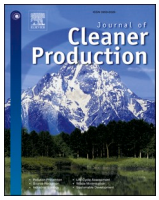
Journal of Cleaner Production 471 (2024) 143436

Contents lists available at ScienceDirect

Journal of Cleaner Production

journal homepage: www.elsevier.com/locate/jclepro



Concept for recycling a small-scale plastic-based bioreactor in a close-loop – Technical approach

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ARTICLE INFO

Handling Editor: Giovanni Baiocchi

Keywords:
Cell-culture
Bioreactor
Plastic
Recycling
Polycarbonate
Life-cycle-assessment

ABSTRACT

To accelerate biotherapeutic development whilst decreasing development time and project cost, small-scale multi-parallel bioreactors have been developed to maximize product yield and quality. These systems feature single-use plastic-based bioreactors for easy connection and fast turnaround. Despite well-known advantages, the perception of plastic and the lack of recycling options are raising concerns in the scientific laboratories' community. One of the common objections to plastic circularity in life-science is the perceived "downcycling" effect of mechanical recycling. Therefore, the aim of this work was to establish the technical feasibility of a close-loop recycling concept for the main construction material of the small-scale bioreactor. Application tests (cell compatibility and cell culture) were performed and supported by quantitative physical and mechanical tests (tensile, melt flow index, light transmission). Results show that mechanically recycled polycarbonate could be re-used in the same application. A comparative life cycle assessment (LCA), based on a theoretical framework, showed with different scenarios that recycling would have a positive impact on Climate – Carbon – total within the boundaries. Even if the technical feasibility of such a concept is demonstrated through this study, several challenges remain for such a closed-loop recycling concept to be implemented at a commercial scale.

1. Introduction

The increased adoption of single-use technologies over the last two decades and the availability of single-use bioreactors, particularly for mammalian cell culture applications, has enabled the rapid expansion of upstream processing capacities. This shift has gradually replaced glass and stainless-steel bioreactors for operating volumes from milliliters to thousands liters, enhancing process flexibility and cost efficiency, while also providing environmental benefits such as reduced water and energy consumption (Pietrzykowski et al., 2013; Galliher, 2018; Eibl and Eibl, 2019; Budzinski et al., 2022).

Each new batch and experiment start with a brand-new sterile vessel, significantly reducing the risk of cross-contamination from previous experiments and eliminating the need for complex sterilization processes in labs. Single-use bioreactor systems have lower infrastructure costs and smaller laboratory footprints as the need for autoclaves and other sterilization-in-place equipment is reduced. Faster turnaround times between experiments are achieved since there is no cleaning or sterilization of vessels, increasing productivity and reducing downtime. The absence of clean and sterilization in place processes reduce water usage and amount of needed cleaning chemicals. Furthermore, single-use bioreactors offer flexibility for the customer to rapidly respond to different demands should their processes and applications change.

To fulfill required properties such as optical clarity, thermal resistance, impact strength and stability (Domininghaus and Eyerer, 2005; Peacock and Calhoun, 2006), as well as the option to use various sterilization methods (Massey, 2005), the small-scale bioreactors plastic vessels are made of polycarbonate, so far a "virgin" grade, meaning the resin, has never been used or processed before" (Environmental Investigation Agency).

After use, the polycarbonate vessels are classified as hazardous waste and are typically disposed of alongside other consumables exposed to

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https://doi.org/10.1016/j.jclepro.2024.143436
Received 21 May 2024; Received in revised form 1 August 2024; Accepted 16 August 2024
Available online 20 August 2024

biological substances. Initial decontamination is performed using validated chemical disinfectant methods or by autoclaving. Decontaminated waste is ultimately disposed of, through incineration or sent to landfill. The specific decontamination and waste management process can vary across different organizations and geographical regions, depending on internal protocols for handling waste and regulatory directives.

However, due to pressing environmental issues such as climate change and plastic waste related topics, both non-governmental (World Economic Forum and Ellen MacArthur Foundation and McKinsey and Company, 2016) and governmental organizations (Directive on packaging and packaging, 1994; Directive on the reduction of, 2019) are pushing the plastic industry to circularity. Simultaneously the life-science industry is demanding more sustainable solutions (Budzinski et al., 2022; Luu et al., 2022; Health Care Without Harm) and starts considering recycling.

Although a waste hierarchy is clearly established, particularly in Europe (Directive on waste and repealing, 2008), there are still some discussions on recycling definitions and hierarchy. Mechanical recycling is generally considered as the most desirable approach, since it is expected to have the best emission and economical profile (European Commission; Directorate-General for Research and Innovation et al., 2019; European Commission; Joint Research Centre et al., 2023). However, concerns about consistency of quality and material properties in mechanical recycling (Schyns and Shaver, 2021) often hinder its adoption (Alassali et al., 2021), despite the availability of products containing mechanically recycled plastics (Decoded; Covestro; Preserve).

The driver for this study was to challenge these recycling concerns. The assumption of this work is that it is technically possible to recycle single-use items used in bioprocessing labs for the same application.

To explore this, as a starting point, a product that has the potential to be recycled after decontamination and is used for Research and Development purposes, typically not in an environment governed by good manufacturing practice standard (International Society for Pharmaceutical Engineers), where material changes would be far more challenging for customers to adopt due to validation requirements.

Then, within this selected portfolio of products, a polymer with good recycling profiles was selected. Indeed, polycarbonate has been proven to be recyclable through existing route (Decoded)and separate data suggest that multiple recycling loops may be possible with polycarbonate (Moulinié et al., 2022). Polycarbonate parts making more than 50% of the single-use small-scale bioreactors vessels (depending on the configuration), they were selected for his case.

Furthermore, a global warming potential assessment was included, covering the different phases of the product life cycle through a screening life cycle assessment, based on literature data for transparency.

