



Outdoor environmental effects on cleanrooms – A study from a Swedish hospital pharmacy compounding unit

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ABSTRACT

In this study we examined how outdoor climate affects indoor conditions of a cleanroom used for the preparation of radiopharmaceuticals in the Uppsala university hospital pharmacy, Sweden. Further objectives were to identify associated risk factors to ensure a consistent extemporaneous manufacturing process. Data for two years from the facility monitoring system (with one minute resolution for temperature, relative humidity (%RH), differential pressure) were compared with meteorological outdoor data from Uppsala (Swedish Meteorological and Hydrological Institute, 60-minute mean data for temperature, relative humidity, wind speed and air pressure). The findings of this study indicate a linear relationship between indoor and outdoor temperature for the autumn, winter and spring seasons. The typical summer outdoor diurnal pattern is also seen for indoor temperature. During the study period, the minimum outdoor temperature was -17.5 °C and the maximum 31.4 °C. This wide temperature range also entails a wide range of air humidity from 10 %RH to 100 %RH indoors. Cleanroom temperature and %RH are factors that may affect the quality of medications, especially the risk of microbiological growth in aseptic processes, stability of medications during storage but also may affect handling of for example uncoated tablets or weighing of powder, especially at high %RH for hygroscopic drugs or at low %RH due to static electricity. Further the risk of damage on electrical equipment from electrostatic discharge at low %RH is discussed with a focus on the need for humidity control of cleanrooms and/or systems for mitigation of electrostatic discharge in climates with outdoor temperature in the wintertime below freezing point.

1. Introduction

Most of Sweden has a temperate climate, despite its northern latitude, with largely four distinct seasons and mild temperatures throughout the year. According to the Köppen classification system, the climate of the region of Uppsala, where the study was performed, is type Dfb which reads as “warm summer humid continental climate” [1]. Uppsala University has one of the world's longest series of weather observations. The observations date back 300 years since its start in 1722 and today weather observation data are readily available through SMHI, the Swedish Meteorological and Hydrological Institute [2].

When developing systems for controlling the indoor environment of buildings, the type of building and outdoor climate, including season,

should be taken into account [3]. When designing and building cleanrooms, the demands are set to an even higher standard and highly regulated [4,5]. For the aseptic manufacture of medicinal products in Europe, the four A-B-C-D grades can be distinguished and GMP regulations further described in the Annex 1 and 3 of the Eudralex [5]. For radiopharmaceutical preparation in European countries, there is often national regulations for authorised kits and generators excluding these preparations from Annex 1 [6], so often only two room grades are applicable; Grade C (at rest the airborne particle classification is ISO 7 and ISO 8 in operation) and Grade D (at rest, the airborne particle classification is ISO 8) due to the short shelf life of the preparations. The grade divisions are based on maximum permitted number of particles per m³ air volume and in order to create and maintain the requisite level,

Abbreviations: %RH, relative humidity; AH, absolute humidity; DJF, December, January, February; ESD, electrostatic discharge; FMS, facility monitoring systems; GMP, good manufacturing practice; HEPA filter, high-efficiency particulate air filter; HVAC, heating, ventilation and air conditioning; JJA, June, July, August; MAM, March, April, May; MSC, Microbial Safety Cabinets (Class II); SMHI, the Swedish Meteorological and Hydrological Institute; SON, September, October, November.

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cleanrooms are constructed as well-insulated and well-cleaned rooms with high-efficiency particulate air (HEPA) filtered air and air pressure difference between zones. In order to minimize the carrying of particulate by a person, airlocks and protective clothing are further used [4]. Airborne particle levels are tested using particle counters and microorganisms are detected and counted through environmental monitoring methods [7].

Cleanroom temperature and relative humidity (%RH) are factors that affect the stability of medications during storage but also affect weighing of powder or handling of uncoated tablets as well as pharmacoprinting processes [8,9], especially at high %RH for hygroscopic drugs or at low %RH due to static electricity. When moving e.g. a glass container from a refrigerator to a high %RH room temperature environment, condensations take place yielding visual inspections of content more difficult [6]. A high %RH increases the incidence of fungi in cleanrooms jeopardizing the sterility of preparations [7,10]. At low %RH the electrical conductivity of air is decreased causing the build-up of static charge, i.e. the triboelectric effect, influencing the movement of particles that will stick to gloves and clothing or possibly culminating in an electric spark that can cause serious damage to electronic equipment [11,12]. Also worker comfort studies show that skin dryness and eye irritation increased as humidity decreased resulting in cracked skin and worker discomfort [13,14].

