Operating a Cleanroom: Risk Management and Control of Contamination

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This article is a reproduction of Chapter 18 of the Third Edition of *Cleanroom Technology, Fundamentals of Design, Testing and Operation* by Bill Whyte by kind permission of the author. The Third Edition of *Cleanroom Technology*, which was published independently by the author in 2023, was reviewed by the editor in CACR49. The main sections in the reproduced chapter explain how to identify sources and routes of contamination, how to carry out a risk assessment of sources of contamination with examples, how to control and reduce the risk of contamination, how to establish a monitoring programme, how to verify and reappraise the CCC (cleanroom contamination control) system, and what the basic requirements are for documentation and staff training. Editor

18.0 Introduction

The previous chapters of this book have described how a cleanroom is designed, constructed, and tested. The final eight chapters will deal with the operation of cleanrooms to minimise contamination during manufacturing. This chapter introduces the topic by describing the use of risk management to identify the main sources of contamination in a cleanroom, and manage and control the risk from these sources.

A number of risk management systems exist for managing risk in situations not connected with cleanrooms, but two are commonly applied to cleanrooms. These are the Hazard Analysis and Critical Control Point (HACCP) method [ref 1], and the Failure Mode and Effect Analysis (FMEA) method, preferably in its Failure Mode and Effect and Criticality Analysis (FMECA) format [ref 2]. Both the HACCP and FMECA methods need interpretation and modification for use in cleanrooms, and a method known as a Cleanroom Contamination Control (CCC) system is available [ref 3] and described in this chapter. Using this system, the risk from contamination in a cleanroom can be managed by the following steps.

1. Identify the sources of contamination in a cleanroom. Construct a risk diagram, or diagrams, to identify potential sources and their routes of transfer to product.
2. Assess the importance of the sources of contamination to determine the level of hazard they present.
3. Identify methods that can be used to control the hazards and, where appropriate, introduce or improve these methods.
4. Establish a monitoring schedule to monitor hazards or control methods. Establish control levels of contamination, such as 'alert' and 'action'.
5. Verify, on a continuing basis, that the risk management system is effective.
6. Establish and maintain appropriate documentation.
7. Train the staff.

18.1 Step 1: Identify sources and routes of contamination

When operating a cleanroom, it is necessary to minimise the amount of contamination of products or processes. This is carried out through knowledge of the sources of contamination, their methods of transfer of contamination to the product or process, and how the transfer can be controlled. Assembling a risk diagram will assist this process by providing an understanding of what sources of contamination are present in the cleanroom, and the routes by which their contamination is transferred.

The transfer of contamination around the cleanroom can be very complicated as, theoretically, everything in the cleanroom can be contaminated by everything else. However, in practice, it should only be necessary to consider the major sources and direct routes of transfer of contamination. Two risk diagrams are shown in Figure 18.1 and Figure 18.2 that can be applied to a typical production cleanroom where a separative air device, such as cabinet, isolator etc. is used to protect product from contamination. Figure 18.1 deals with airborne sources and Figure 18.2 with surfaces and liquids. The primary sources are given in the red boxes, and secondary sources that are contaminated from the primary sources are given in blue boxes. Routes of transfer of contamination are shown by arrows, and their control methods are given in white boxes.

The greatest risk to product or process is likely to occur at 'critical locations', where product or process is exposed to contamination. At that location, it may be desirable to carry out a more detailed assessment of the process, especially if it is carried out within a separative clean air device, and produce a risk diagram for that specific location. It may also be necessary to construct several diagrams where the process is complex, or where it is necessary to control different types of contaminants, e.g. particles, MCPs, and chemical contamination.

18.1.1 Risk diagram of airborne contamination

Figure 18.1 is a risk diagram that shows possible sources of airborne microbial or particle contamination, the route of transfer to the product, and how this transfer can be controlled. It can be seen that the primary sources of airborne contamination are from personnel, machinery and air supply, and this contamination is often transferred to secondary sources, and then to product.

The airborne sources of contamination and control methods that are common to many cleanrooms are shown in the simple risk diagram in Figure 18.1.

The sources and control methods are as follows:

- The air supplied to a cleanroom or clean air device can be a source of contamination if it is not adequately filtered by high efficiency air filters. Filters with the correct removal efficiency should be provided, and filter installations monitored for leaks.