Last but not least, collaborative practices are essential to achieve circularity goals (Luu et al., 2022; Siems et al., 2023). Therefore, a collaboration between a producer and supplier of small-scale bioreactors, and a producer and supplier of polycarbonate, was established to perform this study and jointly contribute to circularity in life science and bioprocessing industries.

Therefore, the objective of the study is to evaluate the feasibility and environmental benefits of recycling single-use polycarbonate bioreactor vessels used in bioprocessing labs in a closed-loop. The study aims to address concerns about the material properties of mechanically recycled plastic, specifically polycarbonate here, to demonstrate that it is technically possible to recycle these single-use items for the same cell culture application, possibly with a positive impact on global warming potential.

Fig. 1 summarizes the recycling model of this study. Landfill was intentionally excluded as an option. Although it has the lowest carbon footprint for end-of-life disposal, it is the least desirable waste management option in Europe. To obtain a quantity of products for recycling compatible with our study goal, trials were conducted using expired unused bioreactors, autoclaved to simulate decontamination.

2. Materials and methods

2.1. Products and polymer

This study focused on the use of 100% recycled material for the assembly of Ambr® 15 Cell Culture sparged microbioreactors (Item no.: 001–7B01), which are presented in Fig. 2(a) and further named 15 mL scale bioreactor vessels. These vessels feature the largest surface to volume ratio of 2 cm^2/mL in the range of bioreactors available (to be compared to surface to volume ratio of 0.95 cm^2/ml for the largest working volume), and therefore represent a worse case approach for cell compatibility.

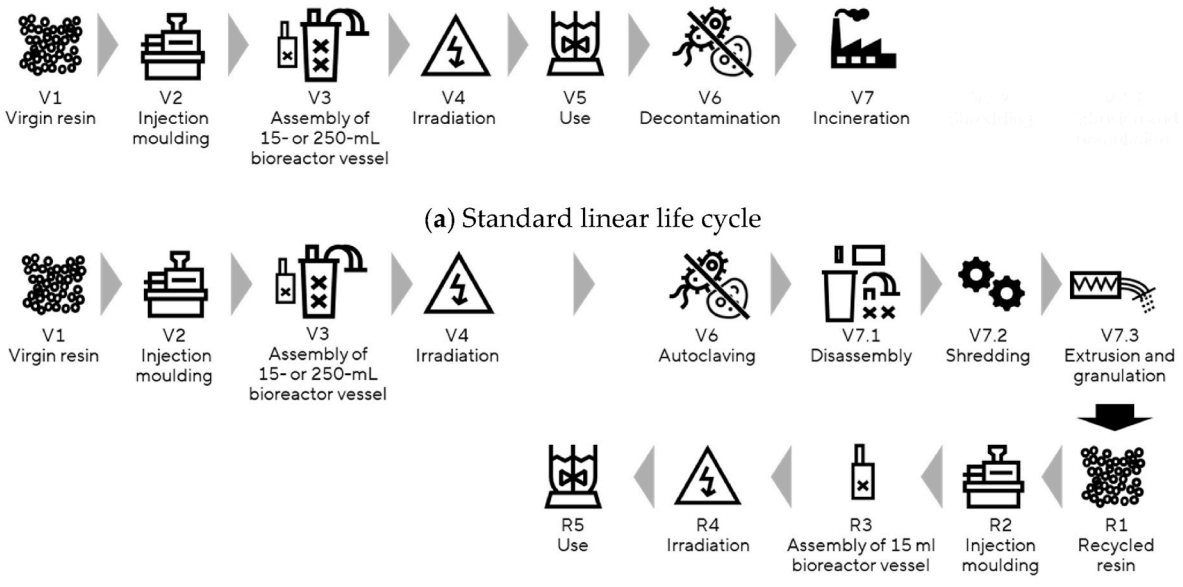

Fig. 1. Schematic representation of life cycle steps of virgin vessels (a) and recycled vessels (b) in this study.

(a) (b)

Fig. 2. Bioreactor vessel Ambr® 15 Cell Culture (a) with a maximum working volume of 15 mL and bioreactor vessel Ambr® 250 High Throughput (b) with a maximum working volume of 250 mL.

But based on availability of materials and to reach an amount of product compatible with our study goals, bigger (i.e. less products in quantity) vessels are recycled, Ambr® 250 High Throughput mammalian bioreactors (Item no.: 001-5G25), shown in Fig. 2(b) and further named 250 mL scale bioreactor vessels.

Polycarbonate used in this study is a Makrolon® grade, formulated for added stability from radiation sterilization with a melt volume rate (300 °C/1.2 kg) of 19 cm^3/10 min supplied by Covestro Deutschland AG.

2.2. Mechanical recycling method

Fig. 1(b) shows schematic representation of the recycling processing steps, that are relevant for the material properties. The products were autoclaved at a temperature of 121 °C for 30 min to simulate decontamination after use. Following the decontamination process, they were manually disassembled, to extract the vessels (Fig. 3(a) composed of polycarbonate. Then, polycarbonate parts were shredded into flakes. The shredding process was monitored to control the size of the flakes for granulation, which is performed in a compounder. Grinding and granulation were performed at lab scale for material characterization, and at a larger scale on industrial equipment, to reach the needed quantities for injection of Ambr® vessels in the industrial process. Fig. 3(b) and (c) relates to the industrial equipment.

The following Lab equipment were used:

- Grinder: Hellweg Maschinenbau GmbH MDS 410/200VF Sieve 6 mm
- Compounder: Coperion GmbH ZSK26 Mc18 L/D 44, extruder temperature 260 °C, throughput 20 kg/h at 225 rpm

The following industrial equipment, still considered as an intermediate scale since it exists even larger scale production machine, were used.

- Grinder Dreher S 34/52 Sieve <8 mm,
- Compounder: Leistritz Extrusionstechnik GmbH, ZSE 40 L/D 40. Extruder temperatures between 240 and 300 °C (different heating zones), throughput estimated to 75 kg/h at 176 rpm.