In the design of the aseptic manufacturing process of the Uppsala university hospital pharmacy cleanrooms, a monitoring system for differential pressure, temperature, particles and relative humidity was installed. The outdoor effects on indoor climate are highly dependent on construction design. The purpose of this study is to examine how outdoor climate affects indoor climate, specifically the controlled environment of a cleanroom. Further objectives are to identify associated risk factors to ensure a consistent extemporaneous manufacturing process.

2. Materials and methods

2.1. Meteorological data

Meteorological data were accessed from SMHI, the Swedish Meteorological and Hydrological Institute [2]. Data are available from circa 1970 until current date, in Swedish, with open access. After defining the study period, parameters and station, the data was downloaded, sorted to match the time frame and further calculations performed using Microsoft Excel. The station used (Uppsala Aut, number 97510) is 1.5 km from the hospital cleanroom (Latitude 59,8471, Longitude 17,6320, Altitude: 23.4 m). The study period was Sep 1st, 2019 to Aug 31st, 2021 and data for wind speed, air pressure, temperature and relative humidity was extracted from the SMHI web database.

The wind speed was analysed using the Beaufort scale.

The absolute humidity was calculated using:

$$\text{Absolute Humidity} = \frac{6.112 \times e^{\frac{(17.67 \times T)}{(T+243.5)}} \times RH \times 2.1674}{(273.15 + T)}$$

where the absolute humidity is expressed in g/m³ and T is the temperature expressed in Degrees Celsius (°C) and RH is the relative humidity expressed as fraction [15,16].

Seasons are normally defined by month; Winter DJF (December, January, February), spring MAM (March, April, May), summer, JJA (June, July, August) and autumn SON (September, October, November). In this study, the seasons were however defined by year-specific season arrival data. The starting dates and durations for seasons defined by meteorological data as spring, summer, autumn and winter are shown in Supplemental Material S1 for the study period.

During the study period the following data were unavailable:

- wind speed data unavailable for September, October and November 2019
- temperature data unavailable for 2020–07-16 at 03:00, 2020–07-17 at 3:00 and 2021–01-14 from 03:00 to 06:00
- relative humidity data unavailable for 2020–07-16 at 03:00, 2020–07-17 at 3:00 and 2021–01-14 from 03:00 to 06:00

2.2. Cleanroom layout

The studied cleanroom (floor area of 70 m²) is situated in the oncology building J3, Entrance 100, Uppsala university hospital, Uppsala, Sweden with operations started on September 9th, 2019. The cleanroom is underground and built in the middle of the nuclear medicine ward. The HVAC (Heating, ventilation, and air conditioning) system is therefore constructed from the basis of the hospital's standard HVAC that is connected to the county district heating network including district cooling for the summer period. There is no system in place to regulate the relative humidity. The air is further filtered through pre-filters and finally HEPA filters mounted in the ceiling of the cleanroom. Outlets are wall-mounted and placed close to the floor. The cleanroom is supplied with 100% fresh air and at least 20 air changes per hour in the Grade C rooms. There are ventilated pass-through hatches for material with interlock system and airlocks for personnel. The differential pressure between adjoining rooms (see drawing in Supplemental Material S2) is maintained using mechanically controlled iris dampers for in- and outlets in addition to pressure relief dampers adjacent to doors. In the three preparation rooms there are also five MSC, Microbiological Safety Cabinets Class II (NinoSAFE Biological Safety Cabinet: Class II Isotope according to EN12469/ANSI49) contributing to the outlet of air by a set amount of exhaust. The MSCs are ducted and mounted with exhaust fans with inflow air speed around 0,45 m/s giving over 300 m³/h in exhaust air flow.

