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Original Article

Operator stress factors and cell contamination risks in cell processing facilities: An online survey-based analysis

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ABSTRACT

The field of regenerative medicine is rapidly evolving, with an increasing number of approved cell preparations. However, cell processing facilities (CPFs) still heavily rely on manual operations by cell processing operators (CPOs). The intricate nature of cell culture and stringent sterility requirements impose a considerable psychological burden on CPOs, particularly the risk of cell contamination. This study delves into the psychological aspects experienced by CPOs in relation to the risk of contamination during cell culture. An online survey was conducted across 47 sites to investigate concerns regarding contamination and the strategies implemented to mitigate contamination risk in cell processing facilities. The survey findings revealed that 72 % of operators expressed concern about contamination, with 18 % reporting direct experiences of contamination. This indicates that the perceived contamination risk in CPFs is higher than the actual reported incidents. Furthermore, this study examines operational practices, such as material handling, and the utilization of biological safety cabinets (BSCs). The results highlight variations in BSC utilization and material handling practices, underscoring potential operational challenges. Implementing risk assessments and leveraging evidence-based data at each site could help address these challenges and alleviate the psychological strain on CPOs. This, in turn, would enhance the quality of cell therapy products and improve the well-being of CPOs.

1. Introduction

Significant advancements in the mechanization and automation of cell processing for regenerative therapy have rapidly evolved in recent years. Despite these advancements, the operation of cell processing facilities (CPFs), including cell processing, still heavily relies on the manual work of skilled operators [1]. These operators ensure the sterility and quality of cell products, a responsibility that requires precise execution of complex procedures and strict adherence to sterility protocols [2–5]. The demanding nature of CPF operations places a considerable amount of psychological stress on operators. Previous surveys have identified various sources of stress unique to CPF work, such as the need for high skill levels, gowning procedures, and adherence to cleanroom conditions [1]. This stress can lead to reduced work efficiency, increased errors, and potential health issues [6,7]. The psychological stress experienced by operators poses a significant challenge in managing cell products, where safety is of utmost importance. Consequently, the optimal means of maximizing operator performance is to eliminate stressors.

This study focuses on contamination risks in cell culture—a critical source of operational stress that directly impacts product safety—highlighted as a high-stress factor in our previous survey.

Abbreviations: BSC, Biological safety cabinet; CPF, Cell processing facility; CPO, Cell processing operator; JSRM, The Japanese Society for Regenerative Medicine; JSTMCT, The Japan Society of Transfusion Medicine and Cell Therapy; JTCA, The Japanese Tissue Culture Association; J-CPO, JSRM cell processing operator; J-ACPO, JSRM advanced cell processing operator; LLM, Large language model; MA, Multiple answer; N/A, Not applicable; No, Number; SOP, Standard operating procedure.

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Contamination within cell products, which cannot be sterilized post-processing, presents a constant challenge for operators and significantly contributes to their stress levels. Contamination events in cell culture involve the unintentional introduction of microorganisms, such as bacteria, viruses, or extraneous contamination. These contaminants can severely compromise cell growth, experimental outcomes, and product viability, frequently necessitating the disposal of affected products [8–12]. For autologous cell products, in particular, the inability to collect additional material may result in the termination of treatment options and loss of critical therapeutic opportunities. These losses are unique to cell production and impose a considerable psychological burden on operators. Therefore, analyzing contamination from a psychological perspective can help identify stress-inducing factors and potential mitigation strategies.

This study aims to identify stress issues faced by operators during the production of cell products, focusing on contamination-related stress. An online survey was utilized to collect data on operators' concerns and experiences of contamination, as well as operational practices related to contamination management within CPFs. Discrepancies between operators' contamination-related anxieties and actual contamination occurrences were analyzed, along with operational factors, such as material handling procedures and the utilization of biological safety cabinets (BSCs) within the CPF. This study aims to identify specific sources of stress among operators by analyzing contamination risks from a psychological perspective. The results of this study are anticipated to aid in the development of improved work environments, enhanced risk management protocols, and enhanced training programs for CPF operators. Ultimately, this study aims to support initiatives to retain a skilled workforce and enhance the safety and efficiency of manufacturing processes for cell products.

2. Materials and methods

2.1. Survey questionnaire

The authors developed an online questionnaire to explore the characteristics of participants, their concerns, and experiences regarding cell contamination in cell processing, material handling, and the operation of BSCs.