- Areas adjacent to the cleanroom. The material airlock(s), clothing change area(s), and outside corridor(s), will be contaminated by activities going on in these areas, and a suitable supply of filtered air is required to minimise their airborne contamination. Also, air should not move from less-clean areas to cleaner areas, and pressure differences are used to ensure the correct air movement.
- Air is a major source of contamination of exposed product, and this contamination is minimised by the ventilation of a cleanroom and, where considered necessary, by the provision of a separative clean air device. To control contamination in non-UDAF cleanrooms, a suitable air volume supply rate is required. In UDAF cleanrooms, and separative clean air devices that use unidirectional airflow, it is the air velocity and direction that should be correct.
- Personnel will generate and disperse contamination into the air, and appropriate cleanroom disciplines, such as avoiding vigorous movements and inappropriate placement of personnel, will minimise the hazard. Cleanroom garments are required to reduce airborne dispersion of contamination.
- Machines and equipment emit airborne contamination. A suitable supply of filtered air to the cleanroom is required to dilute and remove this contamination, or a localised air extraction, or negative-pressure separative clean air device.

18.1.2 Risk diagram – contact routes and liquid

Contact routes allow contamination on surfaces in cleanrooms to be transferred to product or process. These surfaces can be gloves and clothes of personnel, as well as various other items found in a cleanroom such as machines, instruments, containers, packaging, raw materials, etc. An example is personnel touching a contaminated surface and this contamination being transferred to their gloves, which is then transferred to product when it is touched by the glove. Another example is when contaminated packaging touches product. Common sources of surfaces contamination and their control methods are shown in the risk diagram in Figure 18.2. Also shown in Figure 18.2 is the possibility of liquid contamination.

The sources of contamination and their control methods that are shown in the risk diagram in Figure 18.2 are as follows:

- Raw materials, components, containers, packaging etc. that are brought into a cleanroom. These items should be cleaned, and in the case of microbial contamination, sterilised or disinfected.
- Constructional materials such as floor, wall, and ceiling, as well as various furniture and other surfaces can be sources of contamination. These surfaces should be cleaned and, in the case of microbial contamination, disinfected (or sterilised where required) to minimise the amount of surface contamination that is transferred to product.
- Personnel will wear cleanroom clothing, gloves, and masks, and these surfaces may be contaminated by the people who wear them, or by contact with contaminated surfaces in the cleanroom. Replacement of these items at regular intervals by freshly processed or disposable garments, masks and gloves, will reduce the transfer of this type of contamination. Contact transfer should be minimised.
- Contamination can occur from liquids used in cleanrooms, and they should be prepared in a way so they contain a minimum amount of contamination, and then filtered. Liquid sources are included in Figure 18.2 but will not be considered any further in this chapter.

