



Pressurisation of Pharmaceutical Cleanrooms

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Abstract

Cleanroom spaces are maintained with pressure differentials between rooms as an important tool to achieve contamination control. By maintaining the room at a higher pressure, the products can be protected from contaminants from the adjoining spaces. On the other hand, potent products like penicillin and nuclear medicines can be kept in containment by maintaining the room at a lower pressure. Maintaining the required pressure gradient and ensuring that there are no airflow reversals pose peculiar challenges. Movement of personnel and materials between rooms involving opening and closing of doors, changing gaps between doors and frames due to wearing of gaskets and changing supply air, return air and exhaust air quantities are some of the variables which disturb the pressure differentials all the time. This article discusses the means to achieve and control the room pressure differentials for pharmaceutical cleanrooms and also indicates the energy consumed to maintain pressure gradient.

Introduction

The purpose of having pressure differentials in cleanrooms is to prevent cross contamination. When a product needs to be protected from airborne contamination, which may come in from

adjoining spaces, the room is kept at a higher pressure (positive) w.r.t. the surroundings. The room air ex-filtrates and thus follows a 'clean to dirty' axis.

There are potent products like penicillin and nuclear medicines, particles of which should not escape into the adjoining spaces. These need to be 'contained'. Air should only infiltrate from adjoining spaces and not vice versa. These spaces are kept under lower pressure (negative) with respect to the surroundings.

As a result of pressure differential requirements, make-up air needs to be inducted into the system. This poses additional air conditioning load on the system. To keep the ensuing extra energy requirements on a tight leash, it becomes imperative to keep the differential pressures to the minimum required, while ensuring that there are no flow reversals due to pressure disturbances.

About the Author

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How Pressure Differentials are Achieved

Air pressure differentials are created between rooms by introducing movement of air through leakage openings such as the annular space between doors gaskets and door frames, conveyor openings, duct and pipe penetration cracks. This is achieved by controlling the flow rates of supply air, return air and exhaust air in the suite of rooms of cleanroom space.

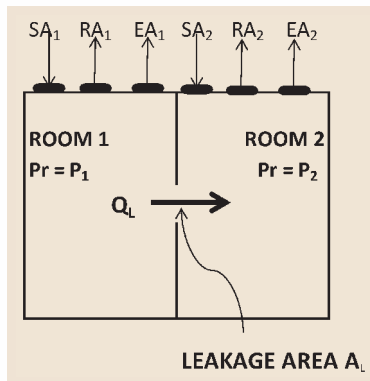


Figure 1: Air flow relationship

SA, RA and EA are the supply, return and exhaust air quantities from the respective rooms, and Q_L is the leakage air flow from Room 1 to Room 2. Both the rooms are leak-proof except for the leakage gap area AL between them.

If SA₁ > RA₁+EA₁, Room1 is at a 'positive' pressure. (1)

If SA₂ < RA₂+EA₂, Room2 is at a 'negative' pressure. (2)

Further,

SA₁ = RA₁+EA₁+ Q_L (3)

SA₂ = RA₂+EA₂- Q_L (4)

The pressure difference ΔP, i.e. (P₁-P₂), is related to leakage area A_L and leakage air flow Q_L as derived from Bernoulli's equation.

$$\Delta P = 0.5 \times \rho \times [Q_L / (A_L \times \mu)]^2 \text{ L} \quad (5)$$

Where, ρ is the density of air in kg.m⁻³; consider 1.2 kg.m⁻³ at 20°C, 60% RH at Mean Sea Level; μ is the discharge coefficient depending on geometry of the opening.

Cleanrooms and other controlled environments have very small leakages (maximum size of 0.01m² ~ 0.02m²). Therefore, coefficient of contraction must be taken into account. The coefficient of contraction for the sizes mentioned is somewhere between 0.66 and 0.75. A figure of 0.72 is usually considered for cleanroom applications (Sauter). However, for large openings such as for conveyors 0.3m x 0.3m, the coefficient of contraction can be considered very close to 1.0.