2.3. Material characterization

Material characterization was performed on virgin and recycled polycarbonate using the following:

A Zwick/Roell Aflow extrusion plastometer was used to measure the melt flow rate of the samples. Tests were conducted according to ISO 1133-1 at 300 °C with a load of 1.2 kg (ISO International Organization for Standardizationa). Three tests were completed per material, with five extrudates being cut per test. Extrudate masses were measured using a calibrated balance with a sensitivity of 1 mg.

The Differential Scanning Calorimetry was carried out using a dynamic heat flow differential calorimeter DSC 300 Caliris Supreme from Netzsch equipped with a compressor cooling system from Huber. Glass transition temperatures were measured according to ISO 11357-2 after the second heating (ISO International Organization for

(a) (b) (c)

Fig. 3. Polycarbonate vessels(a), flakes after shredding process (b) and extruded filament before granulation (c) on industrial equipment.

Standardization). Four samples per material with a resin amount of 10 ± 2 mg were measured in aluminum crucibles at a heating rate of 20 °C.

Five Tensile bars (size A1) were tested respectively using a Zwick/Roell universal testing machine Z010. Tensile modulus and tensile strength were measured at room temperature according to ISO 527-2 with a strain rate of 50 mm/min (ISO International Organization for Standardizationb). Tensile modulus was measured at a strain rate of 1 mm/min.

2.4. Cell compatibility

Cell compatibility (Fig. 4) was performed on polycarbonate recycled with industrial equipment, according to ASTM E3231-19. Virgin and recycled 15 mL scale bioreactor vessels have been manufactured with the existing standard equipment and procedures, in parallel for comparison. The assembled product was subjected to 25 kGy minimum irradiation.

Vessels were extracted in cell culture media ActiCHO™-SM (Cytiva Hyclone™, developed by Sartorius Stedim Cellca GmbH) at a defined extraction volume per vessel (E55 Committee). Extractions were performed for 3 day at 36.8 °C at 80% relative humidity and a shaking speed of 100 rpm.

Vessels were filled at different levels: nominal volume (15 mL), filled at 2/3rd (10 mL) and half-filled (7.5 mL) which led to a plastic surface in contact with media of around 2, 3 and 4 cm^2/mL respectively. Indeed, this is our usual approach to assess the safety margin of the results.

The cell compatibility effects were assessed with the mammalian cell line CHO-DG44 from Sartorius Stedim Cellca GmbH. Spiking experiments were carried out with an initial cell density of 0.2×10^6 cells/mL. Cells were cultured in 250 mL shake flasks from Corning in the extracted media, pure cell culture media (reference) and cell culture media with 2% dimethyl sulfoxide (negative control). The cells were cultivated for 4 days at 36.7 °C, 7.5% CO_2, 80% relative humidity and a shaking speed of 120 rpm.

Afterwards cell growth was measured using the Cedex HiRes Analyzer (Roche Diagnostics AG) and normalized to the reference cell growth.

2.5. Cell culture

Cell culture compatibility was performed on polycarbonate recycled with industrial equipment. Virgin and recycled 15 mL scale bioreactor vessels were manufactured using standard equipment and procedures, in parallel for comparison. The assembled products were subjected to 25 kGy minimum irradiation.

Two commercially available Chinese hamster ovary cell lines (CHO DG44; Sartorius Stedim Cellca GmbH) producing a monoclonal antibody (mAb) were thawed and passaged in shake flasks using the same protocol. The chemically defined and animal component free 4Cell® SmartCHO media system (Sartorius Stedim Biotech GmbH), including the 4Cell® SmartCHO Stock & Adaptation Medium (SAM), the 4Cell® SmartCHO Production Medium (PM), and the two-feeding media 4Cell® SmartCHO Feed Medium A (FMA) and 4Cell® SmartCHO Feed Medium B (FMB), were chosen for cultivation. All media components were supplemented with 6 mM glutamine (Sigma-Aldrich) and the SAM additionally with 15 nM Methotrexate (MTX; Sigma-Aldrich) for the first passages. Cells were expanded and subcultured every 3–4 days to maintain a viable cell density between 0.2 and 5×10^6 viable cells/mL and a viability above 95%. The last three passages were performed without MTX. Incubation of the shake flasks took place at 36.8 °C, 120 rpm, 80% humidity, and 7.5% CO_2 in a humidified shaking incubator (Kuhner).

In a small-scale standard fed-batch process using the multi-parallel Ambr®15 Cell Culture System (Sartorius Stedim Biotech GmbH) virgin and 100% recycled polycarbonate 15 mL scale bioreactor vessels were compared. For this triplicate approach, each vessel was inoculated with one cell line and a cell density at inoculation of 0.3×10^6 viable cells/mL. After inoculation, the working volume was 13 mL, varying during the experiment by sampling and feeding, the latter starting after a 72-h batch phase. For the fed-batch phase, a feeding daily bolus included 4% FMA and 0.4% FMB. For scale-up comparison a volume correction was implemented and resulted in a slightly decreased feeding volume over time. In addition, glucose was topped up to 4.5 g/L from day 5 or day 6 onwards. The temperature setpoint was set to 36.8 °C and the upper pH limit was 7.1, controlled by CO_2 gassing. Vessels were stirred at 1300 rpm and the dissolved oxygen (DO) setpoint was 40%, controlled by O_2 gassing.