2.2. Recruitment

Between February and May 2023, a survey questionnaire was distributed to participants at 47 CPFs in Japan, including universities, clinics, and pharmaceutical companies. Participants completed the online survey using Microsoft Forms.

2.3. Qualitative analysis of open-ended responses

The qualitative analysis of the open-ended responses was conducted using ChatGPT 4.0 to consolidate all responses to each question and distill them into five key points. The specific responses are listed in the Results section. The prompts used for Chat GPT 4.0 were as follows:

The questionnaire was administered and responses were collected. The responses were categorized into questions and answers. Please provide a five-point summary of the claims made from multiple answers. Please also indicate the number of responses covered by each summary, giving a percentage. Each summary should include the number of the answer to which it refers.

As is a characteristic of generative artificial intelligence (AI), the responses obtained from the prompts yielded different results each time. Therefore, the most common responses from six different instances were selected, reviewed, and summarized by the author. These responses align with Elsevier's AI policy for authors and *Regenerative therapy* guidelines for the utilization of generative AI. Notably, these guidelines apply to the writing process and do not restrict the use of AI tools for data analysis and insights generation in research. Therefore, the utilization of AI in this study complies with these guidelines.

3. Results

3.1. Attributes of participants

A total of 125 participants from 47 CPFs participated in the study. The gender distribution was 51 % male and 49 % female (Fig. 1(a)). Most participants were in their 30s (36 %), followed by those in their 40s (27 %), 20s or younger (26 %), 50s (9 %), and 60s or older (2 %) (Fig. 1(b)). In terms of years of experience working in CPFs, 34 % had 3–5 years, 24 % had 1–2 years, 20 % had 6–9 years, 15 % had over 10 years, and 7 % had less than 1 year of experience (Fig. 1(c)). Among the participants, 89 worked in the manufacturing sector (Fig. 1(d)). Participants were affiliated with various organizations, including pharmaceutical companies (31), venture companies (22), CDMO companies (48), and academic institutions, such as research centers and universities (24) (Fig. 1(e)). Organizational sizes varied, with 33 % working in institutions with 1–10 employees, 28 % in those with 11–20 employees, and 28 % in those with 51 or more employees (Fig. 1(f)). Regarding qualifications, 96 participants did not provide information, whereas 15 were J-CPO qualified and 7 were J-ACPO qualified (Fig. 1(g)).

3.2. Concerns and experiences with cell contamination

Concerning cell contamination, 72 % of the participants expressed concern, whereas 28 % were not concerned (Fig. 2(a)). In terms of personal experiences with cell contamination, 18 % reported encountering it, whereas 82 % had not (Fig. 2(b)). Furthermore, the difference in the proportion of Yes responses for beginners and advanced was insignificant (Supplementary Fig. 1). Among those who had experienced cell contamination, 12 participants attributed it to raw materials (cells or tissues), 11 to materials, 5 to a person, and none selected equipment as the cause (Fig. 2(c)).

A total of 123 responses were collected regarding contamination concerns, with 46 out of 125 participants providing responses to the free-text sections. These responses were analyzed and summarized into five categories using ChatGPT 4.0. The results indicated that uncertainties regarding materials utilized and environmental factors accounted for 60 % of responses, the risk of contamination from open handling accounted for 50 %, concerns regarding contamination from physical contact during operation accounted for 47 %, concerns regarding inadequate cleaning and disinfection procedures accounted for 40 %, and lack of self-awareness owing to oversight or complacency accounted for 17 % (Table 1). The percentages may exceed 100 % owing to responses being categorized under multiple themes.

3.3. Operation of the CPF in relation to contamination control

The study also delved into the operations involved in contamination control, focusing on material handling and the use of BSCs. All participants reported manually disinfecting and wiping materials. Additionally, 104 participants removed the outer packaging of multiple packages, and 28 used equipment, such as a decontamination pass-box (Fig. 3(a)). The methods of introducing clean paper