Estimation of Air Leakage Areas for New Cleanrooms

For the purpose of designing new cleanrooms, ASHRAE ELA (effective leakage area) tables are available for building components (doors, walls, joints etc.) for estimation of air leakage.

For existing rooms, air leakage can be calculated from the power equation (Wei Sun) as follows:

$$Q_L = C \times (\Delta P)^n \quad (6)$$

Where,

Q_L = flow in l/s

C= flow coefficient, l/s/Paⁿ

ΔP= pressure in Pascals

Evaluating Leakage of an Existing Cleanroom

Through ASTM 'Blower Door' test using a pressurisation blower, a set of Q_L and DP is generated for the room. 'Power Equation' curve fit with calculated constants (C, n, ELA) that define a room's unique and dynamic leakage characteristics are established (Wei Sun).

$$n = \frac{\sum_{k=1}^m \ln Q_k \cdot \sum_{k=1}^m \ln \Delta P_k - m \cdot \sum_{k=1}^m (\ln Q_k \cdot \ln \Delta P_k)}{\sum_{k=1}^m (\ln \Delta P_k)^2 - m \cdot \sum_{k=1}^m (\ln \Delta P_k)^2}$$

$$C = \text{EXP} \left(\frac{\sum_{k=1}^m \ln Q_k - n \cdot \sum_{k=1}^m \ln \Delta P_k}{m} \right) \quad (7)$$

Room Pressurisation Effect of Parameters

Effect of a difference in volume flow in an air-tight room (i.e. no leakage)

Assumption:

Room volume = 200m³ (basic area 8m x 8m, 3.12m ht)

SA = 2000m³.hr⁻¹ (10 ACH)

RA < SA

Duct pressure, SA = 800Pa

Duct pressure, RA = -300Pa

Suppose volume flow difference is 4% between SA and RA

Therefore, difference = 4% of 2000 = 80m³/hr = 0.022m³.s⁻¹

Due to difference in volume flow into the fixed volume room, the pressure increases thus:

$$\frac{100,000 \text{ Pa} \times (200 + 0.022)}{200\text{m}^3} \text{ m}^3 \cdot \text{s}^{-1} - 100,000\text{Pa}$$

$$= 11\text{Pa} \cdot \text{s}^{-1}$$

The room pressure can change to the level of the supply air duct pressure. The time taken will be:

$$\frac{800 \text{ Pa}}{11\text{Pa} \cdot \text{s}^{-1}} = 73\text{s}$$

Thus, for a totally air tight room, the room pressure quickly achieves the supply air duct pressure when supply air quantity is more than return air quantity!

Effect of increase in air quantity on a room with very low leakage (leakage area 0.001m²)

Assumption:

Room volume = 200m³

Supply air volume flow = 2000m³.hr⁻¹ (10 ACH)

Leakage area = 0.001m²

A sudden difference in volume flow of 1% (e.g. from short term changes in duct pressure),

Volume flow increase = 20m³.hr⁻¹ (1% of flow)

Using equation (5),

$$\Delta P = 0.5 \times 1.2\text{kgm}^3 \times \left[\frac{0.0055\text{m}^3 \cdot \text{s}^{-1}}{0.001\text{m}^2 \times 0.72} \right]^2$$

$$= 35\text{Pa}$$

When dealing with pressure differentials in the range of 15Pa, a variation of 35Pa can result in flow reversals.

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Effect of increase in air quantity on a room with moderate leakage (leakage area 0.01m²)

Assumption:

Room volume = 200m³

Supply air volume flow = 2000m³.hr⁻¹ (10 ACH)

Leakage area = 0.01m²

A sudden difference in volume flow of 1% (e.g. from short term changes in duct pressure),

Volume flow increase = 20m³.hr⁻¹ (1% of flow)

Using equation (5),

$$\Delta P = 0.5 \times 1.2 \text{kgm}^3 \times \left[\frac{0.0055 \text{m}^3 \cdot \text{s}^{-1}}{0.01 \text{m}^2 \times 0.72} \right]^2$$

= 0.35Pa

When dealing with pressure differentials in the range of 15Pa, a variation of 0.35Pa is unlikely to result in flow reversals.