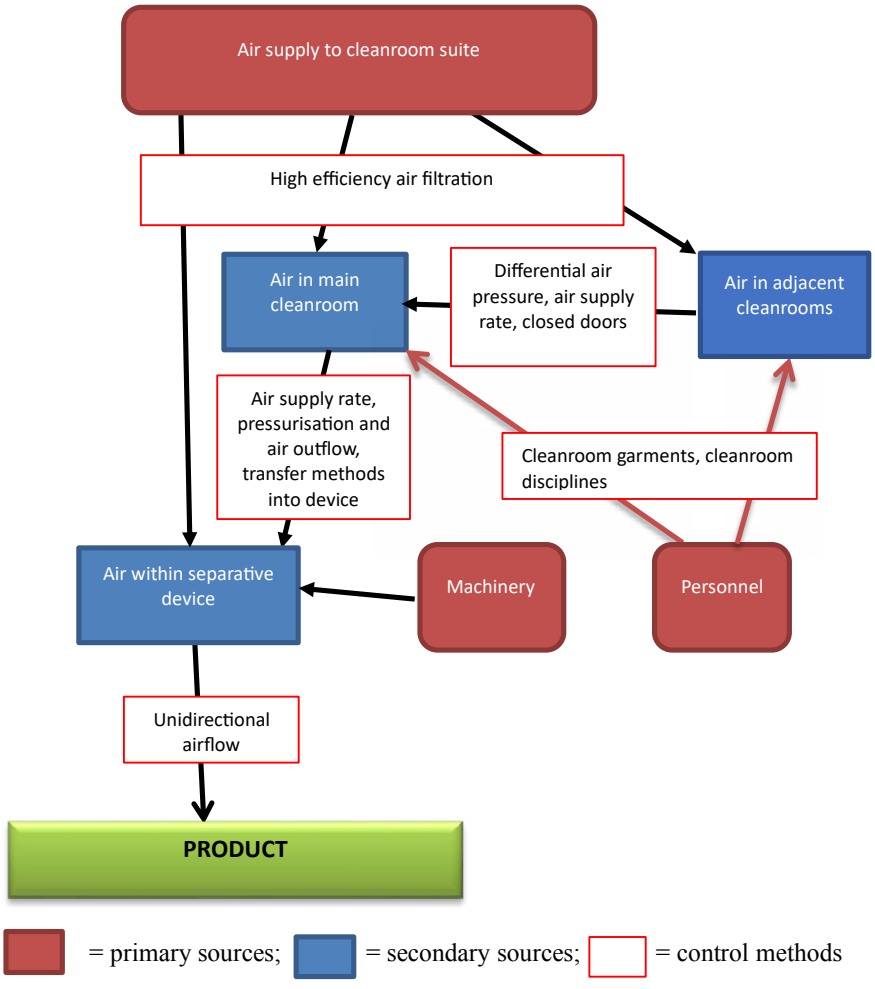

Figure 18.1: Airborne risk diagram

18.2 Step 2: Risk assessment of sources of contamination

When all potential sources of contamination in the cleanroom and their routes of transfer have been identified, a risk assessment is carried out. Risk assessment is also called hazard or risk analysis, and is used in cleanrooms to ascertain the potential importance of the risk that sources have to contaminate product or process.

Risk assessment can be a difficult step to carry out, especially when the cleanroom is new and information is missing. However, lack of information should not prevent a preliminary risk assessment being made, as a later stage (Step 5) is used to reappraise the conclusions of the risk assessment, and improvements can be made.

18.2.1 What does 'risk' mean?

In its universal application, risk is considered to be a combination of the criticality (which is also known as severity or importance) of harm, and the frequency of occurrence of this harm. This can be expressed mathematically as follows:

Equation 18.1

Risk = criticality of occurrence x frequency of occurrence

This concept is shown graphically in Figure 18.3, where it can be seen that as the 'criticality' and 'frequency' increase, either separately or in combination, the risk increases.

In the risk assessment method known as Risk Priority Number (RPN), 'detectability' is added as a third variable to Equation 18.1. Detectability is the probability of detection of the risk, and is useful in situations where it can be identified and the degree of detectability is known. However, in cleanrooms, this information is normally unavailable, or considered to be constant at 100%, and it can be ignored in the risk assessment.

In cleanrooms, 'criticality' of contamination can be considered to be a combination of three risk factors, namely,

A. the concentration of contamination on a surface, air, or liquid source,

B. the proportion of contamination that is transferred from a source and deposited onto, or into, a product, and,

C. the surface area of product that is contaminated by the transfer of contamination.

The 'frequency' of contamination (D) can be considered to be the number of surface contacts, or the length of time that product or process is exposed to airborne contamination. Using this approach, a risk model that combines these four risk factors is given in Equation 18.2 [ref 4].

Equation 18.2

Risk from contamination (risk rating) = A x B x C x D

Where,

A = concentration of particles or microbial contamination on, or in, a source;

B = proportion of contamination that is transferred from source of contamination to product i.e. transfer coefficient;

C = surface area of product that is exposed or contacted;

D = frequency of transfer of contamination.

18.2.2 Risk descriptors and scoring methods

The importance of risk of contamination to product from each source of contamination in a cleanroom can be assessed by inserting values of the risk factors into Equation 18.2 and calculating the risk rating. However, actual numerical values of the risk factors are often unavailable, and 'descriptors' are used. Descriptors are surrogates for the actual values, and words such as 'high', 'medium' and 'low' are assigned to each risk factor, and given risk scores such as 3, 2 and 1, respectively. The scores of each risk factor are then multiplied together in the manner shown in Equation 18.2 to obtain the risk rating of each source of contamination.

