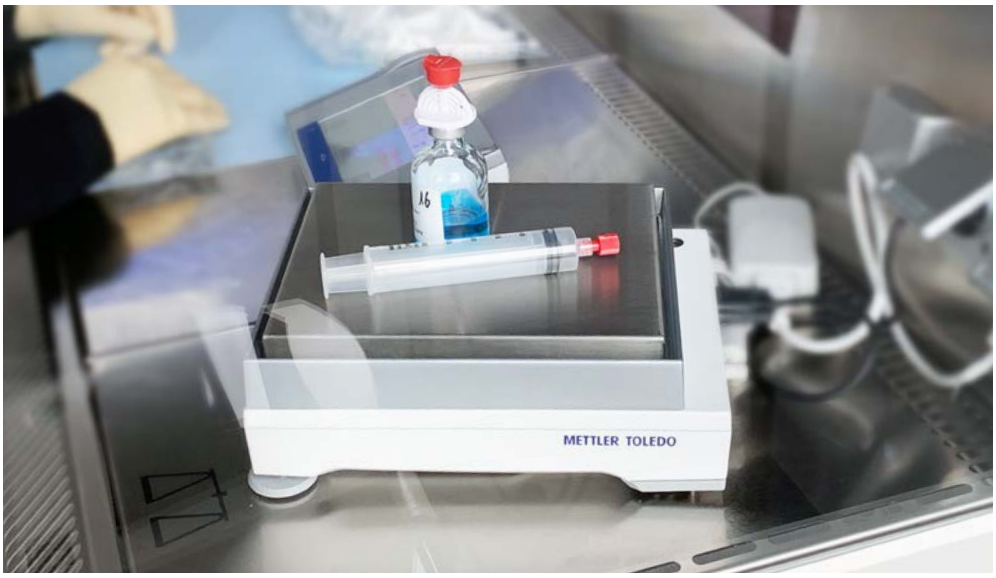
White Paper

Staying Safe When Weighing

Hazardous or Sensitive Materials



This paper describes 13 steps for safe, accurate weighing in safety cabinets or other enclosures. Technical aspects of protective gear and enclosures are also covered, as are strategies to address the challenges inherent to weighing under such conditions to ensure high user safety, weighing accuracy, and product purity and quality.

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1. Introduction

Many substances processed in today's working labs or production environments must be kept pure. Many of these substances also pose a risk to user safety, particularly in microbiological and pharmaceutical settings. To ensure purity and avoid dangerous cross-contamination, personal protection for the user as well as protection for weighed substances is essential.

The right containments for sensitive and hazardous materials that pose a threat to human health yet require a highly clean environment are safety cabinets and specialized isolators. These enclosures provide a higher degree of protection than standard fume hoods or weighing cabinets, where turbulent airflow is a major drawback for weighing scenarios where aseptic or particle-free conditions are required.

Unlike fume hoods or weighing cabinets, safety cabinets and specialized isolators ensure that all air from the lab environment entering the weighing workspace is guided via unidirectional airflow through a high-efficiency particulate air or HEPA-grade purification system to remove contaminants in a practical manner. This helps to ensure product purity.

As shown in the following, the unidirectional system also provides a high degree of protection against exposure to vapors, aerosols or particles for the operator. However, it may be difficult to avoid exposure risk completely, particularly in the case of accidental minor or major spills. To further limit exposure risk, operators must adopt safe weighing principles including appropriate operational protocols (e.g. training, SOPs, hygiene management).

This requires thorough knowledge of safe operating principles in order to protect product purity as well as assure that weighed substances do not come in contact with skin, eyes, mucosa, or lungs. A discussion of safe operating principles follows, as does a detailed discussion of the benefits of safety cabinets and specialized isolators for effectively improving operator safety and product quality.

2. Mandatory Personal Protective Equipment (PPE)

Even though the operating principles of safety cabinets and isolators are sound, PPE is always mandatory. This is due to potential toxicity or to the carcinogenic, mutagenic, reprotoxic (CMR) or teratogenic properties of many substances in use in the modern lab.

These PPE items, detailed in Figure 1, provide an added level of protection in the event of unforeseen environmental circumstances or equipment malfunction. They should be part of your lab's SOPs and followed consistently for every weighing or service task.

Does Your Protective Gear Meet Safety Requirements?