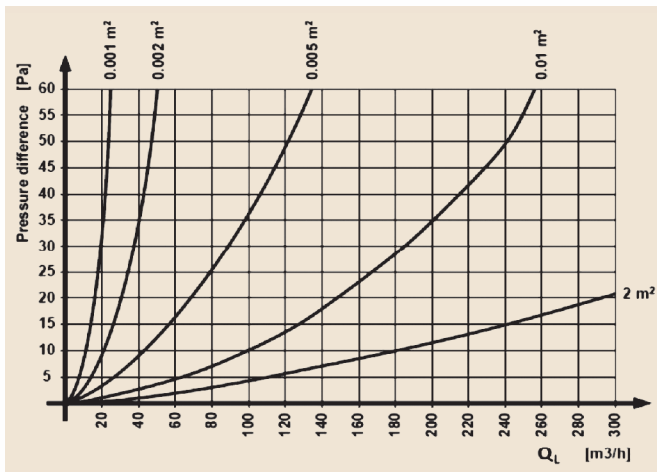


Figure 2: Room pressure versus leakage air flow for various leakage areas

Effect of air tightness

Slight room leakage fundamentally improves room pressure retention. When room leakage is doubled, room pressure retention is improved by a factor of 4.

Influence of change of air quantity on quality of pressure control

Assumption:

Room volume = 200m³

Supply air volume flow = 4000m³.hr⁻¹ (20 ACH)

Leakage area = 0.01m²

A sudden difference in volume flow of 1% (e.g. from short term changes in duct pressure),

Volume flow increase = 40m³.hr⁻¹ (1% of flow)

Using equation (5),

$$\Delta P = 0.5 \times 1.2 \text{kgm}^3 \times \left[\frac{0.011 \text{m}^3 \cdot \text{s}^{-1}}{0.001 \text{m}^2 \times 0.72} \right]^2$$

= 1.4Pa

Compare this with a variation of 0.35Pa for half the flow in the previous example. The variation is not as dramatic as the change in air tightness of the room. Between the degree of room tightness and air change rate, room pressure retention is mainly dependent on the leakage area of the room.

Room Pressure Control Strategies

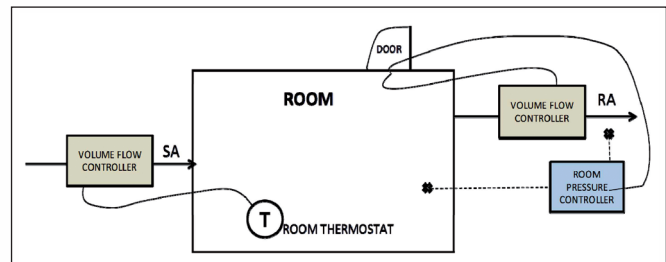


Figure 3: Pressure control strategy #1 – direct pressure differential control

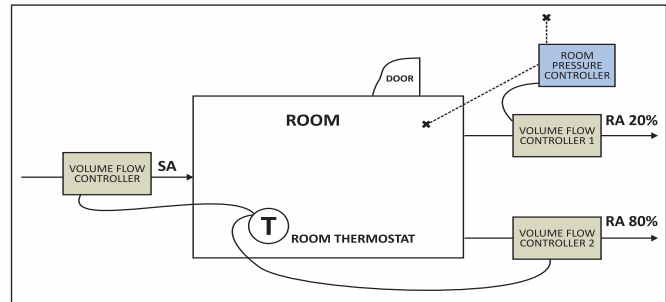


Figure 4: Pressure control strategy #2 – direct pressure differential control on bypass air

