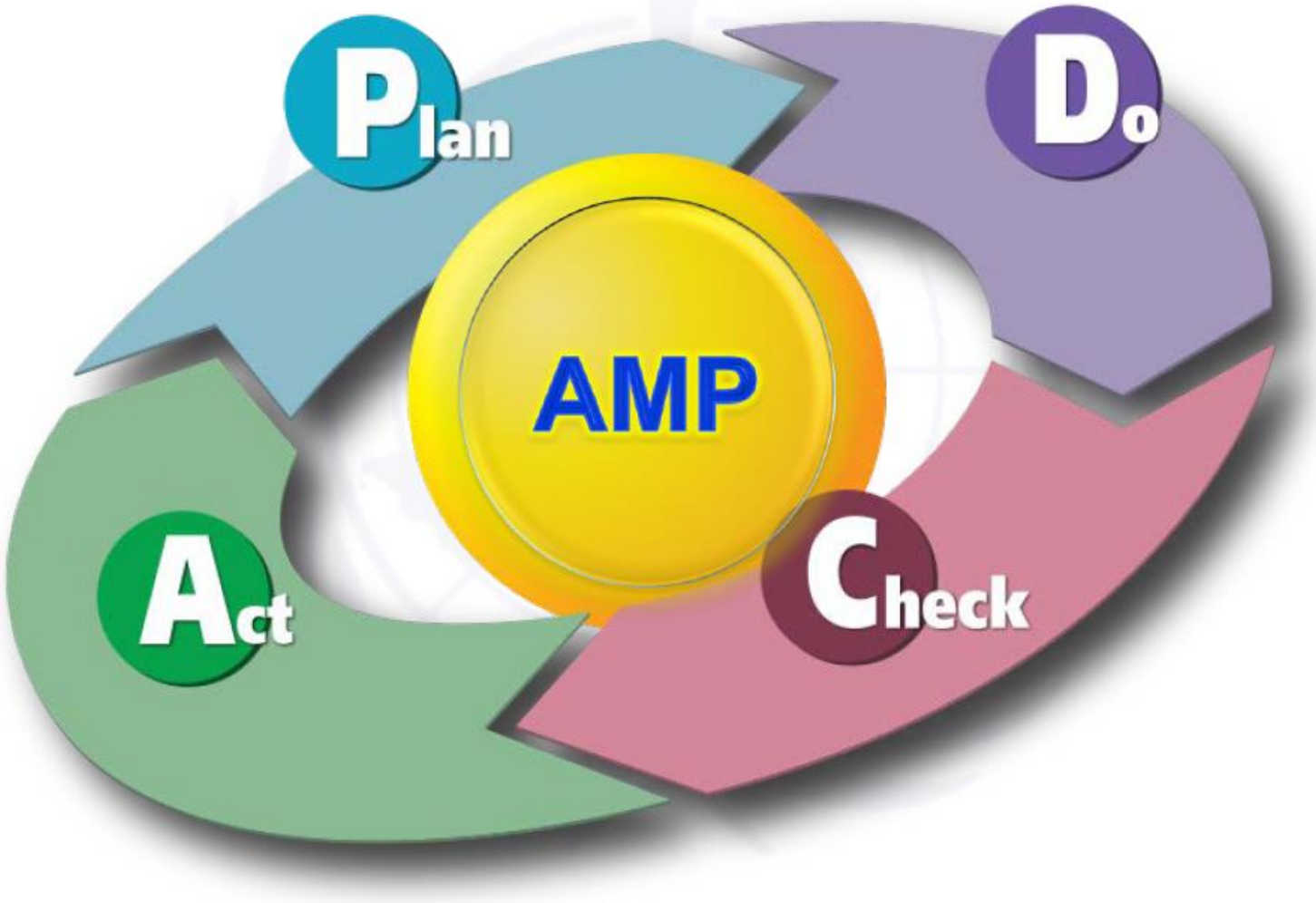

CEN
WORKSHOP
AGREEMENT

CWA 15793

Laboratory biorisk management

WHO Systematic Approach

Systematic Approach



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Biorisk Managment

Biorisk Management = Assessment, Mitigation, Performance

Risk identification	Elimination or Substitution	Control
Hazard/threat identification	Engineering Controls	Assurance
Likelihood evaluation	Administrative Control	Improvement
Consequences evaluation	Practices and Procedures	
	Personal Protective Equipment	

CWA 15793:2011

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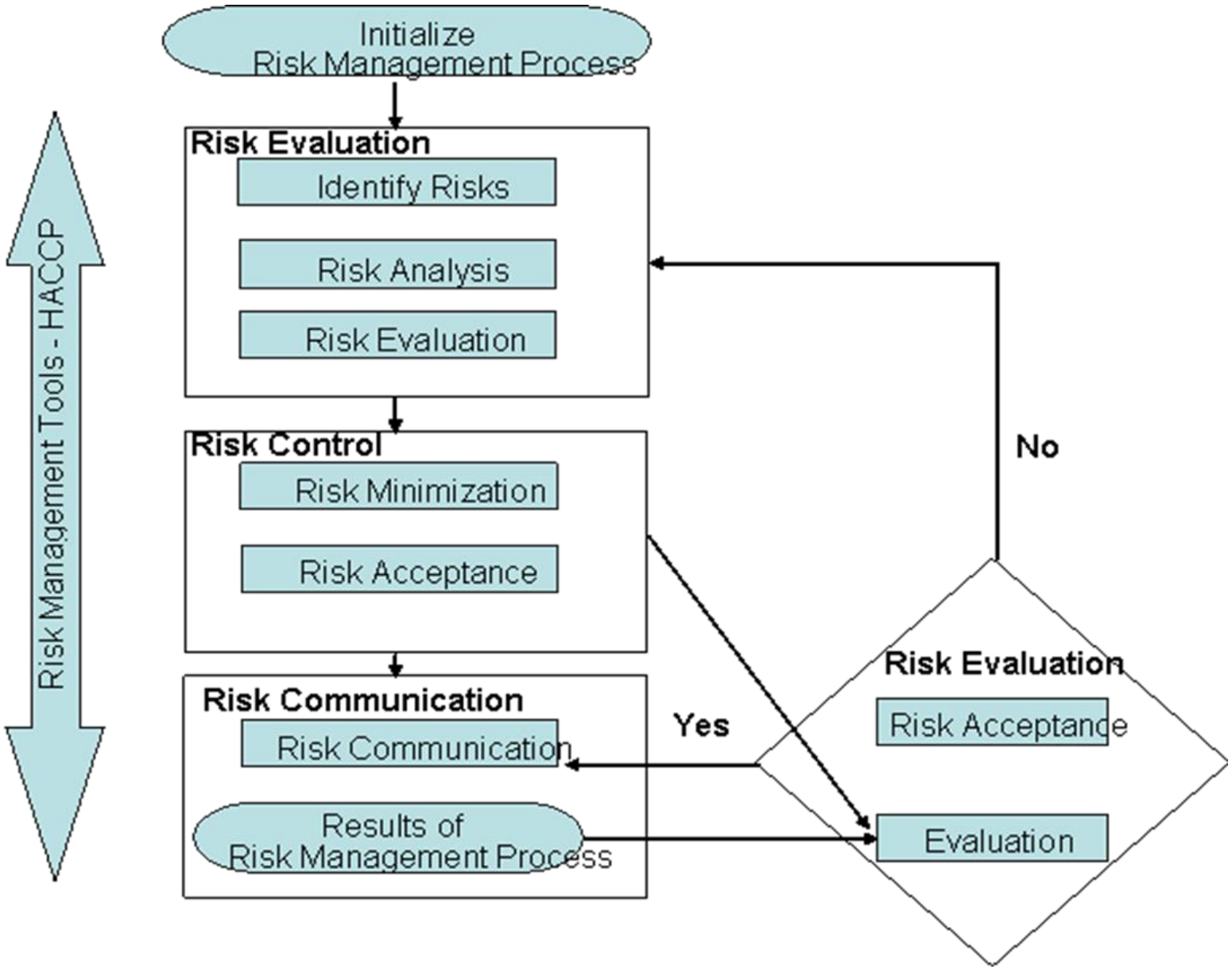
The risk management process



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Scenario A (Pablo) - biosafety

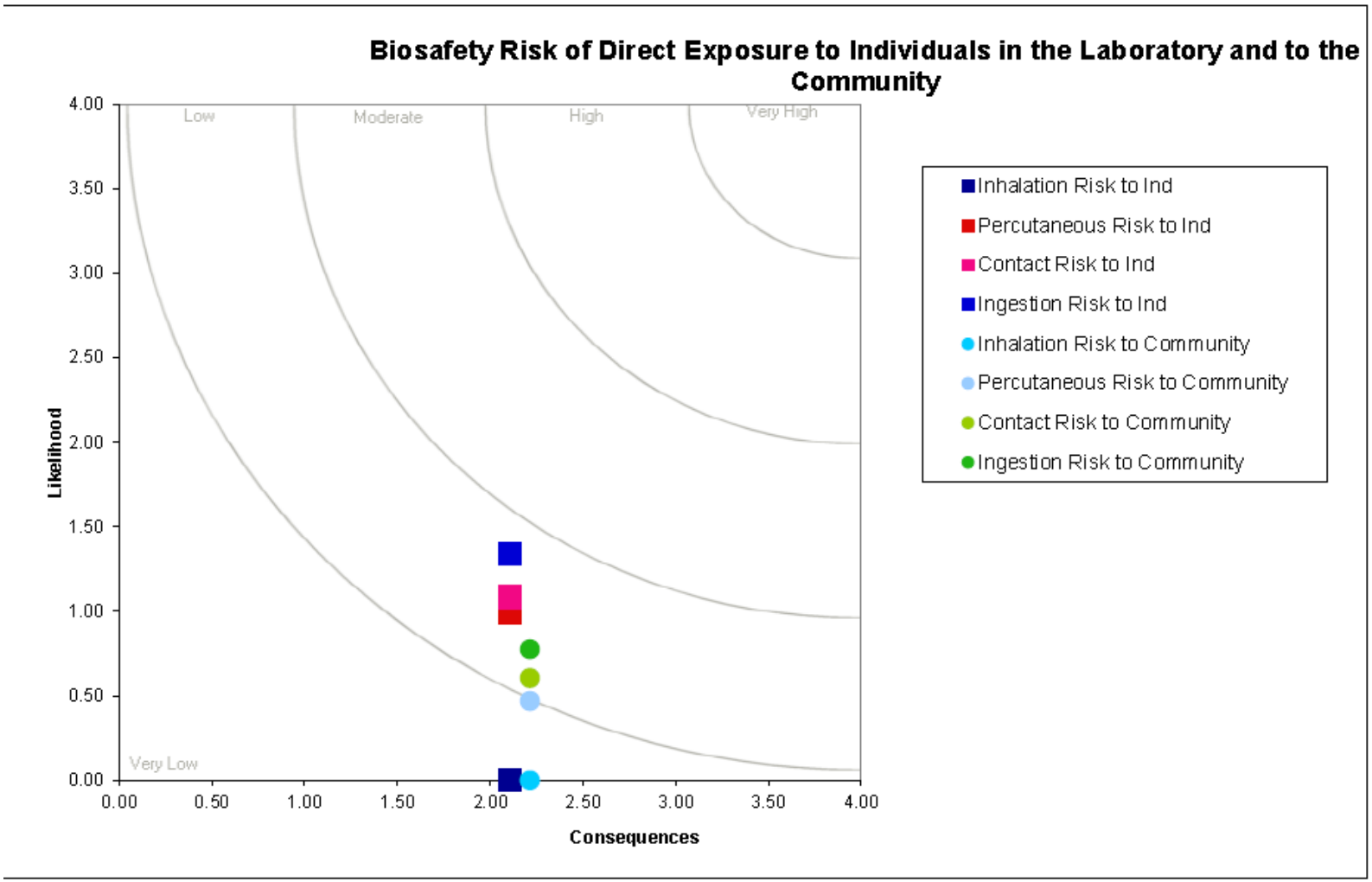

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Table 2. ***Relation of risk groups to biosafety levels, practices and equipment***

RISK GROUP	BIOSAFETY LEVEL	LABORATORY TYPE	LABORATORY PRACTICES	SAFETY EQUIPMENT
1	Basic – Biosafety Level 1	Basic teaching, research	GMT	None; open bench work
2	Basic – Biosafety Level 2	Primary health services; diagnostic services, research	GMT plus protective clothing, biohazard sign	Open bench plus BSC for potential aerosols
3	Containment – Biosafety Level 3	Special diagnostic services, research	As Level 2 plus special clothing, controlled access, directional airflow	BSC and/or other primary devices for all activities
4	Maximum containment – Biosafety Level 4	Dangerous pathogen units	As Level 3 plus airlock entry, shower exit, special waste disposal	Class III BSC, or positive pressure suits in conjunction with Class II BSCs, double-ended autoclave (through the wall), filtered air

BSC, biological safety cabinet; GMT, good microbiological techniques (see Part IV of this manual)

WHO Laboratory Biosafety Manual

Table 3. ***Summary of biosafety level requirements***

	BIOSAFETY LEVEL			
	1	**2**	**3**	**4**
Isolation[a] of laboratory	No	No	Yes	Yes
Room sealable for decontamination	No	No	Yes	Yes
Ventilation:				
— inward airflow	No	Desirable	Yes	Yes
— controlled ventilating system	No	Desirable	Yes	Yes
— HEPA-filtered air exhaust	No	No	Yes/No[b]	Yes
Double-door entry	No	No	Yes	Yes
Airlock	No	No	No	Yes
Airlock with shower	No	No	No	Yes
Anteroom	No	No	Yes	—
Anteroom with shower	No	No	Yes/No[c]	No
Effluent treatment	No	No	Yes/No[c]	Yes
Autoclave:				
— on site	No	Desirable	Yes	Yes
— in laboratory room	No	No	Desirable	Yes
— double-ended	No	No	Desirable	Yes
Biological safety cabinets	No	Desirable	Yes	Yes
Personnel safety monitoring capability[d]	No	No	Desirable	Yes

[a] Environmental and functional isolation from general traffic.
[b] Dependent on location of exhaust (see Chapter 4).
[c] Dependent on agent(s) used in the laboratory.
[d] For example, window, closed-circuit television, two-way communication.

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BIOHAZARD

WHO 0464

ADMITTANCE TO AUTHORIZED PERSONNEL ONLY

Biosafety Level: _____

Responsible Investigator: _____

In case of emergency call: _____

Daytime phone: _____Home phone: _____

Authorization for entrance must be obtained from the Responsible Investigator named above.

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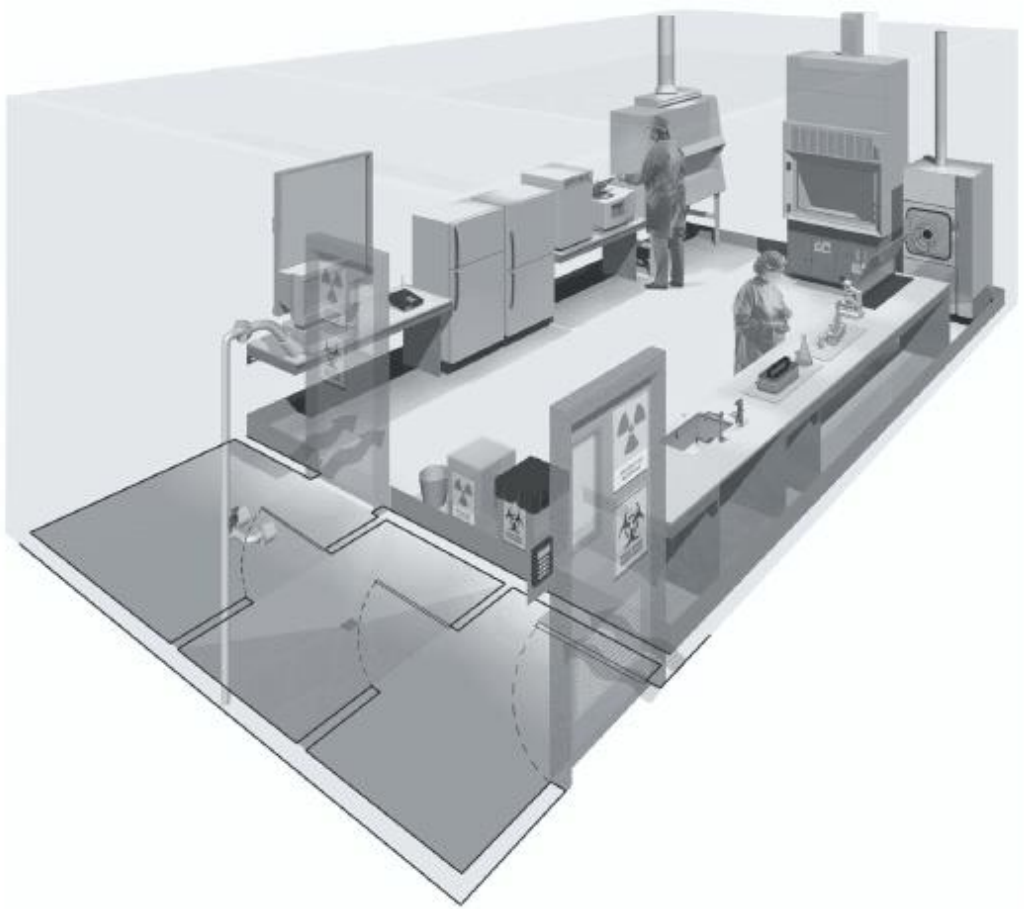

Figure 4. **A typical Biosafety Level 3 laboratory**
(graphics kindly provided by CUH2A, Princeton, NJ, USA). The laboratory is separated from general traffic flow and accessed through an anteroom (double door entry or basic laboratory – Biosafety Level 2) or an airlock. An autoclave is available within the facility for decontamination of wastes prior to disposal. A sink with hands-free operation is available. Inward directional airflow is established and all work with infectious materials is conducted within a biological safety cabinet.

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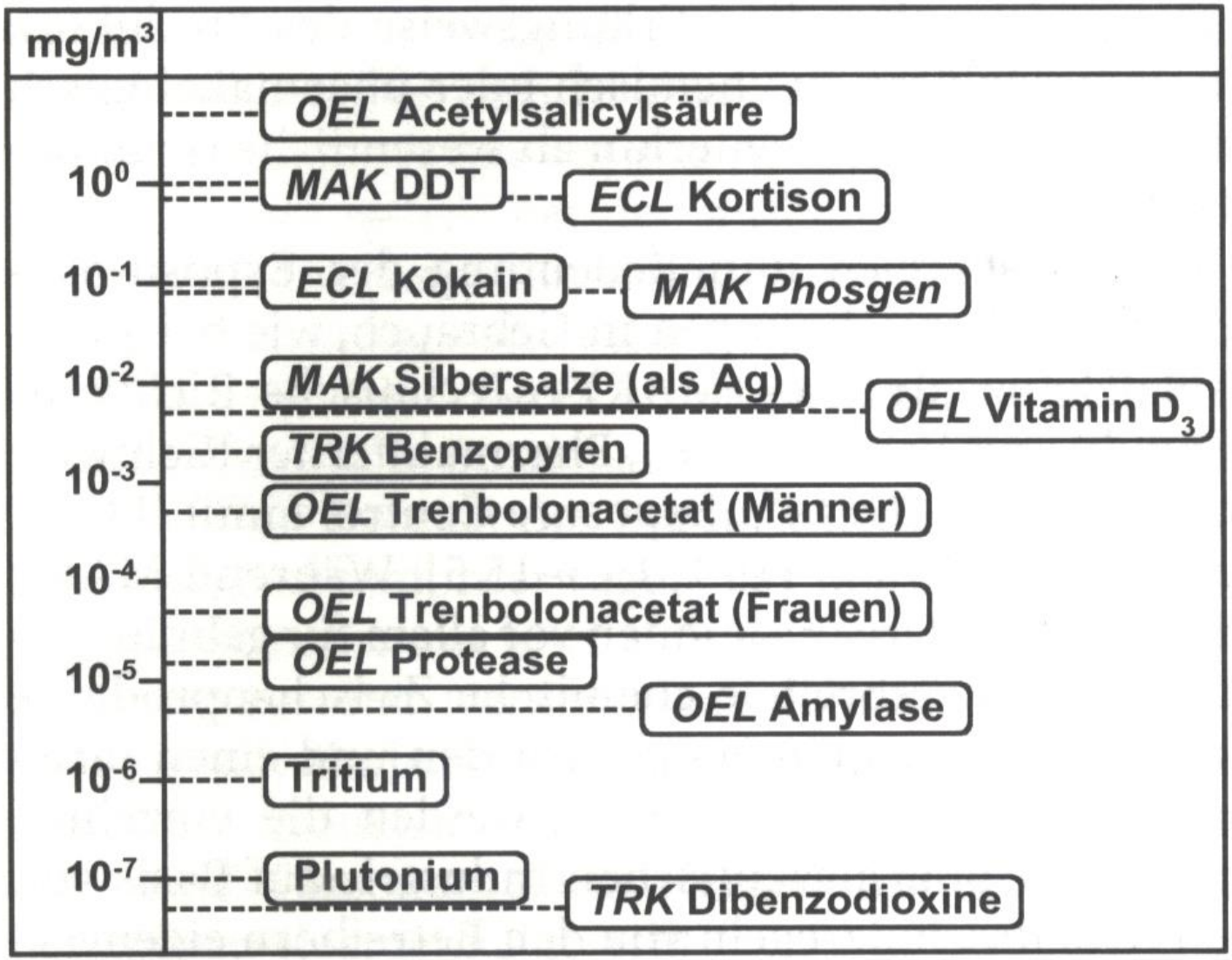

Occupational Exposure Limits for Some Drug Substances and Hazardous Material, VDI 2083

Safety: Protection of Personnel / Environment

For the determination of the maximum exposure levels the following aspects should be regarded:

- identity of the compound (analogy with known or similar materiel)
- physical and chemical compound data
- toxicological data: acute or chronic toxicity, carcinogenic, mutagenic, reproduction toxicity)
- pharmacologic properties: function, pharmaco-dynamic, pharmaco-kinetic, secondary and side effects
- epidemic data, experience
- sensitizing properties
- individual compatibility and group of risk
- infecting properties

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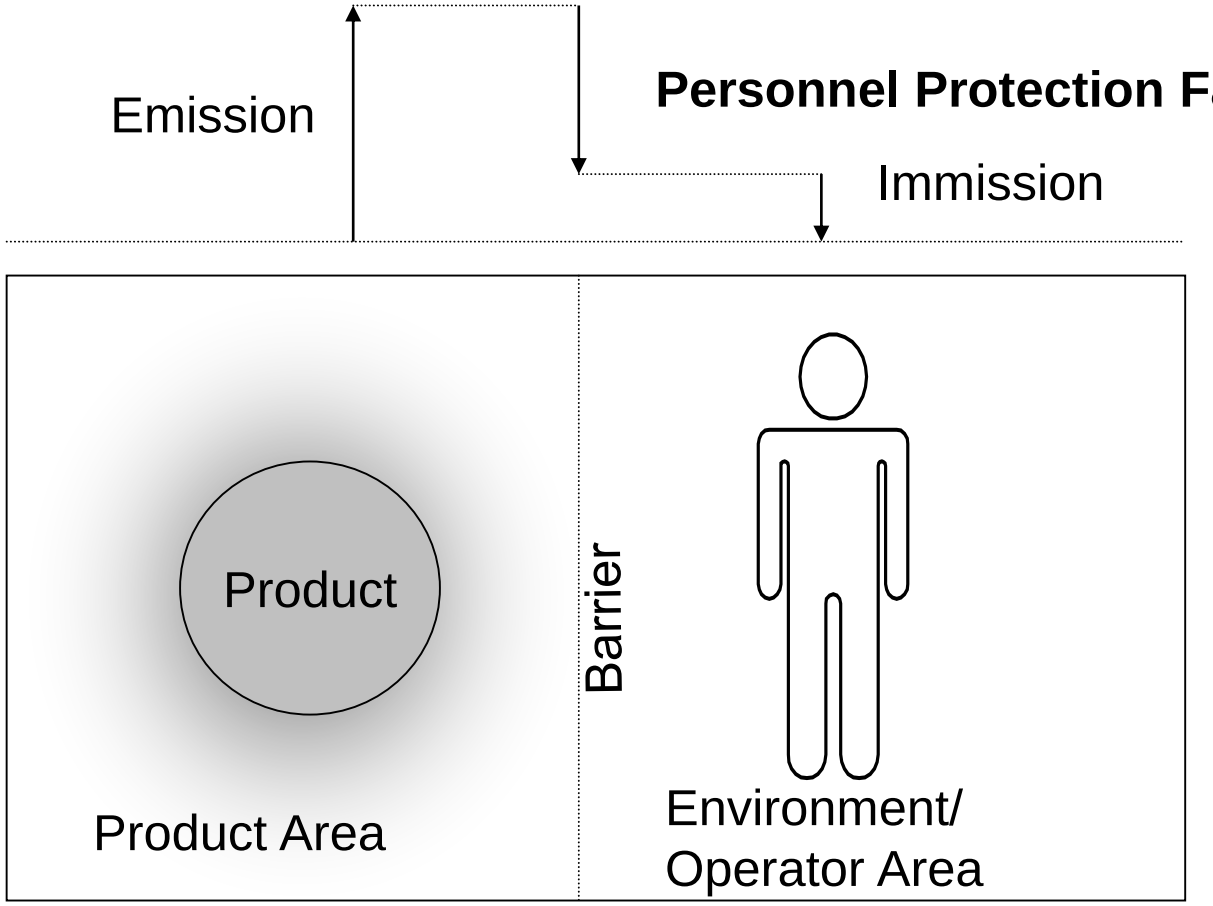

Personnel Protection Factor

Personnel Protection Factor = $\frac{\text{Emission}}{\text{Immission}}$

NOEL: No Observed Effect Level

$$\text{Exposere Level} = \frac{\text{NOEL}}{\text{Respiratory Volume/8 h Shift (10 m}^3\text{) x S}}$$

S: Safety Factor

LOEL: Lowest Observed Effect Level

MAK: Maximum Allowable Concentration
TRK: Technical Concentration Limits
OEL: Occupational Exposure Limit
PIR: Pharma-internal Concentration Limit
STEL: Short Term Exposure Limit
ECL: Exposure Control Limit

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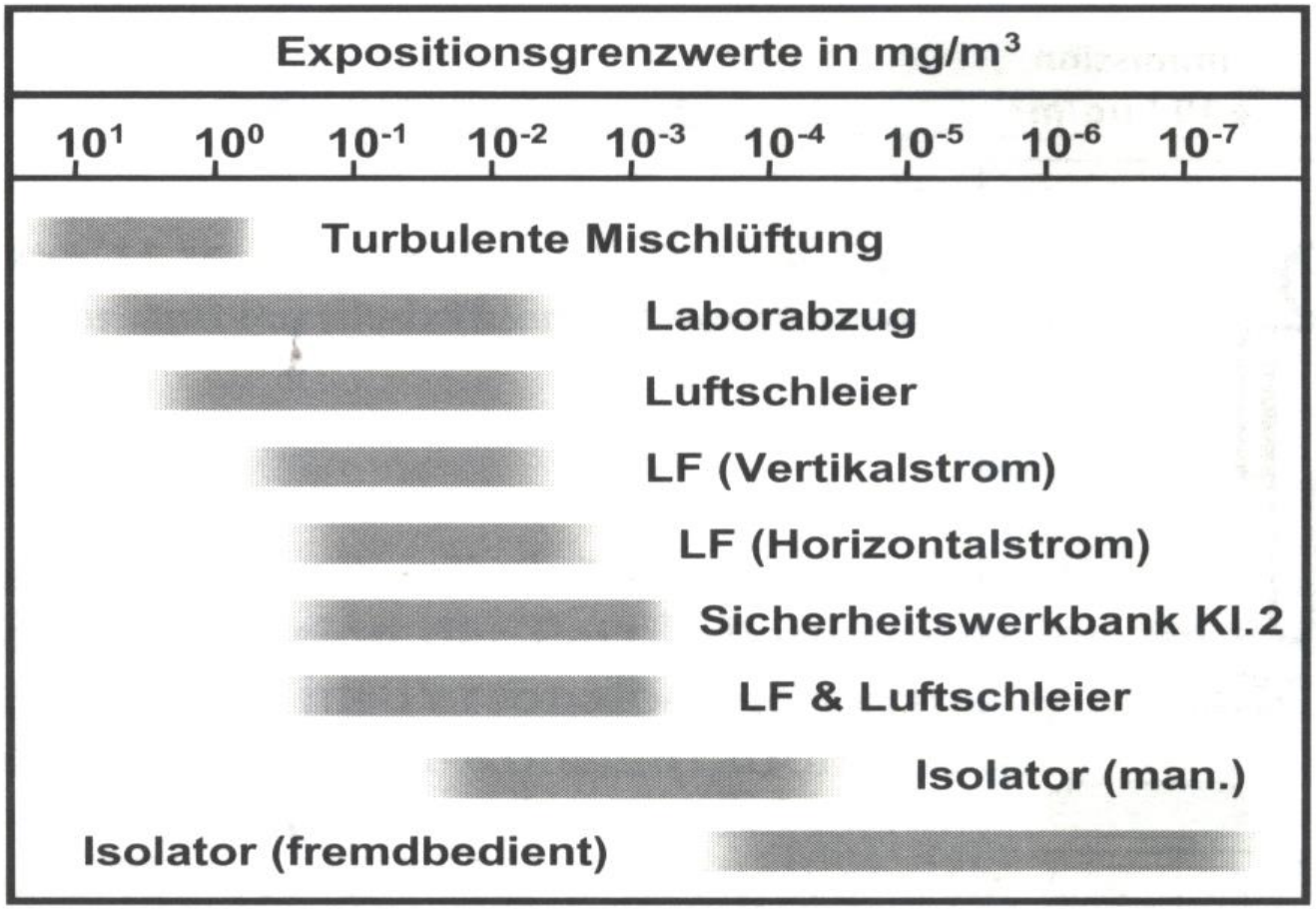
Technical Solutions for the Containment Levels

LF: Laminar Flow
Low Turbulent Displacement Flow



Protection Systems and Applications, VDI 2083, Part 16

Concepts for Protection / Contamination Control

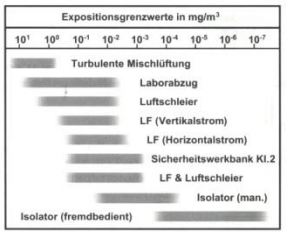
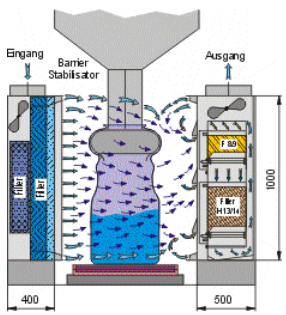
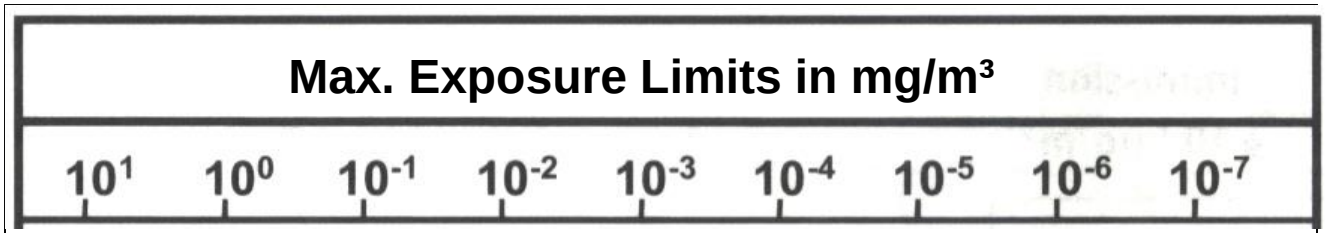
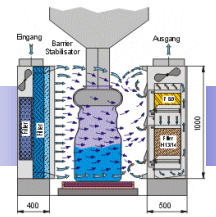


Abb. 15.13 Schutzsysteme mit Anwendungsbereichen





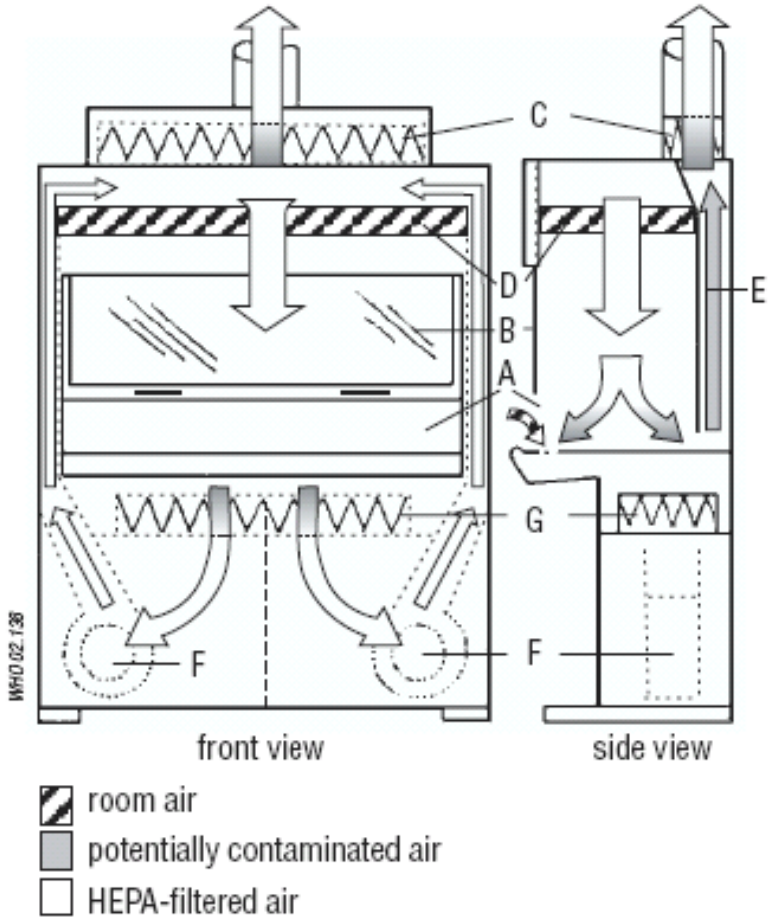


Barrier Systems

Safety Benches Class 2 u. 3

Isolators (manuell and automatic)

Safety Cabinets



WHO BSM

Figure 8. ***Schematic diagram of a Class IIB1 biological safety cabinet.***
A, front opening; B, sash: C, exhaust HEPA filter; D, supply HEPA filter; E, negative-pressure exhaust plenum; F, blower; G, HEPA filter for supply air. Connection of the cabinet exhaust to the building exhaust air system is required.

Table 9. ***Differences between Class I, II and III biological safety cabinets (BSCs)***

BSC	FACE VELOCITY (m/s)	AIRFLOW (%)		EXHAUST SYSTEM
		RECIRCULATED	EXHAUSTED	
Class I[a]	0.36	0	100	Hard duct
Class IIA1	0.38–0.51	70	30	Exhaust to room or thimble connection
Class IIA2 vented to the outside[a]	0.51	70	30	Exhaust to room or thimble connection
Class IIB1[a]	0.51	30	70	Hard duct
Class IIB2[a]	0.51	0	100	Hard duct
Class III[a]	NA	0	100	Hard duct

NA, not applicable.
[a] All biologically contaminated ducts are under negative pressure or are surrounded by negative pressure ducts and plenums.

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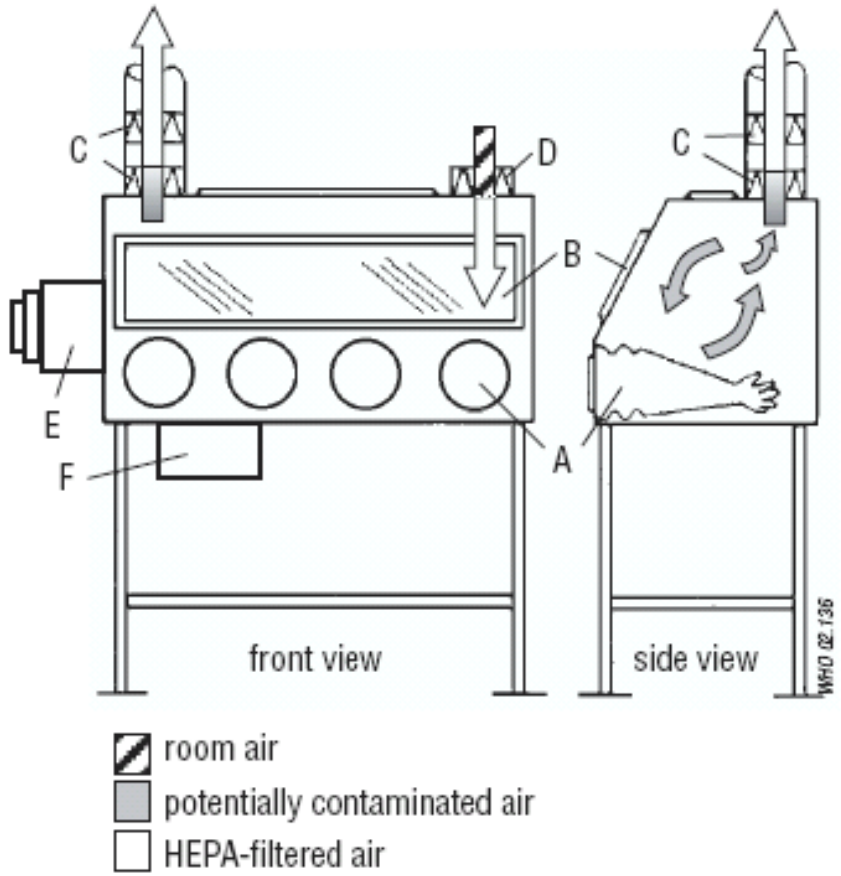

Source WHO BSM

Figure 9. ***Schematic representation of a Class III biological safety cabinet (glove box).*** *A, glove ports for arm-length gloves; B, sash; C, double-exhaust HEPA filters; D, supply HEPA filter; E, double-ended autoclave or pass-through box; F, chemical dunk tank. Connection of the cabinet exhaust to an independent building exhaust air system is required.*

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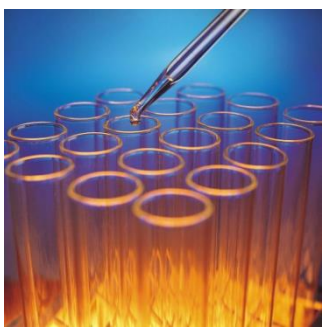
Parallel Engineering and Validation/Qualification



- System Advice
- Validation Advise
- Development
- Validation Master Plan
- Project Planning
- Risk Analysis / DQ
- Production
- IQ FAT
- Assembly
- IQ SAT
- Commissioning
- OQ
- Service
- PQ Assisstence
- Training
- Training
- After-Sales-Service
- Re-Validation

Laws and Regulation

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BSL Laboratory Certification

Ideas from WHO and Capabilities of Certifiers

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Comments:

- There is no international certification board for BSL laboratories.
- Looking onto the following slides there are potential certification organization for model 1 and 2 from WHO due to our services and capabilities
- BV is highly specialized in the field of contamination control
- BV fulfills all requirements for a certification organization as defined and presented below.

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World Health Organization
Regional Office for South-East Asia

Health Systems Commonly Asked Questions:

2. Accreditation:

A formal process by which a recognized, usually NGO body assesses and recognizes that a health care organization meets applicable pre-determined and published standards. Accreditation standards are usually regarded as optimal and achievable, and are designed to encourage continuous improvement efforts within accredited organizations. An accreditation decision about a specific health care organization is made following a periodic on-site evaluation by a team of peer review, typically conducted every two to three years. Accreditation is often a voluntary process in which organizations choose to participate, rather than one required by law and regulation. (USAID, QA Project, 1999)

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World Health Organization
Regional Office for South-East Asia

Health Systems Commonly Asked Questions:

3. **Certification:**

is a process by which an authorized body, either a governmental or non-governmental organization, evaluates and recognizes either an individual or an organization as meeting pre-determined requirements and criteria. Although the terms accreditation and certification are often used interchangeably, accreditation usually applies only to organizations, while certification may apply to individuals as well as to organizations.