Every job has health and safety risks. The most common ones are chemical, biological, physical or electrical hazards. No matter how safe the set up is, certain hazards will always be present. It's important to be cautious and wear the appropriate gear to minimize accidents.

Item	Details, Use
Safety Glasses	Protects eyes; can be worn over corrective glasses; must be certified according to EN166 and EN170.  © BERNER International GmbH
Nitrile Gloves	Chemical protection; protection against cross-contamination; must be certified according to EN374; disposable.  © BERNER International GmbH
Fine Dust Mask	Protects lungs and mucous membranes in the nose and mouth; standard FFP3 to avoid breathing vapors, mist or particulate matter; disposable.  © BERNER International GmbH
200 mL Eye Wash Bottle with Integrated Eye Bowl	Provides extra precaution in case of unforeseen exposure to chemicals or biological agents; disposable. 

Figure 1: Personal Protective Equipment (PPE) to ensure maximum operator safety.

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3. Guideline: 13 Steps to Safe Weighing

While it is important not to fear highly active substances it is important to respect them.

Uniform approaches towards substance-handling will make it easier to comply with SOPs on a consistent basis. This helps to ensure your safety, the safety of those using the enclosure after you, and the purity of the product you are handling.

In general, safe laboratory principles are the rule. This includes:

How to Clean Your Balance

METTLER TOLEDO offers a white paper that will help you increase user safety, reduce the risk of cross-contamination, and prolong instrument life through correct balance cleaning. Download it today at:
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- **Not eating or drinking** in rooms where potentially weighing hazardous materials are present.
- **Using mandatory PPE** for every weighing.
- **Adopting appropriate containment technology.**

The benefits and principles of effective containment technology will be discussed in sections 4 and 5.

The guideline and checklist below offer you a starting point for establishing effective SOPs. Be sure to establish and follow SOPs that are appropriate for substances you handle.

3.1 Safe Weighing in Specialized Enclosures

1. **Schedule enough time for your tasks.** Conscious and concentrated action helps to avoid mistakes, so it is best to avoid working under time pressure.

2. **Always use required PPE.** This PPE should be approved by lab or production-area management.

3. **Maintain workspace tidiness.** Peripherals, cables, power supplies and work surfaces should always be approached using PPE because of the potential for cross-contamination.

4. **Prepare the items you need.** Ensure that you have safety equipment such as eye wash as well as all tare container and tracking/tracing equipment available and within easy reach.

Safe Weighing eLearning

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5. **Ready cleaning agents** for tools, disposable and non-disposable tare containers, and personal items. Ensure they are also within easy reach to limit cross-contamination potential.

6. **Limit unnecessary contact.** Never touch other equipment or yourself—including your cell phone—when you are working with potentially hazardous materials. Change gloves when necessary to avoid cross-contamination.

7. **If necessary, discharge the safety enclosure.** If you are performing maintenance work on the safety enclosure itself, ensure that the ventilation in laminar airflow boxes is switched to the maximum level when working on the extractor hood unit.

8. **Ensure safe disposal.** Gloves, used cleaning materials, tare containers, tools or excess substance should remain in the extractor hood after completing your tasks until they can be safely cleaned or disposed of.

9. **Clean tools, weight boxes, and reusable tare containers** with ethanol. Clean balance work surfaces and windows after each weighing of hazardous materials. Follow your lab's guideline for handling disposable items.

10. **Clean personal items.** Your computer and mobile phone—essentially, any device you may have inadvertently handled during the task—must also be cleaned with ethanol or window cleaner (both the keyboards and the underside of the device).

11. **Ensure completeness.** Check that all work has been completed and all tools and personal items are clean.

12. **Remove protective clothing.** After leaving the workspace, remove protective clothing, observing reverse order. Wash your hands thoroughly with soap and water, rinsing sufficiently and drying with paper towels.

13. **Remember PPE on next use.** When returning to the safety cabinet for additional weighing activities or service tasks, put on PPE again.

Quick-Check: Weighing Safety

Before use, have I:
- Scheduled enough time with the equipment?
- Put on all required PPE (safety glasses, nitrile gloves, dust mask)?
- Prepared all items needed for the task?
- Discharged the safety cabinet to avoid cross-contamination?