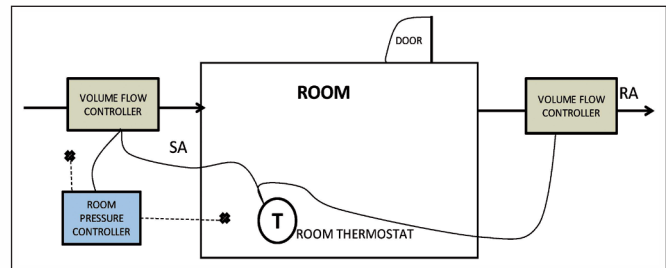


Figure 5: Pressure control strategy #3 – cascade solution

Control System Requirements

(Jurg Blaser, Sauter)

The key to achieving pressure control is the role of the return air damper and its actuator. For rooms with moderate leakage, longer running time (>20 seconds) does not have a negative impact on the control. However, for low leakage rooms, this will result in high control deviations. For this reason, for low leakage rooms a short running time is desirable (<10 seconds). Further, for good differential pressure control, the controller should have as little hysteresis as possible.

Direct Pressure Differential Control (Pressure Control Strategy #1)

Refer Figure 3.

Control components:

1. Volume air controller on return air working on room pressure.
2. Interlock of differential pressure controller with door opening.
3. Volume air controller on supply air, working on temperature.

The return air damper is throttled as per the room differential pressure signal so that the required room pressure is achieved.

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However, when the door is opened, room pressure drops due to high leakage. The room pressure controller affects the damper to its closed position. When the door is then closed, because the return air damper is still in relatively closed position, the room pressure can increase dramatically and can result in flow reversals in adjoining rooms.

By incorporating a door switch contact, it is possible to freeze the damper actuator in the position it was in when the door was opened; the situation of high pressure can be mitigated.

However, when the door is kept open for a long time, if the supply air has a VAV control, incorrect air volume will be admitted because the control loop is interrupted by the door switch. This again will disturb room pressure.

Pressure control strategy #1 is suitable for rooms with low traffic through the doors.

Direct Pressure Differential Control on Bypass Air (Pressure Control Strategy #2)

Refer Figure 4.

This scheme is similar to that of pressure control strategy #1 with the difference that the room pressure is maintained by a return air damper handling partial air volume, typically 10 to 20% of total volume. Since the volumes handled are much less, even though door openings result in fully closed damper position, the influence when the door is closed is minimal.

This control strategy thus provides for considerably better control. Other than the extra expense of additional damper box and duct pieces, there is no disadvantage.

Cascade Solution

Refer Figure 5.

This control strategy gives similar result as pressure control strategy #2 without the need for an additional bypass damper.

The supply air volume flow controller has input from room temperature and additionally from the room pressure controller. The return air damper position is offset in relation to the supply as per room characteristics, and the setting is done in the field.

Air Leakage Required for Keeping Airborne Particles from Passing through Openings

An outward airflow of 0.5 to 1m.s⁻¹ is adequate to keep the airborne particles from passing through an opening (*ISPE Good Practice Guide: Heating, Ventilation and Air Conditioning*). The differential pressure needed to create this velocity is less than 1Pa. However, after allowing for accuracy of sensors and the pressure variations due to disturbances, the recommended differential pressures between adjoining areas is 10 to 15Pa in pharmaceutical cleanrooms.

Need for Airlocks

Airlocks are provided as effective obstacles to airborne contamination.

For a door of the size of 2m², the airflow through leakage area in door closed condition for a pressure differential of 10Pa can be less than 160m³.hr⁻¹.

However, in door open condition, to achieve the minimum 0.5m.s⁻¹ transport velocity for airborne contamination, the air quantity

required will be 3000 m³.hr⁻¹. This may be impractical to achieve.

One way to reduce the need for high air quantity flow through open doors is to provide airlocks, also called ante-rooms. The doors leading from the room to the airlock and from the airlock to the adjoining space are not opened simultaneously.

Types of Airlocks

(Illustrations courtesy *ISPE Good Practice Guide: Heating, Ventilation and Air Conditioning*).