When applied to individual practitioners, certification usually implies that the individual has received additional education and training, and demonstrated competence in a specialty area beyond the minimum requirements set for licensure. An example of such a certification process is a physician who receives certification by a professional specialty board in the practice of obstetrics. When applied to an organization, or part of an organization, such as the laboratory, certification usually implies that the organization has additional services, technology or capacity beyond those found in similar organizations. (USAID QA Project, 1999)

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Laboratory Biosafety and Biosecurity

7-8 April 2005, REDI Centre, Singapore

Nicoletta Previsani

Biosafety

Department of Communicable Disease Surveillance and Response

WORLD HEALTH ORGANIZATION

Source

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WHO Laboratory Biosafety Manual

Biosafety:
To promote the use of safe practices in the handling of pathogenic microorganisms
- •in the laboratory
- •during transportation
- •in field investigations
- •in manufacturing facilities
- •in health-care facilities

- **Laboratory Biosafety Manual, 3rd edition**
  - lab commissioning and certification
  - lab biosecurity concepts

1983 1993 2003 2004

- translated into F, S, P, Ch, Ru
- available on web, CD-Rom, hard copies

WORLD HEALTH ORGANIZATION

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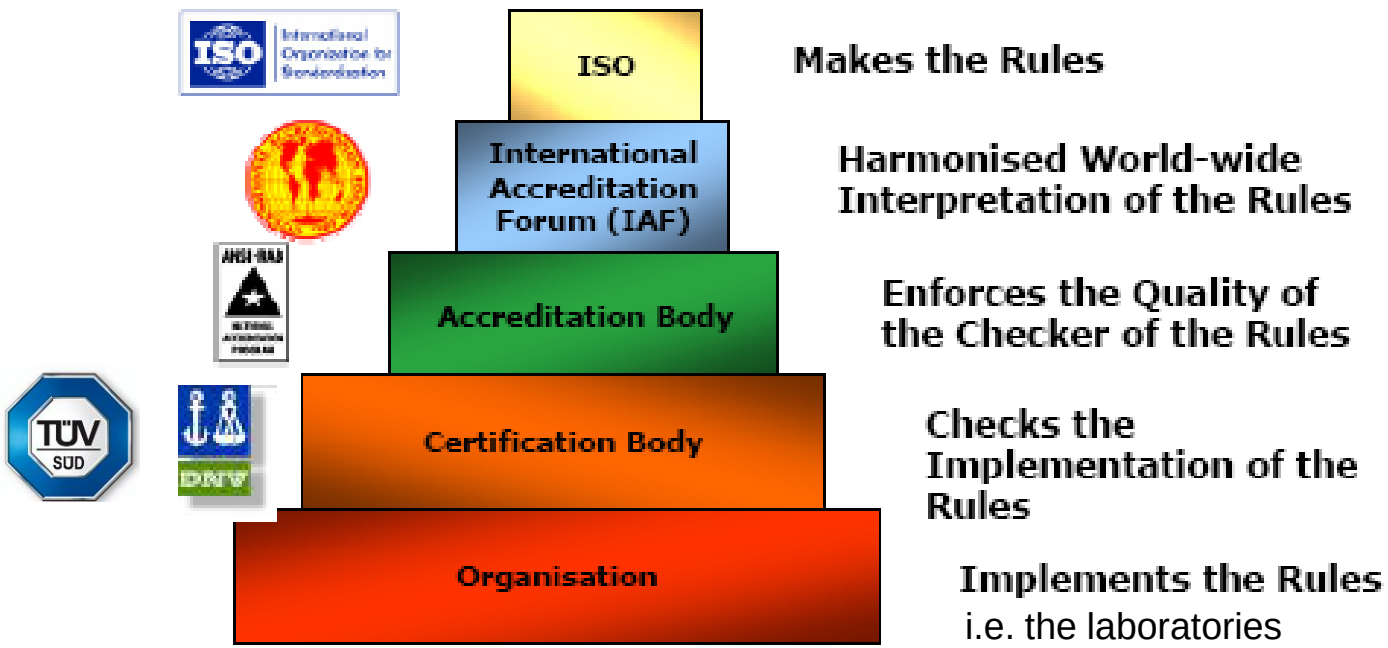
Model 1 for potential BSL Laboratory Certification System

Players in an ISO Management System



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Model 2 for potential BSL Laboratory Certification System

Potential Players in a Laboratory Biosafety & Biosecurity Certification System

WHO

International Accreditation Forum (IAF)

Accreditation Body

Certification Body

Organisation

Produces guidelines (i.e. Laboratory Safety Manual)

Produces standard based upon Laboratory Safety Manual (e.g. EBSA, ABSA, UN, others?)

Ensures certification bodies conduct assessments effectively (ABSA, EBSA, others?)

Checks the Implementation of the Rules (e.g. DNV and other certification bodies) like TUEV

Implements the rules (i.e. laboratories)

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Von der Industrie- und
Handelskammer zu Köln
öffentlich bestellter und
vereidigter Sachverständiger
für Reinraumtechnik

Background to ISO 14698

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Pharmagraph
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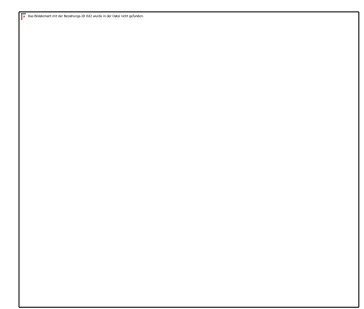

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ISO standards

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- ISO = International Organisation for Standardisation
- ISO made up of 161 countries world-wide
- ISO standards are consensus documents, with agreement from >75% of member countries
- ISO documents are typically adopted by member countries as their national standard

ISO 14644

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- Regulators inspect to GMP, which defines target cleanliness levels
- But GMP does not tell you the procedure to follow to classify your cleanrooms
- EU GMP & CGMP call up ISO 14644 for the methodology

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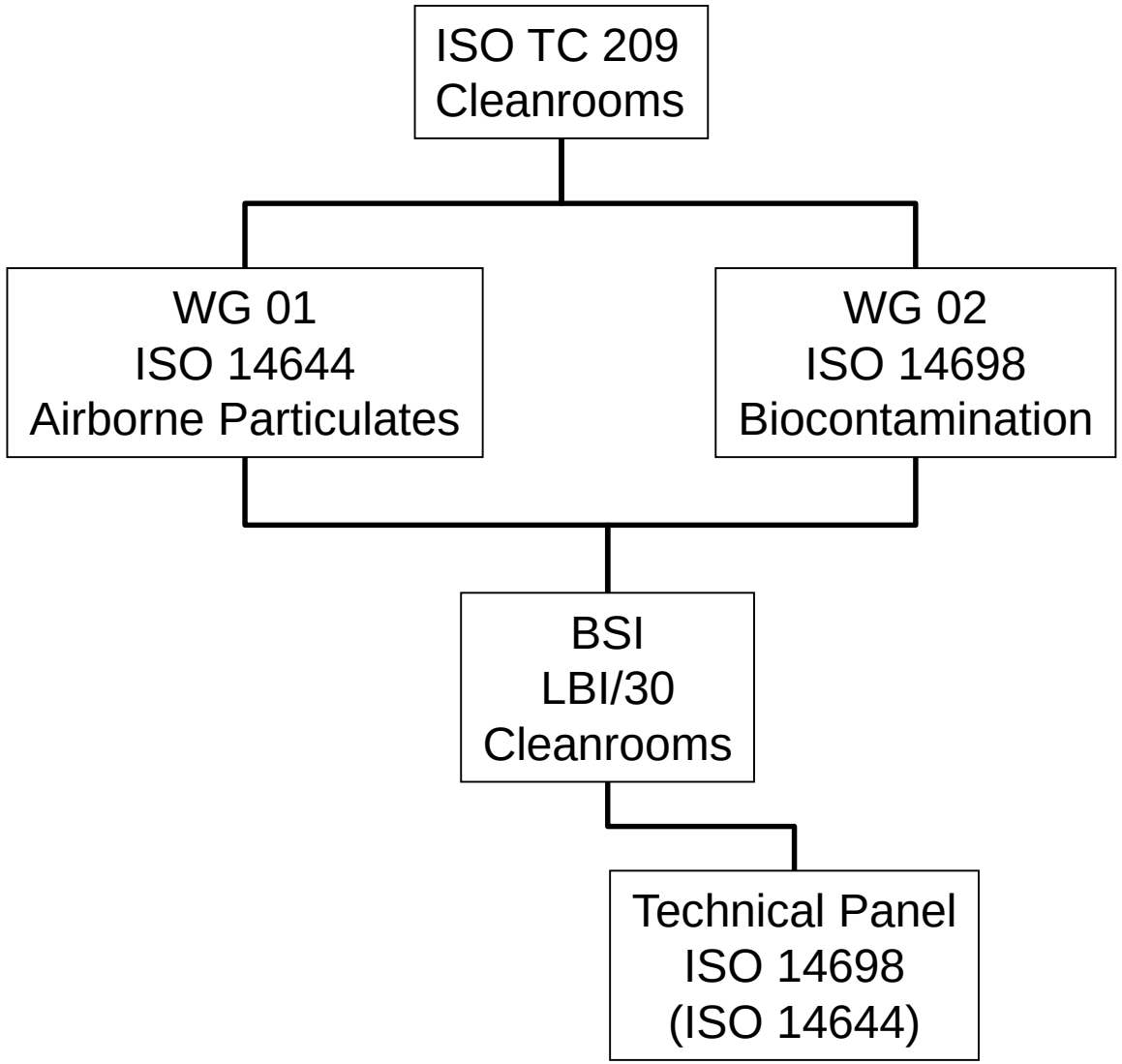
ISO and BSI



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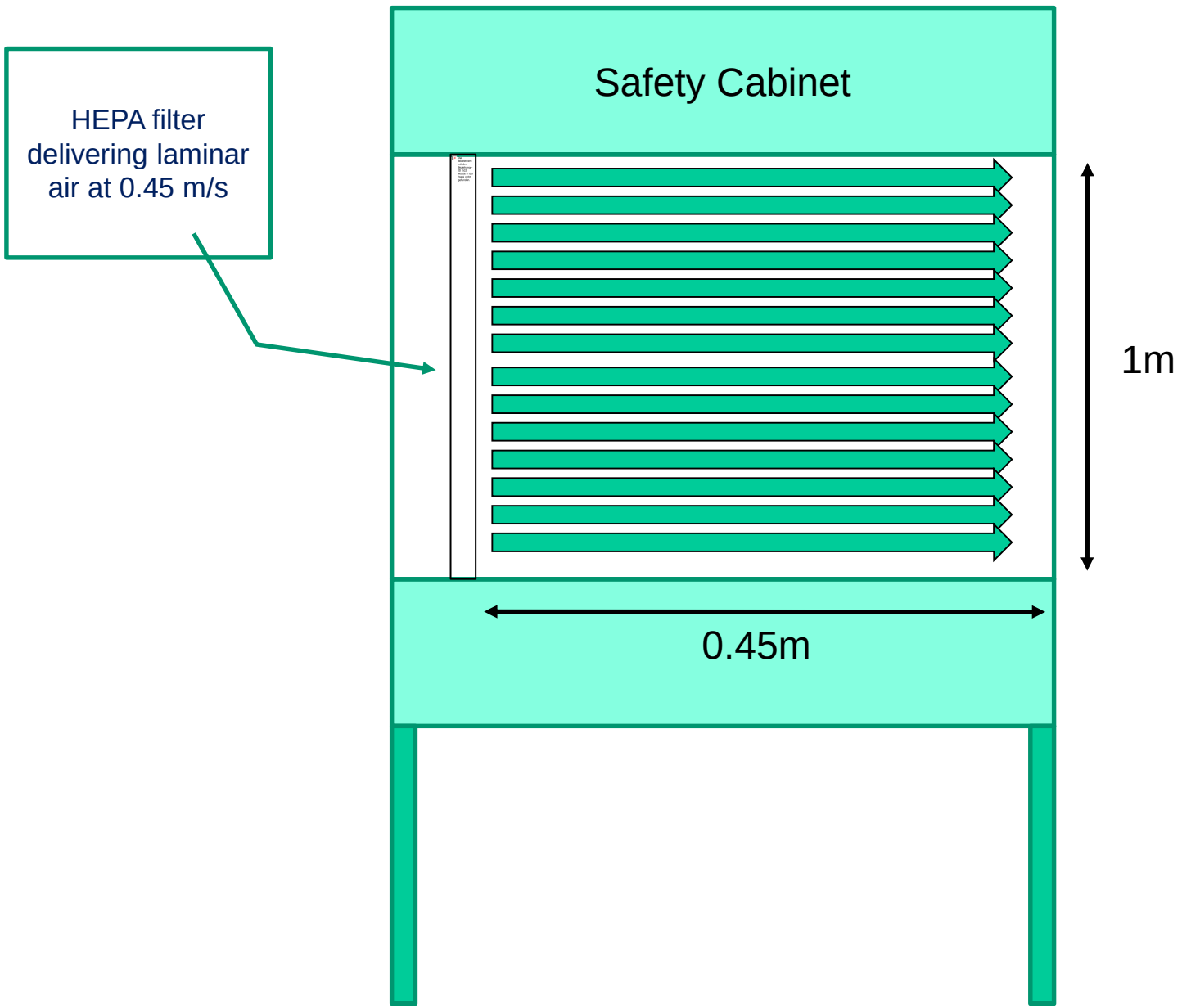
Concept of airborne viable counts vs. settle plate & product risk



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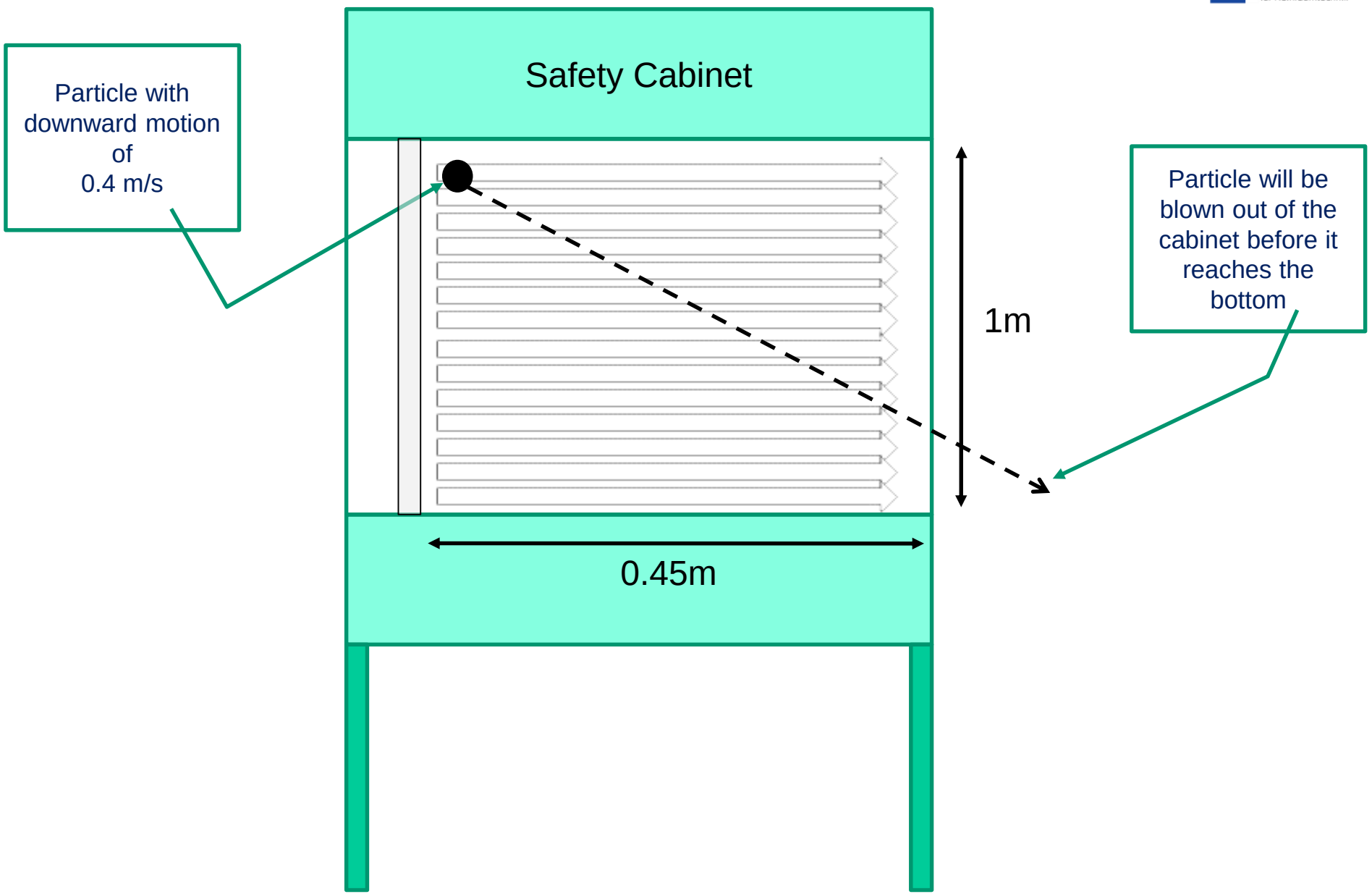

Concept of airborne viable counts vs. settle plate & product risk

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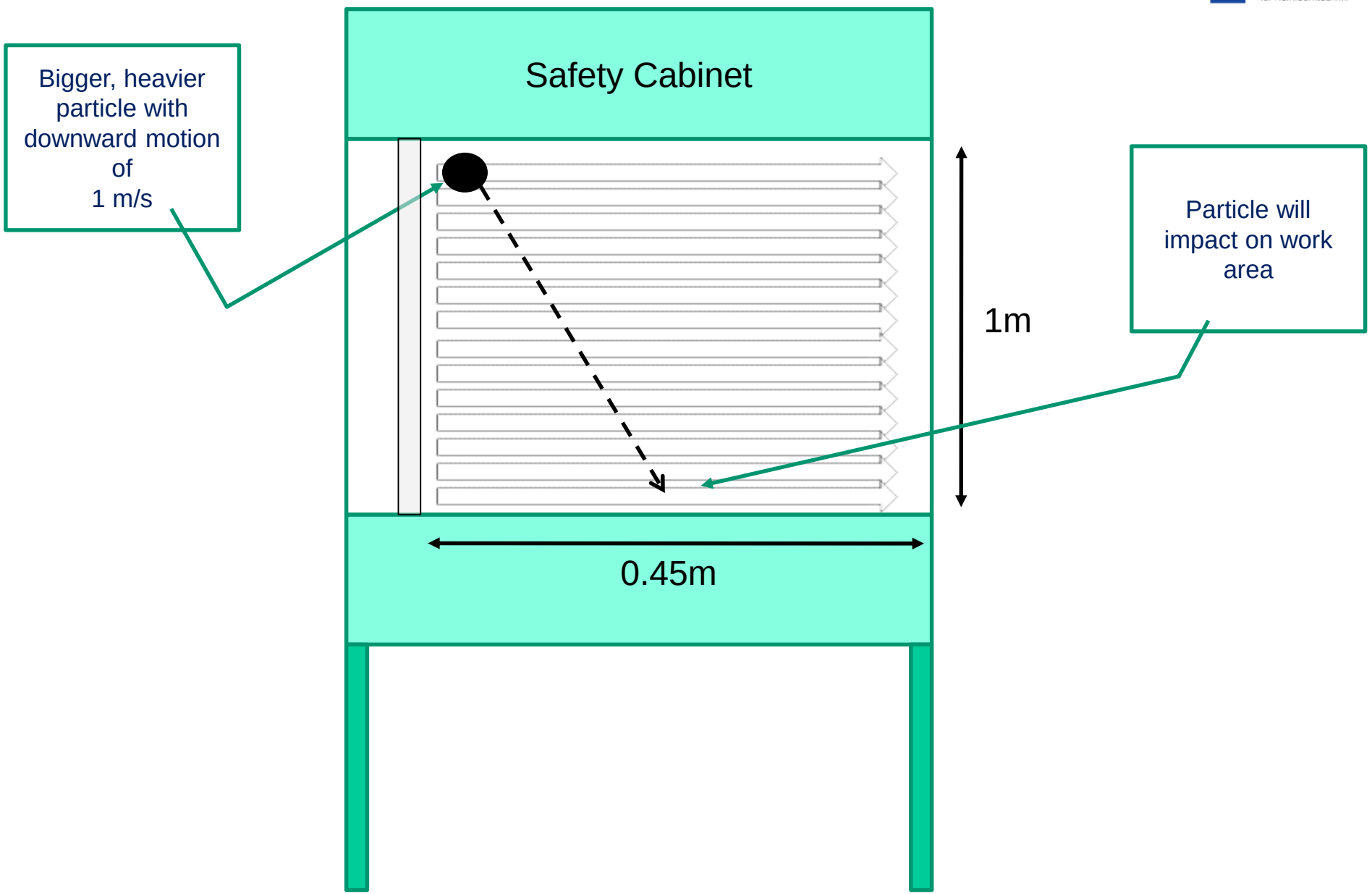

Concept of airborne viable counts vs. settle plate & product risk

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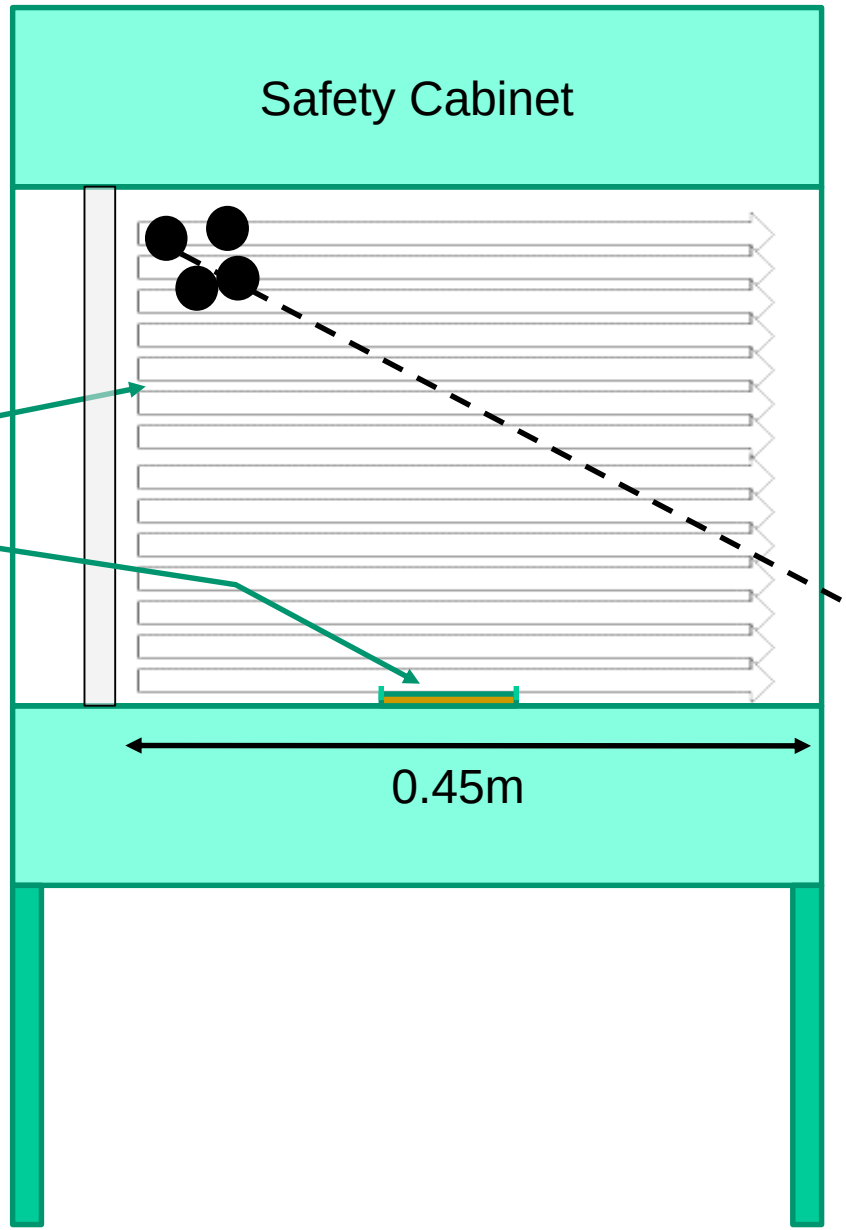
This air system will tolerate a certain level of airborne contamination before some falls out into the work area

Settle plate gives picture of performance of system vs airborne contamination challenge – true indicator of what may be falling into your product



Particles will be blown out of the cabinet before they reach the bottom

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Concept of airborne viable counts vs. settle plate & product risk

Table 10. Ratio of 5μm counts and RCS counts

	Test Number				
	1	2	3	4	5
Mean particle concentration/m^3 @ ≥0.5μm	205.1	987.8	2712.2	30972.3	117094.2
Mean particle concentration/m^3 @ ≥5.0μm	17.0	20.4	378.8	4566.7	10864.0
Mean RCS count (cfu/m^3)	0.0	0.0	8.5	73.5	218.5
Mean settle plate count (cfu)	0.0	0.0	1.0	4.7	25.2
Ratio of mean RCS count (cfu/m^3)/ mean non-viable particle concentration/m^3 @ ≥5.0μm	0.0000	0.0000	0.0224	0.0161	0.0201
Ratio of mean settle plate count (cfu)/mean non-viable particle concentration/m^3 @ ≥5.0μm	0.0000	0.0000	0.0026	0.0010	0.0023

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Microbiological evaluation of clean rooms and other controlled environments)

Draft USP<1116> - Key Items

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Von der Industrie- und Handelskammer zu Köln öffentlich bestellter und vereidigter Sachverständiger für Reinraumtechnik

- Move from numbers of CFU to incidence rates or “contamination recovery rates”

- Settle plates as qualitative indication of air – prefer the use of active samplers and settle plates are ‘optional’
  - *“The exposure of open agar-filled Petri dishes, or settling plates, is not to be used for quantitative estimations of the microbial contamination levels of critical environments.”*
  - *“Settling plates may be particularly useful in critical areas, where active sampling could be intrusive and a hazard to the aseptic operation.”*

- Suggests air particle counting may be sufficient in aseptic core because microbial sampling during production “may seem unwise” (contamination risk)

Draft USP<1116> -Incidence of contamination

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Grade	Active air sample	Settle Placte (9cm) 4hr	Contact plate or swab	Glove or garment
Isolator or Closed RABS (ISO 5 or better)	<0.1%	<0.1%	<0.1%	<0.1%
ISO 5	<1%	<1%	<1%	<1%
ISO 6	<3%	<3%	<3%	<3%
ISO 7	<5%	<5%	<5%	<5%
ISO 8	<10%	<10%	<10%	<10%

Draft USP<1116> - Key Items

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- Suggests frequency of monitoring in isolators:
  - Active air – once/day
  - Surface sampling – at end of each campaign
  - Glove sampling – left to users discretion
- Zero CFU doesn't indicate sterile, just indicates "below level of detection"
- Can't differentiate between 1CFU and 10CFU with current techniques
- Suggests no practical way to set alert and action levels at very low levels of contamination
- Suggests investigation for 'significant excursion', which is defined as >15CFU for surface, personnel or active air

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Classification Standard ISO 14644-1

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Class	Number of Particles per Cubic Meter by Micrometer Size					
	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1 µm	5 µm
ISO 1	10	2				
ISO 2	100	24	10	4		
ISO 3	1,000	237	102	35	8	
ISO 4	10,000	2,370	1,020	352	83	
ISO 5	100,000	23,700	10,200	3,520	832	29
ISO 6	1,000,000	237,000	102,000	35,200	8,320	293
ISO 7				352,000	83,200	2,930
ISO 8				3,520,000	832,000	29,300
ISO 9				35,200,000	8,320,000	293,000

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GMP uses a sub-set of ISO 14644-1, e.g. Grade B:

Class	Number of Particles per Cubic Meter by Micrometer Size					
	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1 µm	5 µm
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GMP uses a sub-set of ISO 14644-1, e.g. Grade B:

Class	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
	At rest		In operation	
Grade	0.5 µm	5.0µm	0.5 µm	5.0µm
A	[illegible]	[illegible]	3 520	20
B	3 520	29	352 000	2 900
C	352 000	[illegible]	3 520 000	29 000
D	3 520 000	29 000	Not defined	Not defined

ISO 4	10,000	2,370	1,020	352	83	
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ISO 21501 – ‘the best kept secret’

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- Regulators inspect to EU GMP, which calls up ISO14644
- New ISO14644 refers to ISO21501-4
- ISO 21501-4 states – “*Instruments that conform to this part of ISO 21501 are used for the* ***classification of air cleanliness in cleanrooms and associated controlled environments in accordance with ISO 14644-1as well as the measurement of number and size distribution of particles in various environments”***
- Regulators becoming aware because of mention in ISO 14644

Purpose of ISO 21501-4

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Quote from the ISO 21501 Standard:

"*The purpose of ISO 21501 is to provide a calibration procedure and verification method for particle counters, so as to minimize the inaccuracy in the measurement result by a counter, as well as the differences in the results measured by different instruments*."

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Issues with ISO 14698:2003

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- ISO 14698 not in line with ISO 14644
- No Tables of Classification
- Not up to date with technology advances in Rapid Microbiological Methods (eg ATP, Bioluminescence)
- Not up to date with Risk Assessment & Risk Management techniques (eg ICH Q9 QRM)

Issues with ISO 14698:2003

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- No Check Lists of “Things to Consider”
- Cannot “Monitor a process into Control”
- Not enough clarity on differences, issues and guidance on Aseptic vs Non Sterile applications
- Not enough guidance on Airborne vs Surface biocontamination risks and control
- Overall seen as not easy to read & use

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öffentlich bestellter und
vereidigter Sachverständiger
für Reinraumtechnik

Proposed New Structure for ISO 14698

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Preliminary Work Items WG02

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From: **ISO/TC 209 N 187**

Resolutions from ISO/TC 209 Meeting 9-10 November 2007
Résolutions de l'ISO/TC 209 (19ème réunion, 9 et 10 Novembre 2007)

Resolution 1
ISO/TC 209 resolves that WG 2 commences work on these two documents:

a. Classification of airborne biocontamination in cleanrooms, including methods of measurement and their validation.

b. Classification of surface biocontamination in cleanrooms, including methods of measurement and their validation.

At the appropriate time during the development of these documents, the position of ISO 14698 Parts 1 and 2 should be considered, as well as a Risk Management Standard.
(All in favor)

New document

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- Suitable for all industries
- Doesn’t contradict existing regulations
- Reflects current international thinking
- Allows classification by microbiology, enable uncoupling from airborne particulate classification where appropriate
- Does not impose additional costs without improving assurance of product quality
- Keep best parts of existing ISO 14698 documents

New document

- Three parts:

1. Establish control requirements
   - What are you trying to achieve
   - What are the important environmental quality attributes
2. Test methods and validation
   - How are you going to measure
   - How do you demonstrate measurements are accurate
3. Demonstrating control
   - What monitoring are you going to carry out to demonstrate continued control and how to analyse the data captured

Controlled Environments – Biocontamination Control Parts 1, 2 and 3

Establish Control requirements

Relevant topics

Introduction

Overview, Scope, systematic scientific approach, importance of QMS

Establish Control Requirements

- Design Space
- Product Quality Attributes
- Risk Assessment
- Direct vs Indirect systems
- Objectionable Species
- Critical Control Points
- Setting Limits

Controlled Environments – Biocontamination Control Part 1 Establishing Control requirements

Test Methods

Relevant topics

Choice of test methods

Determine Biocontamination of surfaces
Determine airborne Biocontamination
Determine Surface Deposition of Biocontamination
Determine Biocontamination of Raw materials, critical utilities etc
Rapid methods of microbial enumeration and identification
Qualification, Validation and Verification of environment, methods and equipment
Validation of air samplers
Media, qualification and growth promotion

Controlled Environments – Biocontamination Control Part 2 Test Methods

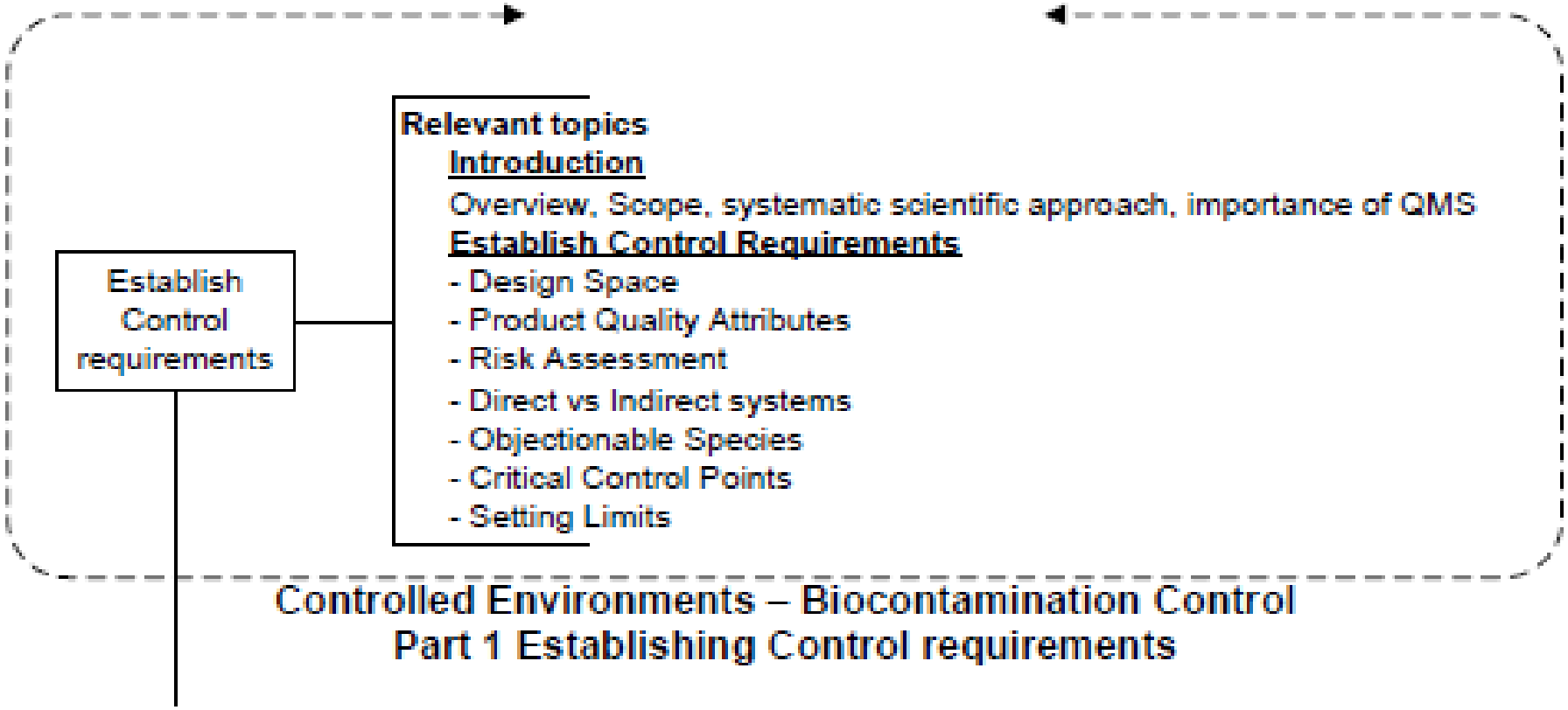
Demonstrate control

Relevant topics

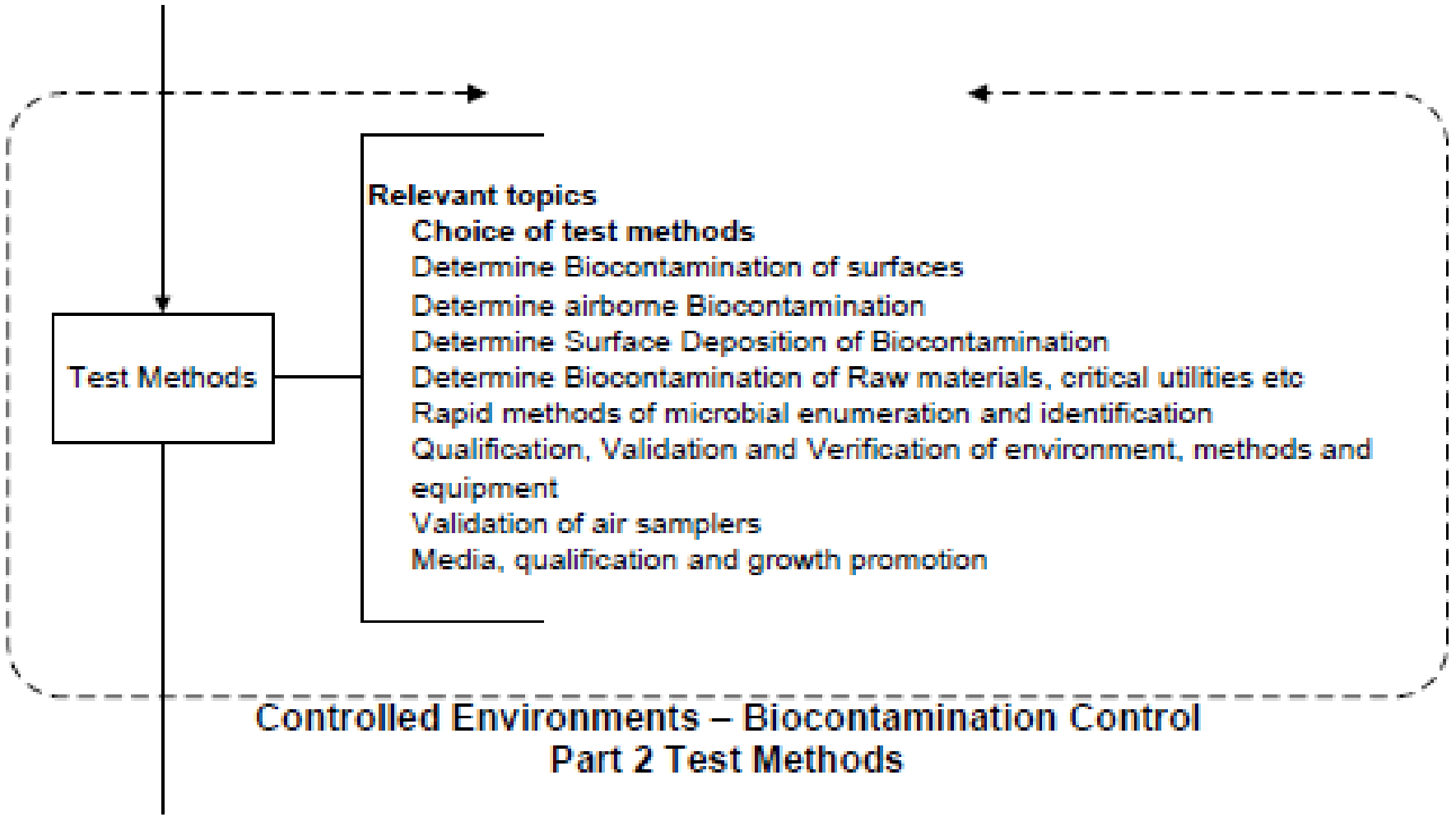
(REMP) routine environmental monitoring plan - Schedules and sampling plans
Expression, interpretation and reporting of results
Trending (plus out of trend results)
Results outside alert/action limits (CAPA etc)
Alert and action levels
Statistics applied to data analysis
Periodic review of data and feedback mechanisms to review limits