In the cleanroom, operations are primarily for preparation of diagnostic and therapeutic medications containing a radioactive pharmaceutical ingredient such as ^{99m}Tc, ¹¹¹In, ¹⁷⁷Lu and ¹³¹I. Due to the short half-life of the radionuclides, all preparations are for immediate use. The shelf-life from an aseptic point of view is maximum 24 h according to local routines. Manufacturing of medications for clinical trials also take place from January 2022 according to the license of the Swedish Medical Products Agency (Uppsala, Sweden) for the PET centre with manufacturing authorisation no. 5.9.2–2021-054962 in accordance with Art. 40 of Directive 2001/83/EC and Art. 13 of Directive 2001/20/EC although the main operations for the PET centre production is in another part of the hospital.

The facility monitoring systems (FMS) for the cleanroom was supplied by Brookhaven Instruments AB (Hallstahammar, Sweden). The system monitors particles, differential pressure, temperature and relative humidity. It is annually revalidated by the supplier according to a service agreement. The study period was Sep 1st, 2019 to Aug 31st, 2021 and data from the FMS software was extracted for i) differential pressure, ii) temperature and iii) humidity with minute resolution. The preparation room (044350) with the highest differential pressure (target > 3x15 Pa = 45 Pa, alarm range 40–60 Pa) relative the outdoor air pressure was selected to be the study subject. For the investigation of outdoor wind effects, the anteroom/airlock (044310) with alarm range –10 to –20 Pa, was also included. Data were exported from the FMS in CSV data format and imported to Microsoft Excel for further calculations of hourly/daily/monthly mean and standard deviations. Data were missing for a large part of the first year, see Supplemental Material S3 for details.

2.3. Statistical methods

Mean and standard deviation of data were calculated using Microsoft Excel pivot tables and later copied to GraphPad Prism 8 for visualisation. By resorting to the analysis function of this program, we conducted

several Pearson correlations according to the seasons defined by meteorological data. This analysis was performed to determine the ratio between the covariance of temperature and humidity variables where the result has a value between -1 and 1 . A value of 0 implies that there is no linear dependency between the variables. The correlation sign is determined by the slope. A value of $+1$, implies that if X increases, Y also increases and a value of -1 , implies that if X increases, Y on the other hand, decreases.

3. Results and discussion

3.1. Temperature

In Fig. 1, the monthly outdoor temperature over a year is presented and the mean temperature ranges from approximately -3 °C to $+21$ °C with the lowest temperatures seen in January and February and the highest in June to August. When single measurements are considered, it can be seen that over the two-year study period the minimum outdoor temperature was as low as -17.5 °C and the maximum 31.4 °C. The great variation in monthly temperatures is also evident from the large standard deviation of e.g. February. The indoor temperature of the cleanroom is however well regulated over the year with small standard deviations of the mean and no measurements outside of the specified range. It can be seen that for the summer months July–August the indoor temperature is lower than the year average (around 18 °C).

By calculating Pearson correlation coefficients (Table 1), the linear relationship between indoor and outdoor temperature is further confirmed however, as discussed above, the dependency during the second summer months is the least likely. It can be seen that the daily mean outdoor temperature varies from -2 °C to $+13$ °C in autumn, -12 °C to $+4$ °C in winter, -5 °C to $+11$ °C in spring and $+7$ °C to $+27$ °C in summer (Supplementary material S4). The outdoor temperature span for each season (approximate 15°) correlates to an approximate 1° indoor span in the spring and autumn. For winter, the outdoor change has less impact, only approximately 0.5° and for summer the outdoor change has a higher impact, around 4° . This can be explained by the HVAC system's temperature control not being responsive enough during the colder seasons, but more efficient at the higher outdoor temperatures during the summer.

In Fig. 2A, data for a summer week is shown using hourly resolution and the typical outdoor summer diurnal temperature variation with an afternoon temperature peak and daily minimum at around 02–04 in the night is evident. A similar pattern can be seen for the indoor temperature variation but to a much less extent thanks to the HVAC system of the hospital, see for example the Friday data (July 17th) with a 13° outdoor temperature variation resulting in approximately 2.2° change indoors.