To monitor the cultivation, daily samples were taken and the viable cell count (VCC), viability, cell diameter, and cell aggregation rate were measured with a Cedex HiRes Analyzer. Additionally, glucose and lactate concentrations as well as osmolality and ammonia levels were analyzed with the Nova Flex2 Analyzer (Nova Biomedical GmbH). The termination criterion was reached when viability dropped below 70% or after 12 days. After harvest, the cell broth was centrifuged at 6600×*g* for 5 min at room temperature (RT), and the supernatant was stored at −20 °C for end point titer measurements using the Octet-R8® (Sartorius Stedim Biotech GmbH), combined with Octet® Protein A (ProA) Biosensors (Martino et al., 2021). This method, based on Bio-Layer Interferometry (BLI), enables rapid, accurate and cost-effective quantification of monoclonal antibodies. 1X phosphate buffered saline (PBS; pH 7.4) was used as a sample dilution and neutralization buffer, while the regeneration buffer was 10 mM glycine (pH 2). As a standard, purified IgG1 with known concentration was used and diluted in a standard dilution series in PBS ranging from 0 μg/mL to 400 μg/mL. The taken samples were diluted in PBS as well and the dilution factor was chosen for the concentration to be within the standard range. Statistical significance was assessed using GraphPad Prism version 9.4.1. and an unpaired two-tailed *t*-test. The sample size for the cell growth and the metabolites data was three for each vessel type, while the sample size for titer measurements depended on the number of vessels harvested at day 12. The significance level was set at $\alpha = 0.05$ to test, whether there was a significant difference between the two vessel types.

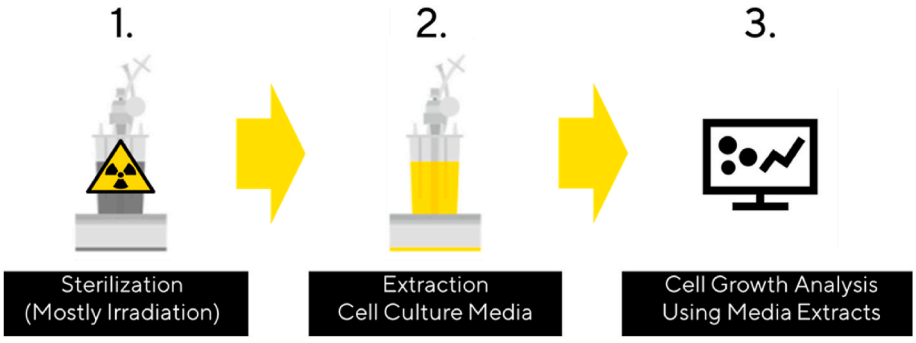

Fig. 4. Steps of cell compatibility testing according to ASTM E3231-19.

2.6. Carbon footprint

This section aims to support the technical assessment of recycling polycarbonate bioreactor vessels with an environmental approach. Due to the focus on Climate Change, a Carbon Footprint study was conducted, though other environmental indicators could also be analyzed. The study compares two routes: using virgin polycarbonate and recycling polycarbonate from discarded 15 mL bioreactors to produce new ones in a closed-loop system as respectively represented on Fig. 1(a) and (b). Given that the annual collection rate of used bioreactors is expected to be lower than production, an intermediate recycled content rate was included, likely below 20% (the return rate of the pilot take-back program of the single-use medical devices Returpen™ ranged between 10 and 15% (Mallick et al., 2022))

Two scenarios were assessed: one with 100% recycled content and another with 20% recycled content, each evaluated at lab-scale (worst case) and industrial-scale (best case), as shown in Table 1 The study uses average and literature data for a screening assessment, employing the EF v3.1 method for Life Cycle Impact Assessment, focusing on "Climate Change - total."

The declared unit is one 15 mL bioreactor vessel, with system boundaries from cradle to grave. Processes included are raw material extraction, production, sterilization, distribution, and end-of-life treatment. For the closed-loop recycling route, polycarbonate parts for secondary raw material production are recycled, while all the other parts are incinerated.

For this screening life cycle assessment, literature data and nominal machine values were used to characterize energy consumption and scrap rates. Databases like Sphera® v2023.2 and ecoinvent v3.9.1 were used to depict virgin material usage. Lab-scale energy consumption was based on machine nominal values for mechanical recycling, while scrap rates were derived from Donatelli et al. (2021) (Donatelli et al., 2021). Industrial-scale energy consumption data for the compounding stage came from Kohlgrüber et al. (2022) (Kohlgrüber et al., 2021), with shredding/milling energy and scrap rates proportionally adjusted from lab-scale data.

Injection molding scrap rates were sourced from the Sphera® database, assuming a 2% scrap rate for quality testing. Manufacturing and testing scraps were sent to recycling but not included in the closed-loop. Sterilization and autoclaving data were obtained from IBA Industries and McGain et al., 2016 (McGain et al., 2017). A manual assembly/disassembly of vessels was considered.

The study focused on the UK for manufacturing and Germany for polycarbonate recycling, using respective residual electricity mixes. Distribution assumed 30% of products sent to Europe and 70% to Asia/America by plane and truck.

Table 1
Screening LCA scenarios of virgin and recycled polycarbonate closed-loop recycling.

Scenarios	Reference	Closed-loop – 100%		Closed-loop – 20%	
		Lab scale	Industrial scale	Lab scale	Industrial scale
Content of recycled	0%	100%	100%	20%	20%
Content of virgin	100%	0%	0%	80%	80%
Energy to recycle	–	0.25 kWh/kg	0.19 kWh/kg	0.25 kWh/kg	0.19 kWh/kg
Losses in recycling	–	1.5%	1.125%	1.5%	1.125%

3. Results

3.1. Material characterization

Results of the material characterization are displayed in Table 2. The recycled polycarbonate exhibited a melt flow index increase of 45% coupled to a 4%–5% lower tensile modulus and lower tensile strength, indicating a potential for chain rupture. It is expected that the molecular weight of the recycled material is decreased compared to the virgin material due to thermal treatment and two irradiation steps. No significant change was observed in the Glass transition temperature (Tg). Consequently, it is not anticipated that the thermal properties of the material will be significantly impacted.