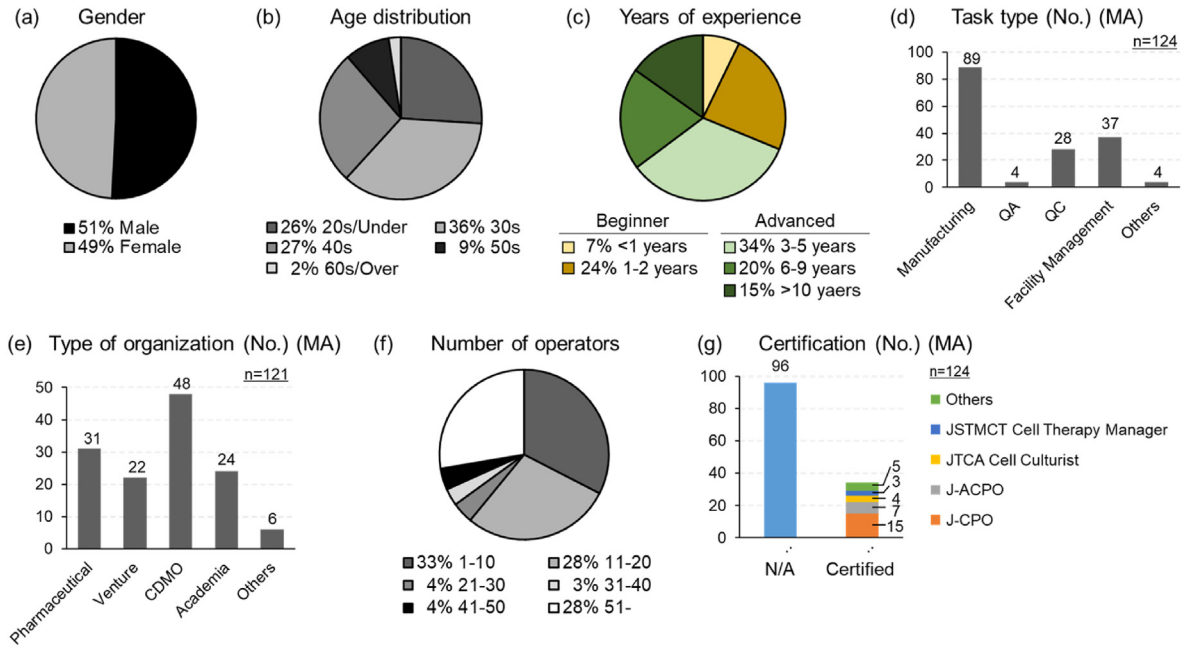

Fig. 1. Attributes of participants. (a) Gender. (b) Age distribution. (c) Years of experience in CPFs. (d) Task type (No.) (MA). (e) Type of organization (No.) (MA). (f) Number of operators in CPFs. (g) Certification (No.) (MA).

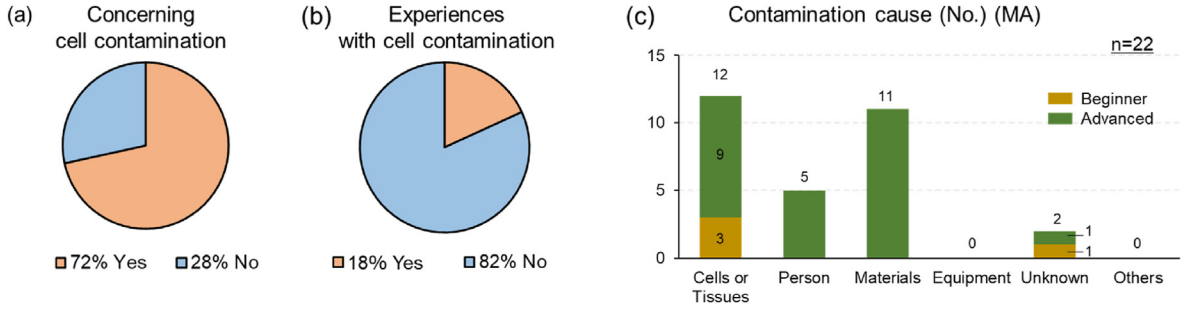

Fig. 2. Concerns and experiences with cell contamination in CPFs. (a) Concerning cell contamination. (b) Experiences with cell contamination. (c) Contamination cause (No.) (MA).

Table 1
Situations and reasons for concern regarding contamination (open-ended responses).