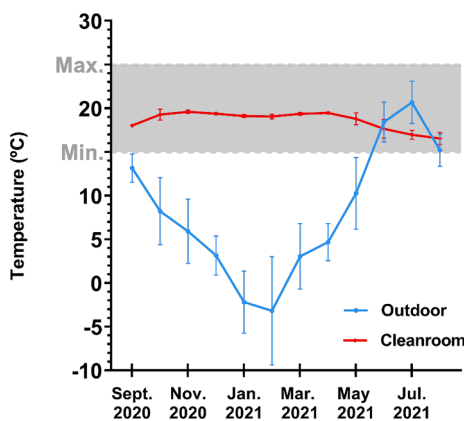


Fig. 1. Mean temperature per month of the 2nd year for Outdoor (blue) and Indoor Cleanroom (red). Error bars are standard deviations of the mean. Grey zone represents the internally set indoor temperature range (15 – 25 °C).

Table 1

Pearson correlation coefficients of temperature and humidity for separate seasons as defined in Supplementary material S1.

	Temperature	Relative Humidity	Absolute humidity
1st year summer correlation between outdoor and cleanroom	$r = 0.7239$ Number of XY Pairs 96	$r = 0.5742$ Number of XY Pairs 96	–
2nd year autumn correlation between outdoor and cleanroom	$r = 0.8742$ Number of XY Pairs 88	$r = 0.2479$ Number of XY Pairs 88	–
2nd year winter correlation between outdoor and cleanroom	$r = 0.7981$ Number of XY Pairs 44	$r = 0.4831$ Number of XY Pairs 44	–
2nd year spring correlation between outdoor and cleanroom	$r = 0.6790$ Number of XY Pairs 74	$r = 0.7002$ Number of XY Pairs 74	–
2nd year summer correlation between outdoor and cleanroom	$r = -0.1598$ Number of XY Pairs 83	$r = 0.2730$ Number of XY Pairs 83	–
Mid week July 2020 correlation between outdoor and cleanroom	$r = 0.7982$ Number of XY Pairs 166	$r = 0.4828$ Number of XY Pairs 166	$r = 0.9509$ Number of XY Pairs 166
Mid week January 2021 correlation between outdoor and cleanroom	$r = 0.6000$ Number of XY Pairs 164	$r = 0.7961$ Number of XY Pairs 164	$r = 0.9945$ Number of XY Pairs 164
Compare r from 1st year summer correlation between outdoor and cleanroom to r from 2nd year summer correlation between outdoor and cleanroom with the same dates	Number of XY Pairs 65 for both correlations 1st year $r = 0.6770$ 2nd year $r = 0.3766$	Number of XY Pairs 65 for both correlations 1st year $r = 0.5936$ 2nd year $r = 0.5050$	–
Compare r from July 2020 to r from January 2021 with the same dates	Number of XY Pairs 163 for both correlations Week July $r = 0.8004$ Week January $r = 0.5908$	Number of XY Pairs 163 for both correlations Week July $r = 0.4927$ Week January $r = 0.7937$	Number of XY Pairs 163 for both correlations Week July $r = 0.9512$ Week January $r = 0.9944$

For a typical winter week (Fig. 2B) there is no diurnal pattern, instead the outdoor temperature varies from 1.6 °C to -13.6 °C during the week, independent of time of day and is rather explained by the synoptic situation. The indoor temperature is stable and varies only 0.7 °C during the week and only slight patterns of causality can be seen when large outdoor changes are happening such as on the Thursday/Friday with a ten degree drop in outside temperature.

3.2. Humidity

Fig. 3 shows that the monthly mean outdoor %RH over a year is around 65–95% with the lowest numbers seen in late spring and early summer and the highest in autumn and winter. When single measurements are considered, values around 20 %RH are seen on an April day but during night-time the same day also values around 90 %RH were measured. The indoor mean values have a larger variability over the year from 75 %RH in July to 20% in the winter-time where single measurements as low as around 10% RH in January to March are seen.

Absolute humidity represents the number of water vapour molecules (in g water per m^3 of air). The relative humidity represents the amount of water vapour in relation to what is possible at a certain temperature.