Controlled Environments – Biocontamination Control Part 3 Demonstrating Control

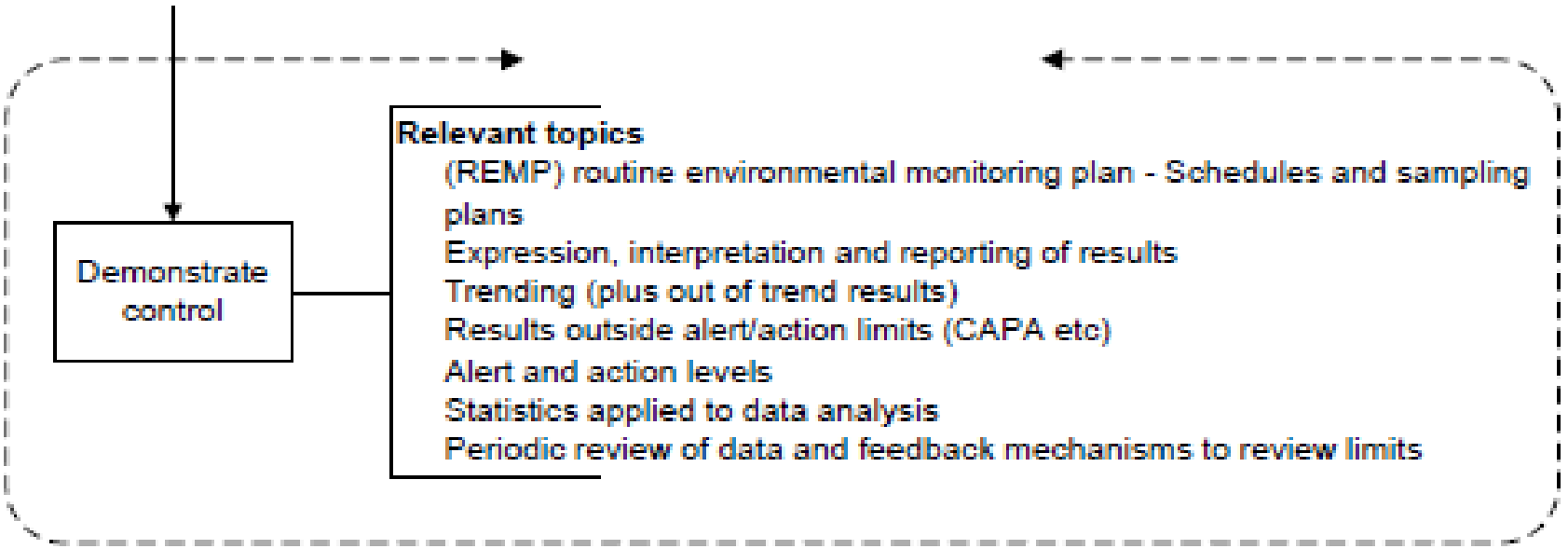
Controlled Environments – Biocontamination Control
Parts 1, 2 and 3



Controlled Environments – Biocontamination Control
Part 1 Establishing Control requirements



Controlled Environments – Biocontamination Control
Part 2 Test Methods



Controlled Environments – Biocontamination Control
Part 3 Demonstrating Control

Current measurement ‘technologies’

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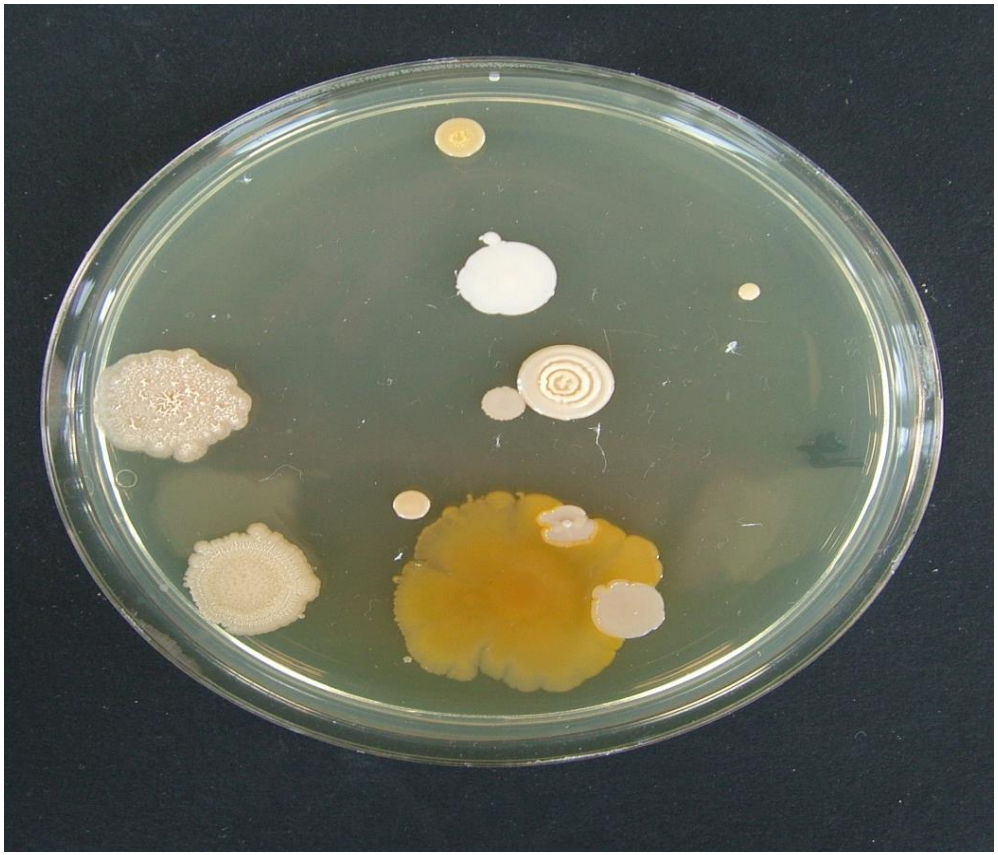
Plates – incubated to grow Colony Forming Units



Current Techniques Look for ‘Total Mesophilic’

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- Total mesophilic = species cultivate at ambient temperatures in normal atmosphere
- Incubate at: 20 to 25^{o}C and 30 to 35^{o}C (roughly equivalent to ambient and human body temperature)
- Ignore thermophiles (between 45 and 80°C)
- Ignore anaerobes (some killed by oxygen)

Necrotizing fasciitis - from streptococcus throat infection

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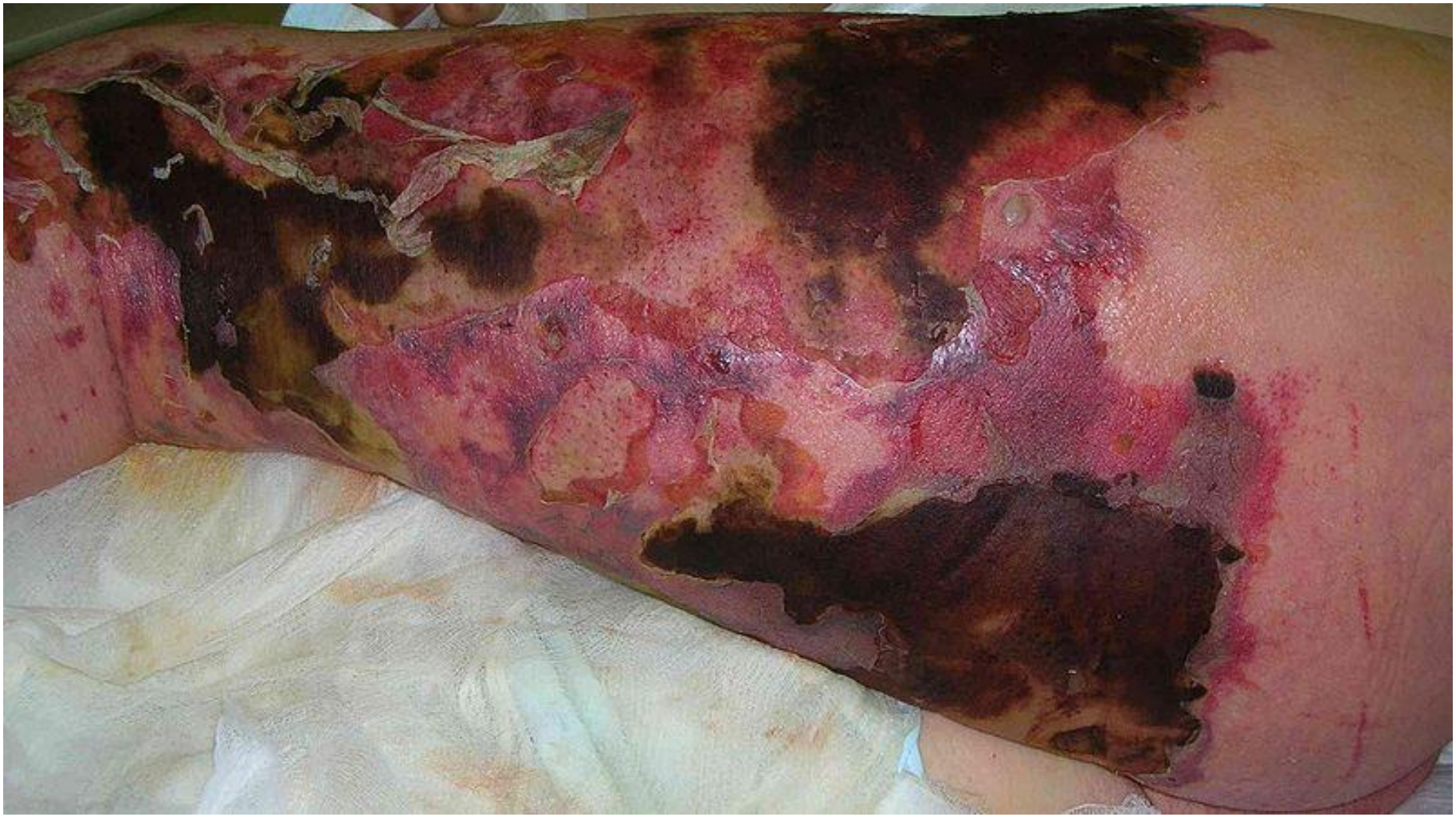

2. Issues in very clean spaces

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- Below limit of resolution for current technologies
  - i.e. 1 cfu recovered may be indicative of contamination of 1cfu or perhaps 10cfu, impossible to accurately and repeatedly determine
- Risk of false positives high due to likelihood of accidental contamination during collection and incubation

3. Process/application specific

- In some cases, all species are considered harmful
- In some cases there is ‘background counts’ of cfu of species considered ‘normal and non-harmful’
- In some cases, some species are considered ‘objectionable’ and are not tolerated at all

Surface Cleanliness by Viables

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Surface Contamination Class (SCV)	*Surface Count Limit (CFU)	Sampled Area
SVC_X 1	<4	1 m^2
SVC_X 2	<40	1 m^2
SVC $_X$3	<40	1 cm^2
SVC_X 4	<300	1 cm^2
SVC $_X$5	>300	1 cm^2

1. *Combined with an appropriate incidence rate
2. '$_X$' is the species of interest
3. Intermediate classes are permitted. For example SVCx 3,5

Airborne Classification by Viables

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Class	*Airborne limit In Operation cfu/m^3
ACV_x 1	$<10^{\#}$
ACV_x 2	< 100
ACV_x 3	< 1000
ACV_x 4	< 10000

1. *Combined with an appropriate incidence rate
2. ‘x’ is the species of interest
3. # still under discussion (added error by air collection method)
4. Intermediate classes are permitted. For example SVCx 3,5

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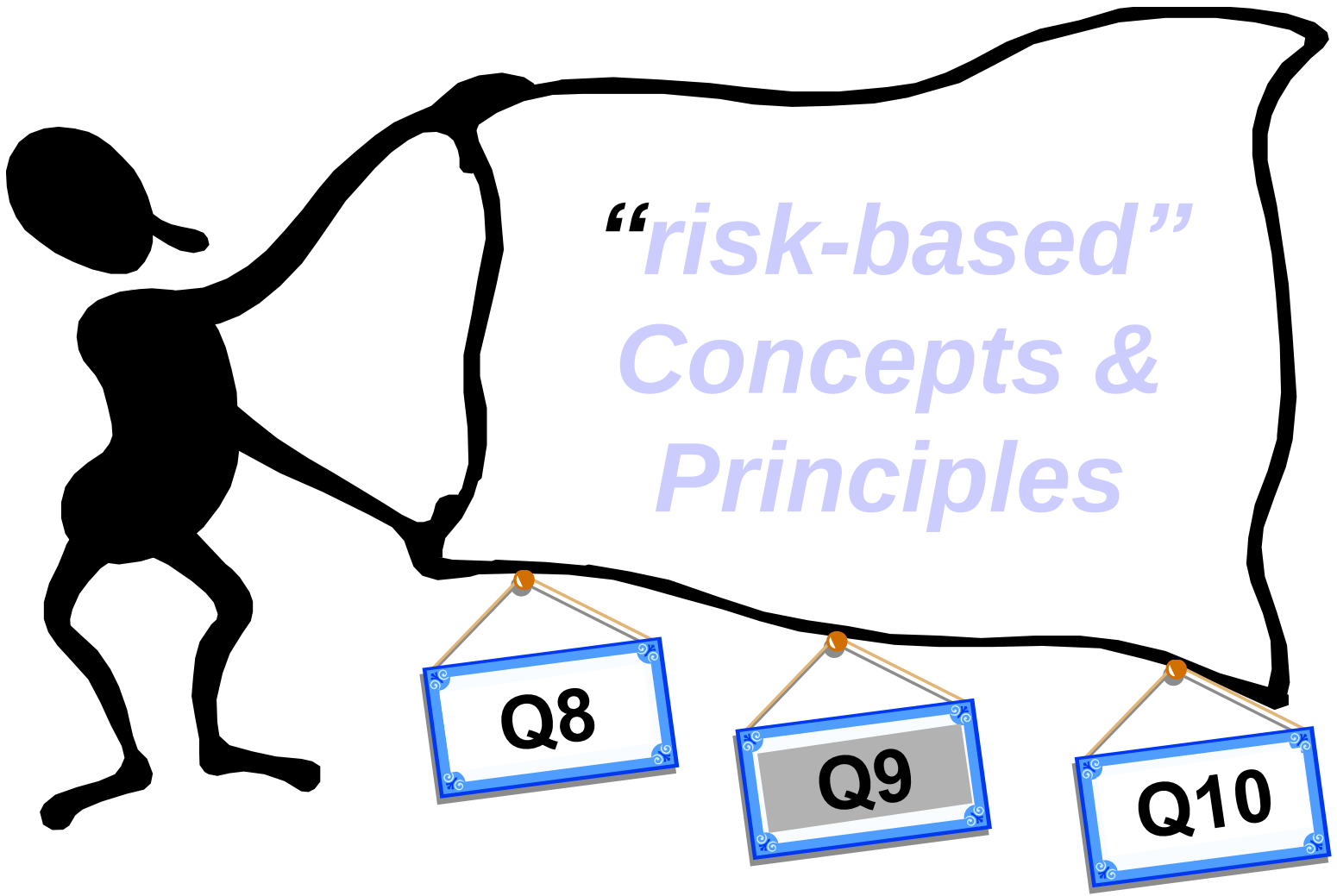
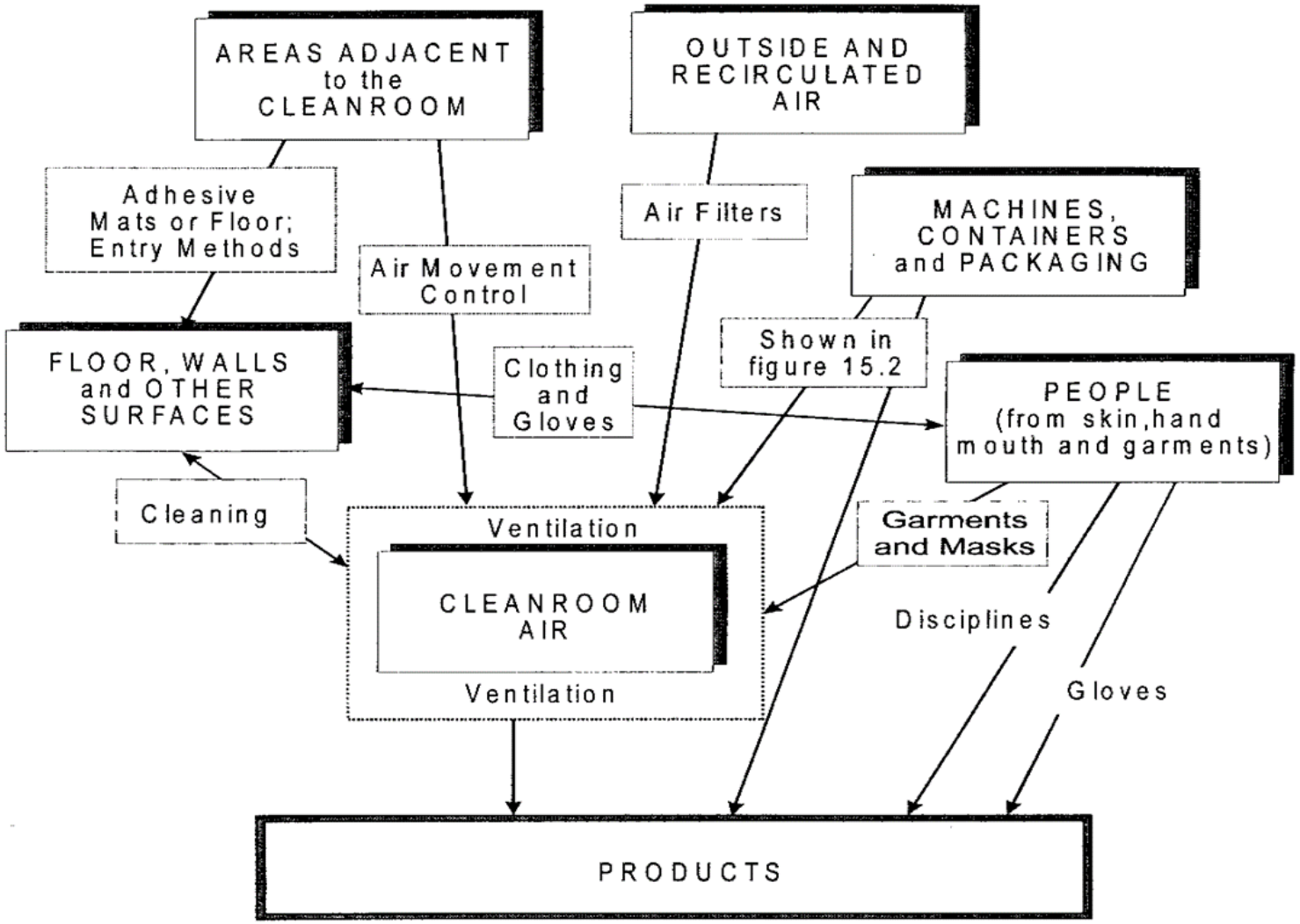
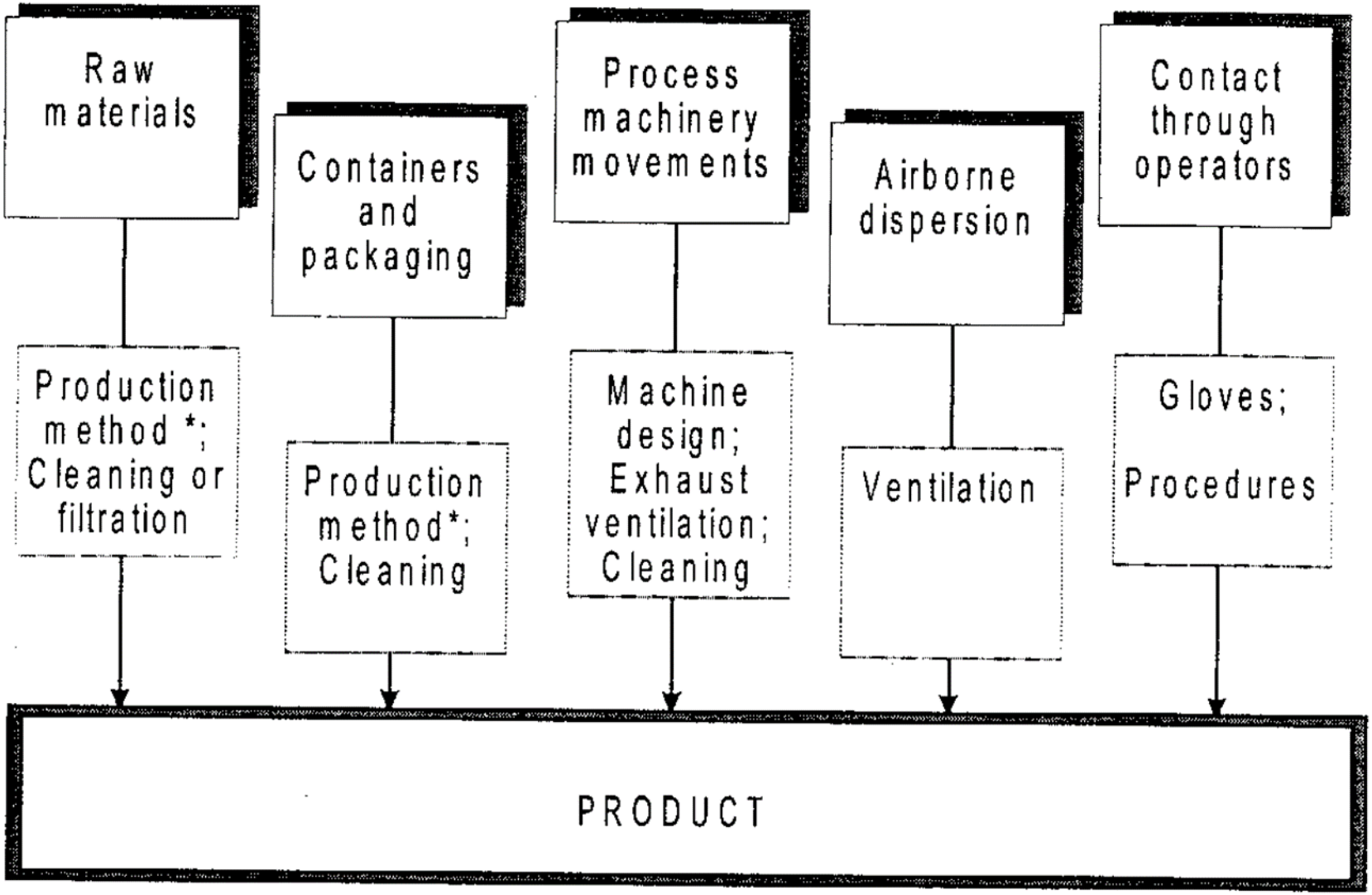
Risk Based Approach





Sources and routes of particle and microbial contamination in a cleanroom along with preventative measures



Sources and routes of control associated with Process Equipment

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Assessment of the Importance of Contamination Hazards

- Possible sources of contamination →routes of transmission→ risk assessment
- Risk factors:
  - Risk factor A: the amount of contamination on, or in, the source that is available for transfer
  - Risk factor B: the ease by which the contamination is dispersed or transferred
  - Risk factor C: the proximity of the source to the critical point where the product is exposed
  - Risk factor D: how easily the contamination can pass through the control method

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Risk factors for assessing Contamination Hazards

Amount of contamination on, or in, a source (A)	Ease of dispersion, or transfer (B)	Proximity from critical area (C)	Penetration through control method (D)
0 = nil	0 = nil	0 = outside corridor	0 = barrier protection
0.5 = very low	0.5 = very low	0.5 = air lock	0.5 = very good control
1 = low	1 = low	1 = periphery of cleanroom	1 = good control
1.5 = medium	1.5 = medium	1.5 = general area of cleanroom	1.5 = some control
2 = high	2 = high	2 = critical area	2 = no control

- Risk rating = A x B x C x D
- Low: a risk rating of less than 4
- Medium: between 4 and 12
- High: higher than 12

ID Methods to Control Contamination Hazards

- Identify the contamination hazards
- Assess the degree of risk
- Select the appropriate method to control the risk(s)

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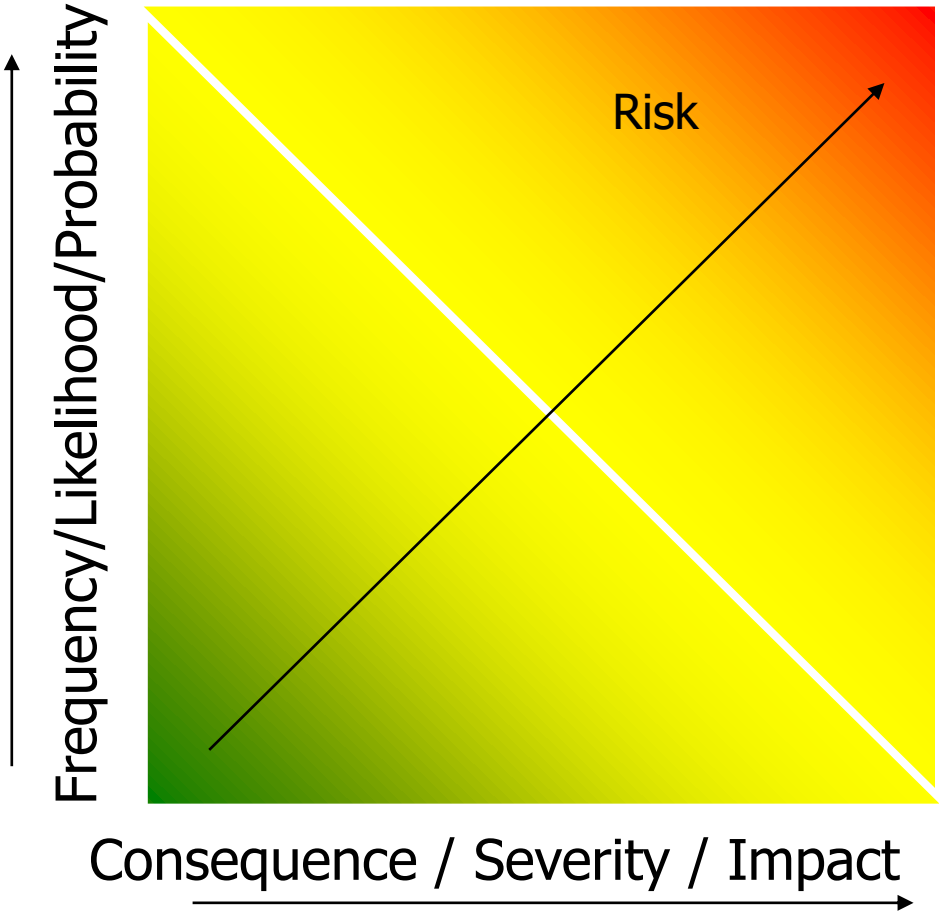
ID Methods to Control Contamination Hazards

- HEPA or ULPA air filters - supply air
- Airborne contamination from areas outside the cleanroom - air moves from the cleanroom outward
- Contamination from the floors, walls and ceiling - cleaning
- People's mouth, hair, clothing and skin - Cleanroom garments and gloves
- Contamination from process – equipment design, exhaust air systems to draw contamination away, cleaning
- Raw materials, containers and packaging – non shedding, manufactured in a cleanroom, double packaged to ensure contamination free transfer

Risk Matrix

- Criticality of the occurrence x Frequency of occurrence

- Two dimensions
  - Consequence
    - (Impact or severity)
  - Likelihood
    - (Frequency or Probability)
- How to use
  - Define for a risk:
    - Its consequence
    - Its likelihood
  - Read off the risk level



Biocontamination Control

- Other References

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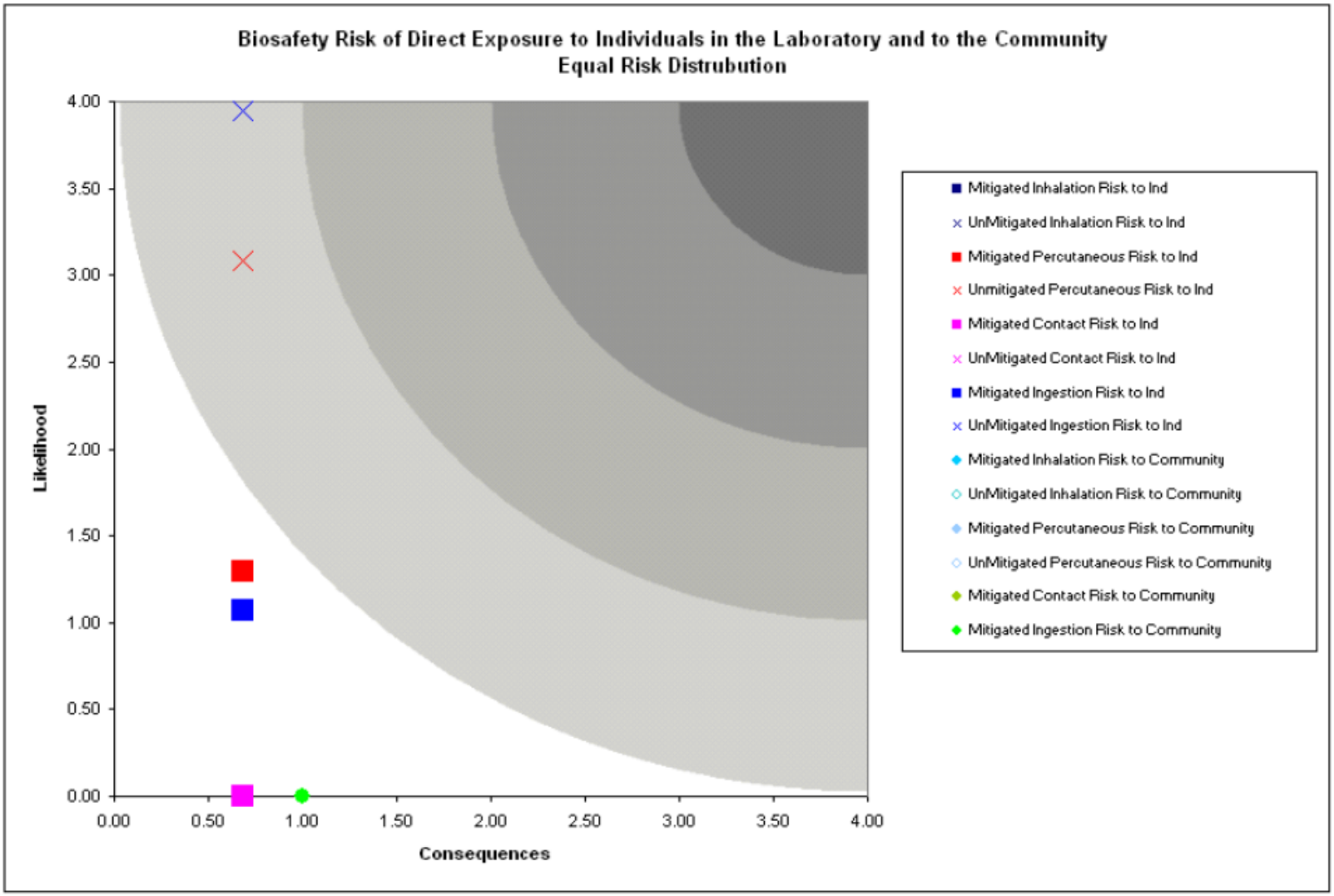
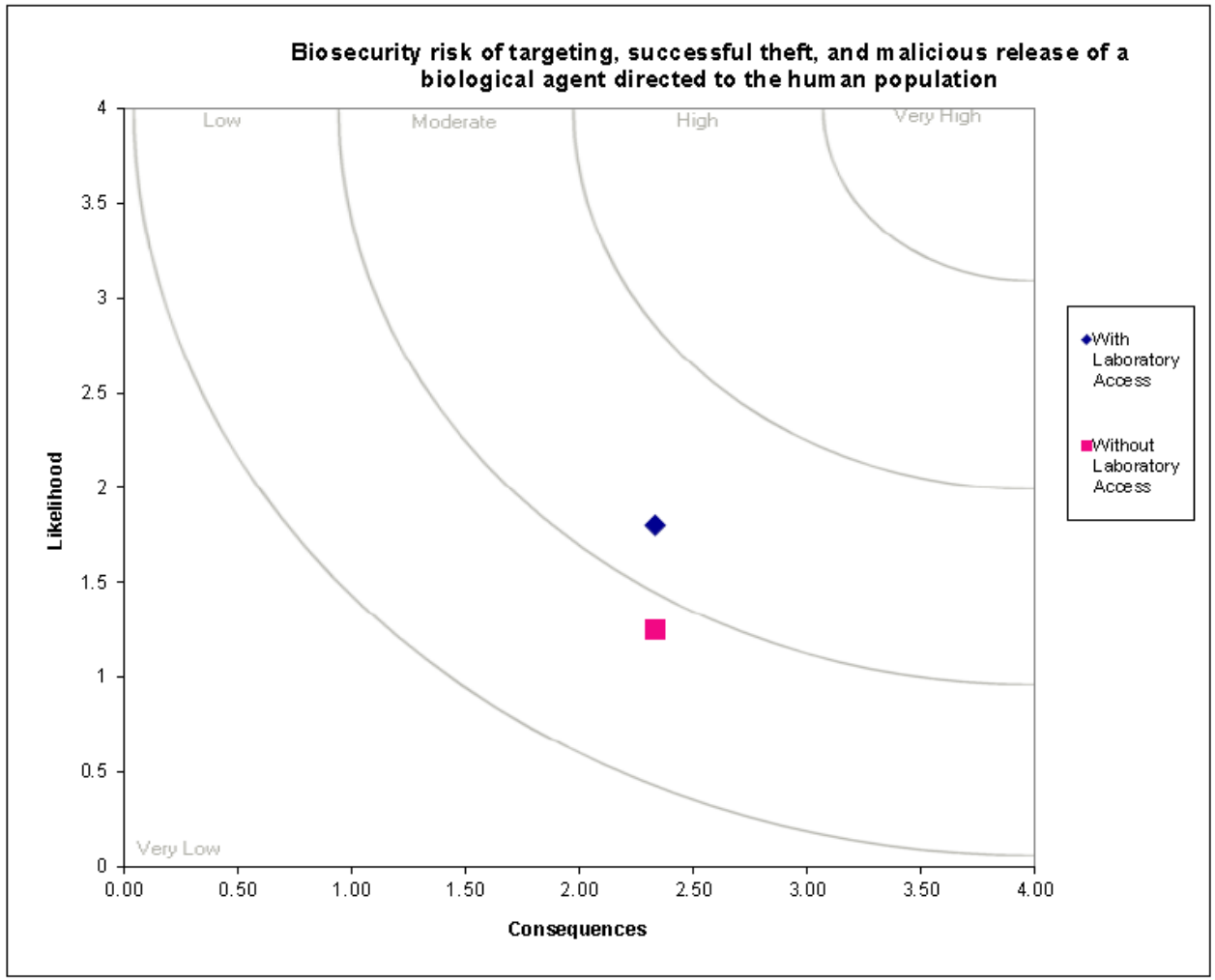
Risk Appreciation



WHO Risk Evaluation

Scenario A (Pablo) - biosecurity



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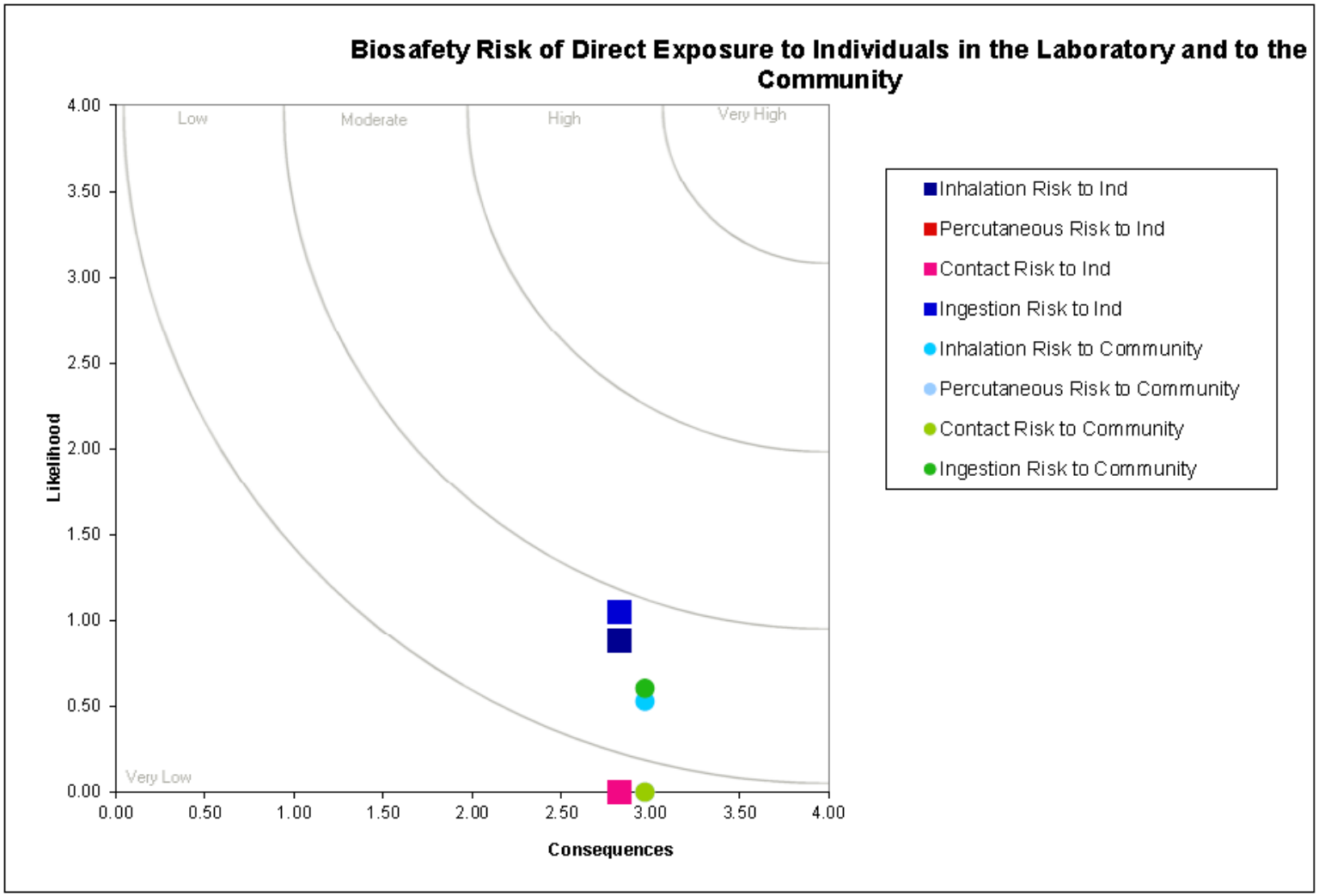
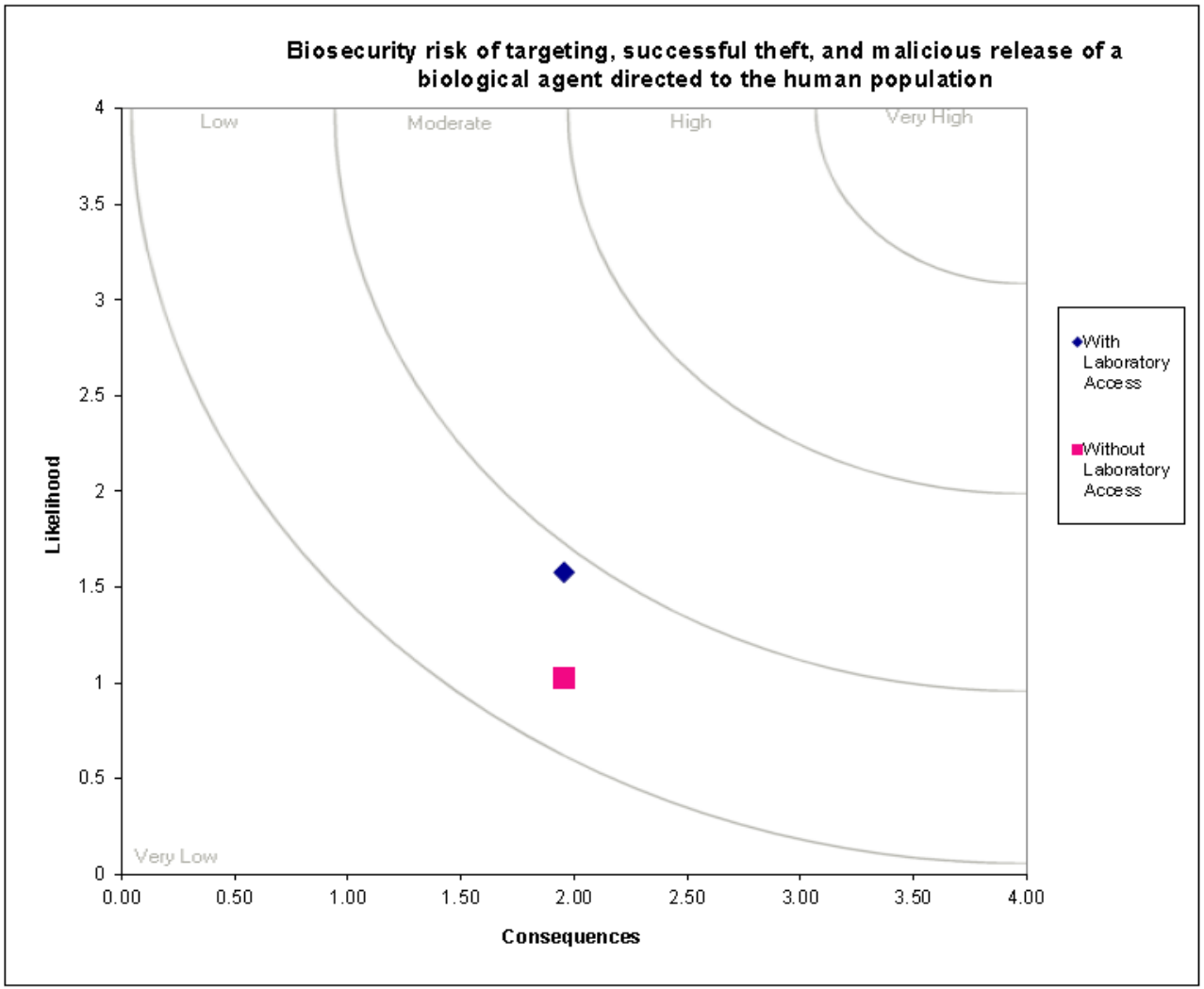
Scenario B (MDR-TB) - biosafety