During use, have I:
- Limited unnecessary contact with personal items and work surfaces?
- Maintained safety items, cleaning items, and tare containers within easy reach?
- Changed gloves when necessary to avoid cross-contamination?
- Left used gloves, tare containers, or cleaning items in the hood until I can dispose of or clean them?

After use, have I:
- Cleaned used tare containers, tools, and personal items with ethanol?
- Ensured that I did not miss any items during cleaning or disposal?
- Removed protective clothing in a safe manner?

If I return to the safety enclosure, have I:
- Put on PPE again, as per user-safety guidelines?

4. Technical Principles of Safety Cabinets and Isolators

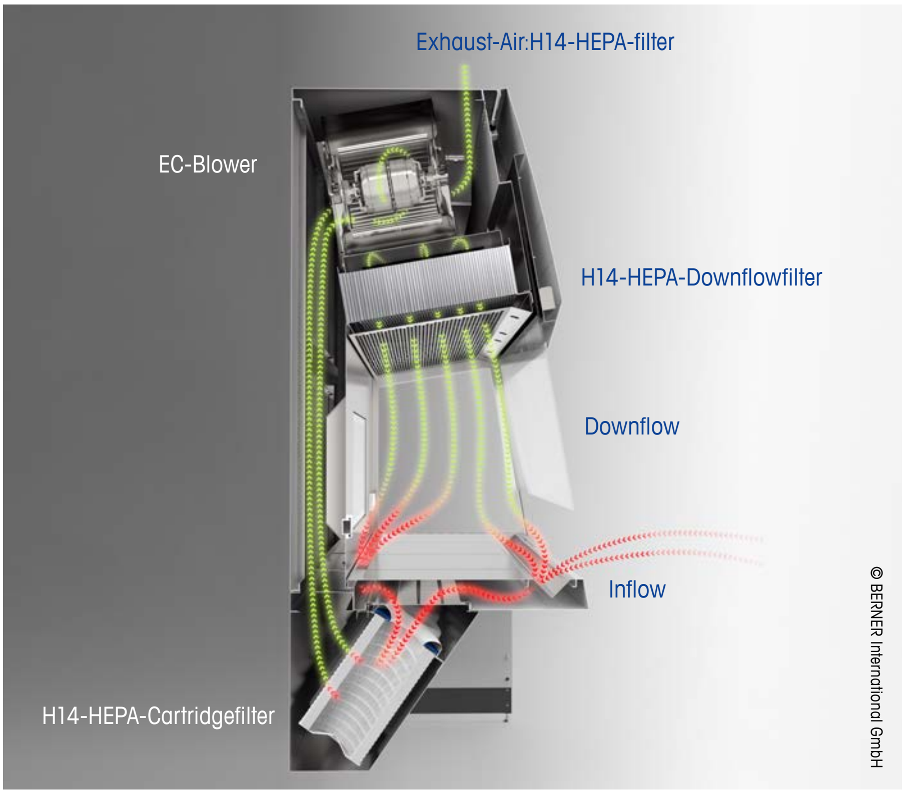

Figure 2: Cross-section and functional principle of a safety cabinet for cytotoxics with 3 filter levels.

After establishing the need for PPE and appropriate weighing protocols, we are ready to review the technical principles and benefits of a modern safety cabinet. These technical principles can be illustrated by the cross-sectional example shown in Figure 2.

The high level of personnel and product protection provided by the safety cabinet is achieved by HEPA filtration, the interaction of downflow and inflow at the access opening, and the guidance of the air system itself. All factors combine to determine overall safety-cabinet performance.

The image itself is of a safety cabinet dedicated to the preparation of cytotoxics for individualized cancer infusions. In Germany, the requirements of safety cabinets and isolators used for such applications are defined in a relatively new version of a national standard called DIN 12980 established in 2017 [1].

Strict aseptic conditions according to GMP regulations [2] are required, as is the highest safety for the user because of cytotoxics' CMR properties. Safety cabinets for cytotoxics, according to DIN 12980, act as a model for many other applications in pharmaceutical, biotechnological and other laboratory settings.

4.1 Air Guidance

As shown in Figure 2, the air path through the safety cabinet is driven by one or more energy-efficient EC blowers typically located in the upper area which is called the plenum. Lab air is sucked in at the front opening. The medial air velocity must be ≥0.40 m/s according to DIN 12980. The airstream is guided under the worktop through the front grid to the first and main H14-HEPA filter level and then through a double-walled backside up to the plenum. Here the total air volume is split into approximately 30 percent exhaust air and 70 percent recirculated air.