Classifications	Summary	Rate (%)
Uncertainty regarding materials utilization and environmental uncertainties	The possibility that materials may not be adequately wiped or disinfected, or that materials utilized may not be completely sterile. Concerns regarding contamination risks in the work environment, particularly in safety cabinets and isolators.	60
Risk of contamination from open handling	Open system operations, particularly working outside safety cabinets or temporary open operations. Concerns related to airflow disturbances, external contaminant ingress, and operational procedures.	50
Concerns regarding contamination from physical contact during operation	Potential for contamination from physical contact, such as opening flask lids, handling centrifuge tubes, and handling tissue on Petri dishes, as well as the opening and closing of tubes and dishes.	47
Concerns regarding inadequate cleaning and disinfection procedures	Questions about the sufficiency of ethanol wipes and other methods of disinfecting objects and equipment. Concerns about the risk of contamination, particularly on uneven surfaces that are difficult to wipe clean, and the risk of contamination from wipe remnants.	40
Lack of self-awareness stemming from oversight or complacency	Operational laxity and complacency that “this is sufficient.” lack of experience or training.	17

Number of respondents: 46; total number of responses: 123; average response length: 51.0 characters.
ChatGPT 4.0 was utilized to aggregate the open-ended responses obtained from respondents into five summaries. The percentage of each summary among all responses was calculated.

and sterile water varied—79 participants wiped the paper with ethanol before introducing it; 36 participants autoclaved it; and two participants did not introduce it at all (Fig. 3(b)). Clean paper was primarily used for record-keeping purposes, as reported by 118 participants (Fig. 3(c)). In terms of sterile water, 82 % of participants introduced it into the CPF, whereas 18 % did not (Fig. 3(d)). Among

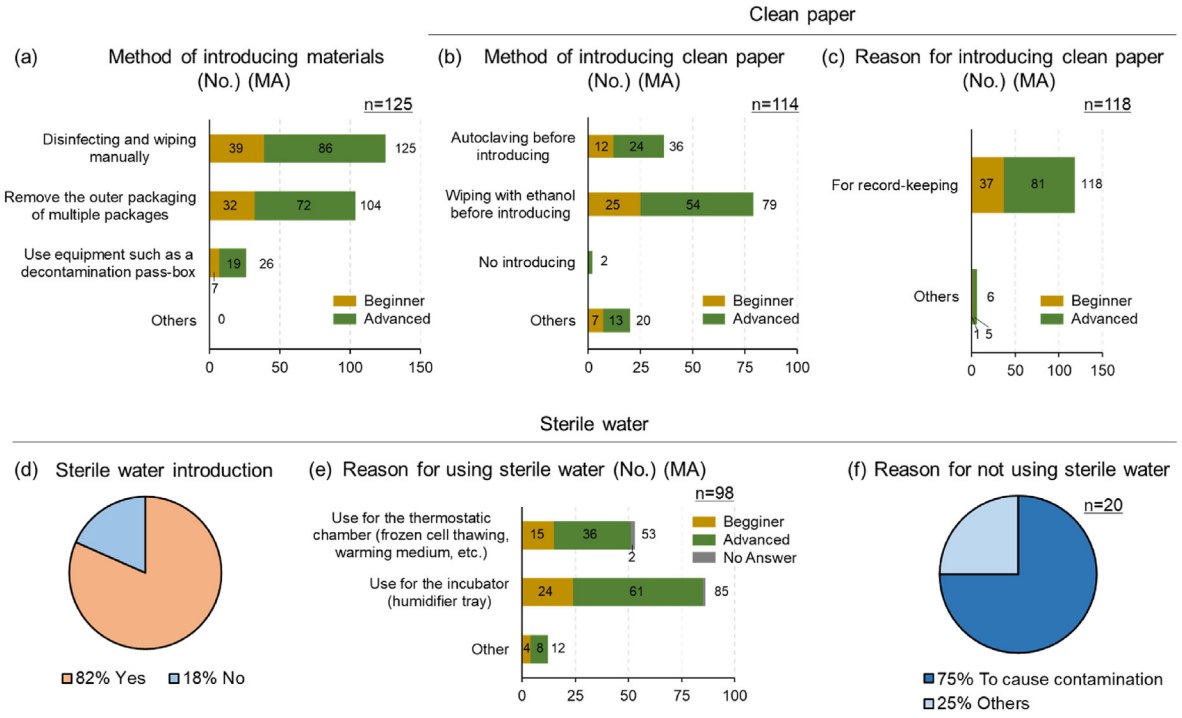

Fig. 3. Introducing materials in CPFs. (a) Method of introducing materials (No.) (MA). (b) Method of introducing clean paper (No.) (MA). (c) Reason for introducing clean paper (No.) (MA). (d) Sterile water introduction. (e) Reason for using sterile water (No.) (MA). (f) Reason for not using sterile water.

those who utilized sterile water, 86 individuals used it for the incubator (humidifier tray) and 51 for the thermostatic chamber (Fig. 3(e)). Conversely, 75 % of those who did not use sterile water cited the risk of contamination as the primary reason (Fig. 3(f)). These results regarding the use of sterile water did not reveal any significant differences in the response percentages when comparing between beginner and advanced (Supplementary Fig. 2).