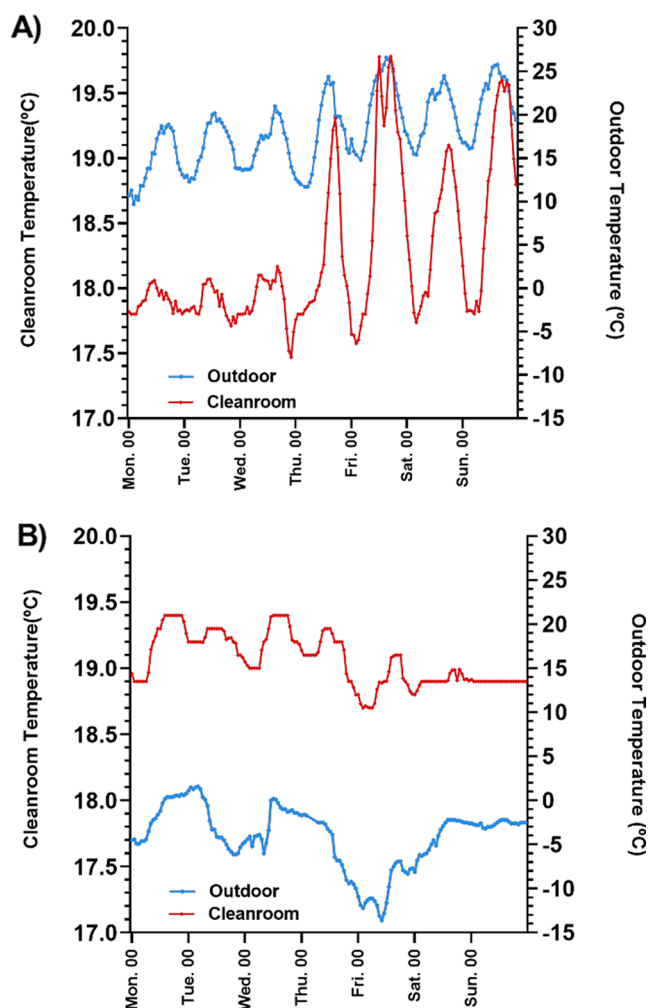


Fig. 2. Mean temperature per hour A) July 13th to 19th, 2020 and B) January 11th to 17th, 2021 for Outdoor (blue) and Indoor Cleanroom (red).

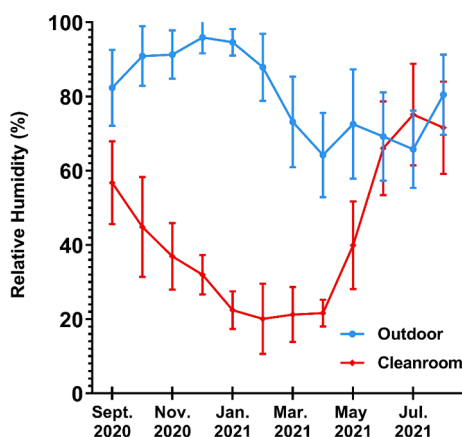


Fig. 3. Mean relative humidity per month of the 2nd year. Error bars are standard deviations of the mean.

Thus, the relative humidity is much more closely related to how human beings experience humidity. Data for a summer week is plotted using hourly resolution for indoor (Fig. 4A) and the typical outdoor summer diurnal temperature variation is seen (Fig. 4B) accompanied by a co-varying %RH depending on air being able to hold more water vapour at higher temperatures. The corresponding graphs for winter

(Fig. 4C and 4D) show a very low, (approximately 20 %RH) relative humidity in the cleanroom although the outdoor RH% is high (almost 100%).

The warmer the air is, the higher is the potential of absolute humidity level. Conversely, the cooler the air is, the less water vapour can be present. The absolute humidity variation pattern has an almost perfect correlation between indoor and outdoor for both the studied winter and summer weeks (Fig. 5). The dynamic pattern is similar and only a slightly lower humidity is seen indoors, and this could be attributed to losses in HVAC or because of the different measuring methods, outdoor being SMHI data from a site nearby hospital and indoor coming from the FMS system.