The Melt Flow Index increase is consistent with an observed lower injection pressure of the vessels during the manufacturing process. However, the injection molding process adhered to standard manufacturing parameters, like those used for the virgin vessel. The dimensions of the components were found to be within the specified range, thereby confirming the robustness of the manufacturing process, and the assembly process was fulfilling manufacturing specifications.

3.2. Cell compatibility

The results are displayed in Fig. 5. A slight reduction in cell growth in virgin vessels was observed with an increased surface to media volume ratio. However, these reductions were within the typical deviations of the test, indicating that they are not significant. No significant cell growth reduction was observed in the recycled vessel, even at higher surface to media volume ratios which gives an additional safety margin.

The results suggest that the recycling process does not impact cell compatibility. Yet, it is recommended that if recycled vessels are to be introduced to the market, further tests should be conducted with validated process and recycling conditions. This will ensure that the results are applicable to the specific conditions of the recycled vessels and can reproducibly be tested against a wider range of cell lines and applications to support market adoption.

3.3. Cell culture

Fig. 6 shows the results of the viable cell count (VCC) and the cell viability for the virgin vessels compared to the recycled vessels. The triplicate measurements were averaged and plotted with their standard deviation. Both the viable cell density and the viability reveal a consistent trend until day 5 when comparing the growth in virgin vessels to the recycled vessels. Exponential cell growth is visible during this period and the peak cell density is reached after 8 days for Clone A and 7 days for Clone B. After six days the standard deviation increased in all approaches, and with two exceptions no significant difference ($p > 0.05$) between the two vessel types was observed. Two data points of Run 2 with Clone B, marked with asterisks and brackets in Fig. 6D), showed significantly higher viable cell densities in recycled vessels compared to virgin vessels ($p < 0.05$). Overall, no impact of the recycled material on viable cell density and cell viability could be demonstrated, indicating that the recycled vessels are suitable for cell growth.

A comparable evaluation was also carried out for cell diameter, cell aggregation, osmolality, and different metabolites, such as glucose,

Table 2
Property comparison of virgin polycarbonate and polycarbonate resin recycled in the lab recycling process.

Test method	Virgin	Recycled
Melt Flow Rate	20 g/10min	29 g/10min
Glass transition temperature	145 °C	146 °C
Tensile modulus	2400 MPa	2300 MPa
Tensile strength	64 MPa	61 MPa

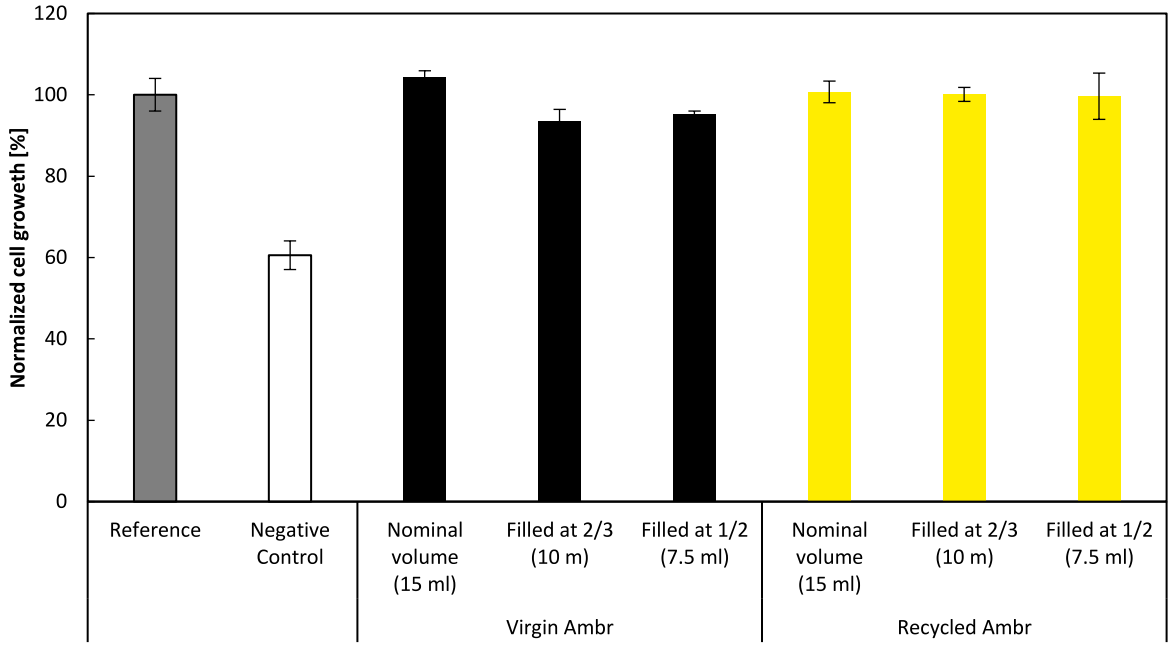

Fig. 5. Results of a triplicate cell growth test. Reference: untreated medium; Negative Control: Medium with 2% Dimethyl sulfoxide.

lactate, and ammonium. No significant effect of the recycled material compared to virgin material was observed (data provided in supplementary material.

As cell growth and the corresponding metabolites are not the only important factors in characterizing the suitability of the recycled material for the final application, the product titer was also analyzed. This was done by an end point measurement at the time of harvest. Only the data points of vessels harvested on day 12 were considered to provide a fair end point comparison between the virgin and recycled vessels, vessels harvested at earlier timepoints were not included since different product titers would be expected and not considered directly comparable. As displayed in Fig. 7, the mAb titer produced by Clone B was higher than that of Clone A. This increase was +10.6% in the recycled and +10.4% in the virgin vessels for Clone B compared to Clone A. Fig. 7 also shows that the mAb production in the virgin vessels was slightly higher compared to the recycled vessels. The increase in the virgin vessels is +3.7% for Clone A and +3.6% for Clone B, but the performed *t*-test did not provide any evidence that the difference in mAb titers between recycled and virgin vessels was significant ($p > 0.05$). Even within replicates using the same vessel types some biological variation is expected, and there will be a margin of error introduced from sampling, dilution, and analysis.