The utilization of the BSC fan and UV lights, as well as the rationale behind their use, were examined. A total of 68 % of participants always turned the BSC fan ON, whereas 27 % turned it ON during use and off after use (Fig. 4(a)). Among those who consistently kept the BSC fan ON, 70 % did so to prevent airflow disturbance/contamination, and 29 % did so because it was outlined in the SOPs (Fig. 4(b)). For those who reported turning the BSC fan ON during use and OFF after use, 63 % did so because allowing it ON continuously was not necessary, 22 % did so because it was outlined in the SOPs, and 9 % did so to prevent contamination (Fig. 4(c)). Regarding UV light usage in BSCs, 44 % did not utilize them, 37 % turned them ON for a specified time and then turned them OFF, and 16 % left them ON continuously (Fig. 4(d)). Seventy-five participants provided reasons for using UV lights, 71 % to achieve a sterilizing effect, and 25 % because it was outlined in the SOPs (Fig. 4(e)). Forty-seven participants provided a reason for not using UV lights, and 87 % mentioned that the BSC fan was consistently ON (Fig. 4(f)). These results on the use of fans and UV lights in safety cabinets were consistent when comparing between beginner and advanced levels (Supplementary Fig. 3).

4. Discussion

Regenerative medicine is rapidly advancing in Japan, with a growing number of approved cell preparations. The process of cell manufacturing is crucial, as it directly impacts both the effectiveness and safety of these preparations. Despite recent technological advancements, many aspects of cell manufacturing still rely heavily on the manual skills of operators, indicating the lack of automation and standardization. Consequently, CPOs are crucial in the manufacturing process and are indispensable assets for the future of the regenerative medicine industry. However, the risk of contamination looms large in the cell production process, which is challenging to sterilize and remains a primary concern faced by CPOs daily. Contamination represents a significant source of stress for CPOs due to its severe consequences, including halted shipments of cell preparations and disruptions to ongoing treatments. This study delved into the attributes of CPOs, focusing on their anxiety and stress levels related to contamination. Additionally, we explored current operational practices aimed at preventing contamination and identified key issues that must be addressed to empower CPOs to be more effective in the regenerative medicine industry.

When comparing the attributes of participants in this survey with those from a previous study, no significant changes in gender or age demographics were observed [1]. Nevertheless, an increase in experienced CPOs was observed, with 69 % of participants in the current survey having over three years of experience in CPFs, compared with 47 % in the previous study. This trend indicates that CPOs are increasingly establishing themselves in the industry. Out of the 34 qualified CPOs who responded, 26 were certified through the Japan Society for Regenerative Medicine (JSRM) accreditation system, underscoring its effectiveness in shaping CPO career paths. A continuous investigation of CPO attributes is essential for identifying future trends.

The survey results revealed that 72 % of CPOs expressed concerns about contamination during the manufacturing process, whereas 18 % reported actual instances of contamination. However, the differences in these percentages were insignificant when the beginner and advanced groups were analyzed separately. This suggests that anxiety about contamination is not dependent on experience, but is a universal concern specific to cell