Exhaust air is directed to the outside through a second H14-HEPA filter to further protect the environment from potentially hazardous or infectious material. Through the largest and third H14-HEPA filter, which covers the complete work space, clean recirculated air enters the work space as a uniform, downwards airflow, also called laminar airflow or downflow. The uniformity is important to prevent the spread of contaminants in a horizontal direction which can promote cross-contamination in the enclosure.

Particulate material set free during operations inside the safety cabinet is guided to the main filter level by the strong downflow. The medial air velocity should be 0.45 m/s ±20 percent when working under GMP regulations.

In total, the design enables the highest level of protection for both personnel and product and reduces potentially contaminated areas inside the cabinet to a minimum. This design also enables easy and simple cleaning and disinfection procedures.

4.2 HEPA Filtration

High or ultra-efficient particulate air filters (HEPA/ULPA) are basic elements of safety cabinets. Most are made from micro-glass fiber material and can separate airborne particles like dust, aerosols, spores, bacteria and viruses effectively.

According to international standards these filters need to fulfill defined requirements. In Europe, they must be at least class H14. That means they need to remove ≥99.995 percent of particles of the most penetrating particle size (MPPS) [3], typically in the range of 0.12 to 0.25 µm. For larger or smaller particles, the separation efficacy is even higher.

The filter technique enables work conditions with a very low particulate concentration inside the safety cabinet. Typically clean room class A according to GMP Annex 1, ISO class 5 according to ISO 14644-1 [4] or better can be achieved.

Safety cabinets for cytotoxics with three filter levels improve filtration significantly because the air passing into the workspace to create the laminar airflow and the exhaust air is filtered twice. With this design, the main filter retains practically the entire particle load and is typically the only filter element that needs to be replaced during maintenance. The downflow filter and exhaust filter have very little contact with particulate matter and thus have a very long service life.

4.3 Interaction of Downflow and Inflow

Most critical for basic safety-cabinet function is the interaction of inflow and downflow at the front access which creates an air barrier. This barrier effectively prevents contaminants from the outside from entering the workspace as well as the release of hazardous particulate matter into the laboratory air.

The personnel and product protection function is intensively evaluated during type testing of safety cabinets with internationally harmonized and defined microbiological test procedures. For proof, bacillus subtilis spores are set free in different settings to document either product protection or personnel protection. In the European standard EN 12469 for microbiological safety cabinets [5] to date, only the standard settings for inflow and downflow velocity given by the manufacturer are evaluated.

Other standards like the US standard ANSI NSF49 [6] or the above mentioned new German standard DIN 12980 for safety cabinets for cytotoxics require more extensive evaluations. For these, safety-cabinet performance is verified by microbiological tests at not only the standard setting (BP) but also on other settings with increased or decreased values for medial inflow or downflow at so-called provocation points PP1, PP2 and PP3. Figure 3 shows the scheme for varying inflow and downflow according to DIN 12980:2017-05. These intensive tests lead to a known performance range for this type of safety cabinet with increased user and material safety.