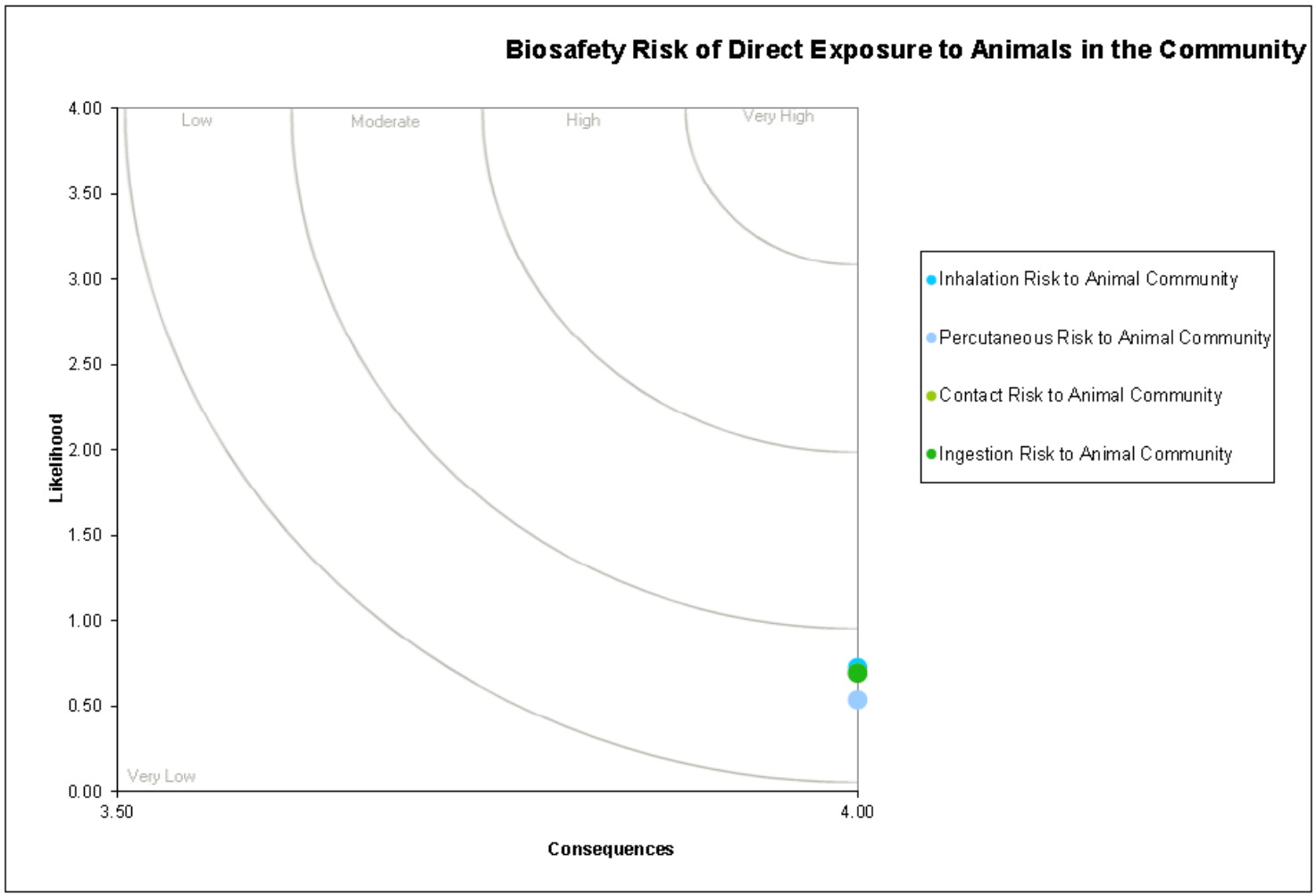
WHO Risk Evaluation

Scenario B (MDR-TB) - biosecurity



WHO Risk Evaluation

Scenario C (FMD) - biosafety



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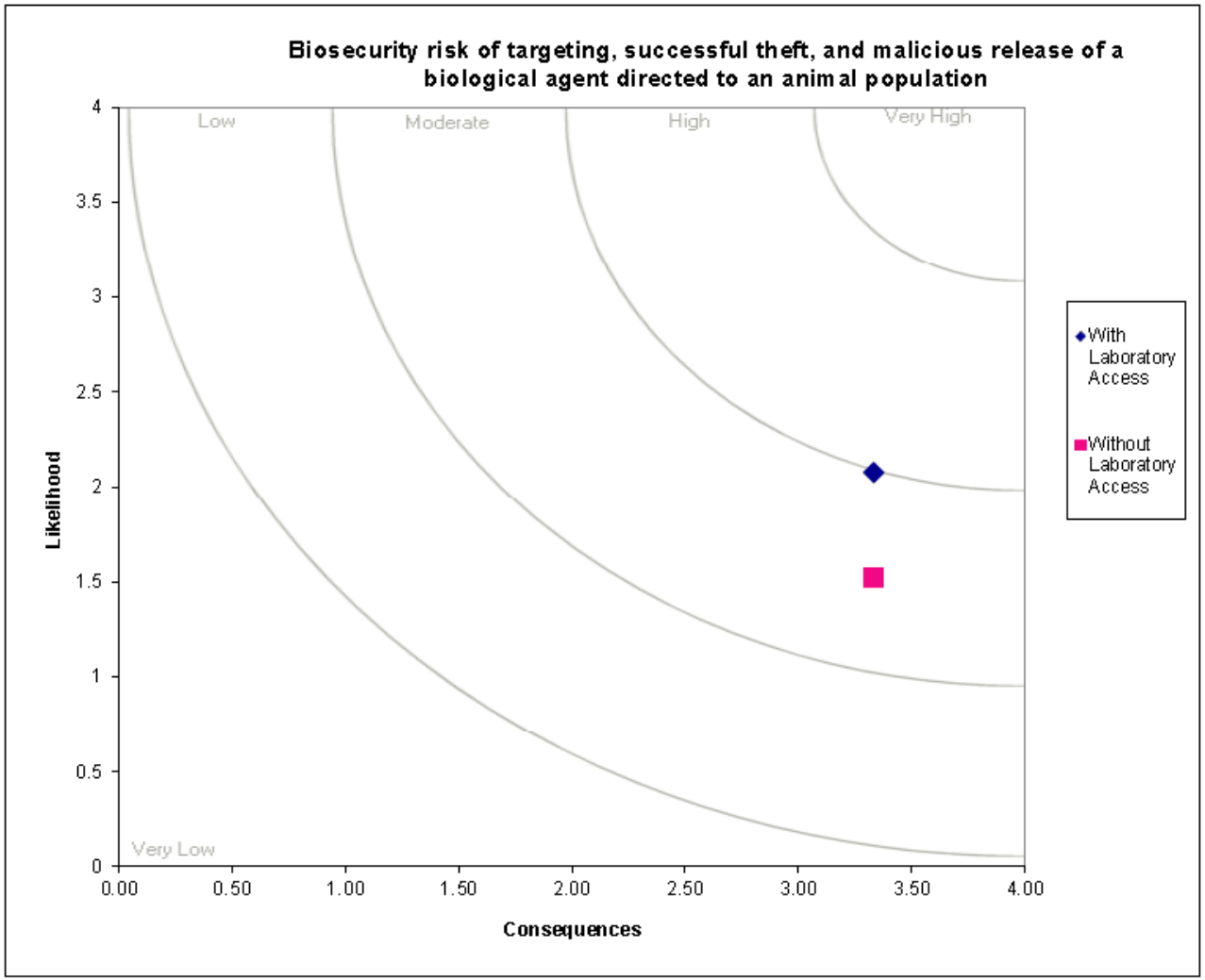
Scenario C (FMD) - biosecurity



SANDIA REPORT
SAND2009-8070
Unlimited Release
Printed December 2009

Strengthening Risk Governance in Bioscience Laboratories

Jennifer Gaudioso*, Susan A. Caskey*, LouAnn Burnett+, Erik Heegaard#, Jeffery Owens**, and Philippe Stroot++

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+ Independent consultant, Franklin, TN, USA
# Biosecurity Institute, Lyngby, Denmark
** DLS Inc, Atlanta, GA, USA
++ Xibios Biosafety Consulting, Brussels, Belgium

Prepared by
Sandia National Laboratories
Albuquerque, New Mexico 87185 and Livermore, California 94550

Sandia is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the United States Department of Energy's National Nuclear Security Administration under Contract DE-AC04-94AL85000.

http://www.biosecurity.sandia.gov/BioRAM/Biorisk%20Framework%20Report.pdf

Sandia National Laboratories

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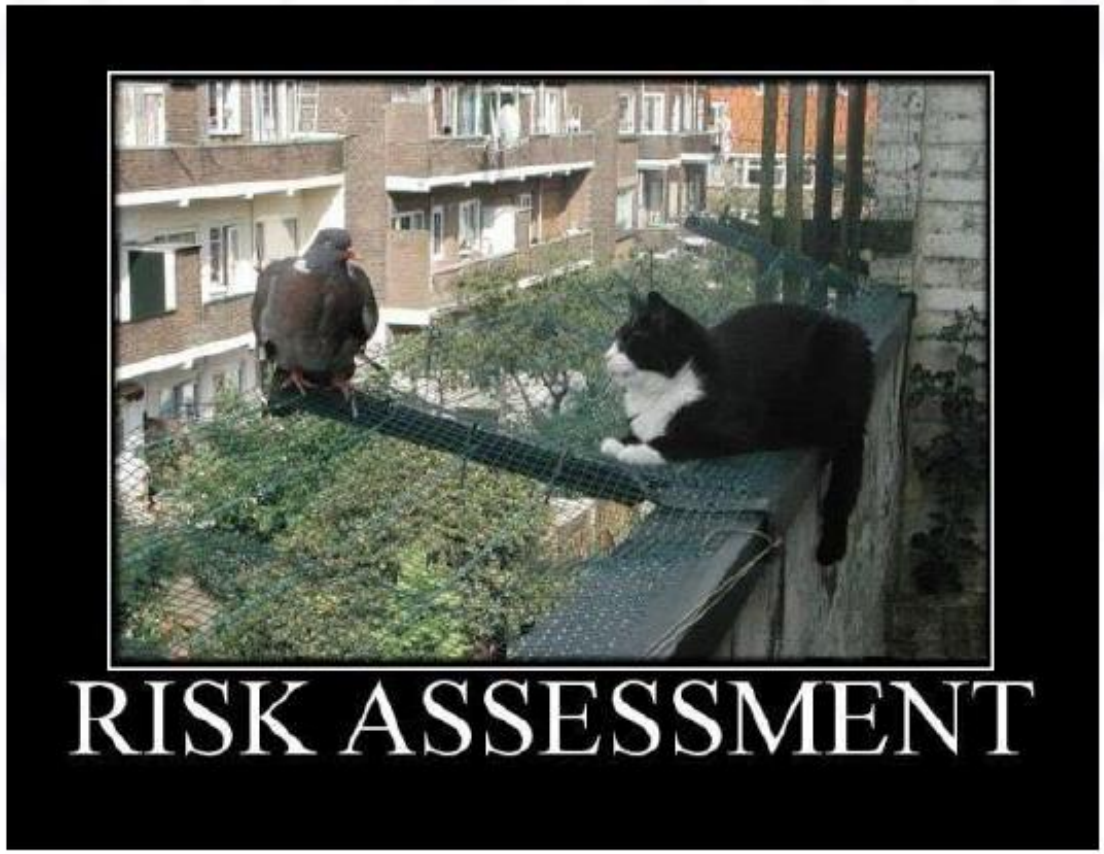
What are the benefits of a robust risk assessment?



THE PARENTERAL SOCIETY
and
THE SCOTTISH SOCIETY FOR CONTAMINATION CONTROL

RISK MANAGEMENT OF CONTAMINATION (RMC) DURING MANUFACTURING OPERATIONS IN CLEANROOMS

Technical Monograph No. 14 ISBN No. 1-905271-12-3

W Whyte, University of Glasgow, Scotland, UK,
and
T Eaton, AstraZeneca, Macclesfield, UK.

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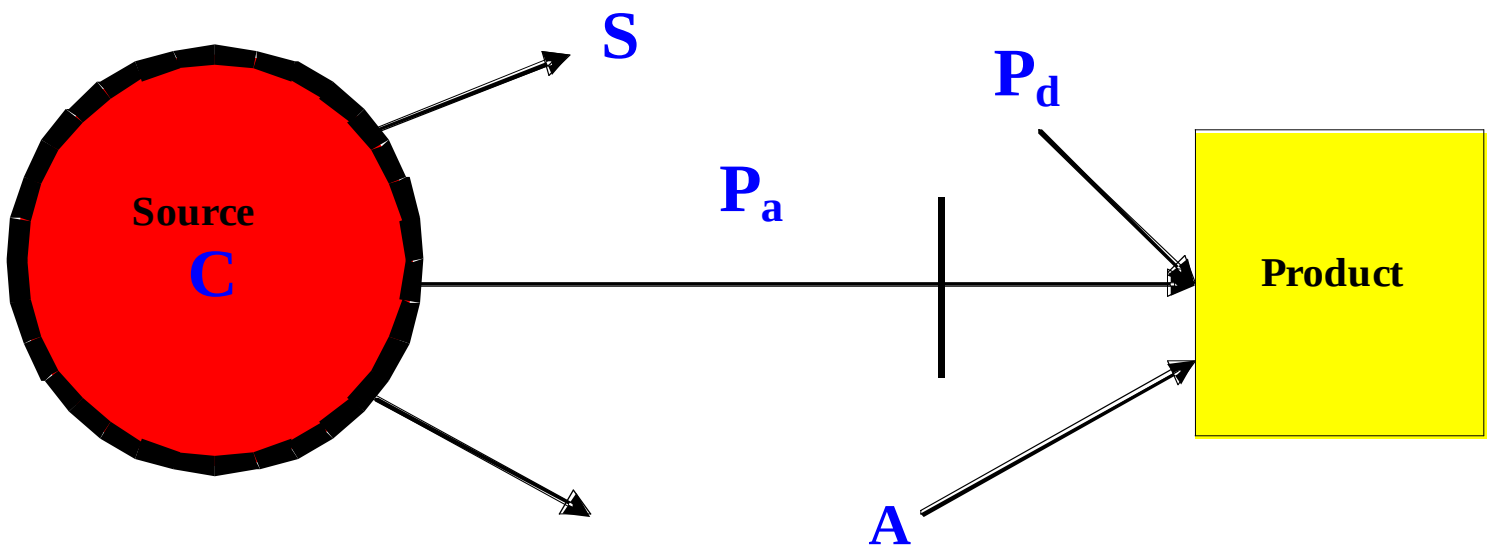
Contamination Deposition Method



Contamination deposited on a product

= C × S × Pd × Pa × A × T

Contamination Deposited on a Product

$$= C \times S \times P_d \times P_a \times A \times T$$

C = concentration of microbial contamination on or in a source (number/cm^2 for surface, or number/cm^3 for air)

S = quantity of surface material or air that is dispersed from the source in a given time (cm^2/s for surfaces, or cm^3/s for air); also expressed as the quantity dispersed per frequency of occurrence

P_d = proportion of micro-organisms dispersed from the source that are transferred to the area adjacent to the product

P_a = proportion of micro-organisms in the adjacent area that are deposited per unit area of the product (cm^{-2})

A = area of surface onto which microbes are deposited (cm^2)

T = time, during which transfers occurs or frequency of occurrence

Correlation with FMECA

Contamination deposited

= Concentration on contaminating surface (a)
x quantity dispersed and transferred (b)
x quantity deposited (c)
x time (or frequency) (d)
$\Rightarrow$ (a x b x c x d)

FMECA Risk = (a x b x c) x (d)

Criticality of occurrence x frequency of occurrence

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Identification of Sources and Routes of Contamination

- Sources of contamination
  - dirty areas adjacent to the cleanroom
  - unfiltered air supply
  - room air
  - surfaces
  - people
  - machines, as they work
  - raw materials
  - containers
  - packaging

Airborne and contact routes of transfer

- The two main routes of transfer are airborne and contact
- Airbone: particles are small; fibres, chips or cuttings fall directly on to the product
- Contact: machines, containers, packaging, raw materials, gloves, clothes, etc

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Conclusion

We live in Interesting times!

It’s good to talk!

Get involved!

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Hmmh!

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Expect the Unexpected

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Communications is Key

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Thank You for Your Attention So Far

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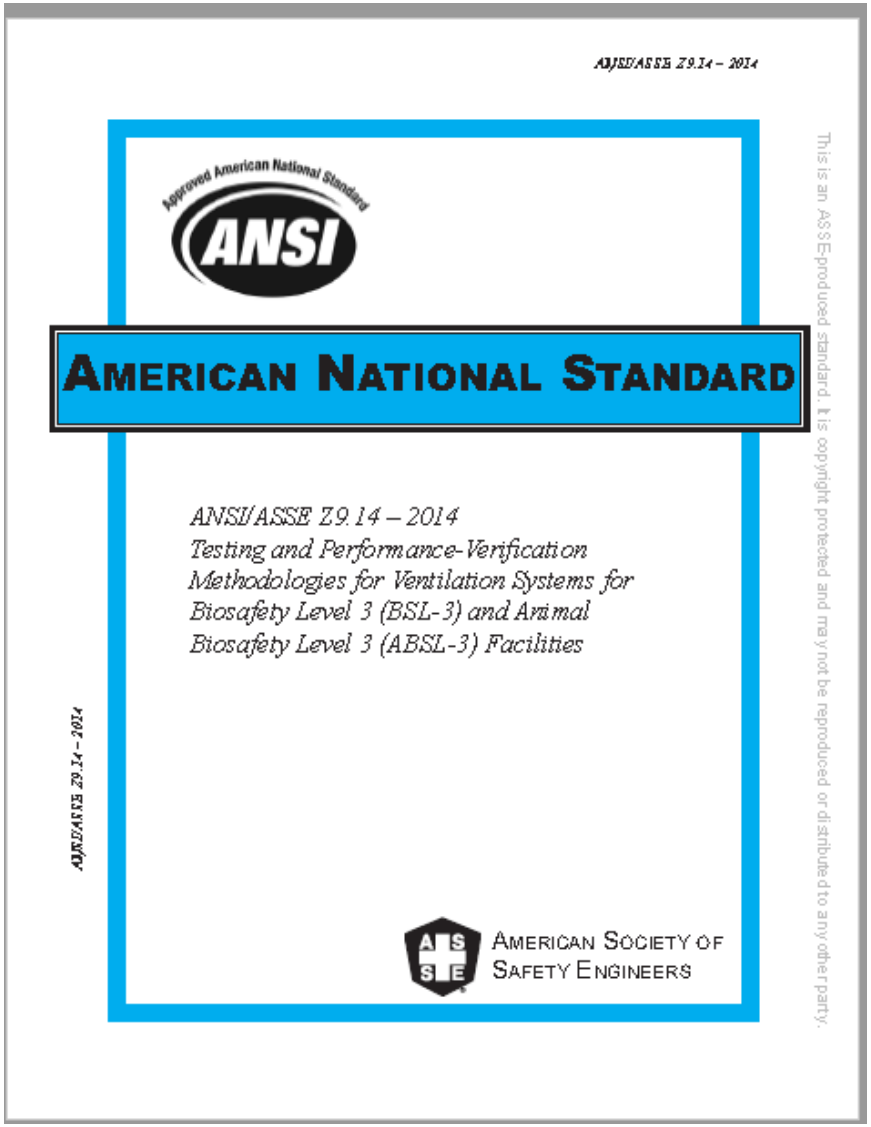
ANSI Standard



ANSI/ASSE Z9.14 – 2014

Approved American National Standard

ANSI

AMERICAN NATIONAL STANDARD

ANSI/ASSE Z9.14 – 2014
Testing and Performance-Verification Methodologies for Ventilation Systems for Biosafety Level 3 (BSL-3) and Animal Biosafety Level 3 (ABSL-3) Facilities

ANSI/ASSE Z9.14 – 2014

AMERICAN SOCIETY OF SAFETY ENGINEERS

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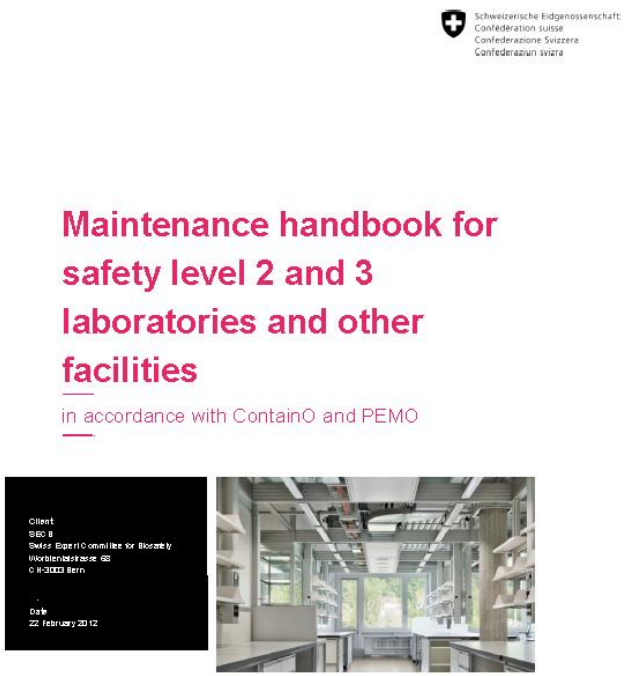
SECB SUISS

- The Swiss Expert Committee for Biosafety (SECB) is an independent expert committee which advises the Federal Council on drawing up laws and ordinances, and the federal and cantonal authorities on implementing these regulations.



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ContainO

These activities are regulated by the Ordinance on the contained use of organisms (Containment Ordinance, ContainO). According to the species or organism, or the class of activity, laboratories and other facilities must adhere to a particular safety level and fulfil various safety measures. Switzerland has so far lacked uniform instructions for the operation and maintenance of these facilities.

PEMO

In the event of exposure to microorganisms during maintenance, the Ordinance on Protection of Employees from Dangerous Microorganisms (PEMO) must also be observed.

3.4 Maintenance and inspection as laid down by the AMEV and the SWKI

AMEV

In its current edition of "Wartung 2006", the German AMEV (Mechanical and Electrical Engineering Working Party of National, Regional and Local Authorities) defines the German terms "Wartung", "Inspektion" and "Instandhaltung" (maintenance, inspection and repair), in conformity with DIN.

ACCREDITATION

Health Systems Commonly Asked Questions:

World Health Organization
Regional Office for South-East Asia

2. Accreditation:

A formal process by which a recognized, usually NGO body assesses and recognizes that a health care organization meets applicable pre-determined and published standards. Accreditation standards are usually regarded as optimal and achievable, and are designed to encourage continuous improvement efforts within accredited organizations. An accreditation decision about a specific health care organization is made following a periodic on-site evaluation by a team of peer review, typically conducted every two to three years. Accreditation is often a voluntary process in which organizations choose to participate, rather than one required by law and regulation. (USAID, QA Project, 1999)

Health Systems Commonly Asked Questions:

World Health Organization
Regional Office for South-East Asia

3. **Certification:**

is a process by which an authorized body, either a governmental or non-governmental organization, evaluates and recognizes either an individual or an organization as meeting pre-determined requirements and criteria. Although the terms accreditation and certification are often used interchangeably, accreditation usually applies only to organizations, while certification may apply to individuals as well as to organizations.

When applied to individual practitioners, certification usually implies that the individual has received additional education and training, and demonstrated competence in a specialty area beyond the minimum requirements set for licensure. An example of such a certification process is a physician who receives certification by a professional specialty board in the practice of obstetrics. When applied to an organization, or part of an organization, such as the laboratory, certification usually implies that the organization has additional services, technology or capacity beyond those found in similar organizations. (USAID QA Project, 1999)

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Position paper of the Committee for Biological Agents (ABAS) concerning CWA 16335:2011 "Biosafety professional competence"

(formerly CEN Workshop 53)

I. Summary

A current demand exists to establish requirements for competency and technical qualification/s in particular within the scope of the BioStoffV. It would be desirable to achieve this during revision of the Biological Agents Ordinance (BioStoffV) or in a subordinate Technical Rule for Biological Agents (TRBA).

The contents of CWA 16335 could deliver some input for this purpose. CWA 16335 aims at specifying the professional competence and therefore also the training required for "biosafety professionals". The European directives in this area and national regulations such as the German Biological Agents Ordinance do not currently contain any detailed requirements concerning technical qualifications.

However, CWA 16335 specifies an extensive set of responsibilities and tasks focussed on one person. German law does not provide for such a concentration of tasks. It is also questionable whether this concentration is in fact reasonable, as it must be doubted that one single person possesses the expertise to cover such a broad catalogue of tasks. The fact that many of the tasks assigned to the biosafety professional (BSP) are related to health and safety at work may lead to overlaps with existing regulations in this area. Addressing health and safety aspects in CEN Workshop Agreements is therefore not generally useful.

CWA 16335 may be useful in countries in which corresponding legal provisions do not yet exist. The CWA 16335 is not necessary in Germany because a large number of rules and regulations already exist.

Position Paper of the ABAS on the CWA 16335:2011 "Biosafety Professional Competence"
(formerly CEN Workshop 53)

Position paper of the Committee for Biological Agents (ABAS) concerning CWA 16335:2011 "Biosafety professional competence"

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b) Certification

As already mentioned, the document is structured in such a way that it could be used as a basis for future certification. As a result, it increases the significance of certification bodies and other commercial institutions. Running the required advanced training courses for BSPs and certifying and auditing CWA-compliant organisations opens up new business opportunities to these institutions and serves commercial interests. This might become a problem for small organisations in particular, as they possess neither the required structures nor the financial means for certification.

V. Possible implications of CWA 16335

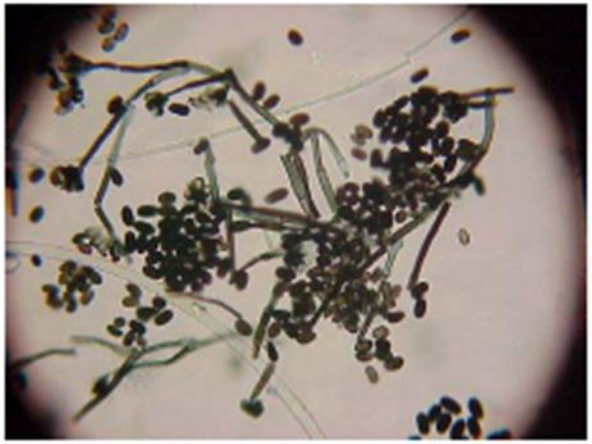
a) General

As a matter of principle, application of a document such as CWA 16335, which is developed by a random group of people, is voluntary. Nevertheless, the CWA constitutes an official paper by CEN, the European standards organisation, and can therefore easily be confused with a standard. A CWA can become binding in cases where regulations, legal acts or directives make reference to the CWA as constituting the "state of the art in Europe", or where its contents are incorporated into revisions of such provisions, as was the case for example with the GMP guidelines for the manufacture of medicinal products[5], which also governs personnel and management aspects, or as is theoretically conceivable for the revision of the Biological Agents Ordinance (BioStoffV). An example of a reference to a (different) CWA in an official document can be found in the CBRN Action Plan of the European Union, which calls for application of CWA 15793:2008 "Laboratory Biorisk Management Standard" or comparable documents for certain organisations unless binding statutory provisions exist.[6]

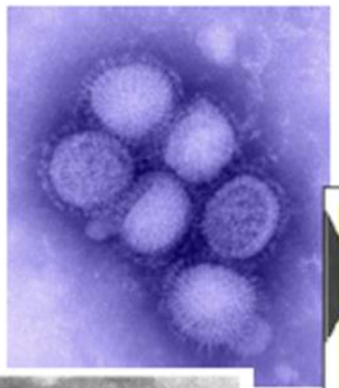
BIOAEROSOLS

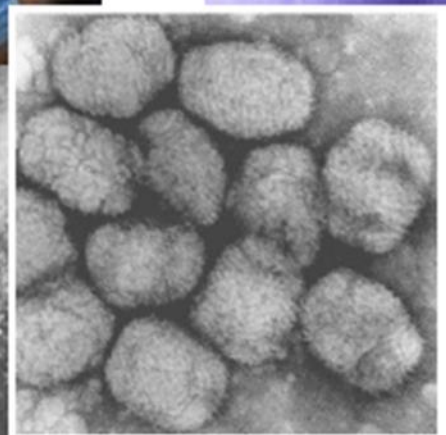
See also www.aerosols.wustl.edu

- **Introduction**
  - Terminology
  - Characteristics
  - Sources
  - Transmission
- **Instrumentation**
  - Traditional Methods
  - Bridging the Gap in Real-time
  - Aerodynamic Sizing
    - APS & UV-APS
- **Research Examples**
  - Indoor/Outdoor Air
  - Aircraft
  - Healthcare
  - Agriculture
  - Basic Bioaerosol Research
  - Bioterrorism Threats



Stachybotrys chartarum is a greenish-black mold that is commonly referred to as Black Mold. Health problems related to this mold have been documented in humans and animals since the 1930s and S. chartarum has been linked with so-called sick building syndrome.





Cover your Cough

HEALTH ALERT NOTICE
H1N1 FLU VIRUS (HUMAN SWINE FLU)

Public Health Agency of Canada
Message for All Travellers Arriving in Canada

DURING YOUR TIME OUTSIDE OF CANADA, YOU MAY HAVE TRAVELLED THROUGH AN AREA AFFECTED BY H1N1 FLU VIRUS (HUMAN SWINE FLU).

What is H1N1 flu virus (human swine flu)?

- H1N1 flu virus (human swine flu) is a respiratory illness that causes symptoms similar to those of seasonal flu (fever **and** cough, runny nose, sore throat, body aches, fatigue, and lack of appetite).

Not all travellers with flu symptoms will have H1N1 flu virus (human swine flu). However, it is important that if you do have these symptoms, you follow the recommendations below.

If you have a fever and a cough, or if you develop a fever and a cough within 7 days:

- **STAY HOME** and avoid direct contact with others for 7 days after your fever and cough start.

Variola Virus. *Smallpox is the only human infectious disease to have been completely eradicated. The British may have used smallpox as a biological warfare agent during the French and Indian Wars*

June 11th: Influenza A (H1N1) Flu Pandemic Alert Raised to Phase 6

- Sustained human to human transmission
- Many regions with wide spread transmission

Map produced: 12 June 2009 07:00 GMT

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

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1918 FLU Pandemic

The second wave of the 1918 pandemic was much deadlier than the first. During the first wave, which began in early March, the epidemic resembled typical flu epidemics. But in August, when the second wave began in France, Sierra Leone and the United States the virus had mutated to a much more deadly form.

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Why Study Bioaerosols?

- Transmit Disease to Humans, Animals & Plants
  - Costs measured in billions, possibly trillions of dollars
- Bioterrorism Threats
  - Regional bacterial census to differentiate normal versus suspicious fluctuations in airborne pathogens
- Influence on the Environment
  - Spread of organisms, cloud & ice formation
- Monitoring Production Facilities
  - Food and Beverage, Pharmaceutical, Biotechnology, Hospitals

Jul 2 2009, 7:57 AM EST
Genzyme Plant Shutdown Could Mean up to $300M in Lost Sales
Special Report

TRUST. SCIENCE. INNOVATION.

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What is Bioaerosol?

- Bioaerosol is broadly defined as organic aerosols that are alive, carry living organisms, or are released from living organisms.
- Natural or Manmade
- Include Viruses, Bacteria, Fungal Spores & Pollen
- Range in size from 0.010 (small virus) to 100 microns (pollen grains)
- More than 1,800 types of airborne bacteria identified [5]

What is Bioaerosol?

- Subset of total course particulate matter in the environment [6]
  - Typically less than 5% by COUNT
  - Typical contribute 20% of the MASS
  - Dynamic & large number concentrations
- Temperature & relative humidity affects bioaerosols
- Affected by gravity, but due to their size air currents play a large role in their movement

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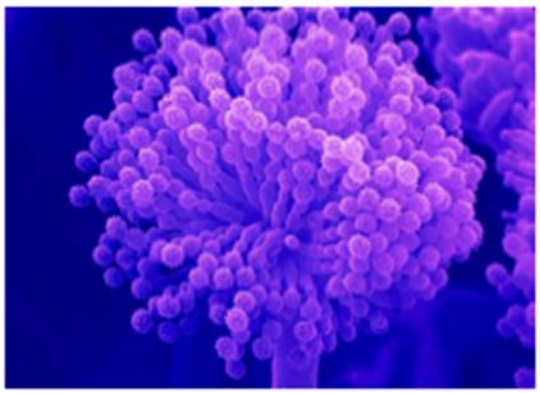
What is Bioaerosol?

- **Viable bioaerosol**: metabolically alive (bacteria, viruses and fungi) with the potential to reproduce. Only viable bioaerosol can be infectious or pathogenic (cause disease).
- **Nonviable bioaerosol**: originate from living organisms but are not currently alive and thus cannot multiply (pollen, animal dander, saliva and insect excreta). Nonviable bioaerosol can cause allergies or toxic reactions.

Important Properties of Bioaerosols

- Particulate, liquids or volatile organic compounds
- Size, viability, infectivity, allergenicity, toxicity and pharmacological activity
- Naturally aerosolized, often occur as agglomerates and properties change



Aspergillus versicolor. *Aspergillus is a genus of mold which can be found in indoor environments. Aspergillus versicolor is very common on gypsum board, floor, carpet, mattress and upholstered-furniture dust, and damp walls. A. versicolor produces high quantities of the carcinogenic substances.*

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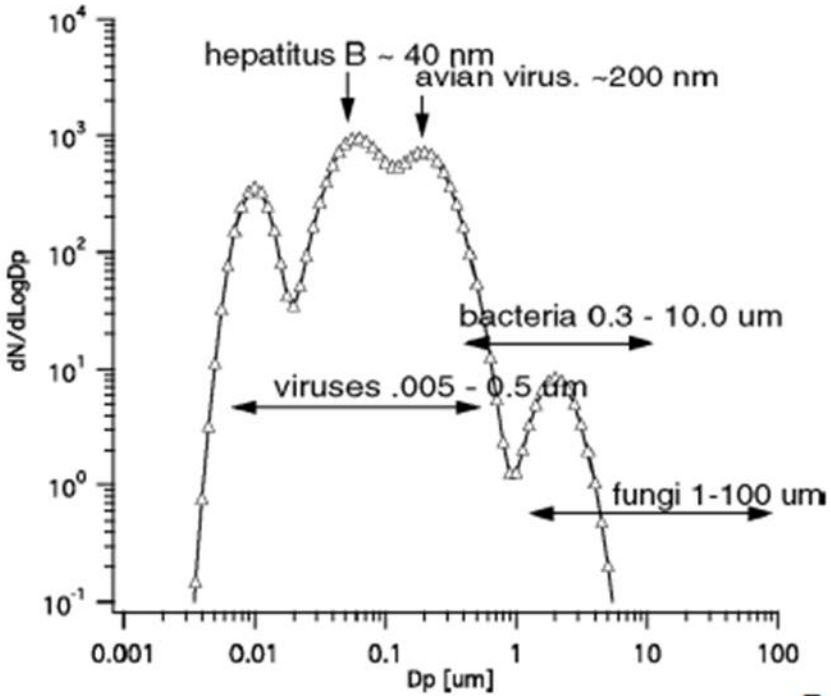
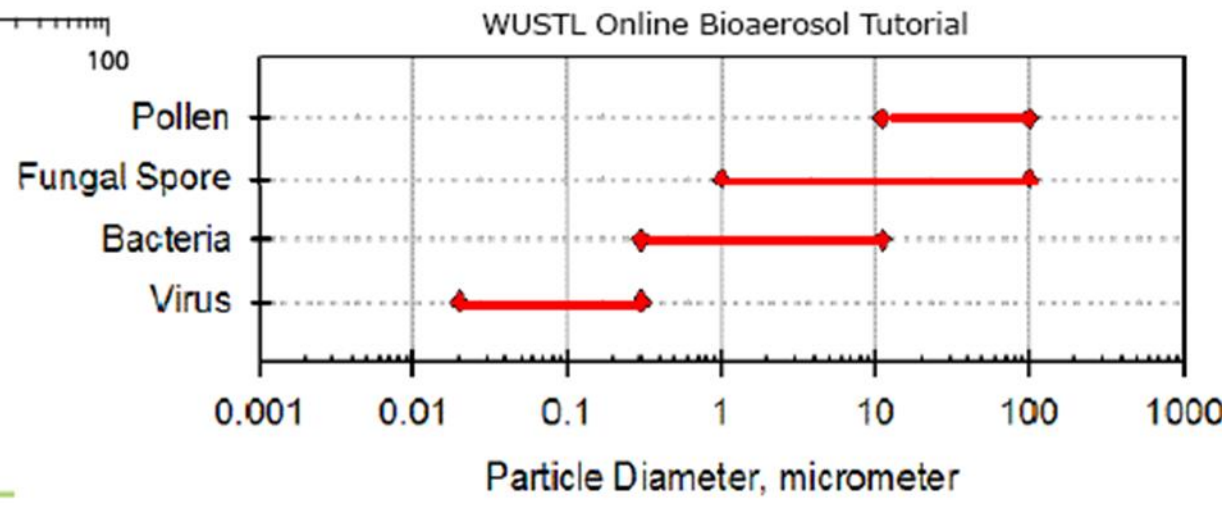
An Important Parameter – Size!