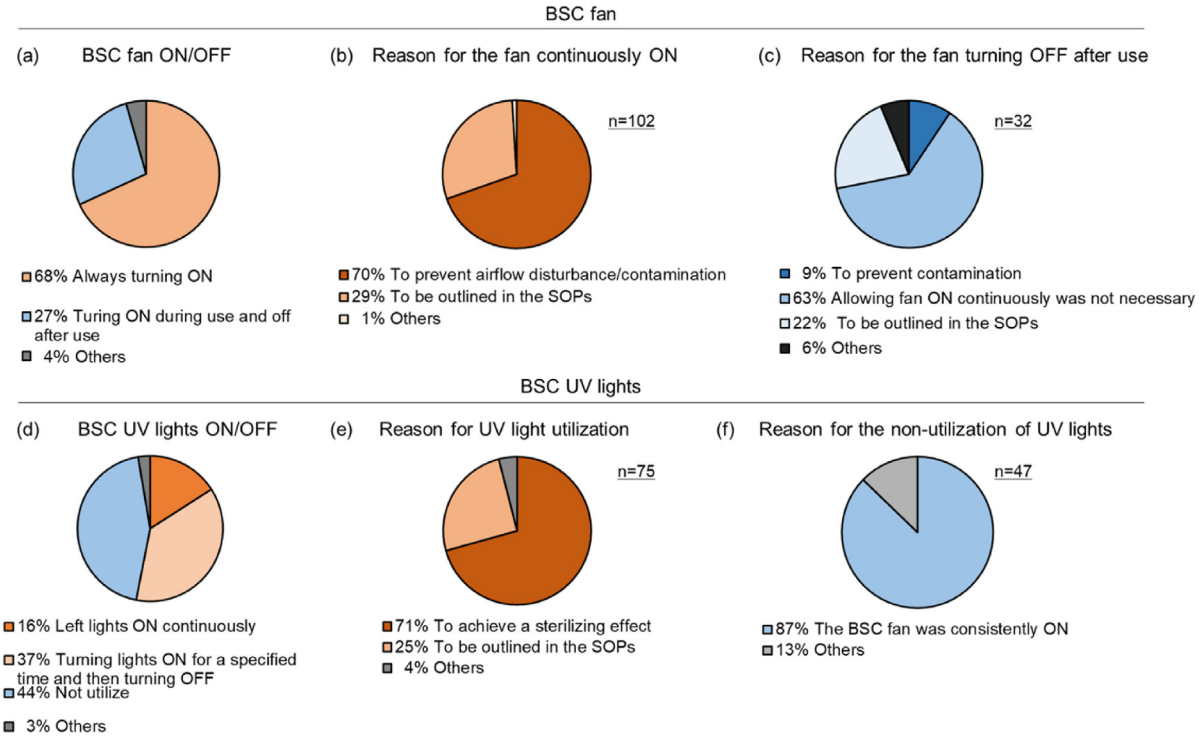

Fig. 4. BSC utilization. (a) BSC fan ON/OFF. (b) Reason for the fan continuously ON. (c) Reason for the fan turning OFF after use. (d) BSC UV lights ON/OFF. (e) Reason for UV light utilization. (f) Reason for the non-utilization of UV lights.

manufacturing. Maintaining a completely sterile environment in cell manufacturing is challenging, leading to contamination risk being a significant issue regardless of the operator's proficiency or years of experience. The perception of contamination risk being excessively high may be attributed to several factors. First, CPOs are still in the process of developing technologies that can accurately and immediately assess contamination risks, with only a limited number of practical technologies currently accessible. Furthermore, the heightened concern regarding contamination risk may be influenced by the realization that any instance of cell contamination can disrupt product shipments or directly impact patient care [8–12]. Moreover, contamination can originate from raw materials, such as human-derived cells, which may inherently contain contaminants despite stringent process controls [13,14]. The survey results indicated that the most common cause of contamination reported by CPOs was the raw materials themselves. This highlights the fact that relying solely on area management may be insufficient to eliminate the risk of exogenous contamination during processing, similar to conventional pharmaceutical production. Concerns about invisible microorganisms and viruses may be fueled by previous contamination incidents within the same facility, even in the absence of recent contamination events. This persistent fear of unseen risks can intensify over time and impact individuals who have not experienced contamination. Efforts to continuously monitor Grade A particles and microorganisms are underway [15,16]. However, sampling at critical points during operations presents challenges, such as reduced operational efficiency. Effectively utilizing these monitoring devices could help alleviate the psychological burden on operators and promote a safer working environment. This study identified a challenge specific to cell products that cannot be sterilized, highlighting the need for appropriate management of contamination risks.