The best types of descriptors are those that describe the actual risk factors in Equation 18.2, but sometimes it is necessary to use a descriptor that is related to the risk factor. For example, the number of people in a cleanroom

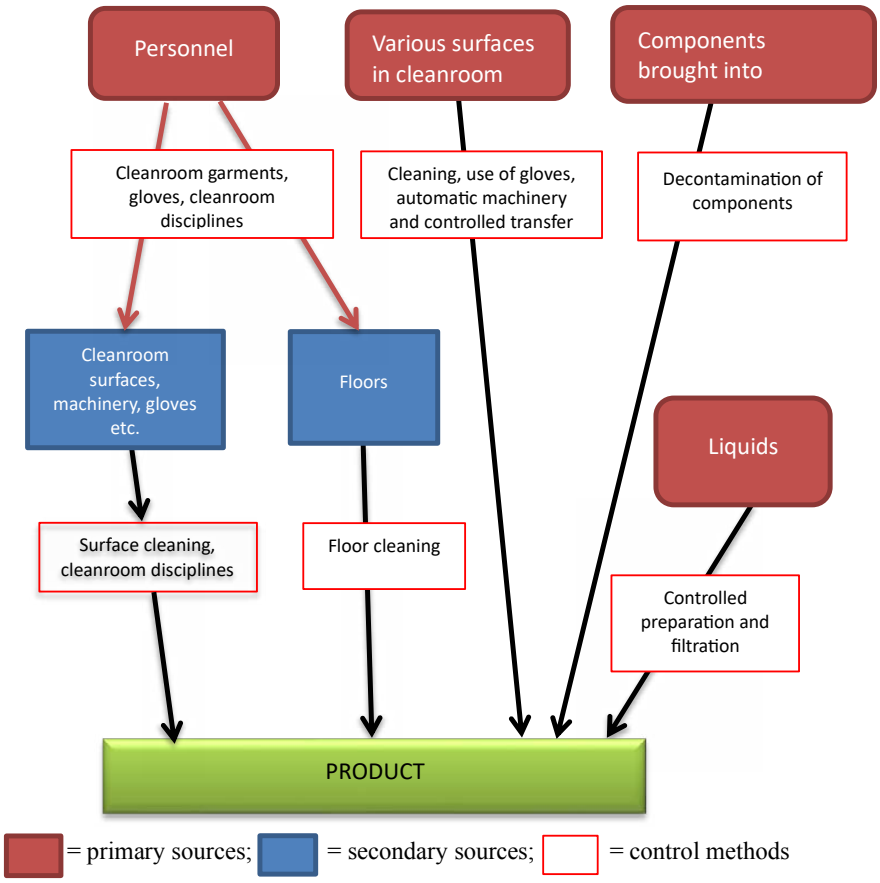

Figure 18.2: Surface contact risk diagram

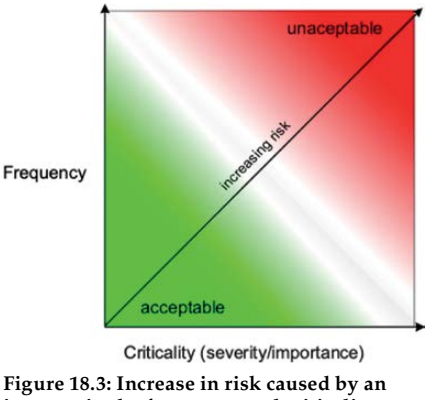

Figure 18.3: Increase in risk caused by an increase in the frequency and criticality

and type of ventilation, can be used as descriptors of the amount of airborne contamination that is likely to be found in the room.

To obtain the greatest accuracy, descriptors and their scores should span the whole range of risk, and, the risk scores should be closely related to the meaning of the words used as descriptors. A variety of scoring systems can be used in a risk assessment, but the system shown in Table 18.1 has been found to be useful in cleanrooms.

Table 18.1 Example of a risk scoring system

Degree of risk	Score
Extremely small	0.001
Very small	0.01
Small	0.1
Medium	0.5
Large	0.7
Very large	0.9
Extremely large	1

The allocation of risk scores is subjective, and it is best that the assessment is not carried out by one person. A Risk Assessment Team can be assembled to decide on the best allocation of descriptors and risk scores.

18.2.3 Examples of a risk assessment obtained by risk descriptors

In normal situations, all potential sources of contamination in a cleanroom should be assessed for risk. However, only two examples are considered here. One is an example of an airborne source, and the other is a surface source.