Ambient aerosol size distribution overlaid with three biological aerosol populations[2]



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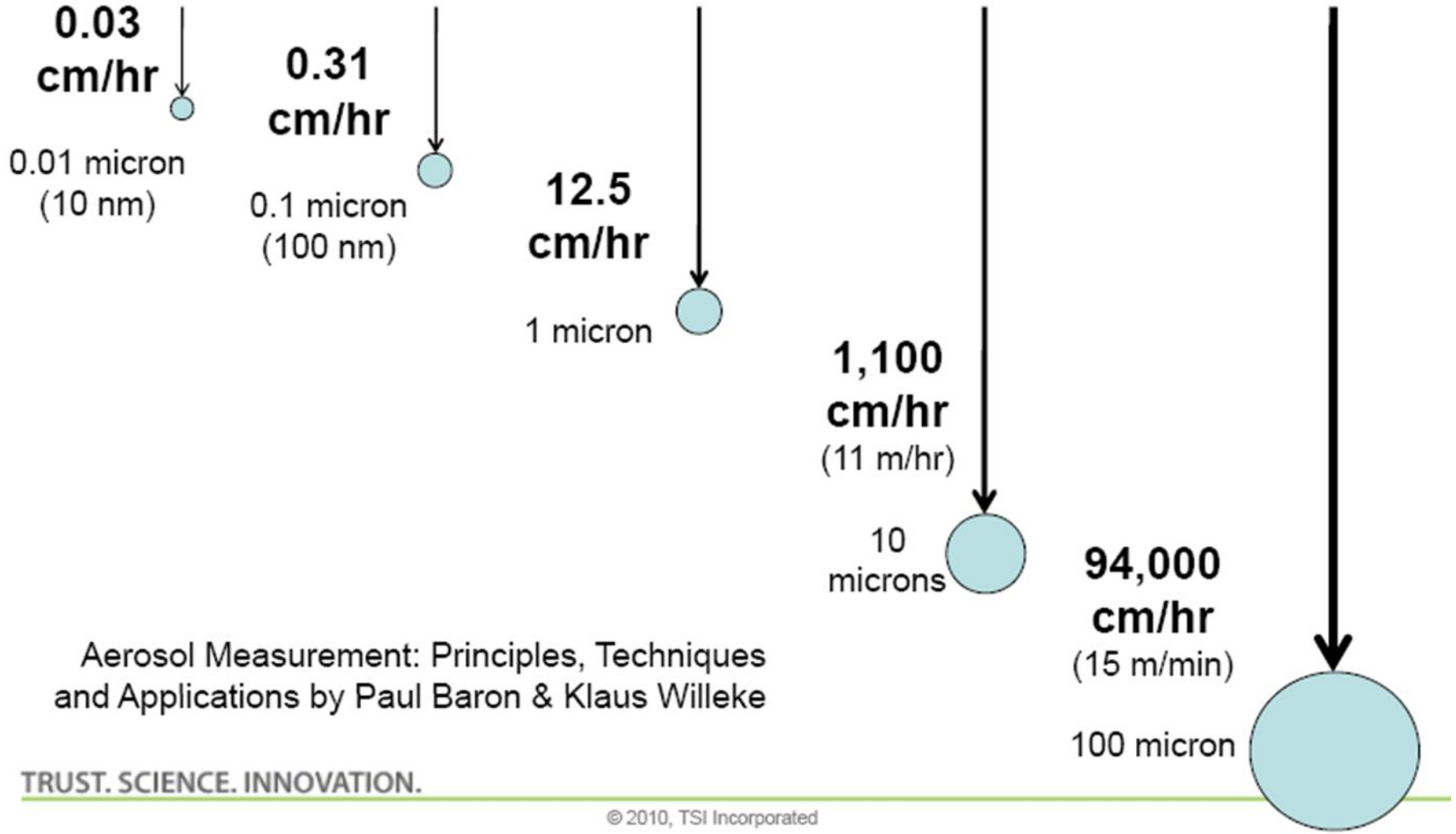
Settling Velocity



Aerosol Measurement: Principles, Techniques and Applications by Paul Baron & Klaus Willeke

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Bioaerosol Transmission – Aerodynamic Diameter

$$d_g = d_{ae}\sqrt{\frac{\chi}{\rho}}$$

d_g = geometric diameter
d_a = aerodynamic diameter
χ = shape factor
ρ = density

Aerodynamic diameter governs:

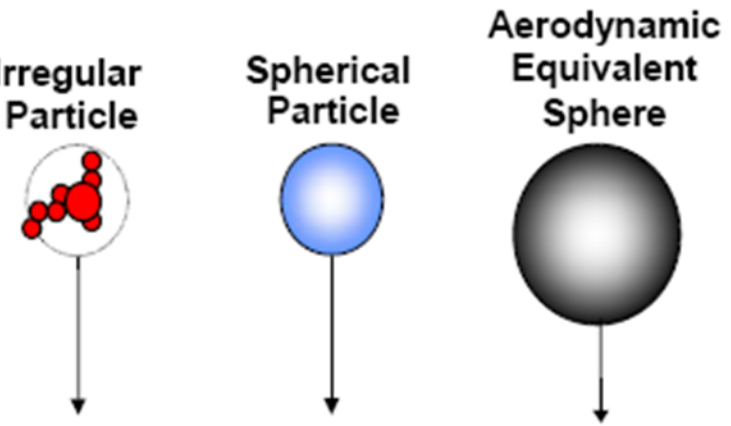
- ❑ Airborne particle transport behavior
- ❑ Cyclone and impactor efficiency
- ❑ Filtration deposition
- ❑ Respiratory behavior and deposition

Based on the balance of:

- ❑ Gravitational force
- ❑ Buoyant force
- ❑ Drag force

Aerodynamic diameter a function of:

- ❑ Particle Size
- ❑ Particle Shape
- ❑ Particle Density



	Irregular Particle	Spherical Particle	Aerodynamic Equivalent Sphere
Settling velocity	= 0.22 cm/s	= 0.22 cm/s	= 0.22 cm/s
Particle diameter	= ~ 3-5 µm	= 4.3 µm	= 8.6 µm
Density	= 4 g/cm³	= 4 g/cm³	= 1 g/cm³

www.aerosols.wustl.edu

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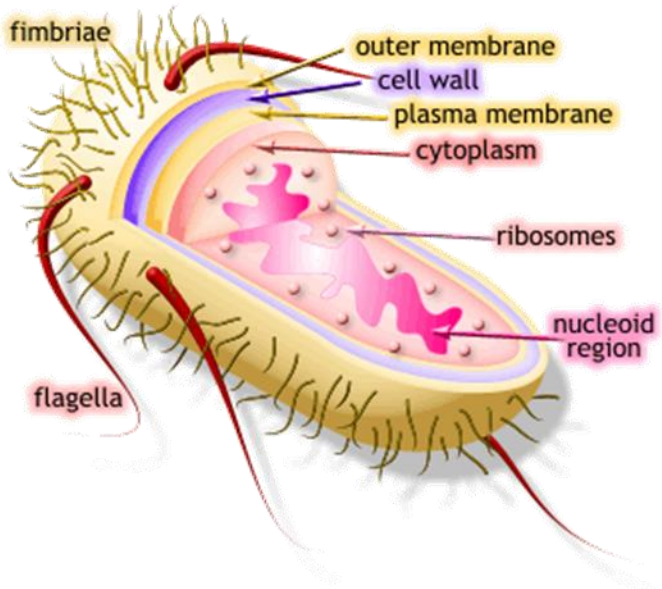
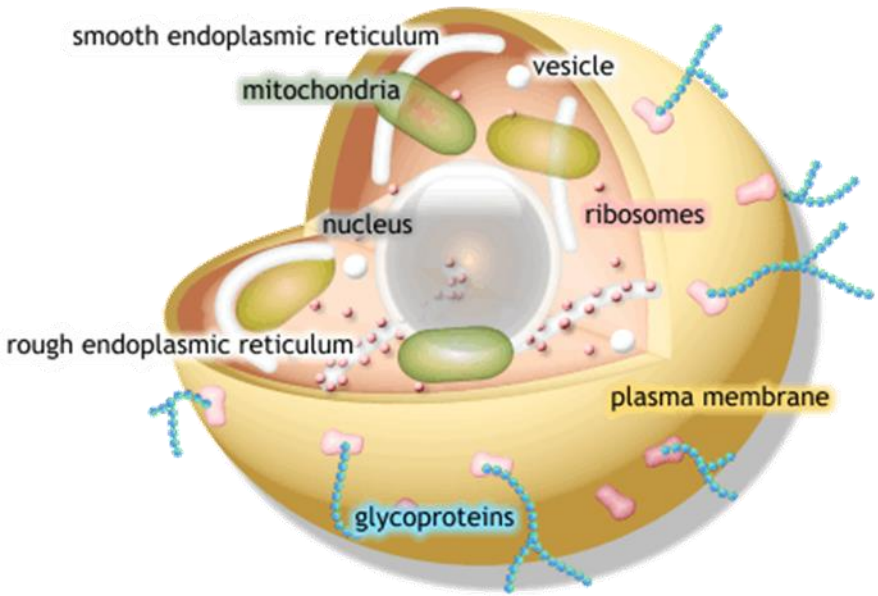
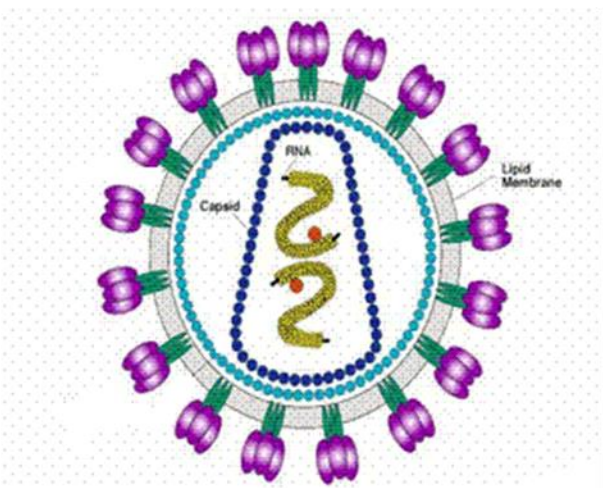
State of the Art & Science



Prokaryotes



Eukaryotes



Viruses

Basics of contamination control technology

Definition

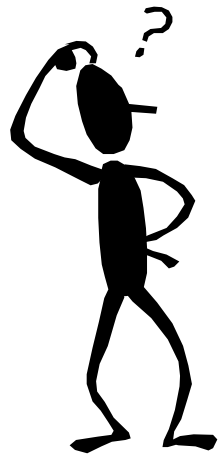
Cleanroom technology is the chain

of all technical and operational measures

in order to avoid or reduce

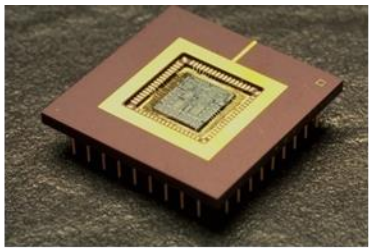
harmful influences of contamination

on pruducts and personel.

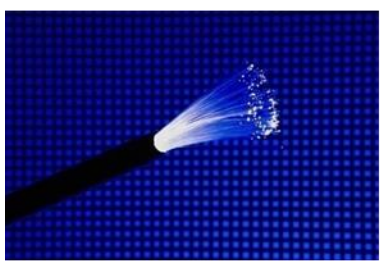


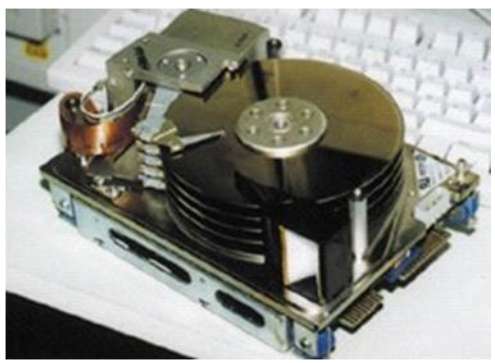
Use of cleanroom technology today

* Microelektronic
* Mikro structures
* Precision mechanics
* Optics, optoeletronics



* Glas fiber technology
* Laser technology
* Space travel
* Multi media technologies





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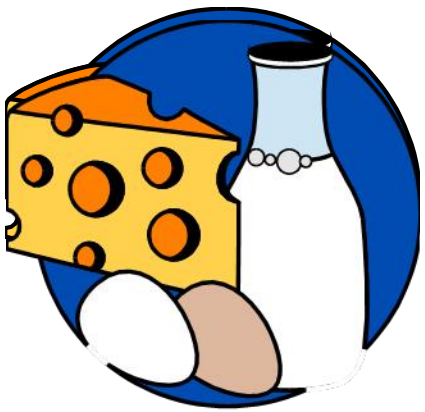
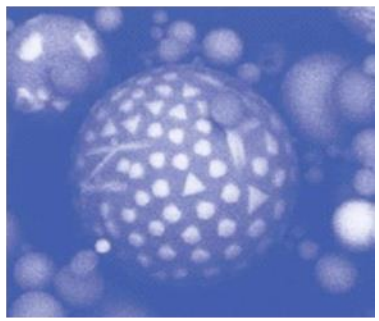
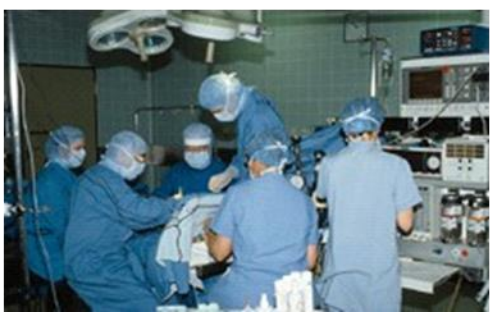
Use of cleanroom technology today

* Pharmaczie
* Food industry
* Biotechnology
* Medicin products
* Laboratories
* Production of active substances





* Hospitals



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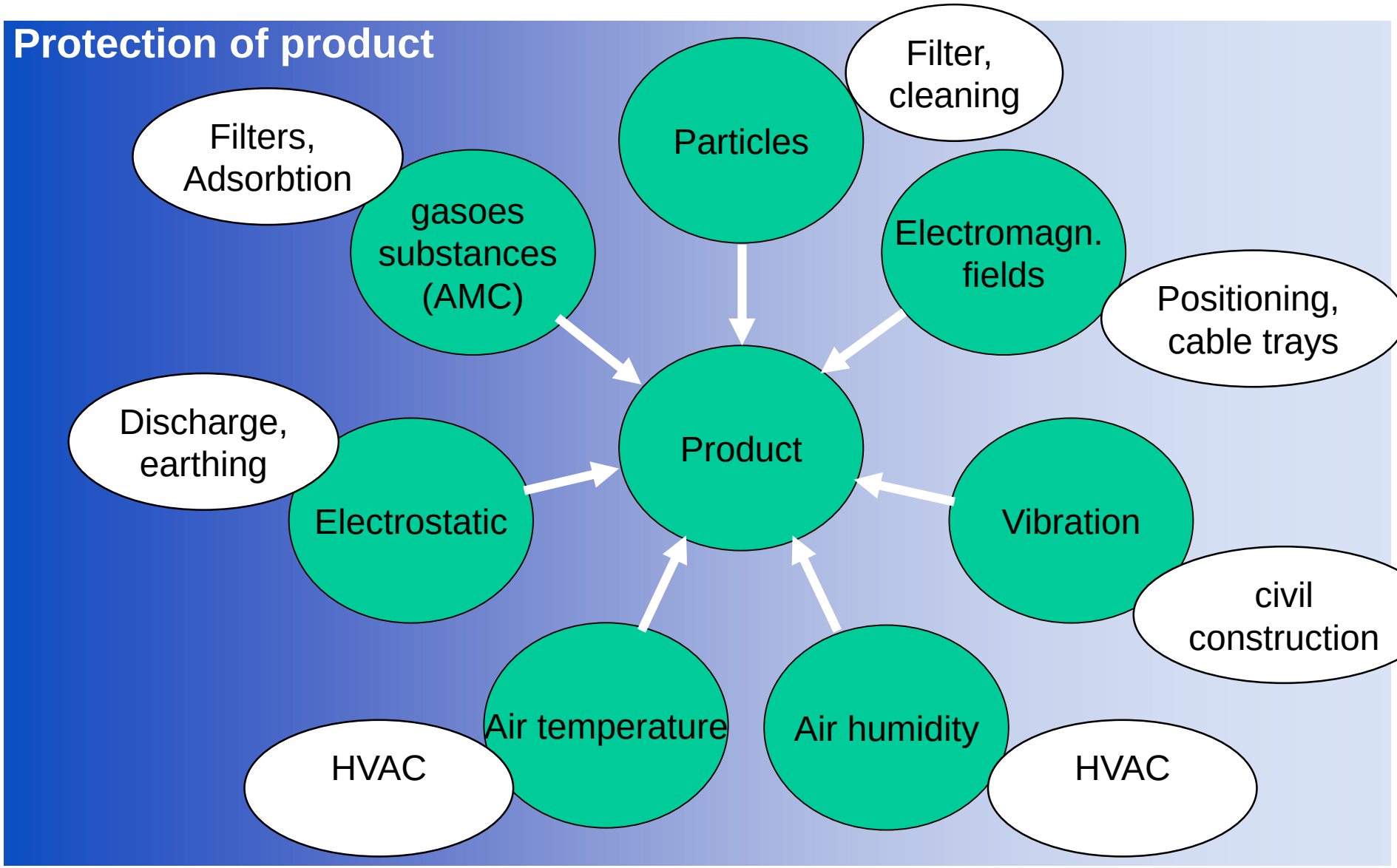
Taks of cleanroom technology

- Protection of products
- Protection of personel
- Protection of environment


Protection of product
Filter, cleaning
Filters, Adsorbtion
Particles
gasoes substances (AMC)
Electromagn. fields
Positioning, cable trays
Discharge, earthing
Product
Electrostatic
Vibration
civil construction
Air temperature
Air humidity
HVAC
HVAC

Cleanroom parameters

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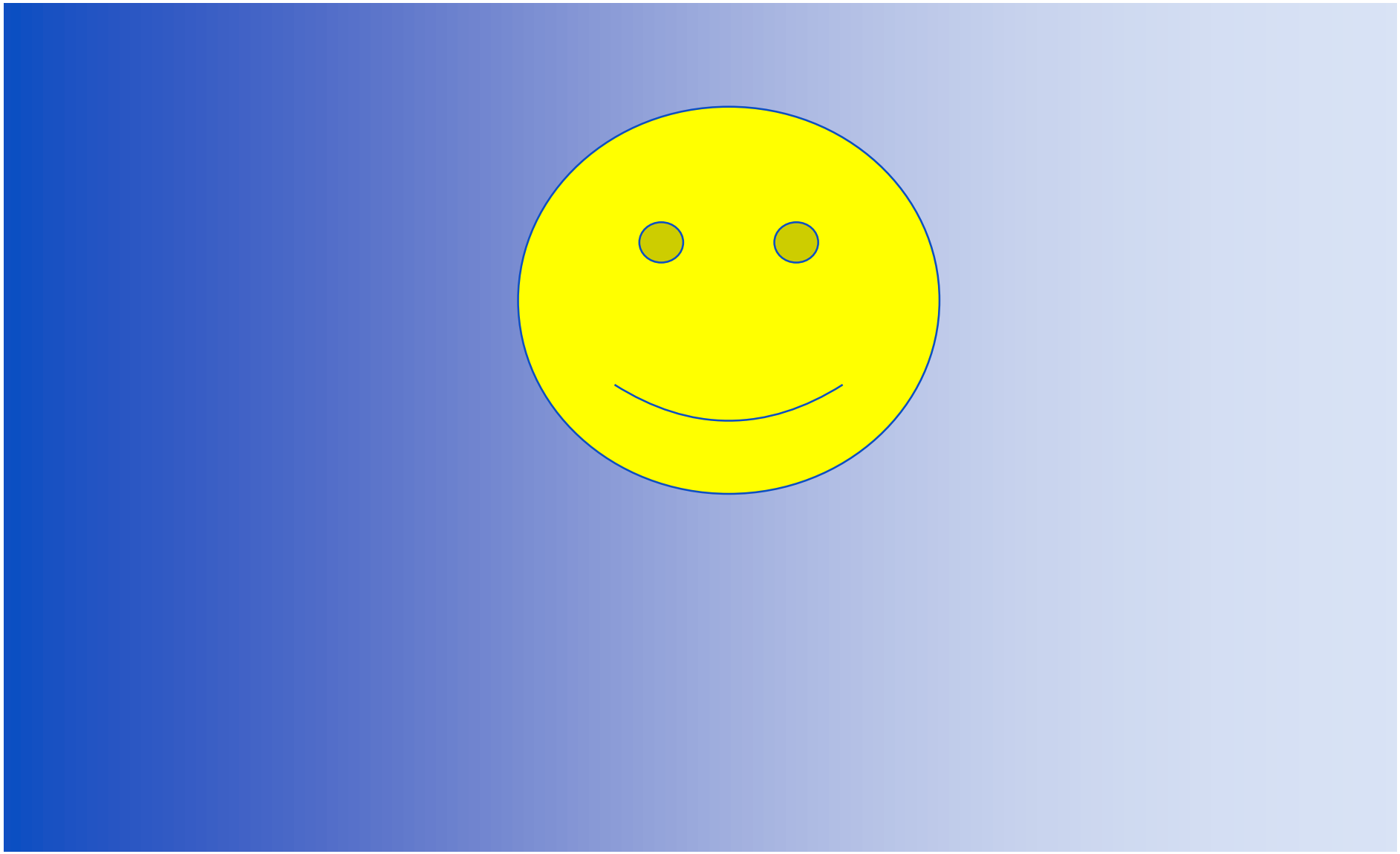
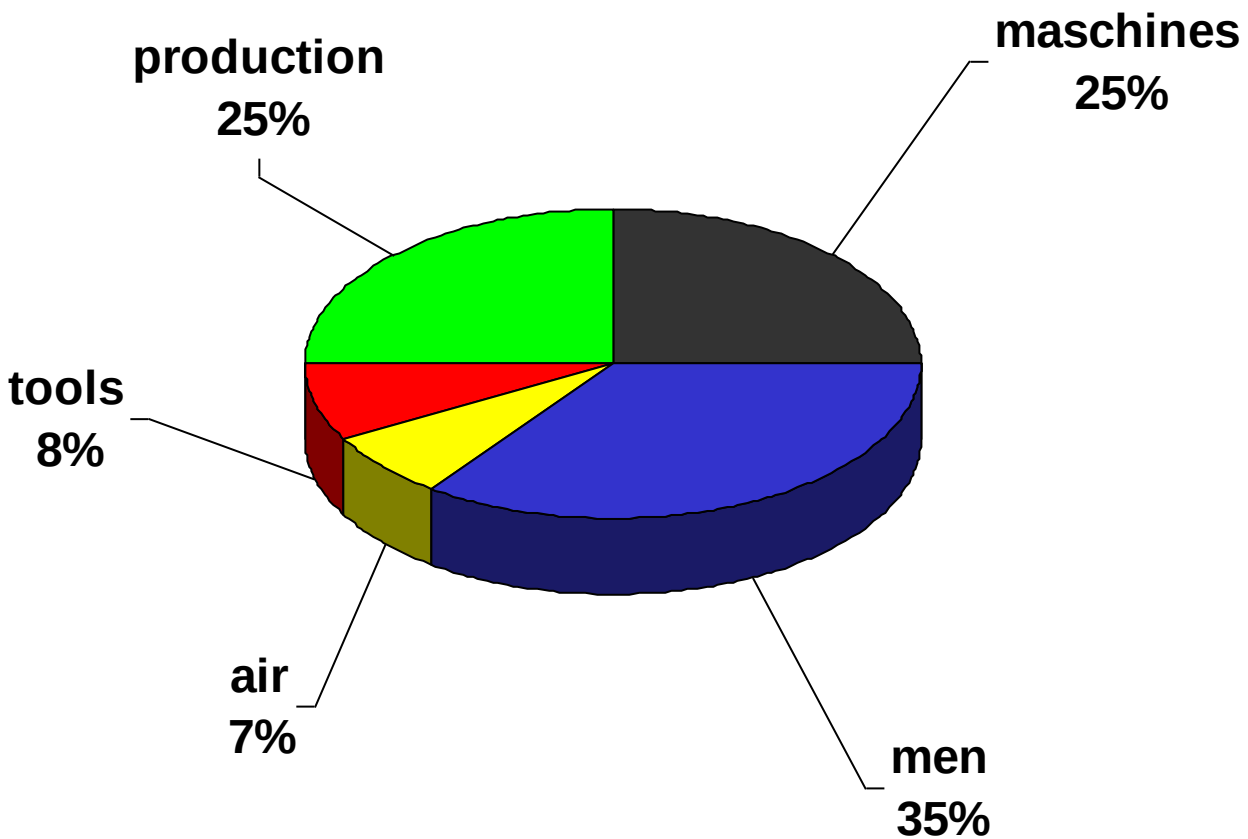


Requirements on cleanroom

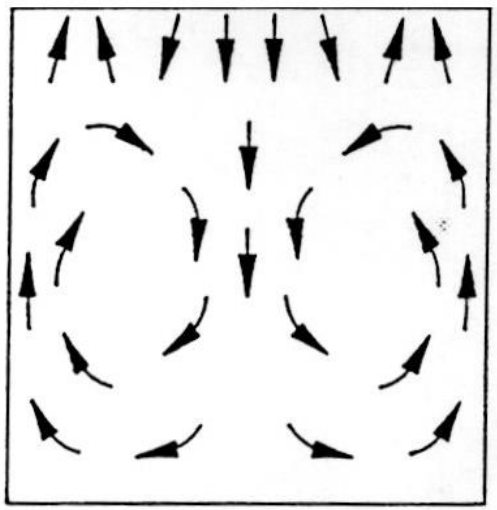
Woolmilkpig laying eggs

Harmful influences in a cleanroom:

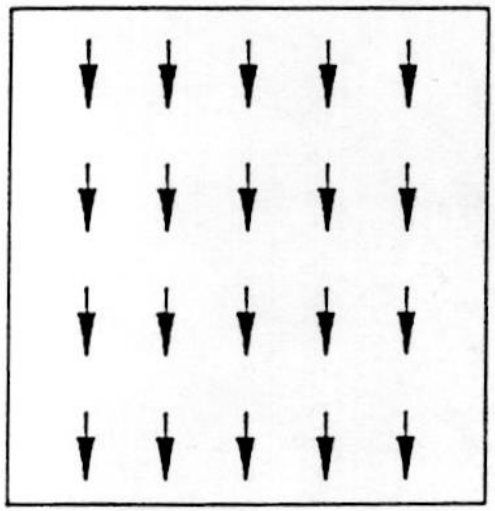
Particle sources in cleanrooms



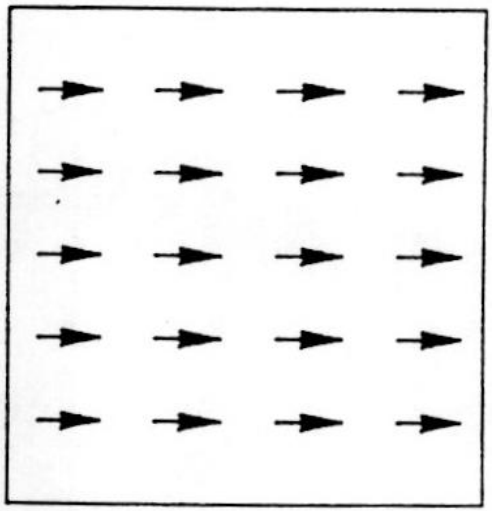
Kind of air flow in cleanrooms



Turbulent air flow

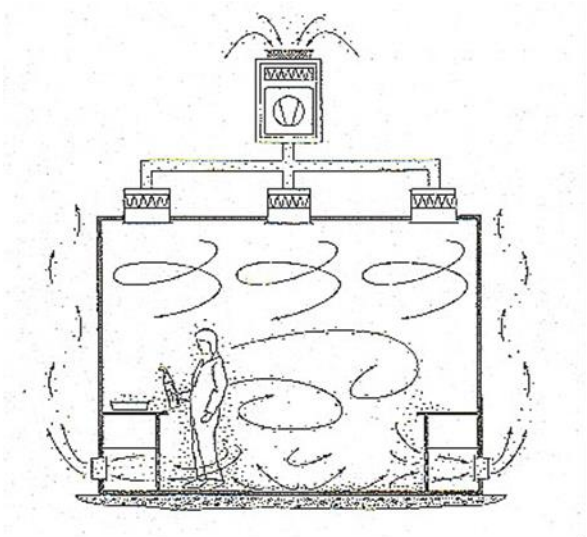


little turbulent displacing (laminar) air flow vertical

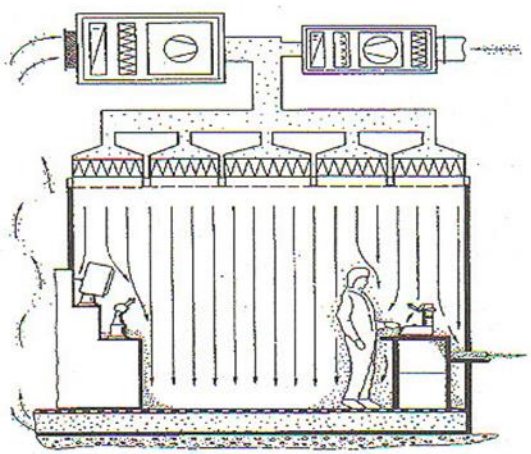


little turbulent displacing (laminar) air flow horizontal

turbulent air flow



laminar air flow



air flow stream

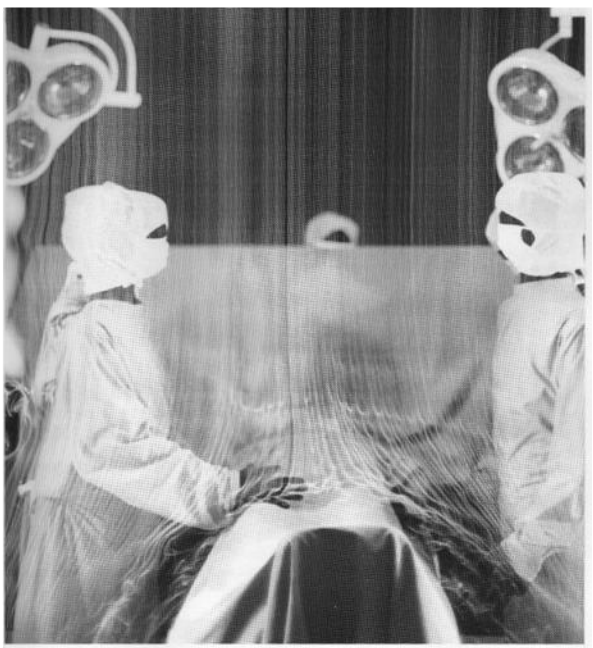


Fig. 6: Laminar displacement flow under a ceiling of an Operation Room.

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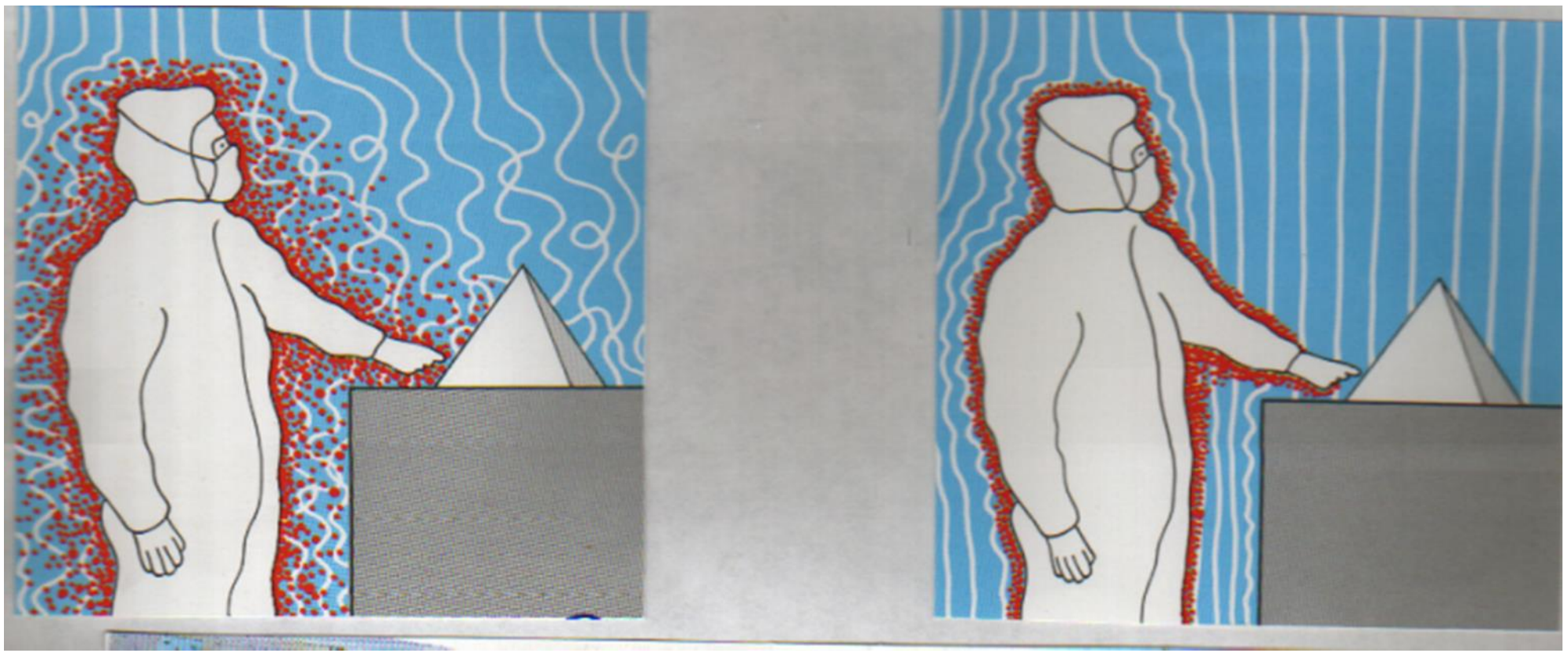
Influences on particles

Turbulent

Laminar



Influence of Air Flow Velocity

Low turbulent displacement air flow with different air velocities

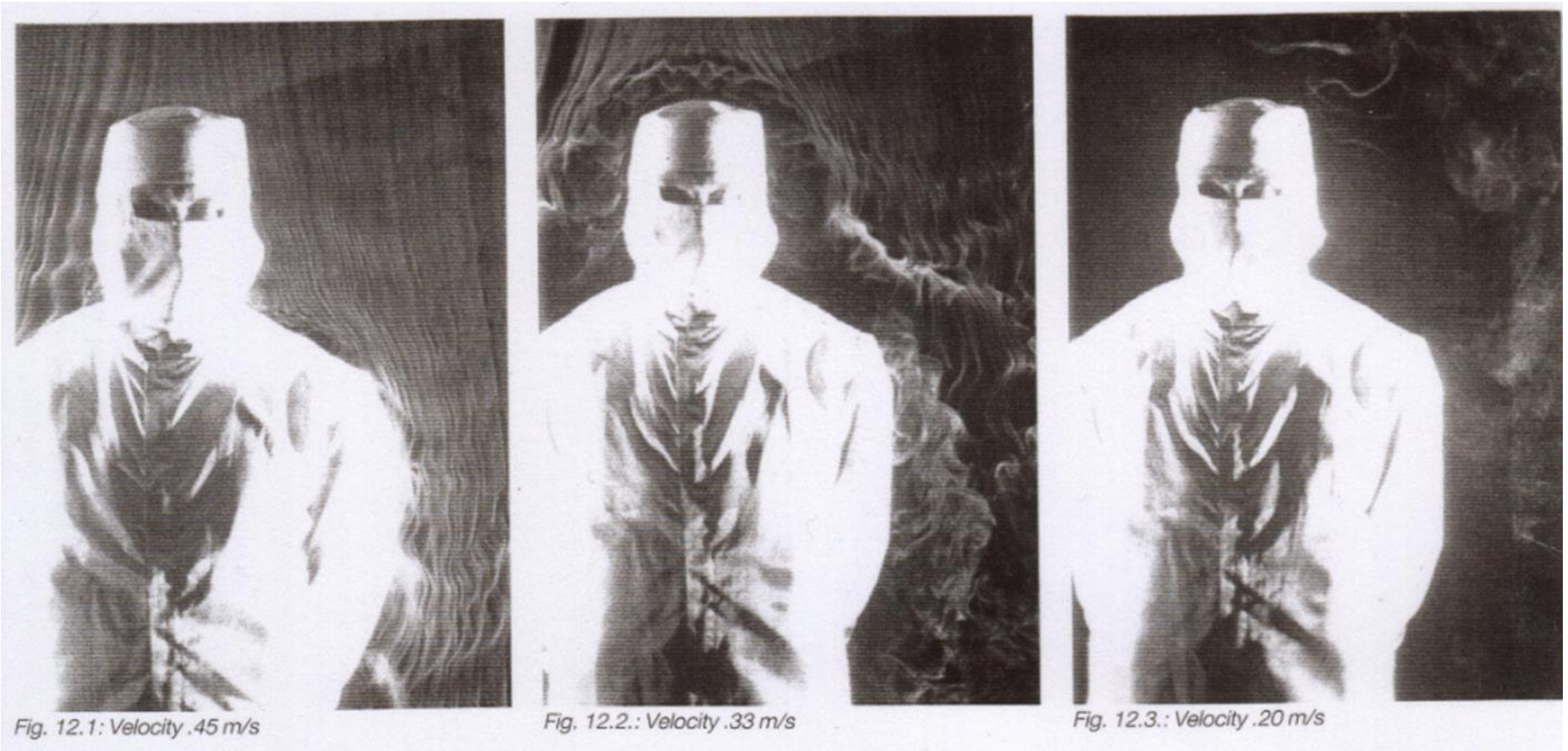


Fig. 12.1: Velocity .45 m/s

Fig. 12.2.: Velocity .33 m/s

Fig. 12.3.: Velocity .20 m/s

Quelle: Siemens, Fertigung unter Reinraumbedingungen

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Regulations and standards

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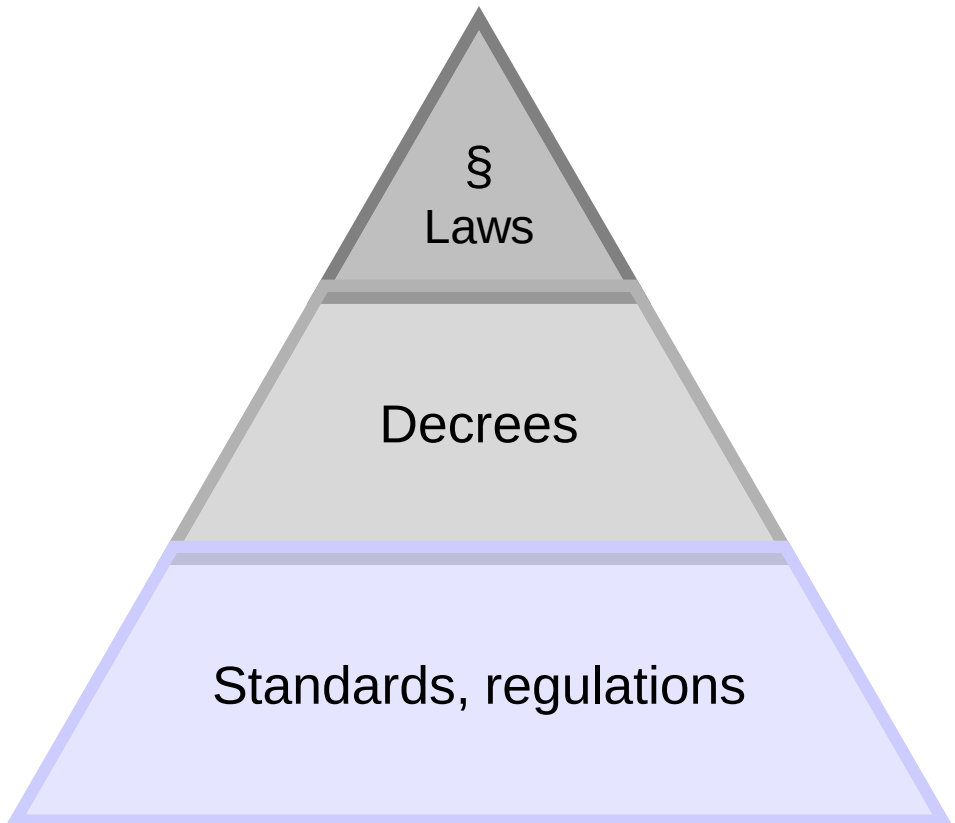
Standard and regulations