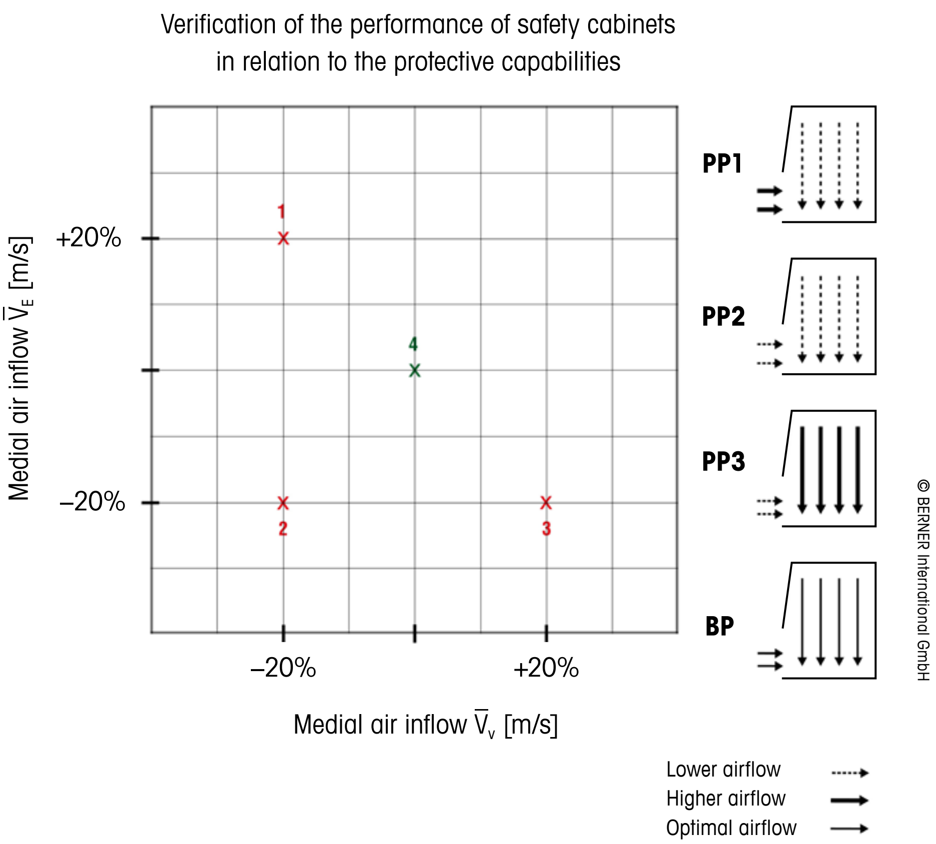

Figure 3: Performance testing for safety cabinets for cytotoxics according to DIN 12980:2017-05.

Air Barrier Note:

It should be noted that disturbing the air barrier can risk the integrity of the protection function. Air can be disturbed by fast movements in front of the safety cabinet, fast arm movements by the user, the opening of interior or exterior doors, and strong HVAC-system airflows. This makes both user training and appropriate positioning of the safety cabinet important.

5. Addressing Challenges in the Weighing Process

The functional principle of a safety cabinet with the interaction of inflow and downflow is of high importance for understanding the challenges in weighing sensitive and hazardous materials.

The primary challenge is obtaining required accuracy in an environment where airflow is a constant presence to ensure safety. Airflow requirements coupled with balance technology that addresses the need for accuracy follow.

5.1 Airflow Velocity and Its Effect on Weighing

Balances in direct combination with a safety cabinet face conditions which usually reduce the overall performance of the weighing equipment, including vibrations and pressure fluctuations caused by airflow. These are both typically in direct dependence to airflow velocity.

High-velocity airflow requires that the blower be run at high speed leading to a higher degree of vibration transmitted to the safety-cabinet housing and work surfaces. Therefore, all international standards during type-testing require measurement of work-surface vibrations expressed as the Root Mean Square Amplitude (RMS value) and must be ≤5 µm.

Increased downflow velocity is also accompanied by increased pressure fluctuations, which add directly to vibration applied to the balance. Taken together, this is why a balance in a safety cabinet under GMP conditions for pharmaceutical applications with a required medial downflow velocity of 0.45 m/s ±20 percent always operates at suboptimal conditions.

In practice, this will be expressed in a higher minimum operating range for balances that are used in safety cabinets in comparison to the theoretical minimum weight under best conditions. It is also possible that, in the worst-case scenario, the calibration of a sensitive balance will fail completely, especially for analytical, micro and ultra-micro instruments. This makes choosing the right balance critical.

5.2 Achieving Accuracy and High Protection

Despite these difficulties, there are several countermeasures you can adopt to adequately operate high-performance balances in a safety cabinet without giving up either the highest personnel or product protection. These include:

- **Use of a draft shield.** Geometry, shield dimensions and the tightness of the enclosure are important factors in how well a draft shield can mitigate changes in air pressure. These factors are highly dependent on the quality of the balance.
- **Solid worktops or enhanced integrated weighing segments.** These worktops can reduce the RMS value by a factor of 2 to 5. Premium safety-cabinet manufacturers will offer such equipment as a normal option in their accessory program to replace standard worktops.
- **Solid weighing stones or specialized metal plates.** These are placed on standard worktops decoupled from vibration. RMS values are 5 to 10 fold lower compared to normal worktops but can create poor ergonomics by adding five or more centimeters to balance height. Despite this, a higher front-access opening should not be considered due to the influence on inflow and downflow settings that can increase exposure risk.