Example 1: Assessment of risk of contamination of product from the air in a non-UDAF cleanroom

Firstly, risk factor A, which is the concentration of particles (or where relevant, microbes) in the cleanroom air, should be allocated a risk score. In comparison to other airborne concentrations within the cleanroom suite, and in similar cleanrooms, the airborne concentration is considered to be 'medium' and, using the scoring scheme given in Table 18.1, a risk score of 0.5 is allocated.

In a non-UDAF cleanroom, the air will mix throughout the cleanroom, and the concentration at the product will be similar to the rest of the room. Therefore, the score of risk factor B, which is the transfer coefficient, would be 'large' and allocated a score of 0.7.

Risk factor C is the surface area of the product exposed to airborne contamination. When compared to other relevant surface areas in the cleanroom and products produced in similar cleanrooms, the exposed area is considered to be 'small' and given a risk score of 0.1.

As the product is continuously exposed to airborne contamination, a risk score of 1 is allocated to the frequency risk factor D. However, if the product is not continually exposed, a smaller risk score would be used.

The risk rating of the air in the non-UDAF cleanroom is obtained by multiplying the risk scores together, and is 0.5 x 0.7 x 0.1 x 1 = 0.035.

Example 2: Assessment of contamination risk associated with touching the surface of cleanroom walls

Firstly, risk factor A, which is the concentration of contamination on the surface of the cleanroom walls, should be assessed. In comparison to other surfaces in the cleanroom, the concentration of particles (and, where relevant, microbes) on the wall is considered to be 'small', and a risk score of 0.1 is allocated.

Particles and microbes on the wall surface can be transferred if a person touches the wall, and then product. The proportion of microbes that is transferred from a contaminated surface when it is touched by a gloved hand i.e. its transfer coefficient, has been shown to be about 0.1 [ref 5]. The transfer of surface contamination is a two-part process, i.e. wall-to-glove and glove-to-product, and the overall risk score will be 0.1 x 0.1 = 0.01. Alternatively, the descriptor approach can be used, and the likelihood of transfer considered to be 'very small' and a risk score of 0.01 allocated to risk factor B.

Risk factor C is the surface area of the product that is touched by a finger of a glove. In comparison to other contaminated surfaces in the cleanroom, it is considered 'medium' and allocated a risk score of 0.5.

Cleanroom disciplines strongly prohibit personnel from touching walls, and the frequency of this action is considered to be 'extremely small', and risk factor D is allocated a score of 0.001.

The risk rating of a wall surface is obtained by multiplying together the scores from the four risk factors to obtain a risk rating of 0.1 x 0.01 x 0.5 x 0.001 = 5 x 10-6. This is a low-risk rating, and other surfaces in the cleanroom are likely to have higher risk ratings, mainly because of the frequency of contact will be higher.

It will be useful to assemble a table that contains all possible sources of contamination, along with their risk factor scores and risk ratings. A possible layout is shown in Table 18.2. When all risk ratings from the various sources in the cleanroom have been obtained, it is possible to see where the highest risk of contamination exists, and where the control of contamination needs the most attention.

It should be noted that when using the descriptor method, care should be taken when comparing the risk rating from different types of transfer i.e. air, surfaces and liquids. As the risk scoring method is likely to be different, the risk ratings should not be compared.

18.2.4 Use of actual values of risk factors in a numerical risk assessment method

The information given in the previous section has explained how the risk from sources of contamination in a cleanroom can be calculated by use of risk descriptors. However, if information is available about the actual numerical values of the risk factors, or accurate estimates can be made, then a more accurate risk assessment can be achieved by use of actual values, although much more time and effort is required. This enhanced approach calculates the actual contamination rate

Table 18.2 Scoring of risk factors to obtain risk rating of sources of contamination in non-UDAF cleanroom

Source	Risk factor scores				Risk rating
	A	B	C	D	
Air in non-UDAF cleanroom	0.5	0.7	0.1	1	0.035
Surface of walls	0.1	0.1	0.5	0.001	5 x 10-6
Other sources to be assessed and added to the table	-	-	-	-	-

that is expected from the various sources of contamination in a cleanroom. Further information about this numerical method is given in [refs 6, 7, 8].

18.3 Step 3: Control and reduction of risk of contamination

When all of the risk ratings are obtained from the potential sources of contamination in a cleanroom, they can be used to decide what sources of contamination, and their transfer methods, require attention.