ISO	-	International Organization for Standardization
VDI	-	Verein Deutscher Ingenieure
DIN	-	Deutsches Institut für Normung
GMP	-	Good Manufacturing Practice
PIC	-	Pharmaceutical Inspection Cooperation
FDA	-	Food and Drug Administration
GAMP	-	Good Automated Manufacturing Practice
IEST	-	Institute of Environmental Sciences and Technology
USP	-	US Pharmacopeia
ICH	-	International Conference on Harmonisation
WHO	-	World Health Organization
CFR	-	Code of Federal Regulations

- **VDI 2083:** Cleanroom Technology
- **DIN ISO EN 14644:** Cleanrooms and associated controlled environments
- **EU Directive 2004/94 EG (GMP) with Guidlines I and II and Annexes**
- **c GMP 21 CFR 11:** Electronic Records, Electronic Signatures
- **c GMP 21 CFR 210:** CURRENT GOOD MAN-UFACTURING PRACTICE IN MAN-UFACTURING, PROCESSING,PACKING, OR HOLDING OFDRUGS; GENERAL
- **c GMP 21 CFR 211:** CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS
- **PIC/S PI 006-1:** Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Valation, Cleaning Validation
- **PIC/S PI 011:** Good Practices for Computerised Systems

- Range of obligations



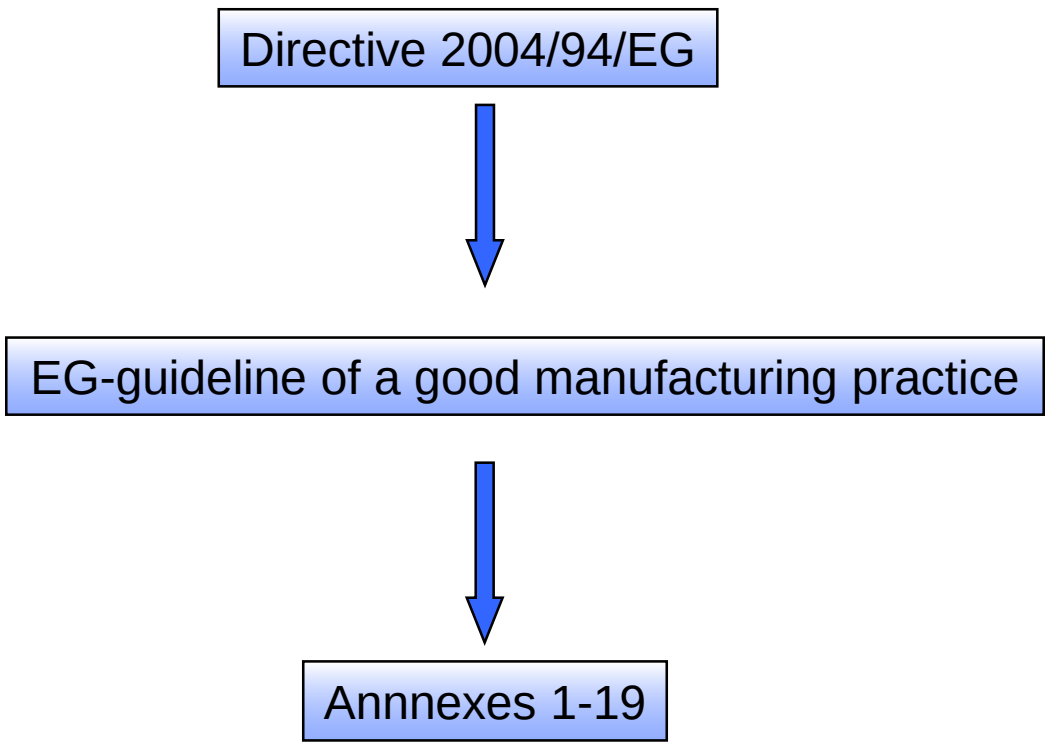
EU-GMP - Good Manufacturing Practice

Concern

Human medicines (drugs)

Animal medicines (drugs)

Structur of EU GMP



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Guideline 2004/94/EG

The principles and guidelines of the GMP deal mostly with

- personnel,
- rooms and the equipment
- documentation,
- production,
- quality control,
- Auftragsherstellung,
- den Beanstandungen
- dem Produktrückruf
- den Selbstinspektionen

Rooms and Eequipment

Special requirements

- take into account the production flow
- access control
- sufficient workplaces and storage capacities
- good ventilation
- careful maintenance
- to avoid access of insects and animals
- surfaces plain, free from cracks and gaps, no pollution of particles, easy to clean and to desinfect
- lounges separated from production areas
- toilets not with direct connection (access9 from production and storage areas
- Separate weighing rooms with dust extraction

Supplement Guideline Annnex 1

für die Herstellung steriler Arzneimittel

Max. permitted no. of particles per m³ air

grade	at rest		in operation	
	0,5 µm	5 µm	0,5 µm	5 µm
A (ISO 5 at rest)	3520 (100)	20	3520 (100)	20
B (ISO 5 at rest)	3520 (100)	29	352.000 (10.000)	2.900
C (ISO 7 at rest)	352.000 (10.000)	2.900	3.520.000 (100.000)	29.000
D (ISO 8 at rest)	3.520.000 (100.000)	29.000	not fixed	not fixed

Recommended limit values for microbiological contamination CFU (Colony Forming Units)

grade	air sample cfu/m³	settle plates Ø 90 mm cfu/4h	contact plate Ø 55 mm cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Supplement Guideline, Annex 1

für die Herstellung steriler Arzneimittel

Which cleanroon class for which activity (example)

Classification	EC	FDA	Activities
Cleanroom class	**Zone A**	Critical	filling of aseptic products, filling of open vials and ampuls and bottles
Cleanroom class	**Zone B**	-	surroundings of class A, transfer of aseptic products in closed systems
Cleanroom class	**Zone C**	Controlled	preparation of solutions, filling of products terminally sterilised, surrounding of Isolators
Cleanroom class	**Zone D**	-	preparation of solutions for filling (products terminally sterilised), packing, handling of componets after washing
other works	**Zone -**	-	Laboratories, administration, workshops, storage

Status of ISO 14644 Cleanrooms and associated controlled environments

Part	Titel	Status	Year
ISO 14644-1	Classification of air cleanliness	ISO-Norm	1999
ISO 14644-2	Specifications for testing and monitoring to prove continued compliance with ISO 14644-1	ISO-Norm	2000
ISO 14644-3	Test methods	ISO-Norm	2005
ISO 14644-4	Design, construction and start-up	ISO-Norm	2001
ISO 14644-5	Operations	ISO-Norm	2004
ISO 14644-6	Vocabulary	ISO-Norm	2007
ISO 14644-7	Seperative devices (clean air hoods, gloveboxes, isolators and mini-environments)	ISO-Norm	2004
ISO 14644-8	Classification of airborne molecular contamination	ISO-Norm	2006
ISO 14644-9	Classification of surface particle cleanliness	CD	

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Status der ISO 14698 Cleanrooms and associated controlled environments -Biocontamination

Part	Titel	Status	Year
ISO 14698-1	General principles and methods	ISO-Norm	2003
ISO 14698-2	Evaluation and interpretation von biocontamination data	ISO-Norm	2003

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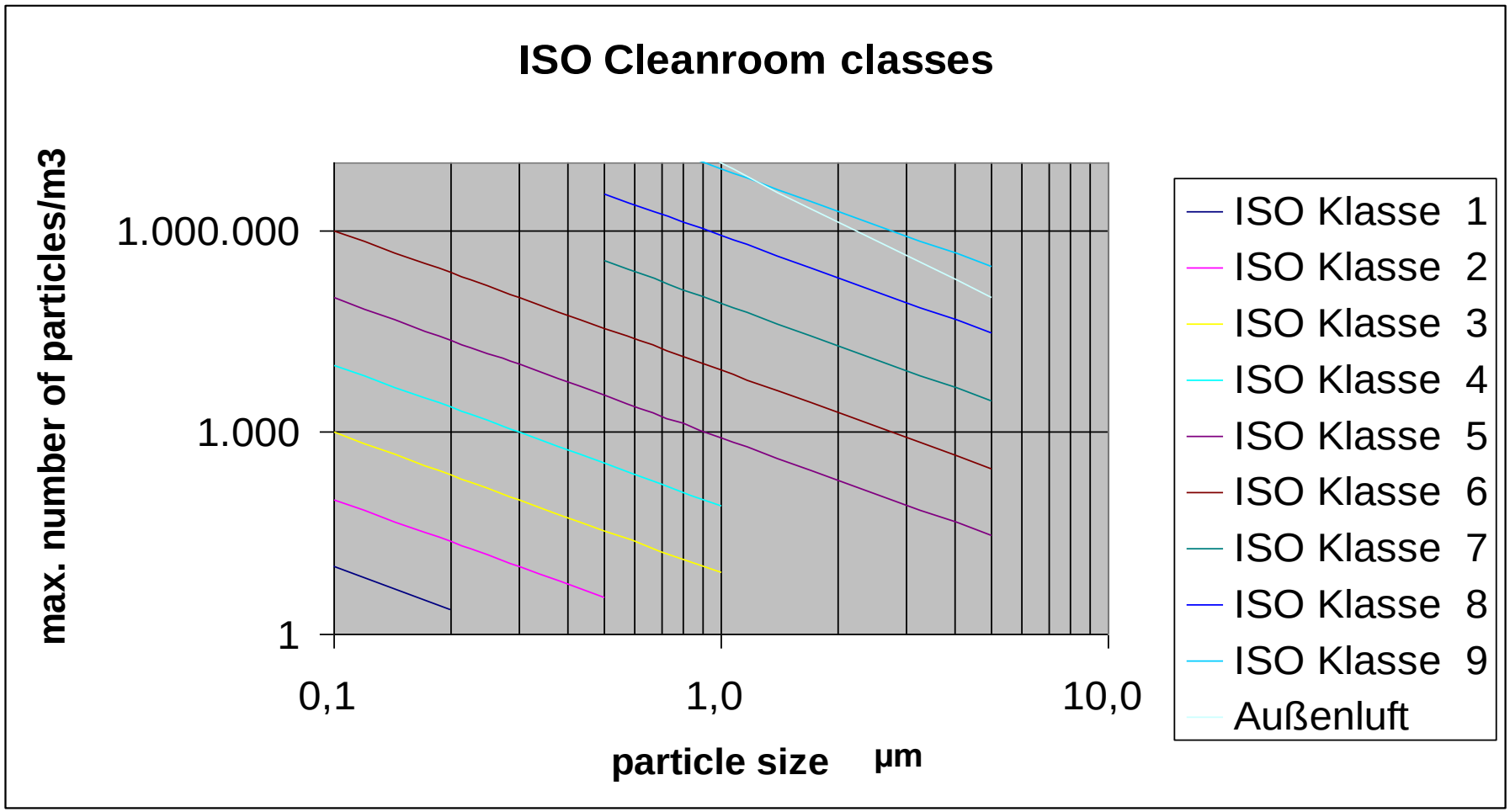
Status der VDI 2083 Reinraumtechnik

Part	Titel	Status	Year
VDI 2083 Blatt 1	Partiiculate air cleanliness classes	Guideline	Mai 2005
VDI 2083 Blatt 3	Metrology and test methods	Guideline	Juli 2005
VDI 2083 Blatt 4.1	Planning, construction and start-up of cleanrooms	Guideline	Okt. 2006
VDI 2083 Blatt 5.1	Cleanroom operation	Guideline	Sep. 2007
VDI 2083 Blatt 5.2	Decontamination of mulit-use cleanroom clothing	Draft	Nov. 2007
VDI 2083 Blatt 7	Cleanliness of process media	Guideline	Jan. 2006
VDI 2083 Blatt 9.1	Conpatibility with required cleanliness and surface cleanliness	Guideline	Dec. 2006
VDI 2083 Blatt 10	High purity media supply systems	Guideline	Feb. 1998
VDI 2083 Blatt 11	Quality assurance	Guideline	Jan. 2008
VDI 2083 Blatt 12	Ssfety and environmental aspects	Guideline	Jan. 2000
VDI 2083 Blatt 13.1	Quality, production and distribution of ultrapure water Fundamentels	Draft	March 2008
VDI 2083 Blatt 13.2	Quality, production and distribution of ultrapure water Microelectronics and other technical applications	Draft	March 2008
VDI 2083 Blatt 14	Airborne molecular contamination in cleanrooms (AMC)	Draft	April. 2008
VDI 2083 Blatt 15	Personnel at the clean work place	Guideline	April 2007


ISO Cleanroom classes
max. number of particles/m3
1.000.000
1.000
1
0,1
1,0
10,0
particle size µm
ISO Klasse 1
ISO Klasse 2
ISO Klasse 3
ISO Klasse 4
ISO Klasse 5
ISO Klasse 6
ISO Klasse 7
ISO Klasse 8
ISO Klasse 9
Außenluft

Cleanroom classes acc. VDI 2083 / ISO 14644

Max. number of particles per m^3 air

	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1,0 µm	5,0 µm
ISO class 1	10	2				
ISO class 2	100	24	10	4		
ISO class 3	1.000	237	102	35	8	
ISO class 4	10.000	2.370	1.020	352	83	
ISO class 5	100.000	23.700	10.200	3.520	832	29
ISO class 6	1.000.000	237.000	102.000	35.200	8.320	293
ISO class 7				352.000	83.200	2.930
ISO class 8				3.520.000	832.000	29.300
ISO class 9				35.200.000	8.320.000	293.000

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NOTICE
OF CANCELLATION
November 29, 2001

FED-STD-209
NOTICE 1

FEDERAL STANDARD
AIRBORNE PARTICULATE CLEANLINESS CLASSES IN CLEANROOMS AND CLEAN ZONES

Federal Standard 209E dated September 11, 1992 is hereby canceled and superseded by International Organization for Standardization (ISO) Standards. International Standards for Cleanrooms and associated controlled environments, ISO 14644-1 Part 1: Classification of air cleanliness; and ISO 14644-2 Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1.

Typical Measurement Devices

Aerosol generator

Particle counter

Fog generator

Pressure difference meter

„Ballometer“

Sound level meter

Contamination and particles

Particles are small parts of substances e.g.:

- Aerosol (consist of free floating particles)
- Soot from Diesel motors
- Fine dust
- Soot from combustion processes

Partiles are of such importance because you cannot see them with the naked eye but they can harm our health (asbestus, allergy, coal dust, fine dust from vehicles).

Particles

Particle characteristics and description

We describe particles by:

a) size

b) concentration

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Cleanliness classes acc. VDI 2083 / ISO 14644

Max number of particles per m^3 air

	0,1 µm	0,2 µm	0,3 µm	0,5 µm	1,0 µm	5,0 µm
ISO class 1	10	2				
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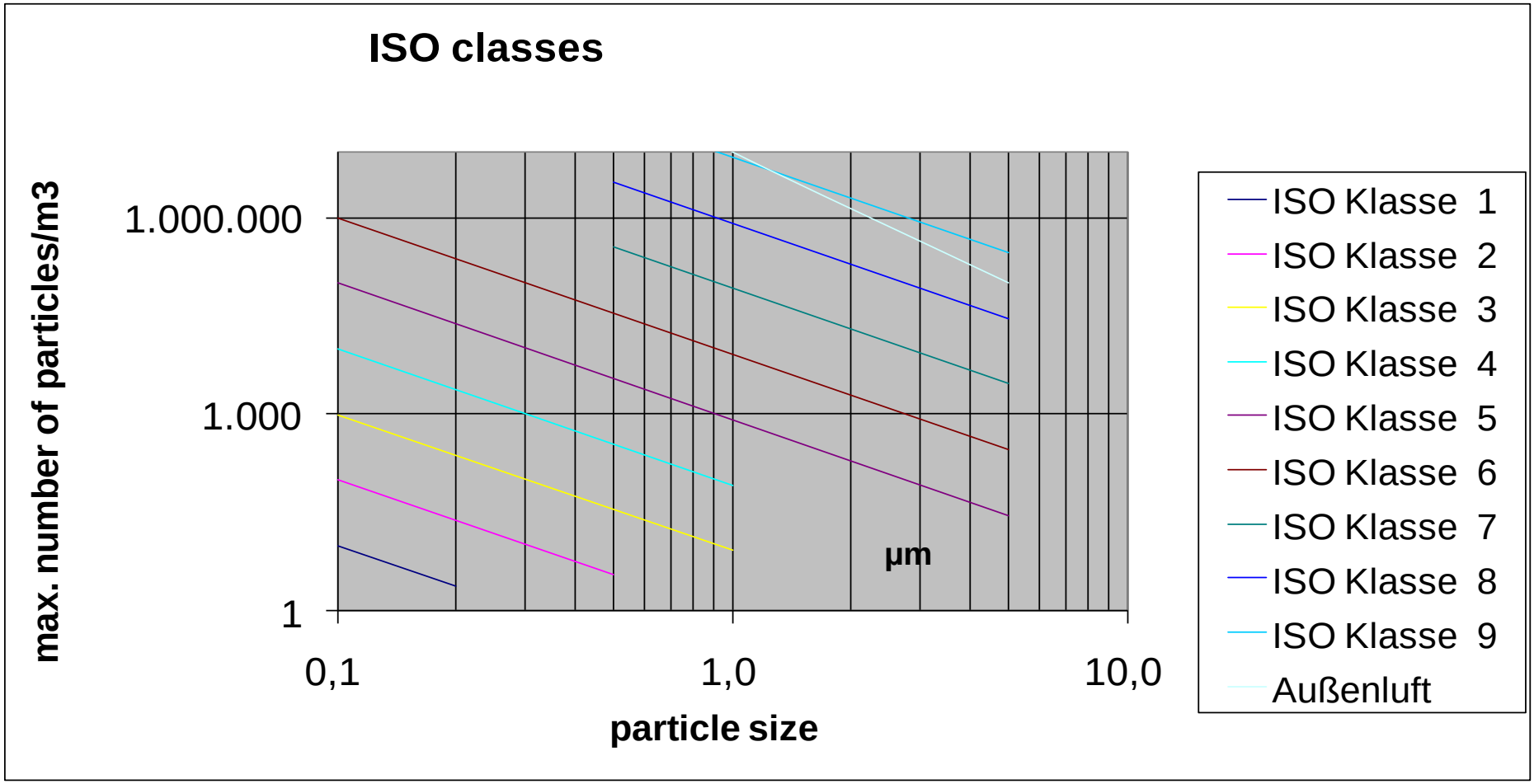

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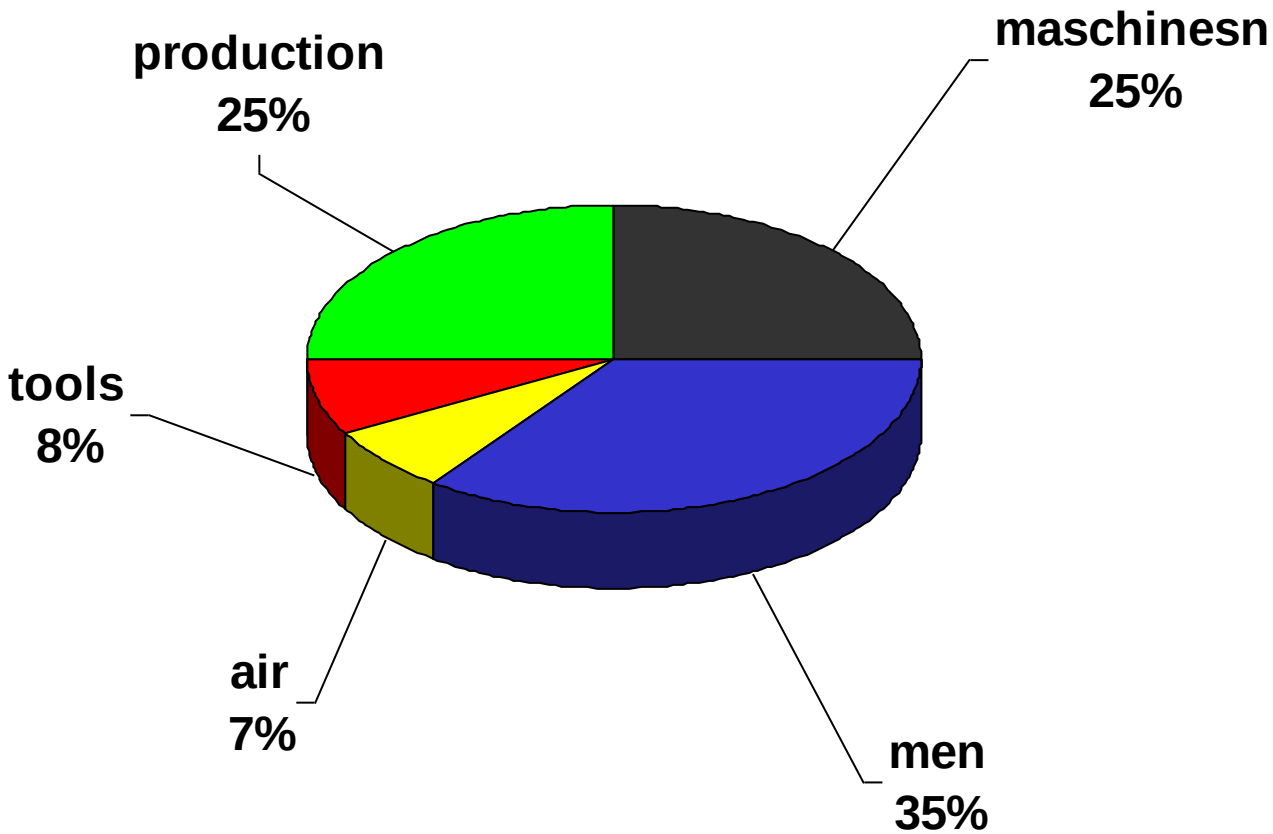
Harmful influences in a cleanroom:

Particle sources in cleanrooms



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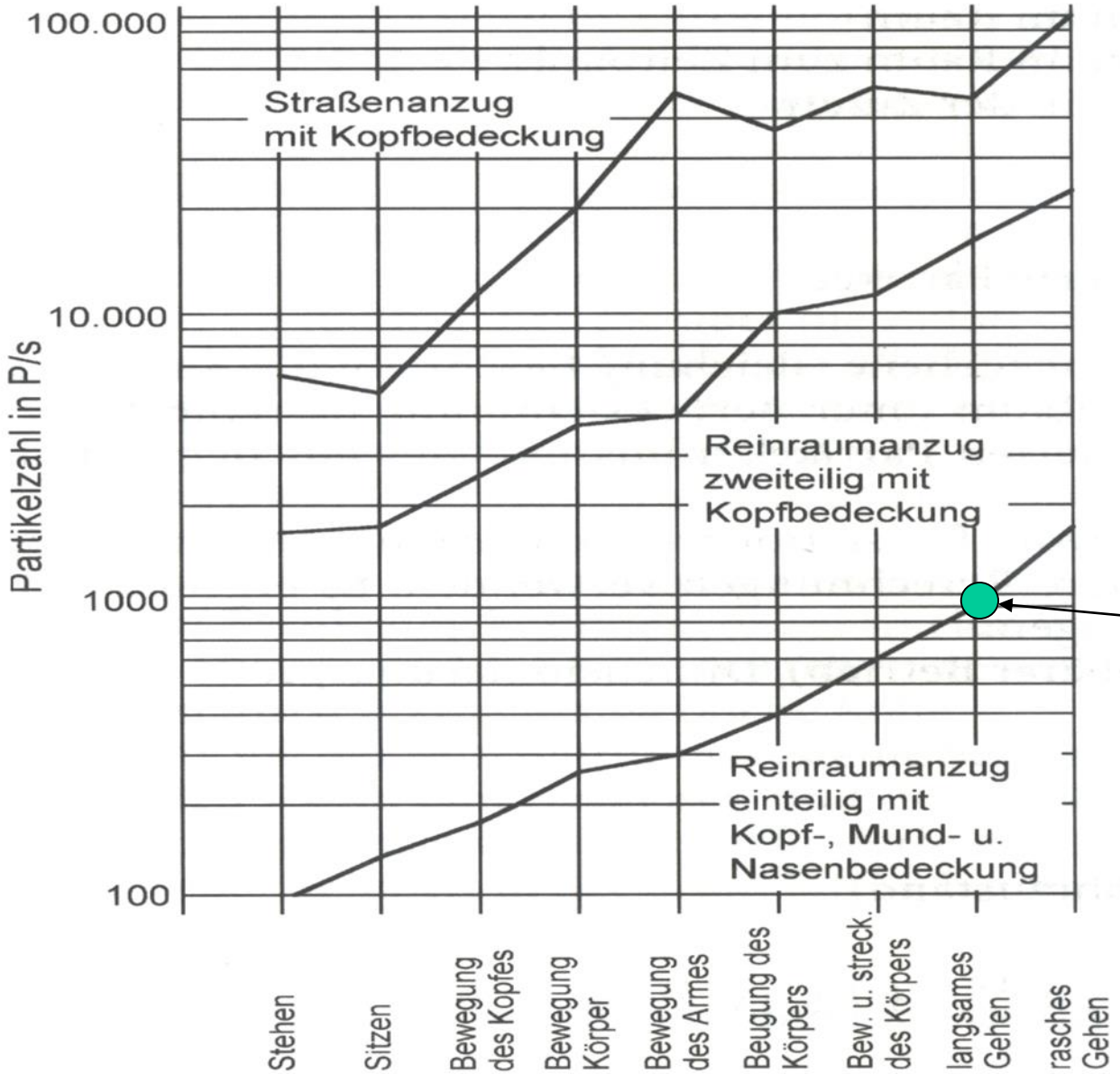

Particle generation depending on clothing and movement
particle size ≥ 0,5 µm

appr. 1.000 P/s
= 3.600.000 P/h

Quelle: Gail. Hortig, Reinraumtechnik, Springer-Verlag 2002

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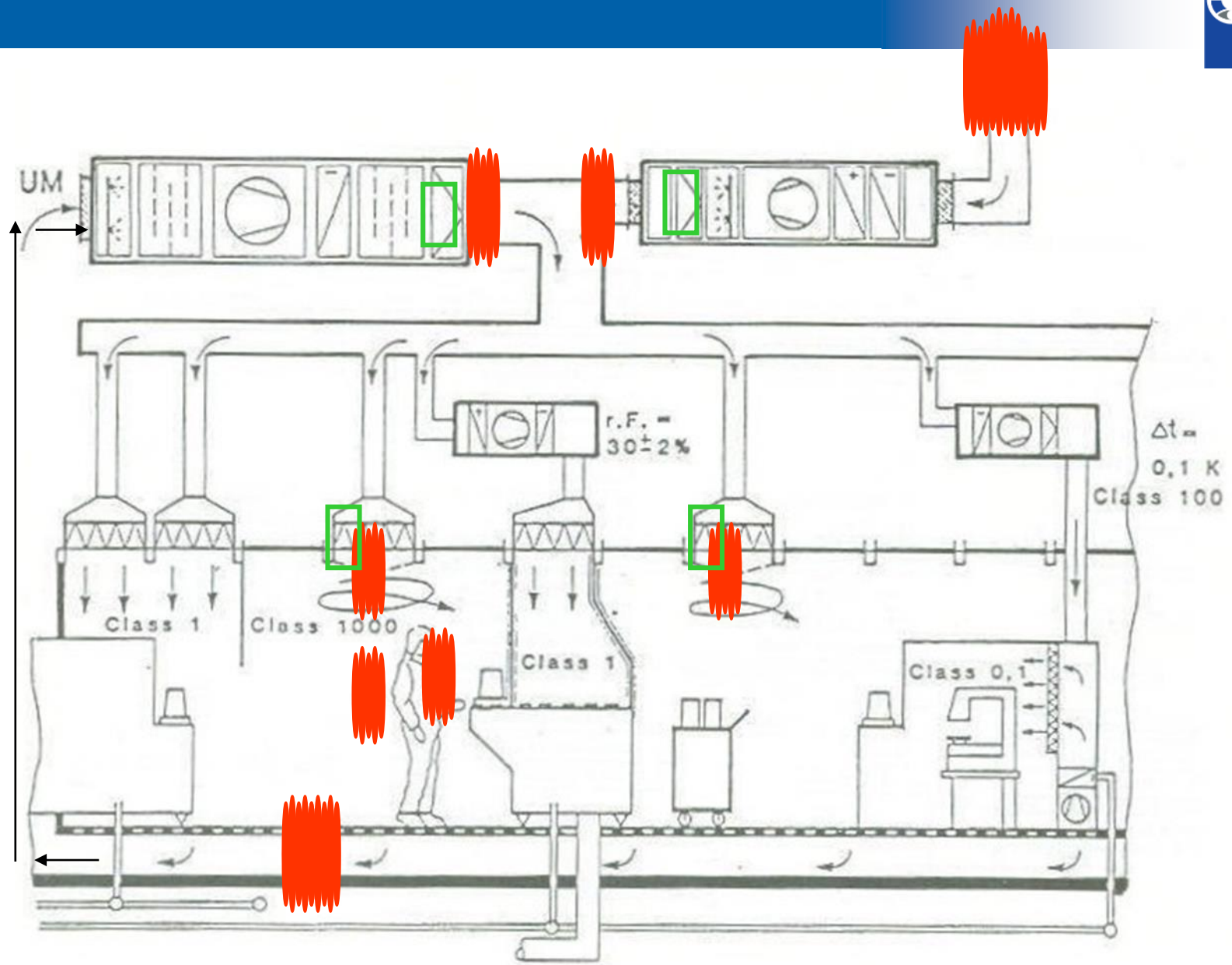
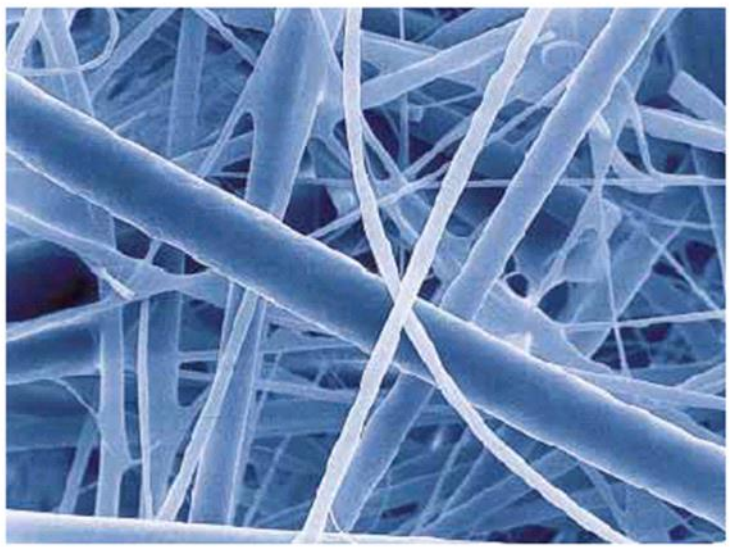


Filter material

500 µm

3-lagiges Vliesstoff-Filtermedium, mittlere Schicht elektrostatisch gesponnene Mikrofasern



5 µm

Hochfestes Glasfaser-Filtermedium mit speziellem Bindersystem

Quelle: Freudenberg „Viledon“

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Filtering effects

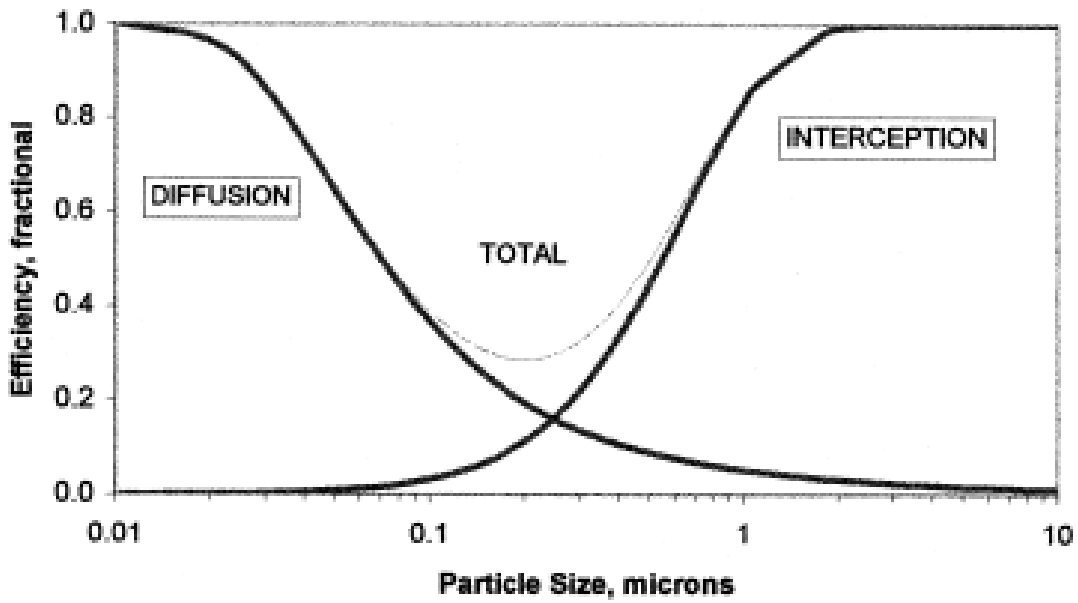


Figure 4 *Generalized comparison of the contribution to total filter efficiency due to diffusion and to interception.*

filtration_of_airborne_microorg

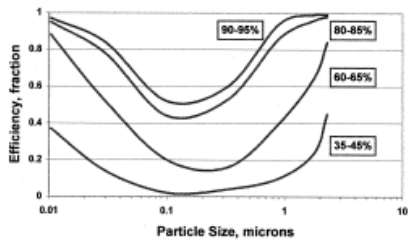


Figure 1 ASHRAE filter performance data (Ensor et al. 1988).

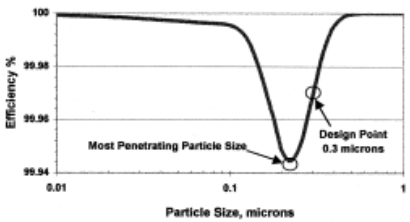


Figure 2 Typical performance of a HEPA 99.9% filter.

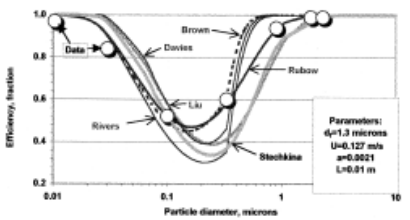


Figure 3 Comparison of various single-fiber filter models with 90% ASHRAE data from Ensor et al. (1988).

equation defining overall filter efficiency (E) for any particle size and set of conditions (Davies 1973) is as follows:

$$E = 1 - e^{-\xi_s S} \qquad (1)$$

where

S = fiber projected area, dimensionless;

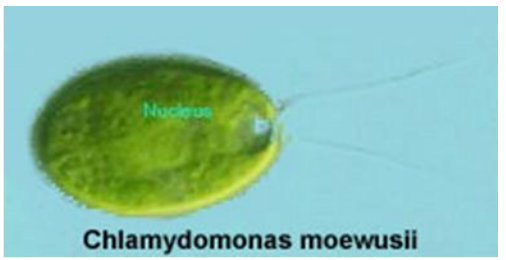
E_s = single-fiber efficiency, fractional.

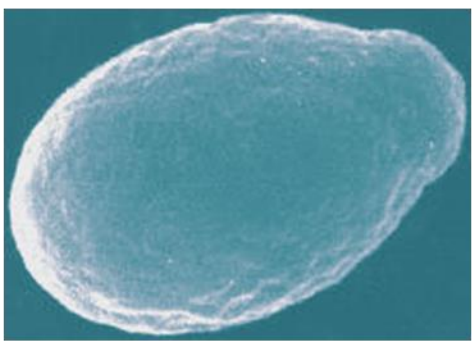
The fiber projected area (S) is a dimensionless constant combining the three main determinants of filter efficiency—filter thickness (length normal to airflow), filter packing

7

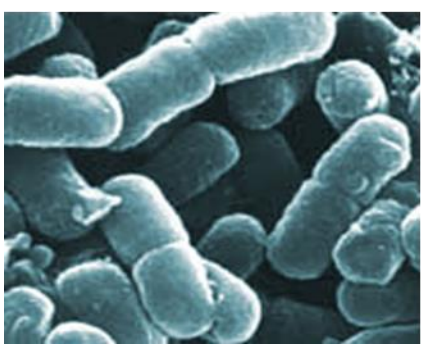
Contamination

- Particles coming from
  - sand/dust
  - soot from chimneys and cars
  - fibers
- Germs
  - pollen
  - spures
  - microorganisme
    - bacteria
    - funghus
    - viruses
- Pyrogene





Chlamydomonas



Hefe (Saccharomyces spec.)

Escherichia Coli

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- size of bacteria: appr. 0,5 thru 1,0 µm
- size of viruses: 0,008 thru 0,5 µm
- air born mikroorganisms occure (appear) preferably tied on particles bigger than 0,5 µm. Germs preferably deposit on dust. **They can be removed by air filters together with particles.**

Why are bacteria so dangerous?

They can reproduce themselve by cell division!

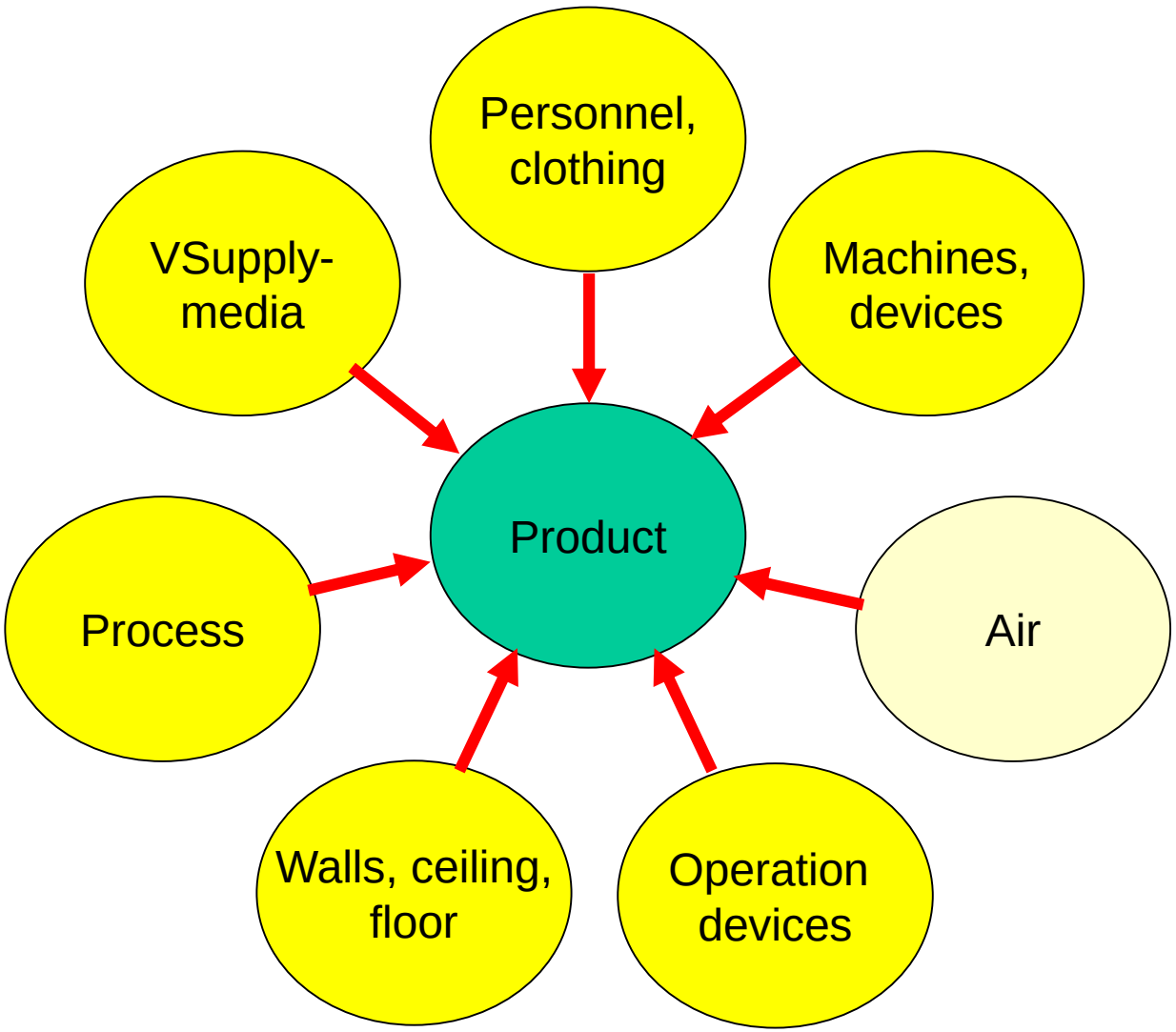
Reproduction of bacteria		
reproduction time:	20 min	
time (h)	number of bacteria	
1	8	
2	64	
3	512	
4	4.096	
5	32.768	
6	262.144	
7	2.097.152	
8	16.777.216	
9	134.217.728	
10	1.073.741.824	
11	8.589.934.592	
12	68.719.476.736	
13	549.755.813.888	
14	4.398.046.511.104	
15	35.184.372.088.832	
16	281.474.976.710.656	
17	2.251.799.813.685.250	
18	18.014.398.509.482.000	
19	144.115.188.075.856.000	
20	1.152.921.504.606.850.000	
21	9.223.372.036.854.780.000	
22	73.786.976.294.838.200.000	
23	590.295.810.358.706.000.000	
24	**4.722.366.482.869.650.000.000**	

Are you able to avoid particles completely in a cleanroom?