'Cascade' pressurisation is used when:

- There are area classification requirements, but few containment issues. Cascade will be outward from the room for aseptic operations.
- There are containment issues, but no cleanliness classification issues. Cascade will be inward into the room for hazardous early intermediates. The normal pressure differential from one air class to the next (i.e. across the airlock) is 10 to 15Pa. The pressure inside the airlock is somewhere between the two adjoining spaces. Pressure differential is measured across the airlock and not across each door.

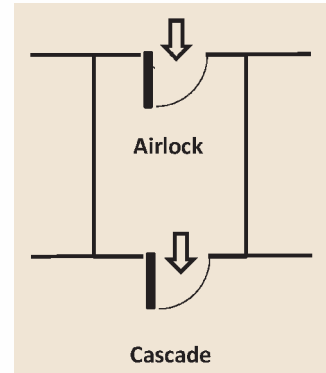


Figure 6: Cascade type of airlock

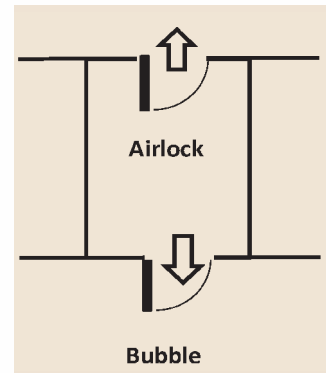


Figure 7: Bubble type of airlock

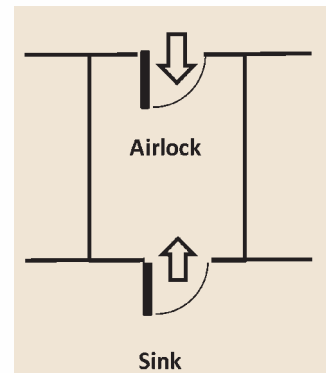


Figure 8: Negative pressure sink type airlock

The bubble airlock provides a means of segregating areas using positive airflows. The bubble airlock should be at the same in-operation air class as the cleaner room it serves, because air infiltrates into the classified area.

The pressure of the airlock is usually designed to be 5 to 8Pa above the higher of the two room pressures. The pressure difference between the cleaner and less clean room across the airlock is maintained at 10 to 15Pa.

The negative pressure sink airlock is used for containing hazardous clean areas. The airlock gets contaminated. The airlock is usually designed to be 5 to 8Pa lower than the lesser of the two room pressures. The pressure difference between the two clean room spaces across the airlock is 10 to 15Pa. Although more