The risk of contamination from a source is controlled by one or more of the risk factors given in Equation 18.2, namely, (a) the concentration of the contaminant at, or on, the source (b) the transfer of contaminant to product, (c) the surface area of product exposed to contamination, and (d) the time of exposure of airborne contamination, or frequency of surface contact. The risk of contamination can be controlled and reduced by lowering the value of these variables. The practical means of how to obtain these reductions will require to be investigated and implemented. The possibilities are not discussed in this chapter but described throughout this book.

18.4 Step 4: Establishing a monitoring programme

The fourth step of the CCC system is to establish a programme to monitor a cleanroom and ensure that contamination is controlled over the cleanroom's lifetime.

Monitoring will normally be carried out by measuring the concentration of airborne particles and, where relevant, other contaminants such as MCPs. In addition, functional properties of the cleanroom that control contamination, such as air volume supply rates, pressure differentials etc. should be monitored. Information on monitoring a cleanroom is given in Chapter 9, and this chapter should be consulted. Using the information gathered in the risk assessment, the sources and their control methods that need attention, are obtained, and this assessment may suggest the need to monitor additional items such as: important surfaces, gloves, clothing, raw materials and components, containers and packaging.

The CCC system requires that monitoring should be carried out by means of valid sampling methods. Therefore, the sampling methods should be fit for purpose, and should use sampling instruments that have known and high collection efficiencies, and are regularly calibrated.

It is necessary to show that the results from monitoring are below the levels required to control contamination in the cleanroom. A common approach is to set 'action' and 'alert' control levels, and this approach has been discussed in Chapter 9.

18.5 Step 5: verification and reappraisal of the CCC system

The CCC system requires regular verification to ensure that the risk management system is effective. Testing manufactured product for functionality and reliability can be carried out to indicate that the contamination rate of the product is satisfactory. When this is not possible, or in addition, the amount of contamination on, or within, product can be measured and used as an indicator of the control of contamination.

In addition to monitoring the manufactured product, the cleanroom environment should be monitored to ensure that the functional properties of the cleanroom that control contamination, such as air supply rates, air filter integrity etc. are as required. The performance of the cleanroom should also be shown to be acceptable, by measurement of the concentration of contaminants, such as particles and microbes. Use of 'alert' and 'action' control levels, should be used to decide if the functional properties and performance of the cleanroom remain within its required performance.

The choice of the risk assessment model and risk scoring method should be considered to confirm that the risk assessment method produces useful information, or if improvements need to be made. The risk ratings assigned to sources of contamination should be reviewed to see if they need modification. Any new information that is available since the previous verification e.g. new control methods, or additional test results, should be included in this reassessment. A change in the risk ratings may require an increase or relaxation of the control of sources of contamination. Monitoring methods may also need adjustment, such as the number and location of sampling points, and frequency of sampling.

18.6 Step 6: Documentation

To be effective, the CCC system should have an effective documentation system. A report on the verification and reappraisal of the CCC system should be produced, perhaps yearly, and contain information of the type discussed in the previous Step 4. An overall analysis of the results from monitoring should also be provided. Standard Operational Practices (SOPs) of the sampling methods used during monitoring, and the methods used to control contamination, should be documented, and kept up-to-date.

Regular reports can be issued to interested people, perhaps monthly or quarterly, that contain monitoring results and any deviations from the expected results. When 'action' levels are exceeded, they should be reported, and actions taken to correct the deviations should be described. 'Alert' levels may also be reported, particularly if they are repeated at a greater than expected frequency, or are unusual, and if any actions have been taken.

18.7 Step 7: Staff training

Training in the principles of risk management is required for the Risk Assessment Team. However, all efforts to control contamination through risk management will fail if personnel working in the cleanroom are not properly trained. They should understand how a cleanroom works and how they should behave to minimise contamination. This training should be completed prior to their first entry into a cleanroom, and at defined intervals thereafter. Suitable items to be included in the training course can be selected from this information contained in this book.

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Bill Whyte has published over 140 journal articles on the design of cleanrooms and operating theatres, and the control of the transmission of contamination within them. He has written four books titled *Cleanroom Technology, Third Edition, 2023* (reviewed in CACR49 page 25); *Advances in Cleanroom Technology, 2018; Cleanroom Testing and Monitoring, 2021* (reviewed in CACR46 page 22) *and Basic Cleanroom Technology* (reviewed in this issue on page 29).

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