- **Avoiding**
  - **discipline**
  - **exhaust**
  - **covering**
  - **suitable clothing**
  - **air locks, cleaning before transport into the clearoom**

- **Reduce**
  - **cleaning**
  - **filtering**

Contamination of the product:



Aim:

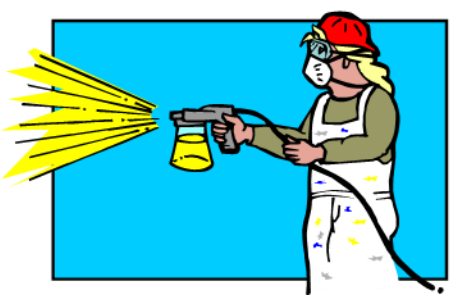
- To fidentify and avoid all possibilities that can harm personnel and product.

Ways

- avoid/keep away
  build a cleanroom, use cleanroom clothes, filter, pressure differences

- remove
  cleaning, filering, use pure supply media

- Inactivate
  Desinfection, sterilisation



Aim of hygenic measures in a cleanroom:

- Keep the transport of germs into the cleannroom as low as possible
- Avoid the reproduction of germs in the aseptic aereas of the cleanroom

.

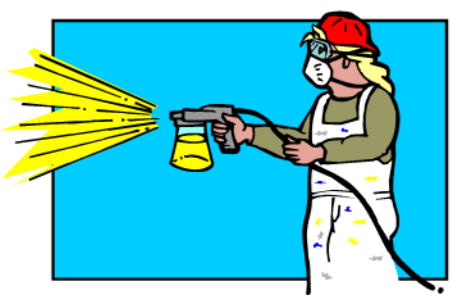
The number of germs usually indicated with CFU **C**olonie **F**orming **U**nits.

GMP grade	Air sample **cfu/m3**	Settle plates cfu/4 h	Contact plates **cfu/plate**	Glove print 5 fingers cfu/glove
A	<1	<1	<1	1
B	10	5	5	5
C	100	50	25	n. r.
D	200	100	50	n. r.

The way to reduce contamination:

a) Hygenic behaviour of personnel

b) Cleaning



c) Disinfection

Personnel hygienic behaviour

EU GMP-Guideline Personnel Hygiene 2.13 – 2.20

- Detailed hygiene programmes should be established and widely discussed during training sessions.
- medical examination upon recruitment
- no infectious disease or open lesions on the exposed surface of the body
- protective garments
- Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice should be forbidden.
- Direct contact should be avoided between the operator’s hands and the exposed product as well as with any part of the equipment that comes into contact with the products.
- Personnel should be instructed to use the hand-washing facilities.

Table 7. Recommendations regarding cleanroom cleaning

ISO class	**8/7**	**6**	**5 and less strict**
GMP class	**D**	**C**	**A/B**
Cleaning agents	aqueous alcoholic solutions such as isopropanol where required: use of disinfectants, see Annex F		
Training intervals for cleaning personnel	12 months		
Equipment	stainless steel or defined plastics		stainless steel or defined sterilisable plastics
Mop-holder system for ceilings and walls	aluminium or defined plastics		anodised aluminium or defined sterilisable plastics
Wipes	commercially available cleanroom wipes		qualified cleanroom wipes
Basic cleaning in microelectronics	12 months		
Basic cleaning in pharmaceutical areas/GMP areas	12 months	6 months	every month
Maintenance cleaning in microelectronics	2 to 3 times a week	daily	
Maintenance cleaning in pharmaceutical areas/GMP areas	daily or as required by campaign		

Quelle: VDI 2083, part 5.1

Table F1. Technical recommendations for the disinfection of aseptic environments and sterile rooms

	Air cleanliness class	
GMP Guide, Annex 1	**A/B**	**C/D**
Comparable class as per ISO 14644-1	**ISO 5**	**ISO 7/8**
Disinfectant	• Change between two or more substance groups, include a sporicide disinfectant in the programme, if necessary • Checked for microbiological contamination • Sterile prior to use • Suitable for planned disinfection technique	• Change between two or more substance groups, include a sporicide disinfectant in the programme, If necessary • Checked for microbiological contamination • Suitable for planned disinfection technique
Equipment	• Not a source of contaminations • Low particle generation • Free of pyrogenes, if necessary • Easy to clean and disinfect • Sterilisable/autociaveable	• Not a source of contaminations • Low particle generation • Easy to clean and disinfect
Materials	• Stainless steel, Sterilisable plastic material • Mop holders made of anodized aluminium, if necessary	• Stainless steel, high-quality plastic material • Mop holders made of anodized aluminium, if necessary
Mops and wipes	• Mops made of autoclaveable, low-particle microfibres (certificate) • Sterile single-use wipes (certificate)	• Mops and wipes made of low-particle micro-fibres (certificate) • Low-particle single-use wipes (certificate)
Disinfection intervals	• Routine disinfection on each working day, several times each day, if necessary • Monthly basic disinfection	• Routine disinfection an each working day • Basic disinfection every six to 12 months
Training of personnel	• Once or twice a year	• Once a year
Further requirements	• Reguler mlcrobiological checks	• Regular microbiological checks

Quelle: VDI 2083, part 5.1

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Table H1. Overview of common wipes
Note: The less frequently used multiple-use articles such as sponge wipes, cleaning brushes and swabs are not considered here.

Cleanroom wipes

Class of wipe	Description Type, structure	Suitable for eieanliness requirements
W1	Polyester/cellulose non-woven	low
W2	Polyester non-woven; polyester fabrics	medium
W3	Polyester fabrics, edges sealed, washed	high
W4	Polyester microfibre fabrics, edges sealed, washed	very high

Quelle: VDI 2083, part 5.1

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Personnel in a Clean Room
Basic knowledge

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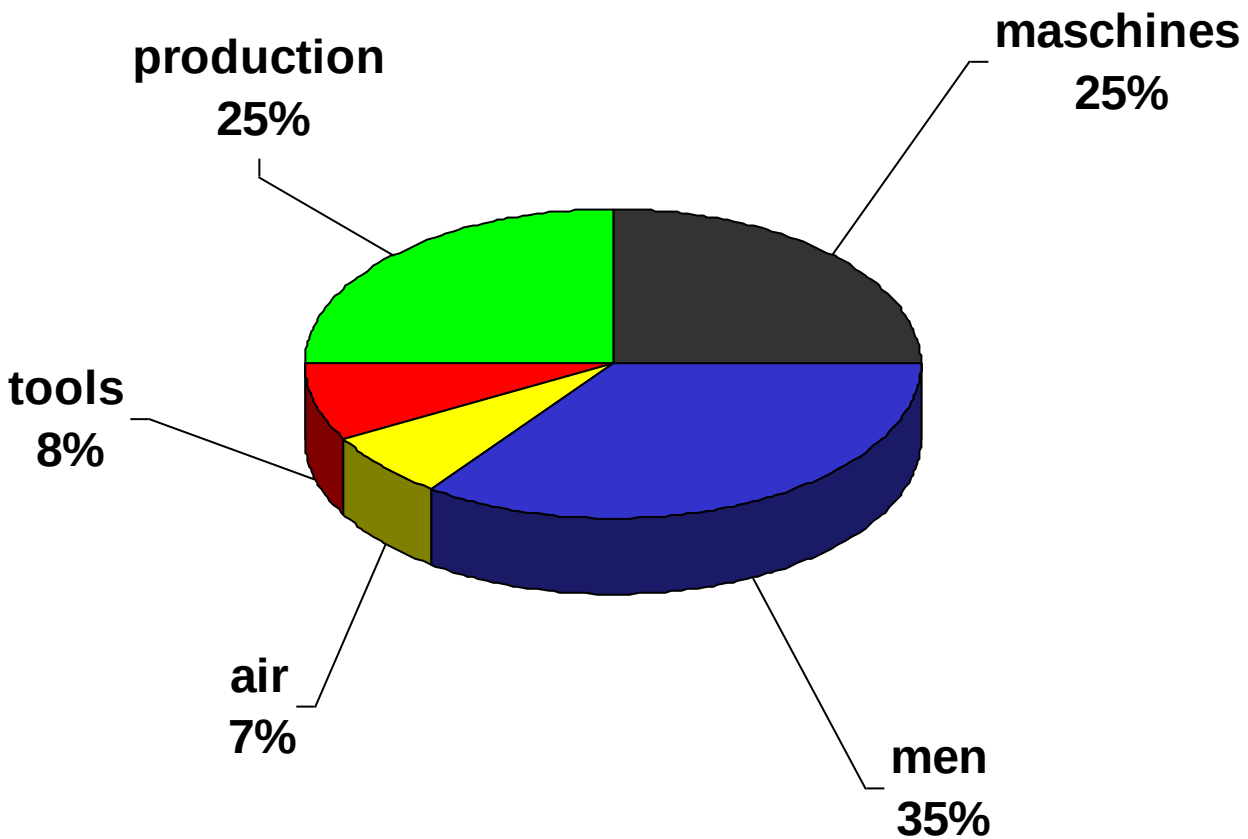
Harmful influences in a cleanroom:

Particle sources in cleanrooms



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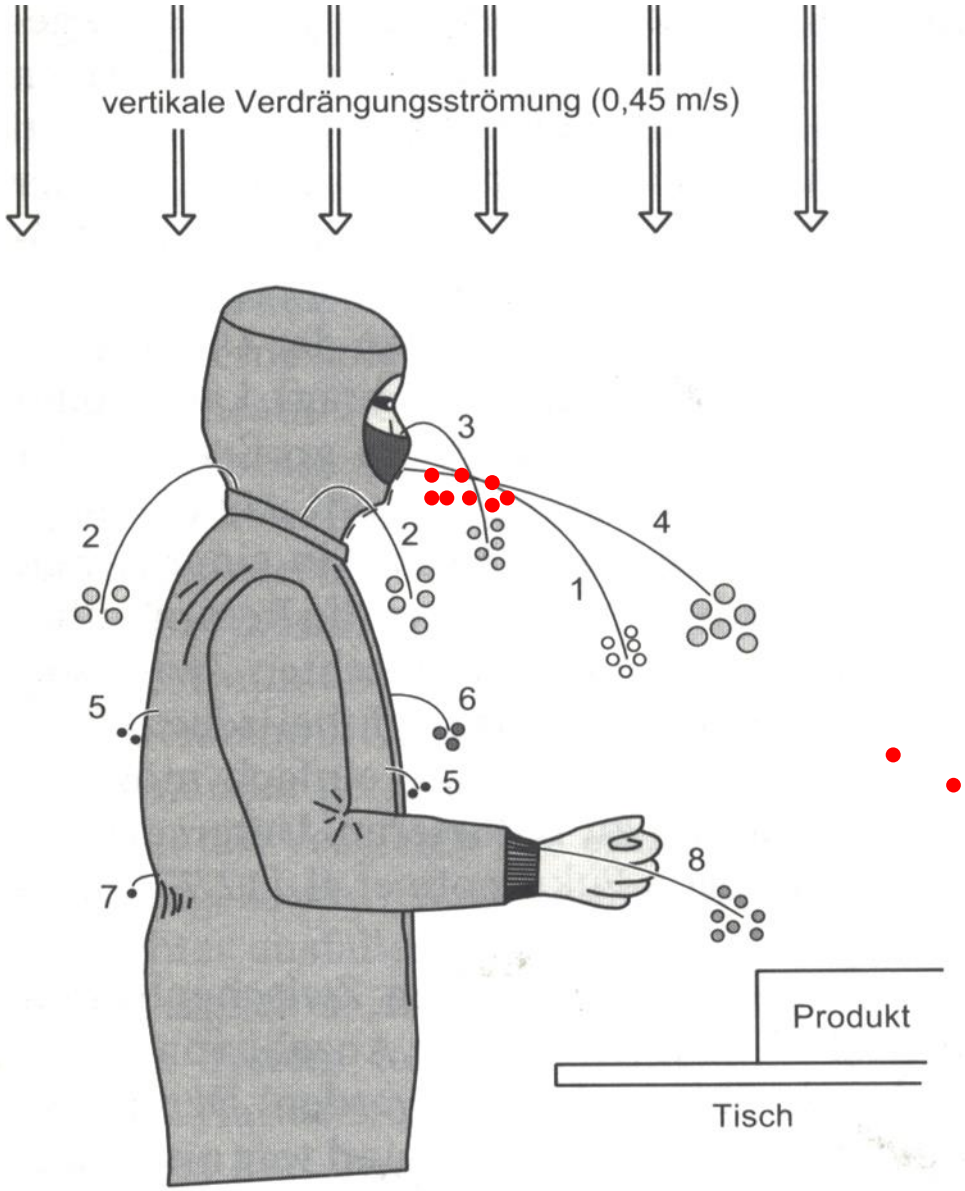

Particle emission and germ emission by men (approximate value):

- **1.000 Particle** ≥ 0.5 µm per person and sec

- **1000 CFU** per person and minute

Quelle: Gail. Hortig, Reinraumtechnik, Springer-Verlag 2002

EU Guidelines to Good Manufacturing Practice

Medicinal Products for Human and Veterinary Use, Annex 1

Generel requirements with respect to personnel and clothing

- Only the minimum number of personnel required should be present in clean areas
- Wristwatches, make-up and jewellery should not be worn in clean areas.
- Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms.
- Gloves should be regularly disinfected during operations.
- Masks and gloves should be changed at least for every working
- session.
- Clean area clothing should be cleaned and handled in separate laundry facilities.

EU Guideline, Annex 1

Special requirements with respect to clothing

Grade D:

Hair and beard should be covered.

A general protective suit

Appropriate shoes or overshoes

Grade C:

Hair and beard and moustache should be covered.

A single or two-piece trouser suit, gathered at the wrists and with high neck

Shoes or

Grade A/B:

Headgear should totally enclose hair, beard and moustach.

Face mask should be worn to prevent the shedding of droplets.

Appropriate sterilised, non-powdered rubber or plastic gloves.

Sterilised or disinfected footwear.

Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves.

For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments should be provided at each work session.

Cleanroom Clothing

Cleanroom Clothing must fulfil different requirements:

- High retention efficiency for particle emission from men
- Protection of personnel from (cold) air
- Permeability for air and
- Air tight
- Abration resistant
- Easy to clean and decontaminate
- Low electrostatic charge
- Good wearing comfort

Suitable cleanroom clothing consist mainly of purely synthetic fibres (multi-filament yarns).

see VDI 2083, part 5.1 chap. 5 and Annex B and part 15 chap. 3.

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Work-place specific requirements for cleanroom clothing

Table 1. Work-place specific requirements for cleanroom clothing

Application	Work-place specific requirements				
	Clothing elements	Fabric	Particle content according ASTM F 51	Micro-biological requirements	Recommended frequency of change
Microorganism-controlled areas in the pharmaceutical industry	half-length jacket or closed laboratory coat, trousers, socks, working shoes, hair cover	abrasion-resistant filament fabrics made of synthetic fibres	no requirements	no requirements	according to soiling
Cleanrooms in the pharmaceutical industry	complete head cover (possibly with face mask), overall or two-part combination, socks, disinfectable working shoes, gloves (where necessary, cuffs)	abrasion-resistant filament fabrics made of synthetic fibres	in particle-sensitive areas class A *)	sterilised or disinfected	at least once a day
Cleanrooms in medicine	hood, face mask, overall or two-part combination, sterilisable gloves and shoes	mixed cotton/polyester fabrics or a abrasion-resistant filament fabrics made of synthetic fibres	no requirements	sterilised	according to soiling; once to several times daily
Cleanrooms in the semiconductor industry with high requirements	complete head cover with face mask, overall with overshoes and gloves; cleanroom-compatible underwear	abrasion-resistant filament fabrics made of synthetic fibres	class A	no requirements	according to standard operating procedure

*) The definition of particle-sensitive areas is in the discretion of the operator.

see VDI 2083, part 15 chap. 3.

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Work-place specific requirements for cleanroom clothing

Annex C Recommendations for specifying cleanroom clothing for a desired particulate air cleanliness class (excluding microbiologically monitored environments)

Air cleanliness class as per ISO 14644-1	ISO 3	ISO 4	ISO 5
Clothing elements	• Non-woven single-use hood (underneath) • Hood with eye slits and single-use face mask (underneath), alternatively full hood with all-round visor and single-use face mask • Coverall • Cleanroom-compliant intermediate garments • Pull-over boots • Cleanroom shoes (underneath) • Cleanroom gloves	• Non-woven single-use hood (underneath) • Hood with eye slits and single-use face mask (underneath), alternatively full hood with all-round visor and single-use face mask • Coverall • Cleanroom-compliant intermediate garments • Pull-over boots • Cleanroom shoes (underneath) • Cleanroom gloves	• Full hood • Single-use face mask or textile multiple-use face mask • Coverall • Cleanroom-compliant intermediate garments • Pull-over boots • Cleanroom shoes (underneath) • Cleanroom gloves
Changing cycle	• Outer cleanroom garments: with each entry into the cleanroom • Intermediate garments: daily	• Outer cleanroom garments and intermediate garments: daily	
Textiles	• Outer cleanroom garments: abrasion-resistant filament fabrics made of synthetic and conductive fibres • Intermediate garments: Filament fabric made of synthetic fibres or, if necessary, so-called meshed lined fabrics (cotton inside, synthetic fibres outside)		

Air cleanliness class as per ISO 14644-1	ISO 6	ISO 7	ISO 8
Clothing elements	• Full hood • Single-use face mask • Coverall • Pull-over boots • Cleanroom shoes (underneath) • Cleanroom gloves	• Non-woven single-use hood • Gown • Overshoes • Cleanroom shoes (underneath) • Cleanroom gloves	• Non-woven single-use hood • Gown • Overshoes • Cleanroom shoes (underneath) • Cleanroom gloves (if necessary)
Changing cycle	• Outer cleanroom garments: two to three times a week	• Outer cleanroom garments: once a week	
Textiles	• Outer cleanroom garments: abrasion-resistant filament fabrics made of synthetic and conductive fibres • Undergarments: personal		

see VDI 2083, part 5.1 annex C

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Work-place specific requirements for cleanroom clothing

Annex D Recommendations for specifying cleanroom clothing for a desired air cleanliness class/hygiene (microbiologically monitored environments)

GMP Guide (EU)	A/B	C/D	Other hygienic production environments
Regarding particle load, this class compares to the following air cleanliness class as specified in ISO 14644-1	ISO 5	ISO 7/8	ISO 9
Clothing elements	• Non-woven single-use hood (underneath) • Hood with eye slits and single-use face mask (underneath), alternatively full hood and sterile single-use face mask; if required, with all-round visor or sterilisable protective glasses • Coverall • Cleanroom-compliant intermediate garments • Pull-over boots • Cleanroom shoes (underneath) • Sterile single-use gloves	• Non-woven single-use hood • Single-use face mask or non-woven single-use beard cover • Coverall or trouser/jacket combination • Overshoes • Cleanroom shoes (underneath) • Cleanroom gloves	• Non-woven single-use hood • Single-use beard cover, if required • Trouser/jacket combination • Cleanroom shoes • Cleanroom gloves, if required
Changing cycle	• Outer cleanroom garments: with each entry into the cleanroom • Intermediate garments: daily	• Outer cleanroom garments: daily	• Outer cleanroom garments: two to three times a week
Textiles	• Outer cleanroom garments: abrasion-resistant filament fabrics made of synthetic and conductive fibres • Intermediate garments: filament fabric made of synthetic fibres or so-called meshed lined fabrics (cotton inside, synthetic fibres outside) • inside: cotton • outside: synthetic fibres	• Outer cleanroom garments: abrasion-resistant filament fabrics made of synthetic and conductive fibres	• Outer cleanroom garments: abrasion-resistant filament fabrics made of synthetic and conductive fibres with high air and water vapour permeability, or cotton/polyester blended fabric (approx. 35 % cotton and 65 % PES)

see VDI 2083, part 5.1 annex D

Example of airlock process

Entry into the associated environment of a sterile production

1. Doff street clothing on the "unclean" side of the airlock; the same applies to all personal items.
2. Foootwear for the target environment is placed ready at the sit-over bench.
3. Don clothing for targetenvironment from head to feet.
4. Sit on sit-over bench, feet on "unclean" side, then lift one foot, don shoe for target environment, put this foot down on "clean" side of the bench.
5. Repeat this procedure for the other foot.
6. Don gloves.

Proceed vice versa for exiting.

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Example of airlock process

Entry into the inner environment of a sterile production

1. Before entering the sterile airlock all clothing except underwear is doffed in the personnel airlock. Cleanroom undergarment is donned, if so required.
2. Bathing shoes are used for the transit into the sterile airlock.
3. Hands and upper arms are washed and disinfected. Don changing gloves.
4. Clothing for the target environment is donned in the sterile airlock, proceed from head to feet.
5. Place cleanroom overshoes ready at the sit-over bench.
6. Sit on sit-over bench, feet on "unclean" side, then lift one foot, don shoe for target environment, put this foot down on "clean" side of the bench.
7. Repeat this procedure for the second foot.
8. After overshoes have been laced securely, don cleanroom gloves.
9. Check in the mirror to make sure proper fit of clothing and that no openings remain.

Proceed vice versa for exiting.

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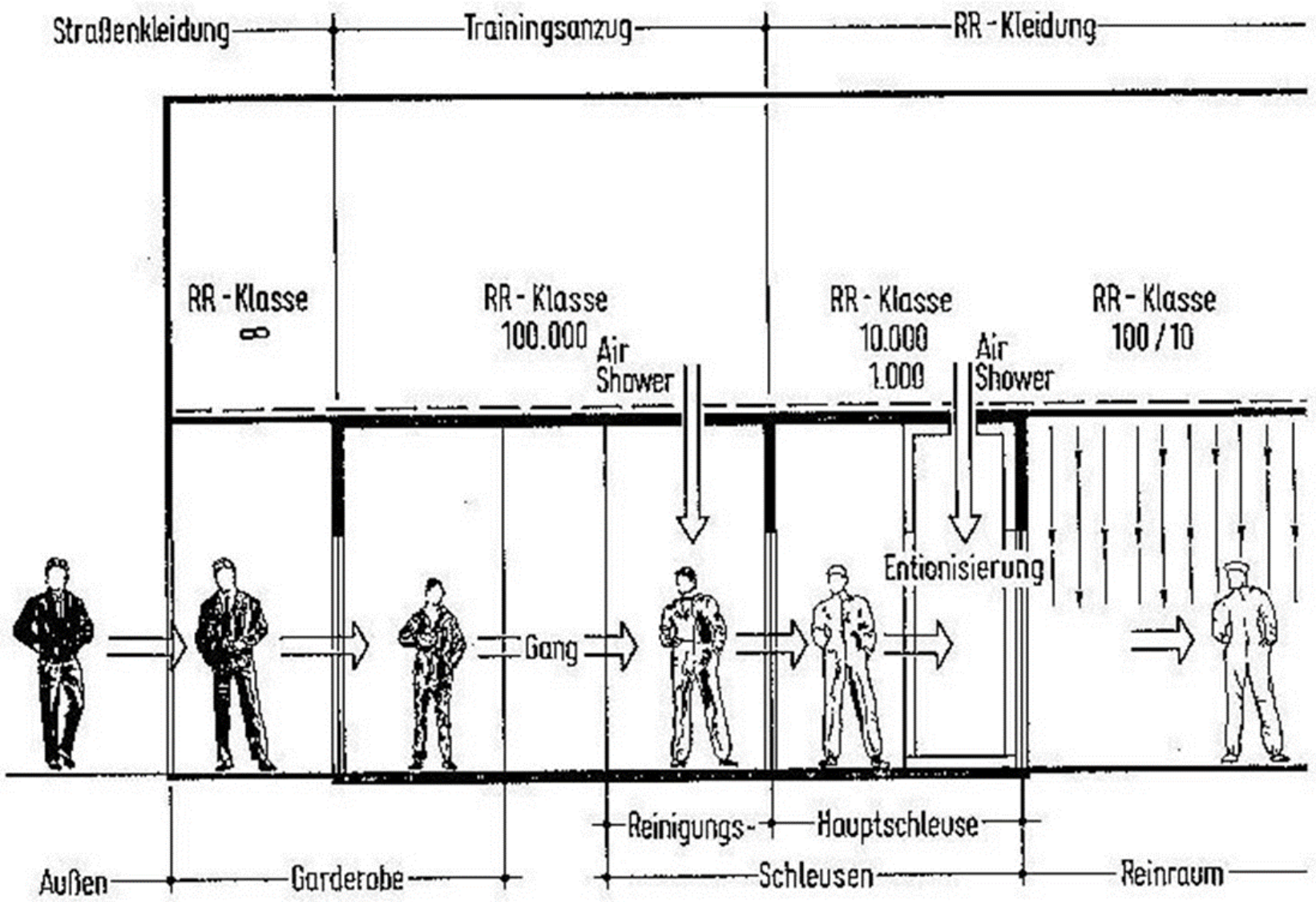
Cleaning devices for personnel

a) Shoe polisher
b) Cleaning device for shoe sole
c) Adhesive mats for cleaning shoe soles
d) Hand wash device consisting of
   wash basin and tap operated by foot, soap dispenser elctric hand
e) Air shower.

Changing


Straßenkleidung
Trainingsanzug
RR - Kleidung
RR - Klasse 8
RR - Klasse 100.000
Air Shower
RR - Klasse 10.000 1.000
Air Shower
RR - Klasse 100 / 10
Entionisierung
Gang
Reinigungs-
Hauptschleuse
Außen
Garderobe
Schleusen
Reinraum

Personnel air lock

To put on the cleanroom clothing keep the following sequence :

1. First head cover,
2. Face mask,
3. Cleanroom overall
4. Finally cleanroom shoes

Proceed vice versa for exiting.

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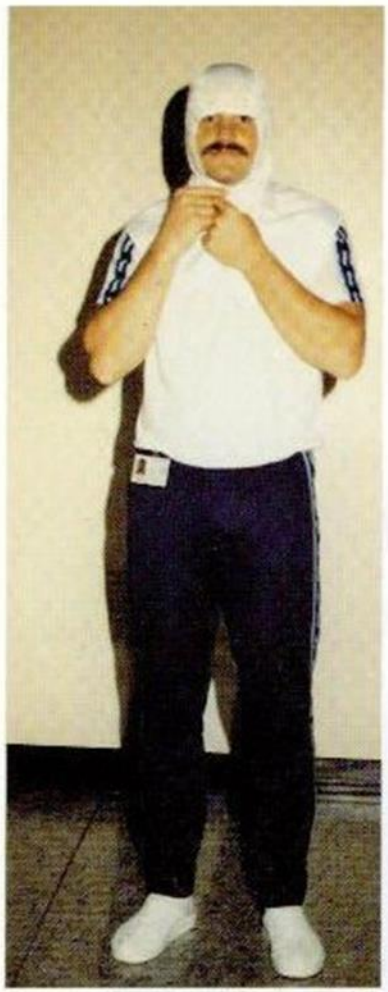
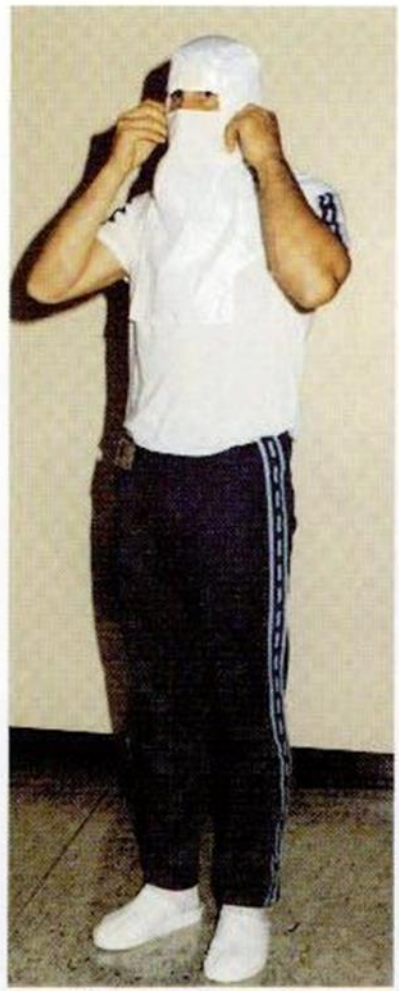
Sequence of clothing



Haube



Mundschutz

RR-Anzug

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Entering a clean room via the personell air lock

Air shower

Quelle: m+w zander

Personnel air lock

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General behaviour rules in a cleanroom

Not permitted:	permitted:
To smoke	in special smoking areas outside
Taking jewellery e.g. watches, bracelets, rings	Wear under the clothing only, completely covered, to wear spectacles
Taking food and beverages, eating and drinking	Only in
Taking other personal possessions e.g. smoking utensils, hand bags	outside
application of cosmetics, powders, fatty skin creams	Under cleanroom clothing only
Hankerchiefs	Under cleanroom clothing only, use if necessary outside or at least apart from production area with disposable handkerchiefs.
Ballpoints, pencils, rubbers	Cleanroom suitable pencils
Manuals, equipment documentation, working instructions	Outside, if necessary inside apart from production area
Identity card, keys	Under cleanroom clothing only

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General behaviour rules in a cleanroom

Not permitted:	permitted:
Hastily movements	Leisurely movements
Quick walk or running	move purposefully and thoughtfully
Assembly of many people	In case of emergency only
To speak loud, to cry, to sing, to whistle	Normal speaking
To open the service doors or the emergency exit doors	Only in case of service or emergency
Blockade or escape routes	never
coughing and sneezing	if necessary outside or at least apart from production area with disposable handkerchiefs.
To bend over the production area	In case of service or disturbance only
disregard of cleanliness at the clean work place and tools	To clean frequently
To lay down and store components and tools on tables and machines	In dedicated areas or cabinets only

Behaviour

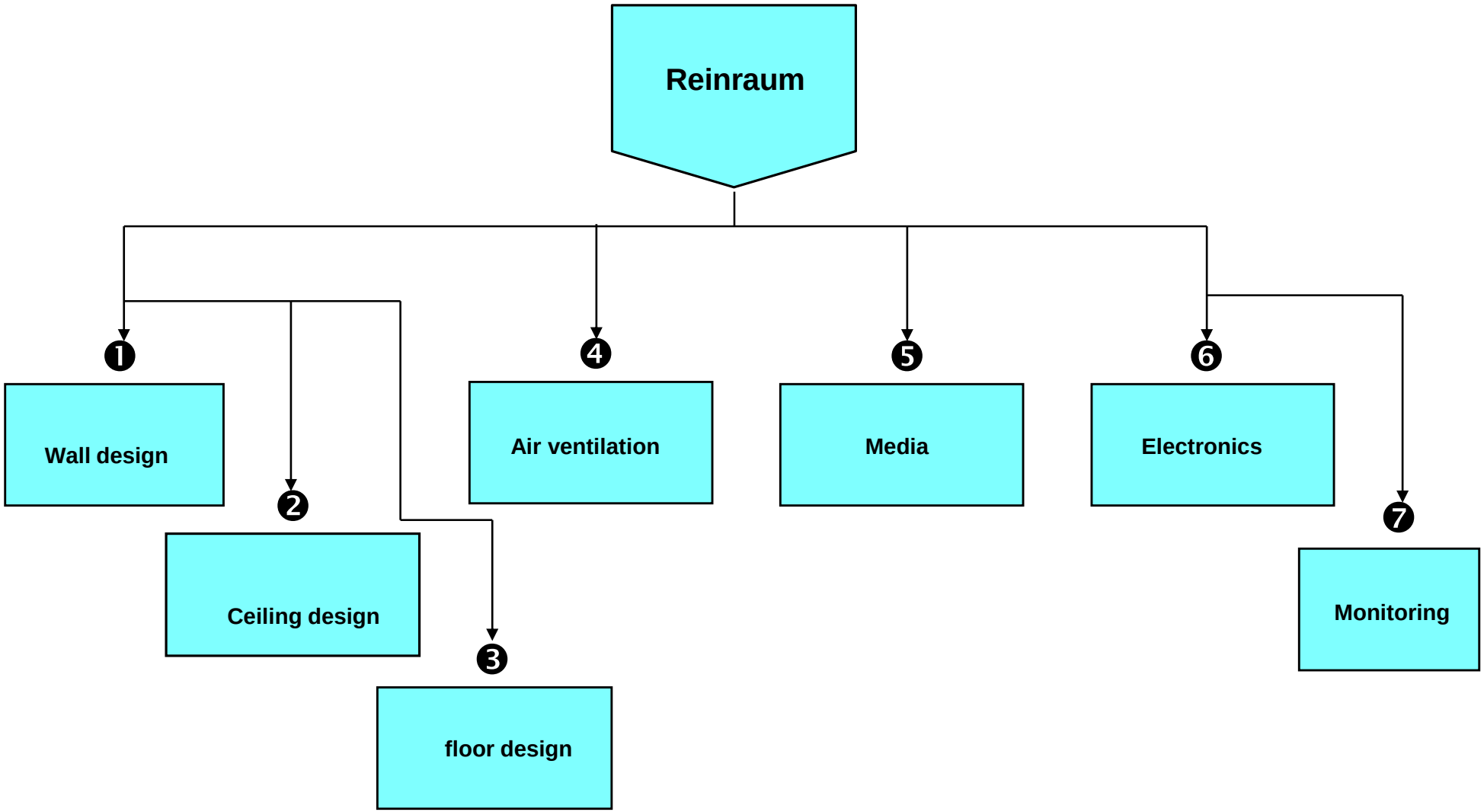
General behaviour rules in a cleanroom

Consequences:

- Cleanroom regulations have the same character as standard operating procedures.
- Disregarding these shall lead to consequences.
- Correct cleanroom behaviour shall be encouraged and commended.