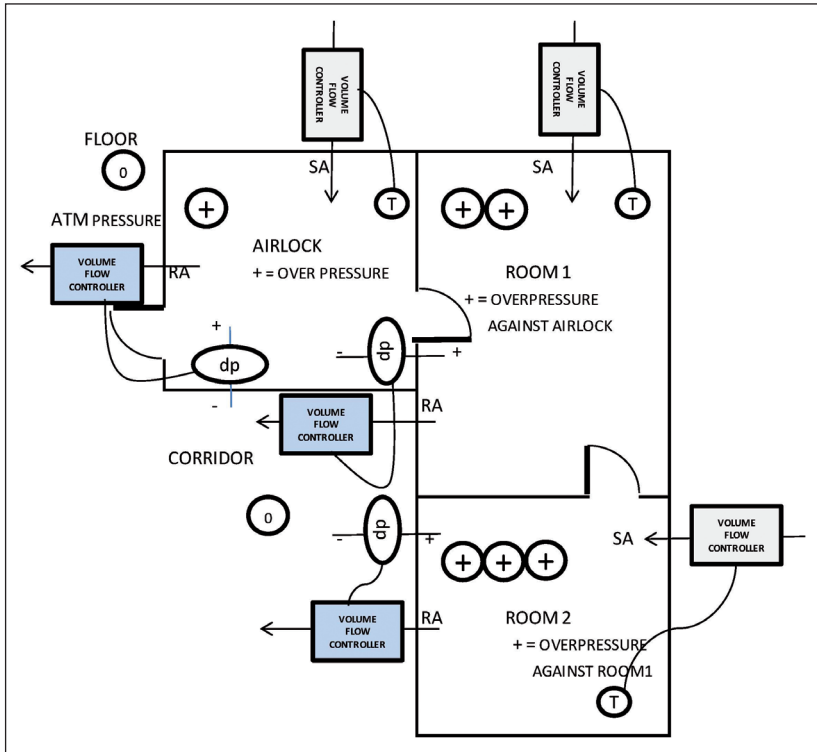


Figure 9: Scheme #1 – Relative pressure measurement sequence

air needs to be removed from the airlock, some supply air is recommended to facilitate quicker recovery of the airlock from the contaminated state.

Room Pressure Measurement for Control

Examples for Figure 9 and 10 are from *Schnieder: Clean Room Technology - Room Pressure Controllers*.

Scheme #1

Room pressure controllers automatically regulate the positive room pressure (+) for each room.

The airlock dp (differential pressure controller) measures and controls the differential pressure between the corridor (0) and the air lock (+), while the Room 1 dp controller measures and controls the differential pressure between the air lock and Room 1. The positive pressure of Room 1, therefore, follows the positive pressure of the air lock with a differential pressure of, say, +10Pa.

The Room 2 dp controller relates to the corridor again and maintains a constant positive pressure of say, +30 Pa.

This model cannot be recommended, as room pressure maintenance is very unstable because increased oscillation occurs when rooms are measured in relation to one another (e.g. Room 1) against the air lock. Room pressure changes, e.g. in the air lock, have an effect on Room 1.

Scheme #2

The dp room pressure controllers automatically regulate the set positive room pressure (+) for each room.

All dp differential room pressure controllers are summarised on the (-) negative pressure side and measured against a common reference point. This preferred measuring method ensures the best stability, provided the reference room or the reference point fulfils the following conditions:

- Pressure stable, non-ventilated room without volume flow or pressure control, without wind load and without connections (e.g. conduits, electrical pipelines, etc.) to ventilated rooms.
- For reference points against the outside atmosphere, the atmosphere must be free of dynamic wind pressure and sufficiently attenuated.

This model is preferable to Scheme #1 due to the previously mentioned control stability.

Effect of Air Leakage on Air Conditioning Load

When a suite of rooms is pressurised, the air which finally leaves the system needs to be compensated with make-up air. This is an additional burden on the air conditioning load.

Likewise, when a suite of rooms is contained, net air infiltration can represent an additional burden on the air conditioning load.

A good door in a pharmaceutical cleanroom typically has a 3mm average crack between door and frame on sides and top, and 7 to 15mm on the bottom. For a 900mm wide x 2100mm high