Overall, no significant effect of the recycled material on cell growth, metabolites, and titer production could be ascertained for the two clones used in this study. Since the cultivation of mAb-producing CHO-cells in a fed-batch mode represents a standard process, this indicates that the application of recycled small-scale bioreactors can also be transferred to other processes with different cell lines, products, and process modes.

3.4. Carbon footprint

Fig. 8 shows the incidence of the recycled content using the "Climate Change – total" impact category for the different recycling scenario studied here. It is expressed as a percentage and compared to the current linear model set to 100%. The options are summarized below, the product considered is a 15 mL scale bioreactor vessel:

1. Baseline: virgin vessels are used, steam sterilized and incinerated.
2. Closed-loop 100%: vessels are used, steam sterilized, sorted, polycarbonate is recycled, and converted into vessel containing 100% recycled content.
3. Closed-loop 20%: vessels are used, steam sterilized, polycarbonate is then sorted, recycled, and converted into vessel containing 20% recycled content. Any other recycled content rate will fall between option 2 and 3.

The worst-case scenario for "Climate Change – total" impact is the single use scenario without any post-use recycling. This finding encouragingly confirms that circularity can save valuable resource and reduce the carbon footprint. In the ideal case of 100% closed-loop recycling, a reduction of about 34% on the "Climate Change – Total" impact category compared to the baseline could be achieved. A closed-loop scenario with 20% recycled content in the vessel results in a decrease of around 7%.

Fig. 8 illustrates that recycled polycarbonate, even when accounting for the impacts of recycling activities, has a lower "Climate Change – total" impacts compared to the production of virgin polycarbonate. Additionally, recycling processes avoid the impacts that would have been caused by incinerating the polycarbonate sent for recycling.

Fig. 9 shows that the industrial scale scenarios have a low impact but is it important to highlight that primary instead of generic data at industrial scale could change the results, even significantly.

4. Discussion

In this study, the recycling process, including several processing and sterilization steps (irradiation of bioreactors before first use, decontamination autoclaving before recycling, and irradiation of recycled bioreactors before reuse), increased the melt flow rate and slightly decreased the tensile strength and modulus of the recycled polycarbonate. This aligns with literature (Rudolph et al., 2017), which states that while polymers are stabilized for initial use, mechanical recycling can cause fragmentation and cross-linking of polymer chains, altering their properties. However, these literature data (Rudolph et al., 2017) indicate a lower impact on polycarbonate's mechanical properties than observed in this study, suggesting that optimized recycling