Temperature and humidity are also an important dyad when examining the cleanroom operator's feelings of comfort or discomfort. To assist with this process a humidex (humidity index) has been devised for cleanrooms that looks at the twin effects of heat and humidity [14] based on meteorological calculations [17]. The humidex is presented as a four-coloured matrix showing %RH and temperature combinations that give rise to recommendations of stopping cleanroom operations or reducing the time spent in cleanroom by operators. Looking at the data from Fig. 4 (A, C) and comparing to the humidex matrix, it is evident that only for occasional hours the conditions are outside of the norm and never sufficiently excessive to stop operations. When considering worker comfort regarding skin dryness and eye irritation the problems are likely more common as humidity is low but in a previous study it was found that work in cleanroom with prolonged wearing of occlusive gloves did not seem to negatively affect the skin with the conclusion that outdoor conditions may also not adversely affect the skin if proper air conditioning is in place [18].

As water is conductive, humidity promotes the flow of electricity and can be a very important factor when examining effects of electrostatic discharge (triboelectric effects). Electrostatic charge is created by the contact and separation of two materials e.g. when an operator is walking across the floor and generates static electricity as shoe soles contact and then separate from the floor surface. In order to prevent damage from electrostatic discharge (ESD), conductive elements such as carbon or metal-coated particles are included in the flooring material to give ESD floors electrical conductivity and create an electrical pathway from the walking surface to ground. Not only the construction and maintenance of ESD floors are important to prevent charge generation but also the type of footwear people will use. With the introduction of more sophisticated equipment in cleanrooms (syntheses modules, robots, pumps etc) there is an increased need for protection from static electricity discharge. Grounding oneself by touching the workbench, or using a special bracelet is standard practice in electronics manufacturing industry and it is important to use ESD protected shoes on specially ESD floors when cleanrooms are operated in low %RH conditions in order to dissipate charge and protect equipment. There are international guidelines available for cleanroom design and control such as the ANSI/ESD 20.20–2021 [19]. Using for example less than 30 %RH as a limit (where polymer spheres become highly charged [12]), this would for a cleanroom of 20 °C without extra humidification, correspond to an outdoor temperature of less than 3 °C (if the absolute humidity is equal in-/ outdoors and 90 %RH outside). These conditions were seen in this study for approximately 3 months in the winter. A rule of thumb may be that cleanrooms in countries where the outside temperature is around or below freezing point during wintertime should be constructed to prevent damages to sensitive electrical devices. This could be accomplished by installing an integrated humidification system including dryers for the summertime. Knowledge about outdoor climate may be a cost-saving tool when designing new cleanroom.

An increased availability of water in the air and further condensed on cold surfaces as is seen in the summer months on the other hand, increases the risk for microbiological growth, especially fungi could be challenging. Movement of people and the associated airflow would induce an influx of fungal spores from the outside. Relative humidity