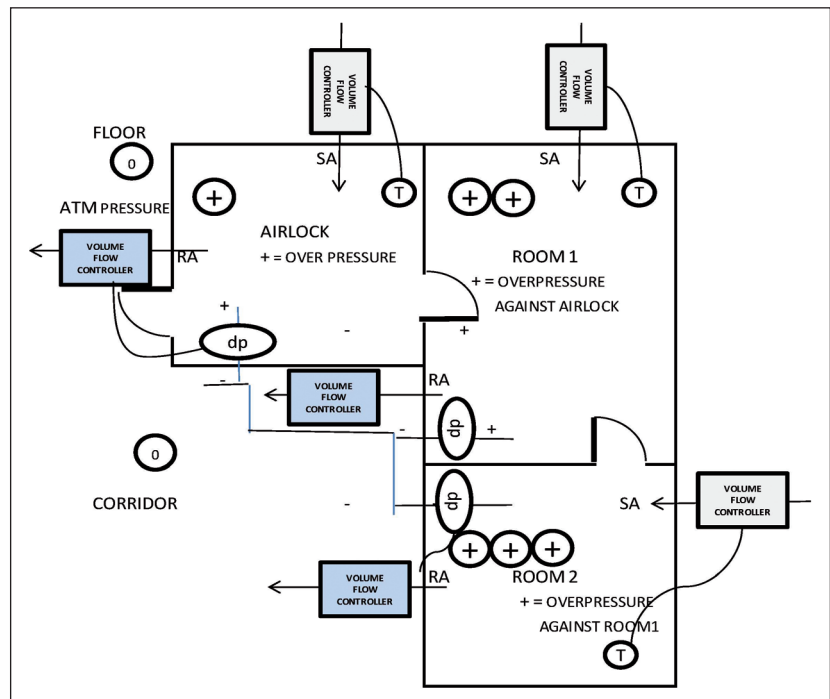


Figure 10: Scheme #2 – Pressure measurement using common reference point

door, this represents approximately 0.024m² leakage area when closed. On the other hand, a 5mm average crack between door and frame on sides and top, and 7mm to 15mm on the bottom for the same door represents approximately 0.036m² leakage area.

The above example considers a typical ambient of 30°C Dry Bulb and 28°C Wet Bulb temperature in monsoon and the make-up air to be cooled from ambient to 11°C ADP to achieve the room conditions.

It is obvious that greater leakage area or pressure will amount to greater energy loss. In general, a 2.5Pa set point increase results in 1% to 2% increase in total energy consumption. (*Jin Wen, Wei Sun and Stephanie Dost.*)

It is thus important to have a careful minimum pressurisation regime and low leakage areas in a cleanroom in order to minimise energy loss.

Conclusion

- Achieving stable pressure gradient is dependent on the total room leakage area. Very low leakage rooms will tend to have more variation in pressures and will thus require much finer controls. On the other hand, low leakage rooms will tend to have more stable pressure.
- Airlocks will be required to help maintain pressure gradients when the room doors are opened for material and personnel movement. The type of airlock and the pressure gradient chosen will be determined by whether protection of the

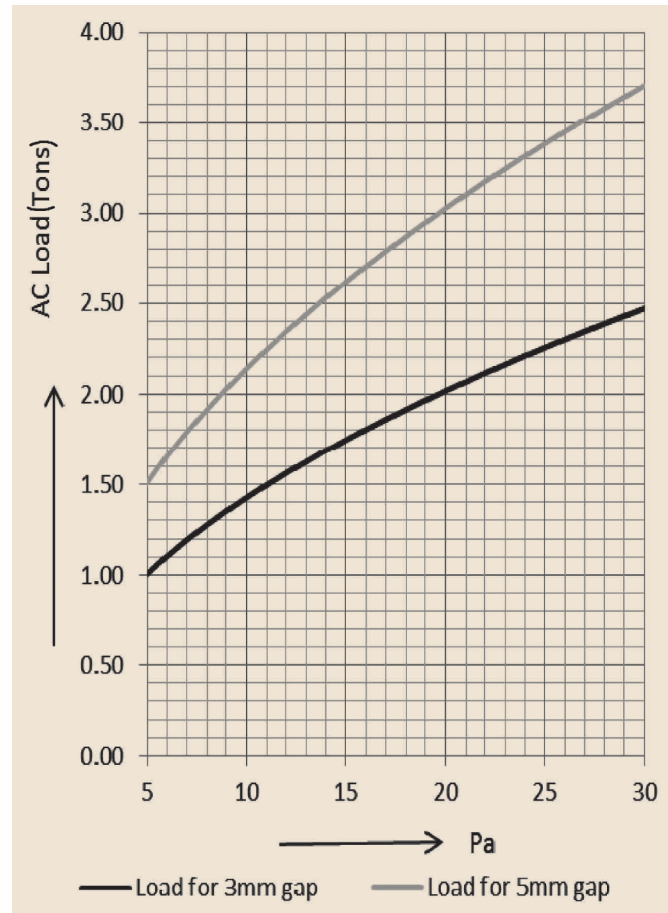


Figure 11: AC loss due to door air leakage out of system

product from contamination is required or containment is necessary.

- Considerable energy is used up in maintaining pressures. Investment in low leakage construction and low leakage doors will minimise energy loss.

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