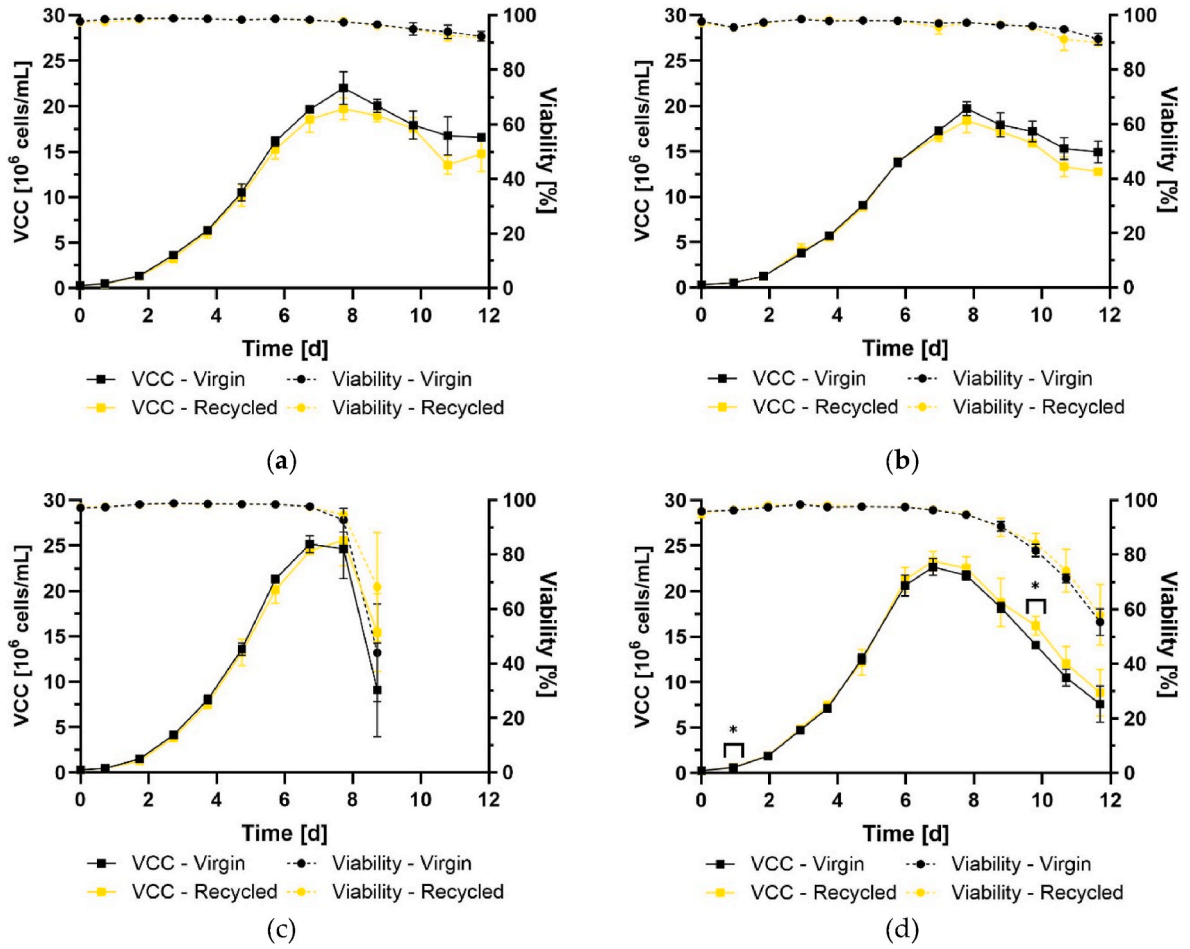

Fig. 6. Viable cell count and cell viability over time for the standard fed-batch cultivation in virgin and recycled 15 mL scale bioreactor vessels. All experiments were performed in triplicates and the results are shown as a mean with the corresponding standard deviation. (a) and (b) results of two independent cultivations of Clone A. (c) and (d) results of two independent cultivations of Clone B. An unpaired two-tailed *t*-test was performed and data points with a statistically significant difference ($p < 0.05$) are marked with asterisks and brackets.

parameters can significantly reduce material embrittlement. Generally, polycarbonate is considered a stable material in the context of recycling due to its lack of residual catalysts, which are present in materials like polyesters, and its aromatic-based chemistry that ensures strong chemical bonds, making it more resistant to thermo-oxidation compared to aliphatic-based materials. Recent reports have highlighted the recyclability of polycarbonates as 100% regrind in a closed-loop system, where an unsorted mixture of various polycarbonate-based materials maintained consistent properties after five to ten recycling cycles (Moulinié et al., 2022; Pérez et al., 2010). Polycarbonate exhibits significantly greater resistance to irradiation compared to most other polymers. The primary impact of irradiation on polycarbonate is chain scission, or the breaking of molecular chains. However, due to the high chain stiffness of polycarbonate, the separated ends of the chains find it challenging to move apart, leading to a higher likelihood of recombination. Additionally, the aromatic structure of polycarbonate allows it to absorb the energy in ways that do not necessarily result in chain breakage (Massey, 2005).

Despite the material alterations due to recycling and irradiation, the robust product design ensured that these material changes did not affect the manufacturability or functionality of the bioreactors. Additionally, the recycled vessels were irradiated twice (once before the first use and once before the second use) resulting in a visible yellowing of the still transparent material (Fig. 10). Virgin polymer contains stabilizers and colorant to decrease the visibility of the yellowing, but it is not formulated for multiple processing or sterilization steps. Literature reports indicate that the yellowing effect doesn't impact material properties such as stiffness or impact strength and diminishes over time (Chung, 1997).

This visual change is confirmed by quantitative data measured by the transmittance of light. Based on this data the yellowness index (YI) and the visual transmission (Ty) have been calculated (see Table 3). This change in color did not impact pH and DO sensor calibration and control.

It is important to note that this study considers a single recycling loop, which includes two instances of material irradiation. Multiple recycling steps will further alter the material due to additional thermal treatments and repeated exposure to irradiation. However, these tests were conducted with 100% recycled polymers, which is not currently realistic given the existing return rate. While 100% recycled polycarbonate is used in open loop applications such as building materials (Rodeca in ArchDaily), this recycling rate is not realistic for closed loop applications. Mixing recycled and virgin materials, will have an overall positive impact on physical and chemical properties and significantly reduce the risks linked to multiple recycling. Indeed, by using a constant mixing ratio between virgin and recycling polymers, the recycled polymer is diluted with each cycle (Rudolph et al., 2017; Goodship, 2007). The composition of a recycled material after multiple recycling steps can be calculated using Equation (1) (Rudolph et al., 2017; Goodship, 2007), where (n) is the number of recycling steps and (q) is the proportion of recyclate, as graphically represented by Fig. 11. If the concentration falls below 1%, it can be neglected because it will not

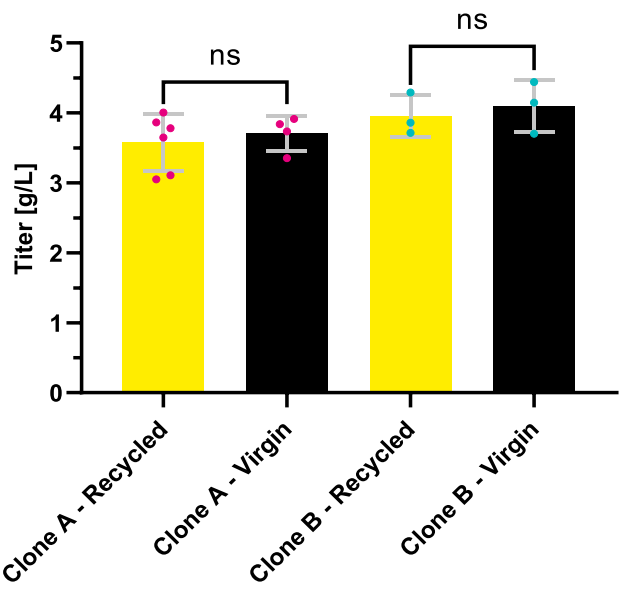

Fig. 7. Average titers produced by the two different clones within 12 days each in recycled and in virgin vessels. The standard deviation is shown in grey, and the separate readings are marked as dots in pink (Clone A) and blue (Clone B). An unpaired two-tailed *t*-test was performed to test for statistical significance between cultivation in recycled and virgin vessels. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

affect the material properties (Goodship, 2007). As expected, the best environmental impact is achieved with the ideal model of 100% recycled content in a closed-loop application. However, a more realistic recycled content of 20–50%, while reducing the impact of the recycling process on the polymer properties, will still have a limited but positive effect (less than 10% of decrease) on the "Climate Change - total" impact as estimated in this study. Several commercial grades are available with recycling contents ranging from 20 to 90% (Avient; Moore). The range of offerings in this sector is expected to grow, especially considering new regulations that may mandate minimum levels of recycled content.

$$\sum_{i=1}^{n} q^{n-1}(1-q) = 1 \quad (1)$$

The cell compatibility and cell culture results showed that small-scale bioreactors could technically be recycled in a closed-loop. However, further studies would be needed to ensure wider applicability across different cell lines and cell culture processes. Long term stress tests would be needed to validate the functionality in worst case conditions. Impact of remaining biomass and or use of chemical decontamination on the recycled polycarbonate quality would have to be evaluated. And finally, these positive results would have to be confirmed by an extractable analysis, comparing virgin and recycled polycarbonate.