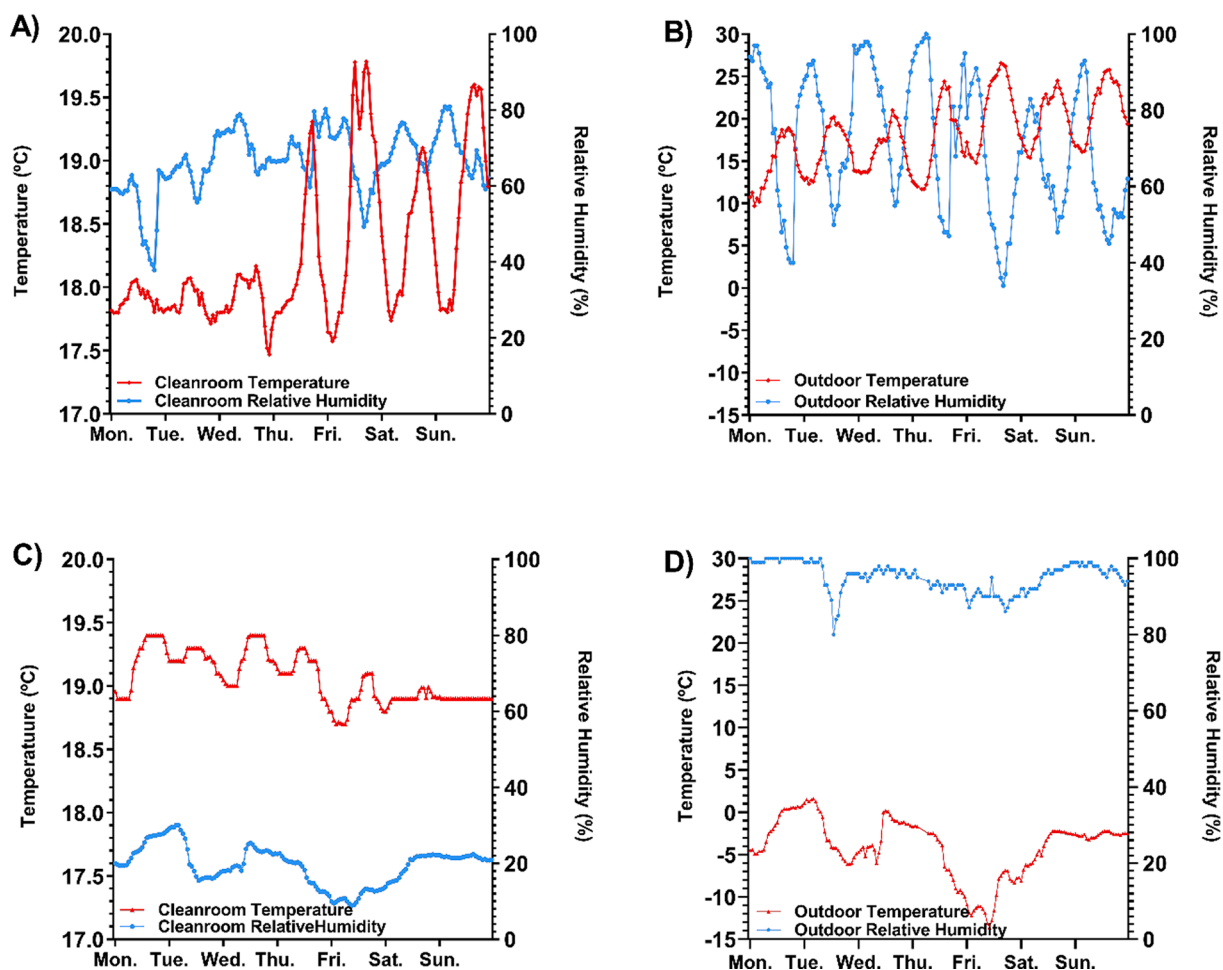


Fig. 4. Mean relative humidity (blue) and temperature (red) per hour in A) Cleanroom in Summer (July 13th-19th, 2020), B) Outdoor in Summer (July 13th-19th, 2020), C) Cleanroom in Winter (January 11th-17th, 2020), D) Outdoor in Winter (January 11th-17th, 2020).

and temperature usually affect the fungal density outdoors with the fungal concentrations being highest in the spring and summer seasons than in other seasons [20]. The typical bacterial flora are primarily those associated with human skin (Gram-positive cocci), although microorganisms from other sources such as the environment (Gram-positive rods) and water (Gram-negative rods) were also detected in a large study over a nine year period in cleanroom grade B (equivalent to ISO 14644, class 7 dynamic), grade C (ISO class 8 dynamic) and grade D (ISO class 9 dynamic) [7].

3.3. Air pressure and wind

The FMS system provided differential pressure data for every separate room of the cleanroom but only one preparation room was chosen as a representative for how the differential pressure values of the whole cleanroom is affected by the outdoor climate. The two first research questions we examined were:

Are there any significant trends over the four seasons regarding differential pressure indoors or other seasonal trends in outdoor air pressure? Outdoor air pressure varies between circa 995–1025 hPa whereas the differential pressure of the studied cleanroom (normalised to outdoor pressure) varies between circa 47.5–51.5 Pa over the two-year period. Based on these examinations, there were no seasonal trends found that were relevant for the cleanroom operations.