We investigated the delivery methods for sterile water and clean paper as potential sources of external contamination. CPOs reported that materials, such as sterile water and clean paper, essential for facility operations, are introduced only after undergoing sterilization and disinfection. Sterile water is crucial for maintaining conditions within thermostatic chambers and incubators. Similarly, clean paper is typically autoclaved or disinfected before use. Although visible contamination can be readily cleaned, wiping as a sterilization method is challenging to standardize and replicate. Moreover, materials can serve as vectors for microorganisms [17,18]. Considering that water is a major source of microbial contamination [19], sterile water poses a risk of becoming a microbial reservoir if not properly controlled at the point of use. Furthermore, in CPF operations, procedures involving human intervention are considered to carry a high risk of contamination, highlighting the importance of conducting comprehensive risk assessments tailored to the specific circumstances of each facility [20]. Despite the meticulous precautions taken by CPOs, situations that could potentially lead to contamination risks may contribute to their unease regarding cell contamination. Our study findings highlight a lack of risk assessment concerning the control of external objects entering the facility, which is a significant exogenous factor of contamination.

Various methods for maintaining and initializing Grade A standards have been explored to effectively manage the contamination of cell products [21]. Isolators and BSCs are commonly utilized in CPF, with many CPOs in our survey indicating regular use of BSCs [1]. In Japan, the 2019 Guidelines for the Installation and Maintenance of BSC at Manufacturing Facilities for Regenerative Medicine Products provide guidance on BSC utilization. However, specific practices for utilization and management are largely left to individual operators, resulting in considerable variations across facilities, particularly in the use of fans and UV lights. For example, regarding the use of the BSC fans, 68 % of CPOs reported always turning ON, whereas 27 % reported turning it OFF after use. Additionally, 16 % of CPOs reported using UV light continuously, 37 %

reported turning them OFF after a specified period, and 44 % stated that they do not use UV lights at all. Keeping the fan running continuously helps maintain a unidirectional airflow inside the BSC, creating an air barrier at the front opening that reduces the risk of contaminants entering from outside and ensures cleanliness within the BSC. Facilities in which CPOs maintain the fan running continuously aim to stabilize the air barrier airflow inside the BSC, minimizing the entry of contaminants from the outside [22]. Furthermore, UV lights are effective in sterilizing microorganisms and maintaining risk reduction within the BSC [3,23]. In facilities where CPOs utilize UV lights, the focus of UV irradiation operation is on reducing residual risks within the BSC after work and minimizing external contamination. This study suggests a discrepancy in the utilization of fans and UV lights in BSCs as a risk management method. Furthermore, it suggests the necessity of establishing a consensus on the appropriate approach to managing these tools effectively.

The study employed ChatGPT, a large-language model, to analyze responses from open-ended questionnaires regarding contamination. With advancements in AI technology, the automatic analysis of text data using generative AI models, such as ChatGPT has become increasingly prevalent [24–26]. ChatGPT efficiently identifies key trends in the response data, facilitating the grouping of similar opinions and themes even amidst a large volume of responses. This capability represents a significant advantage over traditional manual analysis methods, as noted in previous studies that have found questionnaire analysis using ChatGPT to be both efficient and valuable [27]. However, ethical considerations must be considered, as AI-driven analysis may inadvertently distort respondents' intentions and introduce bias [25]. In this study, the reproducibility of the analysis results was ensured by combining AI with human judgment and meticulously documenting the ChatGPT prompts. While this innovative approach to analyzing open-ended questionnaires shows promise, it underscores the importance of carefully evaluating the impact of AI tools on the research process and operating with due diligence.

5. Conclusions

This study shed light on the concerns regarding contamination risks and the operational challenges associated with their management. To address the significant concerns that cell processing operators face regarding contamination risks, comprehensive risk assessments and evidence-based approaches are crucial. Additionally, the study identified disparities in contamination control practices across facilities, underscoring the importance of customizing operational methods based on logical, evidence-based data. By implementing risk assessments and data-informed practices, operators may be able to alleviate the psychological burden associated with their work.

Statement

The authors utilized ChatGPT 4.0 to summarize various responses during the preparation of this manuscript. Subsequent to utilizing this service, the authors meticulously reviewed and edited the content as needed, assuming full accountability for the publication's content.

Author's contributions

Conception and design of the research: YS, MM; data acquisition: MM, YS, NM; data analysis and interpretation: MM, YS; drafting of the manuscript: YS, MM; manuscript revision for important intellectual content: MM, YS, NM, HK, IS. All the authors have read and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests: Mitsuru Mizuno reports financial support from Hitachi Plant Services Co., Ltd.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2025.03.020.

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