5.3 Cable and Peripheral Options

Cables and connected peripherals such as power supplies or control boxes can also interfere with weighing performance. Connections between balance, peripheral devices and data-management interfaces should be kept as short as possible because space is limited inside a safety cabinet and because they increase spill risk. Connecting cables may also transfer vibrations, so any contact between cable wrappings and the balance must be avoided.

Peripheral devices can be positioned on the outside of the cabinet for reduced interference and good accessibility. They can also be integrated below the worktop or behind the back wall. Safety-cabinet manufacturers should be able to offer options that achieve short cable lengths along with integrated interfaces and connections.

5.4 Fully Integrated Balances

The most challenging solution to vibrational interference is the full integration of a balance into a special worktop. This highly specialized solution—while currently only a vision for the future—could potentially provide a significant range of benefits including:

- **Enhanced ergonomics** to promote safe handling of potentially hazardous substances.
- **Elimination of cables or peripheral devices,** helping to provide a best-case scenario for cleaning and the avoidance of cross-contamination.
- **Minimized interference with safety-cabinet airflow** due to inherent design and elimination of cables and peripherals.
- **Improved personnel and product protection** through all of the above.

Full integration when it arrives will require excellent cooperation between the balance manufacturer and safety-cabinet manufacturer with effective decoupling of the weighing instrument from safety-cabinet vibrations as the primary goal.

As mentioned, this type of integration is still a vision for the future at the time of publication, but it would be possible with the right partnership between equipment experts.

5.5 External Influences

Finally, external factors can also have a strong influence on weighing performance, especially when using sensitive micro and ultra-micro balances. As noted above, these external factors can be caused by the cleanroom environment or the HVAC system and include temperature and pressure variations.

These influences can be limited through the application of weighing best practices, including appropriate placement of the safety cabinet and observing practices that limit drafts and changes in temperature and humidity.

6. Summary

Particularly in pharmaceutical and biotechnological applications in GMP conditions, safety cabinets and isolators typically enable the highest personnel and product protection. When combined with appropriate PPE and safe operating procedures such as limiting contact with personal items and work surfaces, cross-contamination risk is practically eliminated.

This level of protection becomes necessary when hazardous and sensitive material is handled, and it is of the utmost importance when the product has CMR properties. GMP Regulations require laminar airflows for safety cabinets of 0.45m/s ±20 percent. The German standard DIN 12980 describes further requirements for safety cabinets and isolators for cytotoxics and other CMR drugs. Safety cabinets fulfilling these requirements are the best choice in such applications.

The high downflow velocity for safety cabinets that conform with GMP is a challenge in weighing processes, especially when using analytical, micro and ultra-micro balances. Due to resulting vibrations and pressure fluctuations, higher minimum operating ranges in comparison to the theoretical minimum weight or even failures in calibration routines can result without appropriate countermeasures.

Ways to minimize the negative effects on weighing performance are:

- Use of solid worktops or special weighing worktops.
- Separate weighing stones or metal plates decoupled from vibration.
- Short cables to power supply and for interfaces.
- Avoiding contact between cable wrappings and the balance.
- Integration of peripheral devices or positioning them outside the cabinet.

Full integration of balances into the worktop is an interesting future goal for enhanced weighing and safety. This type of solution will require excellent cooperation between the manufacturers of balances and safety enclosures.

7. References

- [1] DIN 12980:2017-05. Laboratory installations—Safety cabinets and glove boxes for cytotoxic substances and other CMR drugs. Beuth Verlag, Berlin 2017.
- [2] EU GMP Annex 1: Manufacture of sterile medicinal products, revision Nov. 2008.
- [3] DIN EN 1822-1: High efficiency air filters (EPA, HEPA and ULPA)—Part 1: Classification, performance testing, marking; German and English version. Beuth Verlag, Berlin.
- [4] ISO 14644-1: Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration. Beuth Verlag, Berlin.
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- [6] NSF International Standard/American National Standard: NSF/ANSI 49 -2014: Biosafety Cabinetry: Design, Construction, Performance, and Field Certification. NSF International, Ann Arbor, Michigan, USA.

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