The next research question was: Will outdoor strong winds (high wind speed) affect the indoor differential pressure to such an extent to cause out-of-specification alarms (with risk of suspending cleanroom

operations)? The examination showed that every month there were between 0 and 20 differential pressure alarms (often as short as minutes) that could not be explained by other technical factors. The probability of differential pressure alarm being concurrent with strong outdoor winds (between 8 and 10.8 m/s, so called *fresh breeze*) was analysed, however, no significant correlations were found for the studied positive pressure preparation room nor the negative pressure anteroom/airlock (data not shown). It is likely that in the studied rooms, the amplitude of conceivable differential pressure change caused by outdoor effects is too small to cause differential pressure measurements outside the specified range. It would be interesting for further research to study the correlation between changing outdoor pressure gradient effects on the indoor environment such as differential pressure. This would be especially important in cleanrooms with narrow differential pressure ranges or equipped with MSC Class IIb cabinets that likely are more susceptible to outdoor effects due to the absence of internal cabinet exhaust fans.

3.4. General discussion

Cleanroom construction and operation are highly specialized activities and knowledge about the needs of the aseptic process and the requirements from authorities, guidelines and standards are very important as described by Kastango *et al.* in a paper two decades ago [21]. There is still a lack of evidence-based, scientific papers in this field of manufacturing process design.

Some weaknesses of this study were that we are limited to discuss the setting based on the design of the cleanroom in Uppsala. We are also

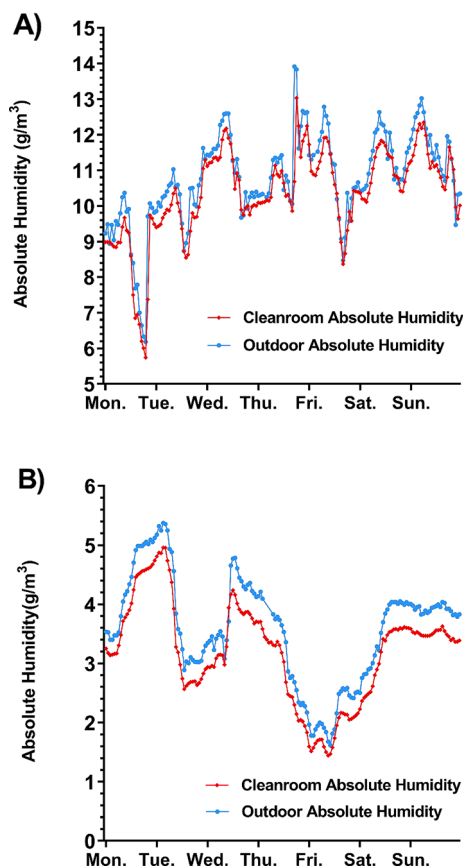


Fig. 5. Mean absolute humidity per hour in A) Summer (July 13th-19th, 2020) and B) Winter (January 11th-17th, 2020) for outdoor (blue) and indoor cleanroom (red).

limited to discuss the outdoor conditions based on the climate type in Uppsala over the four seasons. We have not been able to find an explanation for the missing one-minute resolution data from the FMS for the period of the first year. For an operation to be GMP compliant other means for retrospectively being able to show facility status is in place but data are not available with the necessary resolution to perform this study.

Strengths of the study are the availability of climate data with a high resolution and that Uppsala has a climate with four distinct seasons that reflect the climate of many places around the world where advanced pharmacy cleanrooms are operated.

4. Conclusions

This study highlights the outdoor effects on indoor cleanroom climate and shows the rate as well as amplitude of such changes. This understanding should be taken into account when designing new cleanrooms so that monitoring and controlling cleanroom temperature and humidity is in place to minimize particle release and to create conditions comfortable for the operator as well as safeguarding product quality. The information is further valuable in deviation assessments and quality assurance of cleanroom operations.

We would like to recommend hospital pharmacies with cleanrooms to start humidity monitoring and discussions with landlords or facility managements about the need for humidity control of cleanrooms and/or systems for mitigation of electrostatic discharge in climates with outdoor temperature in the wintertime below freezing point.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejpb.2022.06.003>.

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