Cleanroom systems

The Cleanroom



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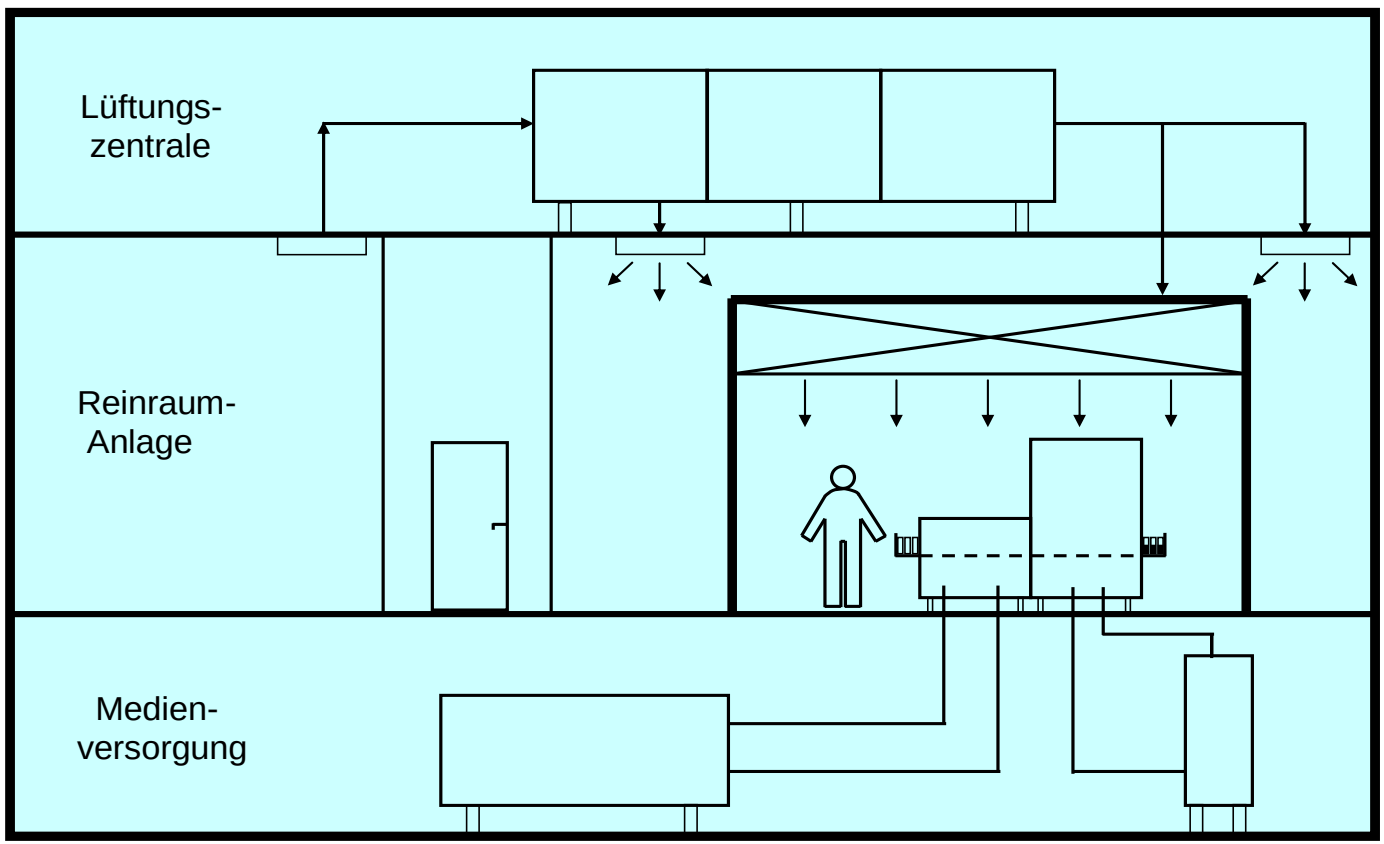
Cleanroom systems



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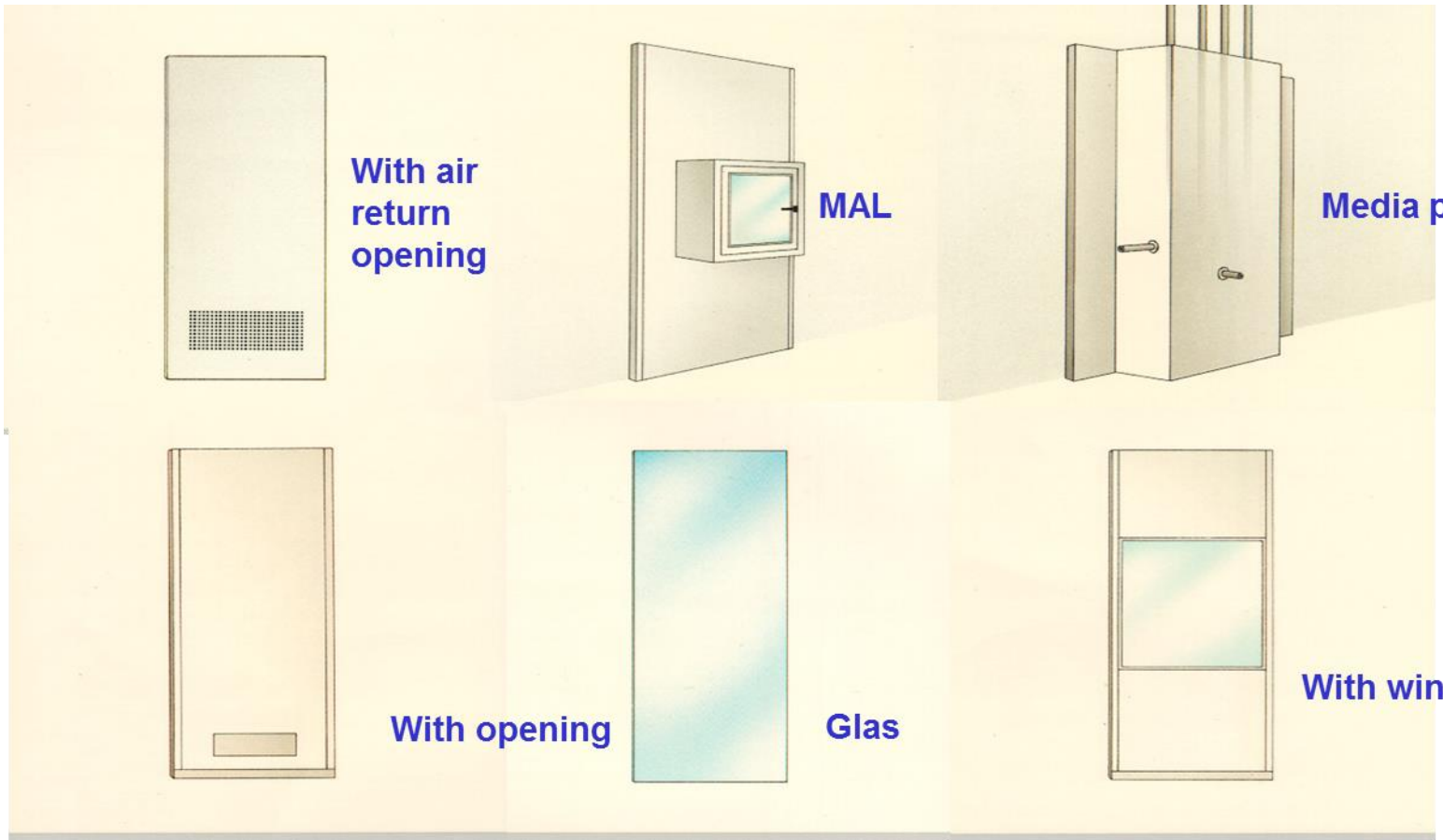
Wall system designs

See also VDI 2083, Blatt 4.1,E



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Wall design system, connection to the ceiling

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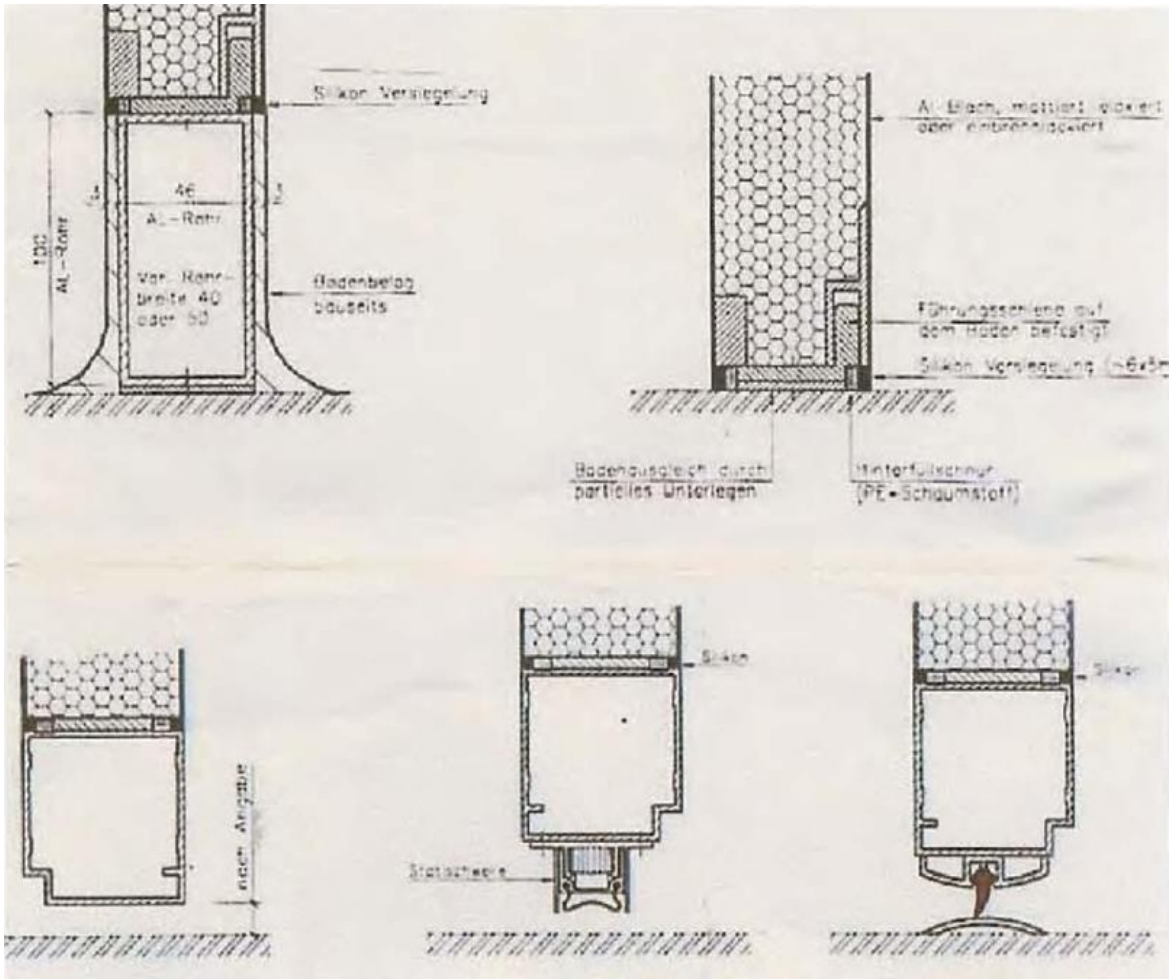
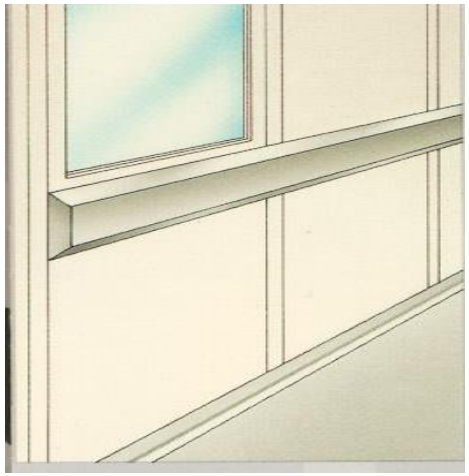
Wall design system, connection to the floor

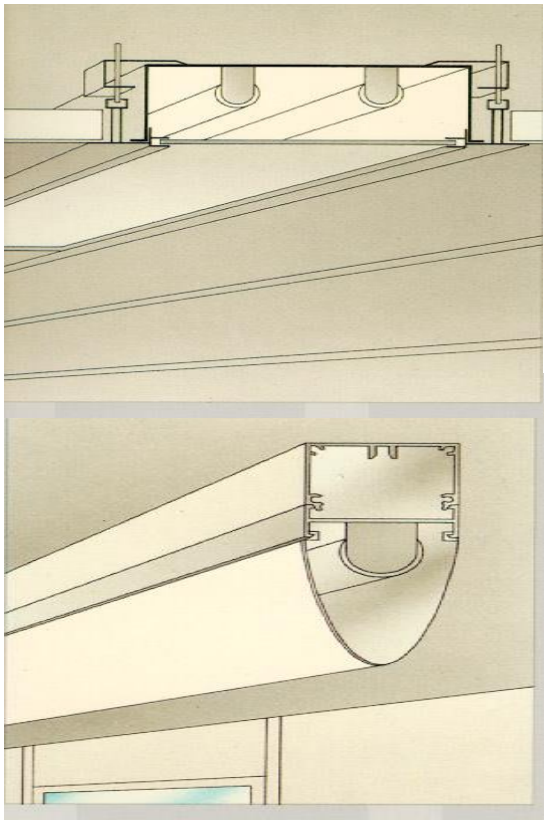




Protection of wall

Protection of floor

Lightning system A



Lightning system B

Door systems in use

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Material Air lock (MAL)

Bringing in and out materials

- Different sizes

- Lock of doors against each other, to keep the pressure difference

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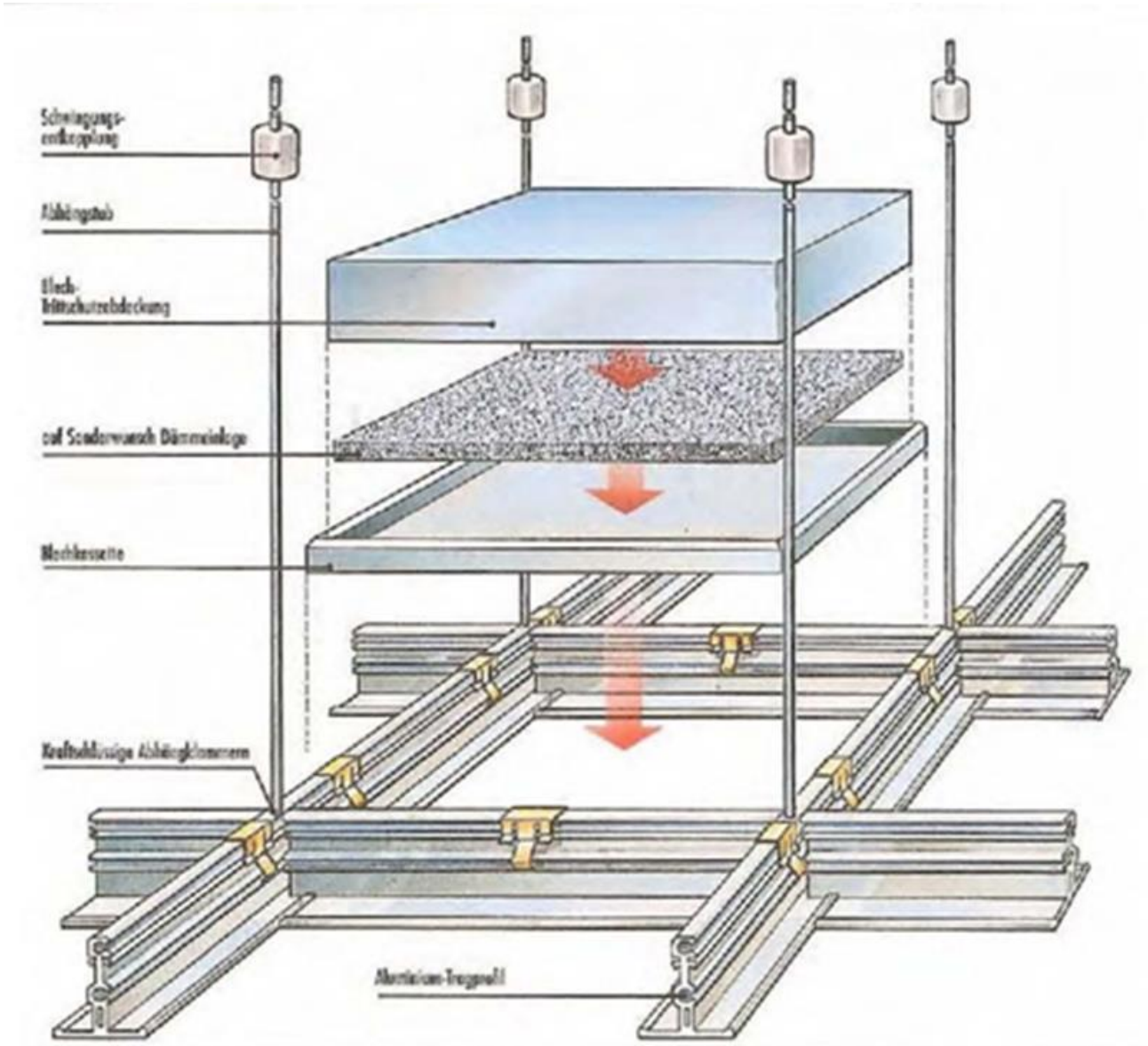

See also VDI 2083, Blatt 4.1,E

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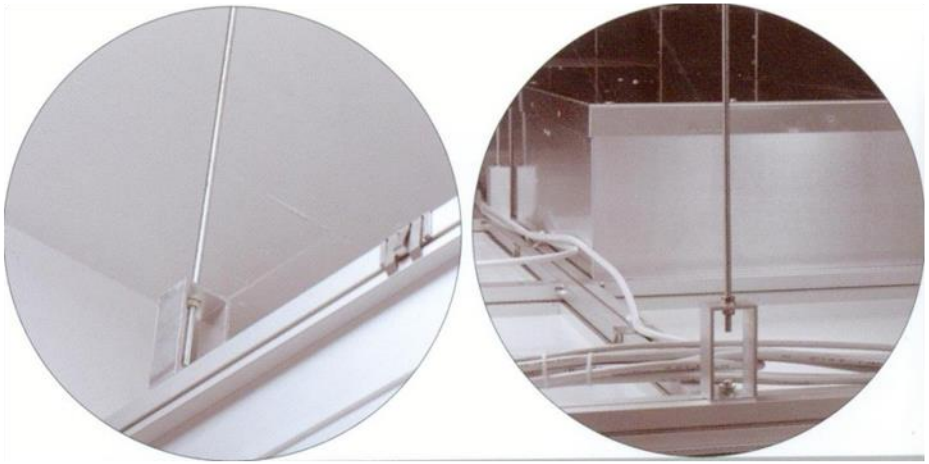


See also VDI 2083, Blatt 4.1, E

Ceiling designs

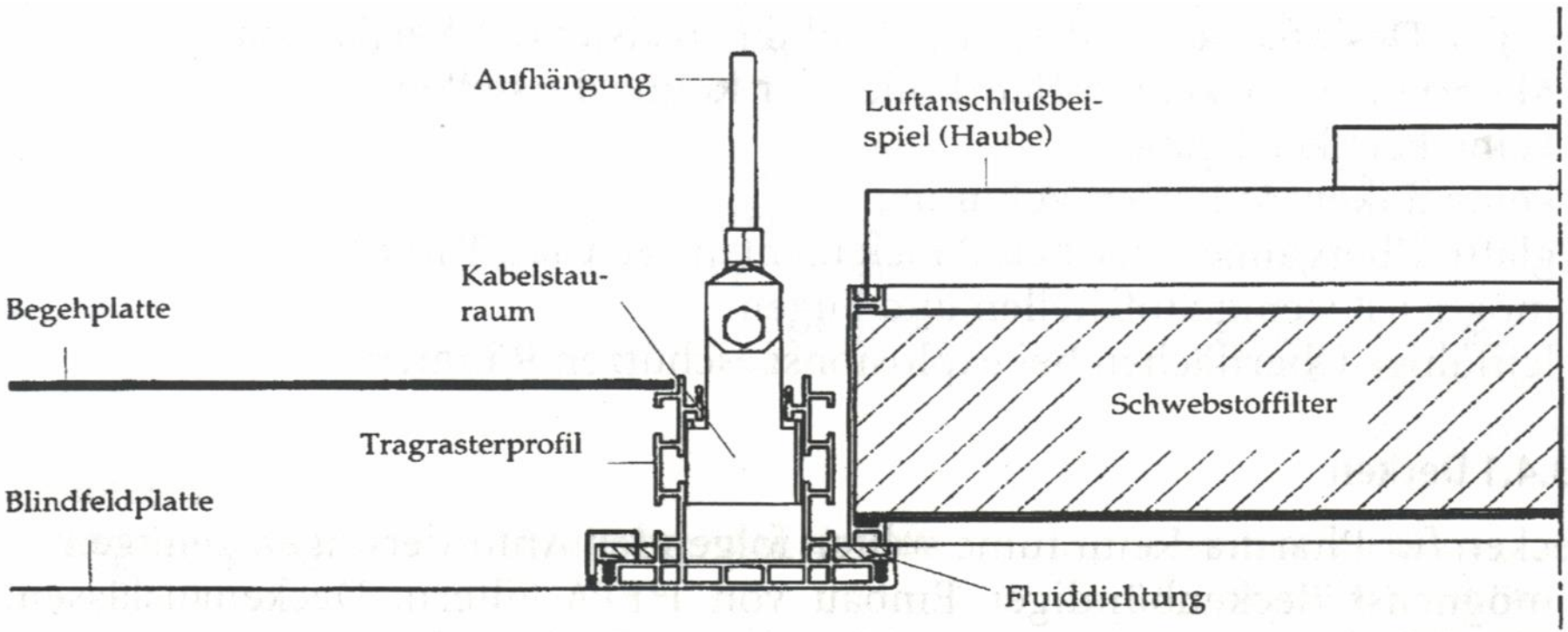
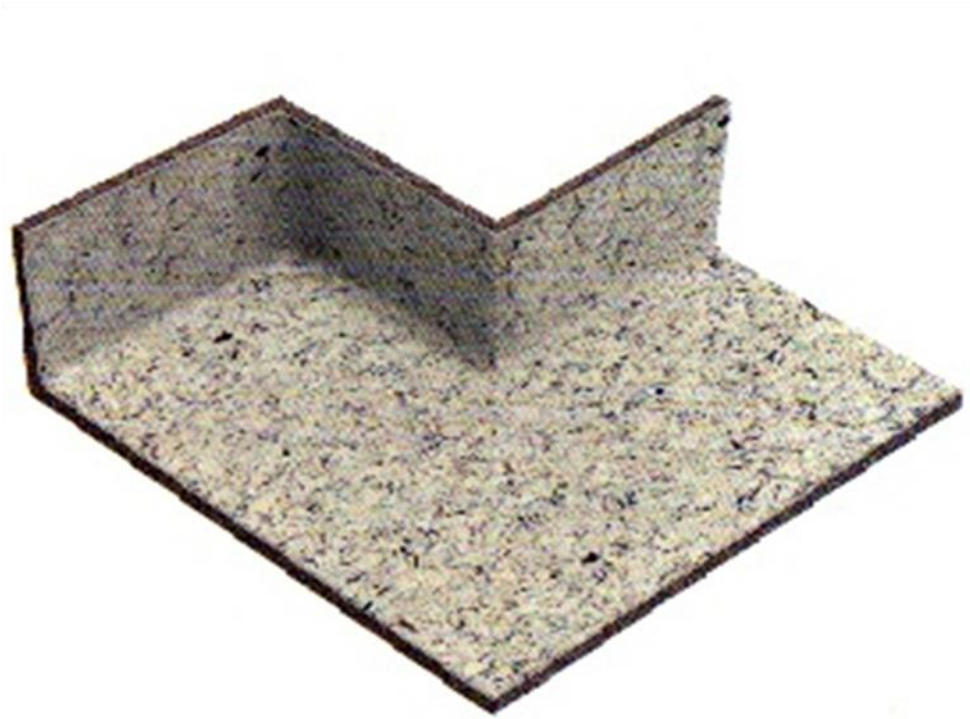


Abb. 7.25 Rasterdecke

Quelle /1/

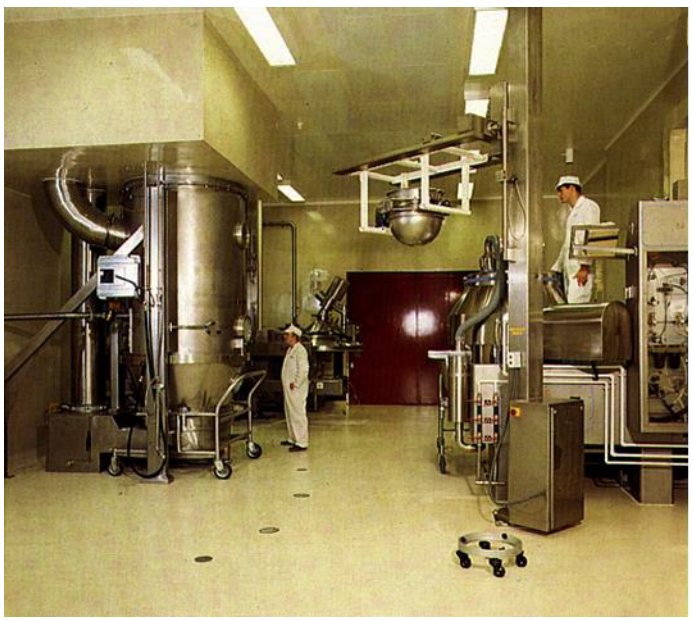
Pharma-Terrazo

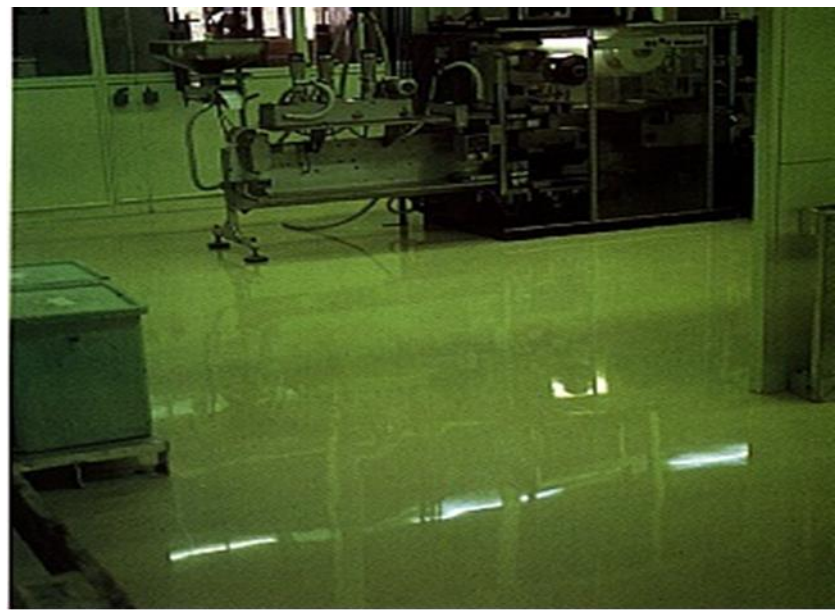
Linoleum/PVC - Fußböden



Connection floor to wall

Epoxy floor





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Filter classes according to DIN EN 1822-1

Filter Class	Integral		Local	
H 10	85	15	-	-
H 11	95	5	-	-
H 12	99,5	0,5	-	-
H 13	99,95	0,05	99,75	0,25
H 14	99,995	0,005	99,975	0,025
U 15	99,9995	0,0005	99,9975	0,0025
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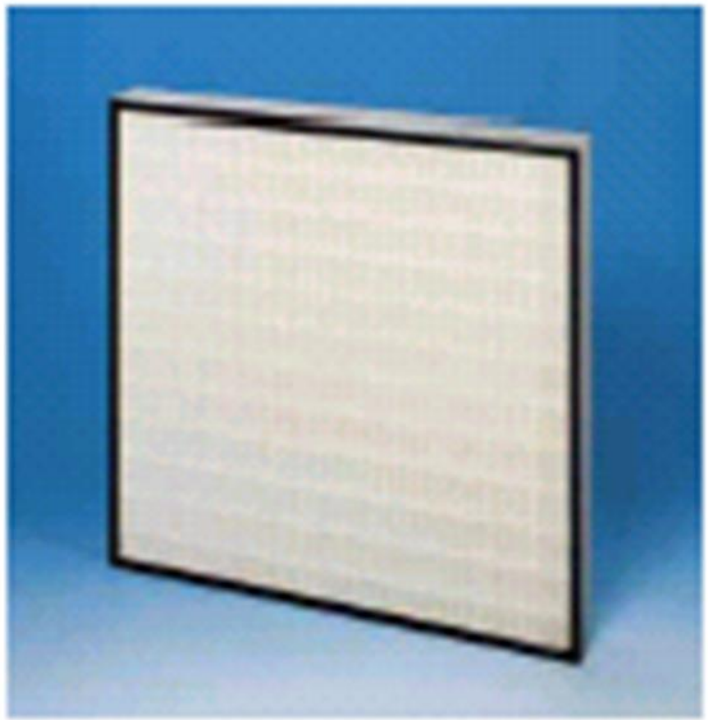
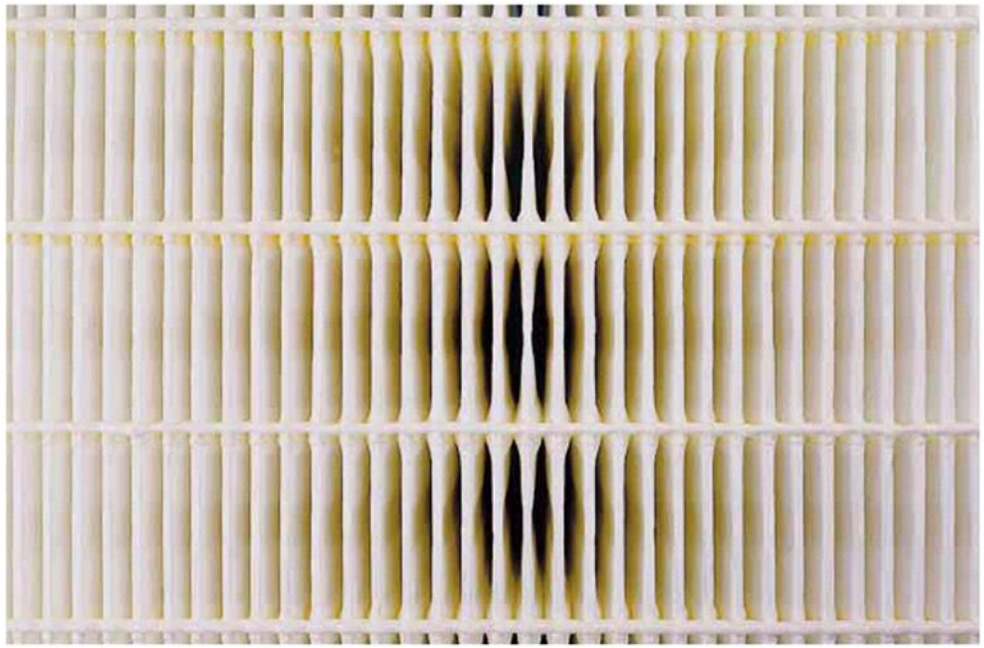
U 17	99,999995	0,000005	99,999975	0,000025



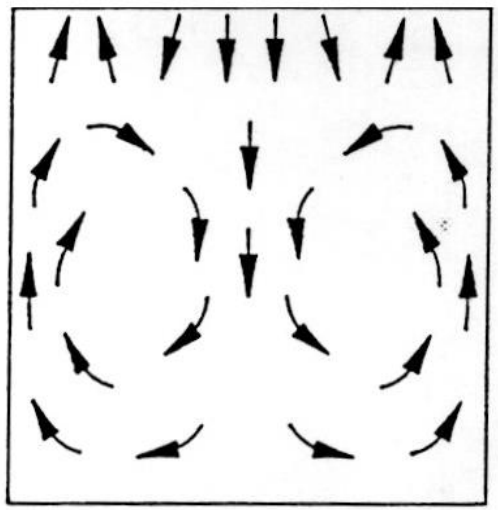
SF 14



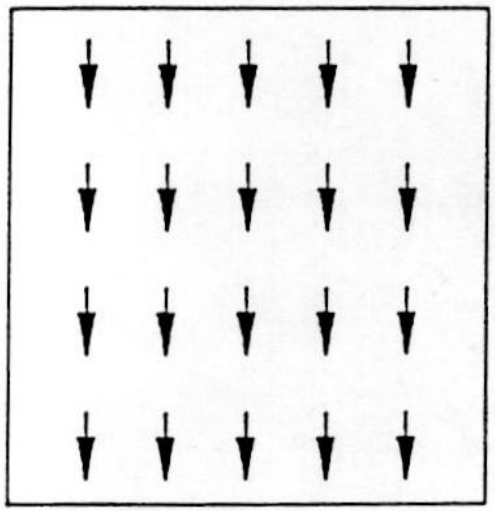
Optimale Faltengeometrie und Äquidistanz durch patentiertes Prägeverfahren

Quelle. Freudenberg „Viledon

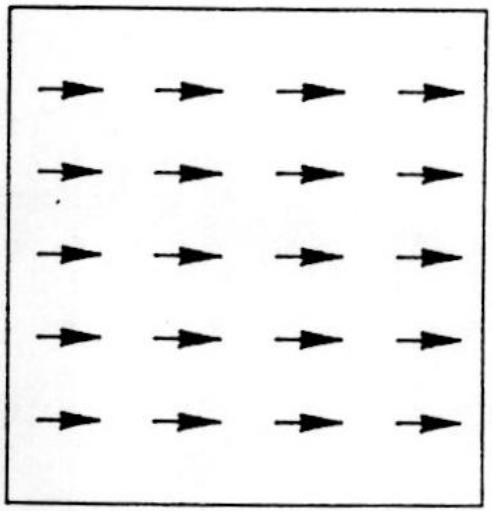
Air flow



turbulent

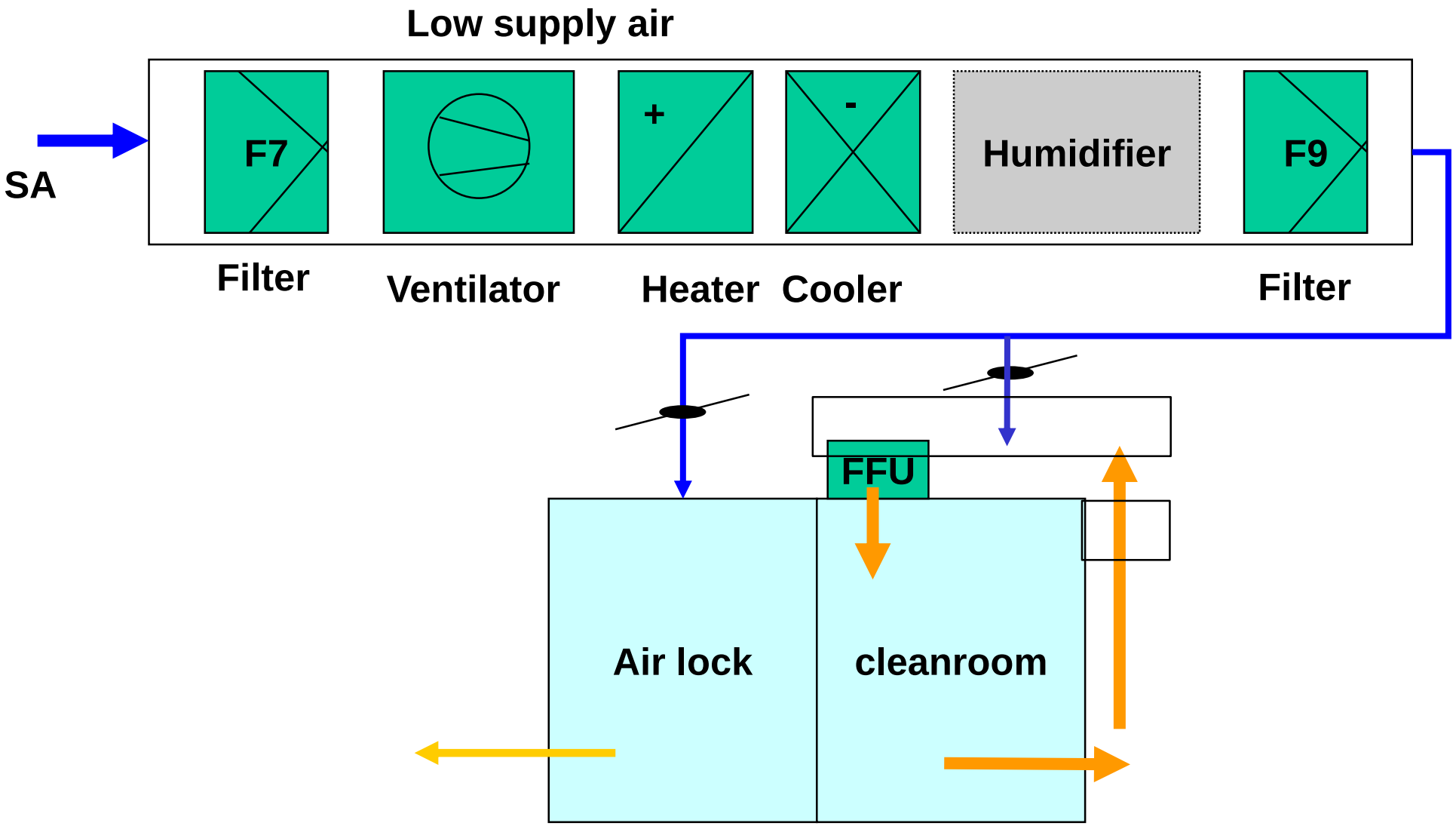


Laminar



laminar

Air ventilation system 2



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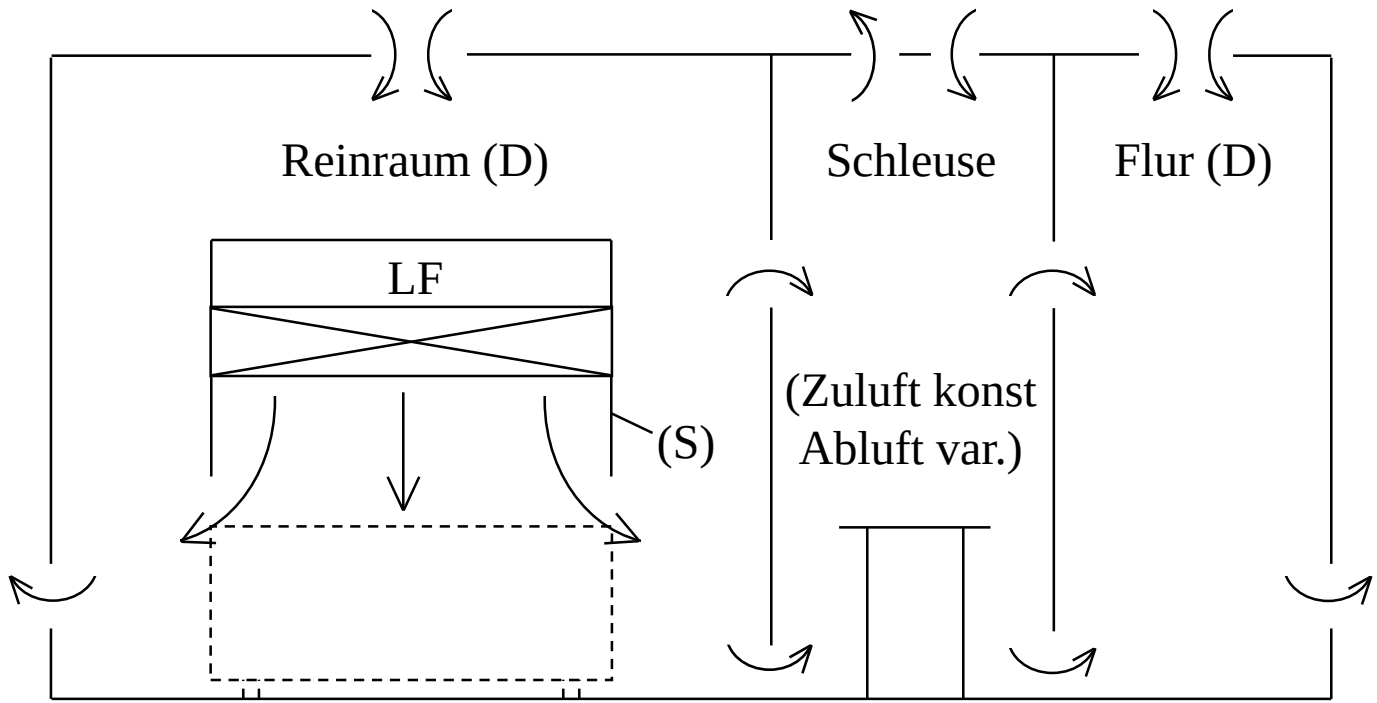
Cleanroom – design (1)



Pressure system 1

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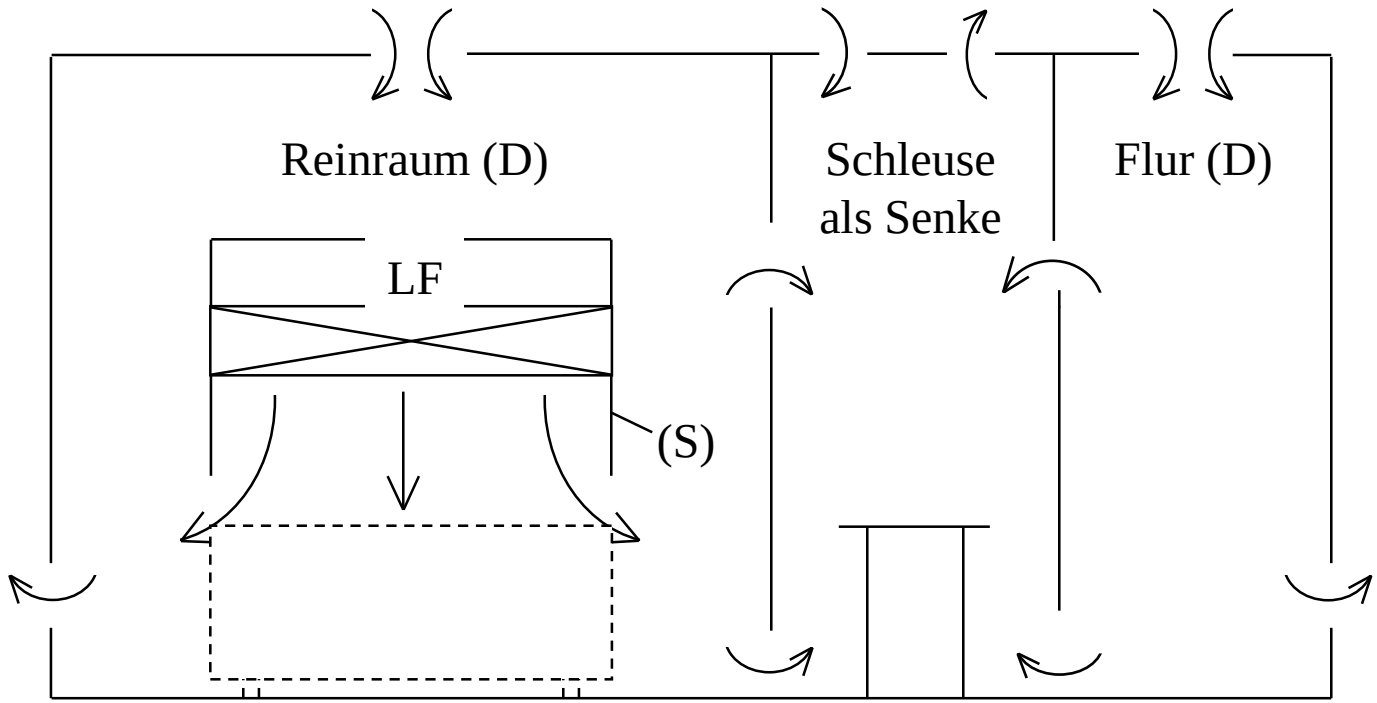
cleanroom design **(2)**



Via preassure differences (D) und airflow (S)