The screening life cycle assessment shows that with the assumptions taken in this study, closed-loop recycling positively impact the "Climate Change – total" impact whatever the amount of recycled content. The scale of recycling (lab versus industrial) was not identified as a critical factor.

In general, the analysis outcomes, indicate that recycling processes in closed-loop scenarios help reduce the impact on Climate Change for two main reasons: raw materials and the end of life. Regarding raw materials, a closed-loop scenario means that the vessel will contain recycled content, as specified in the analysis percentages. t. The data and available information show that the processes for recovering and recycling polycarbonate are less impactful than producing virgin polycarbonate. This results in a decrease in Climate Change impacts, compared to the baseline scenario, which only considers virgin polycarbonate as an input. Additionally, in a closed-loop scenario, the polycarbonate parts of the used 15 mL scale bioreactor vessel are sent for recycling to meet the demand for polycarbonate in the production stage. This reduces the material flows to the incineration and, consequently, the impacts related to the incineration of polycarbonate. Therefore, we observe a decrease in end-of-life impacts compared to the baseline scenario, where all parts are incinerated.

However, given the limited positive impact of a 20% recycled content in a closed-loop system, it became relevant to explore an open-loop model. When a closed-loop recycling is not feasible, collected, sterilized, and shredded polycarbonate can still be effectively utilized. In open-loop recycling, materials from one application are repurposed for another high-value application, thereby reducing the carbon footprint across various sectors. For example, the electronics and automotive industries actively seek end-of-life materials to incorporate into their new products, thus keeping the material in the loop and minimizing waste.

In this study, the end-of-life material was successfully used in producing Bayblend®, a polycarbonate-ABS blend widely employed in these industries. The open-loop model adopted a cut-off approach for the end-of-life allocation. Since the material stream exits the system boundaries of the study, neither the impacts of the recycling activities nor the credits for avoiding the production of virgin material are considered.

With a return rate of 100%, open-loop recycling can potentially reduce the "Climate Change – total" impact by about 20% compared to

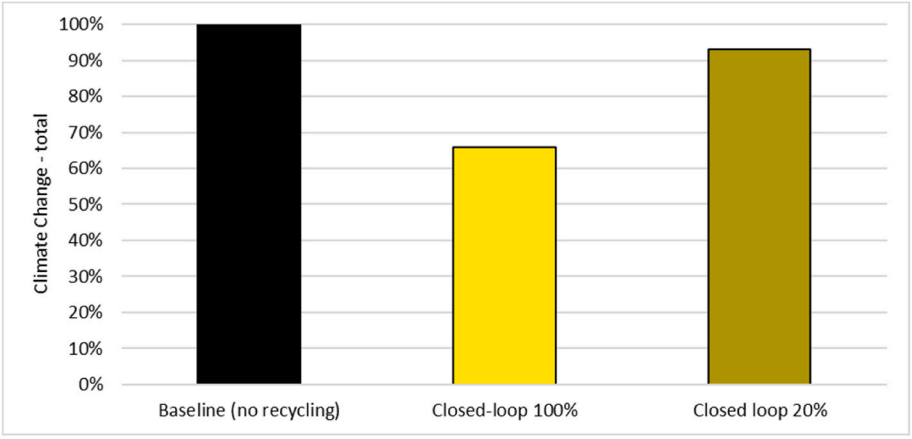

Fig. 8. Total impact on climate change: comparison between the linear base lines and ciruclarity options.

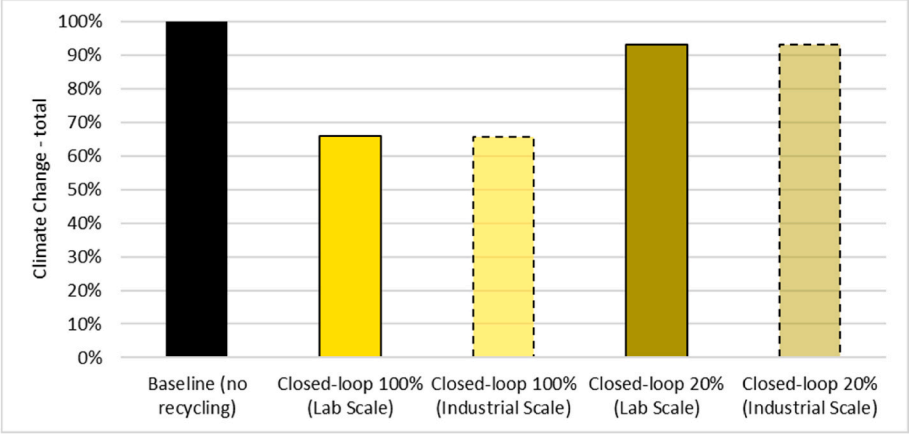

Fig. 9. Impact of the recycling scale.

Fig. 10. 15 mL scale bioreactor cell culture vessels made of virgin polycarbonate (left (a)) and 100% recycled polycarbonate (right (a)), both post irradiation-which means the recycled vessel has been sterilized twice.

Table 3
Visual Transmission (Ty) and yellowness index (YI) respectively calculated according to ISO 11664-3 and ASTM E313 with Observer: 10° and Standard Illuminant: D65.

Test method	Virgin	Recycled
Visual transmission (Ty)	84,77%	78,64%
Yellowness Index (YI)	−0.05	9.96

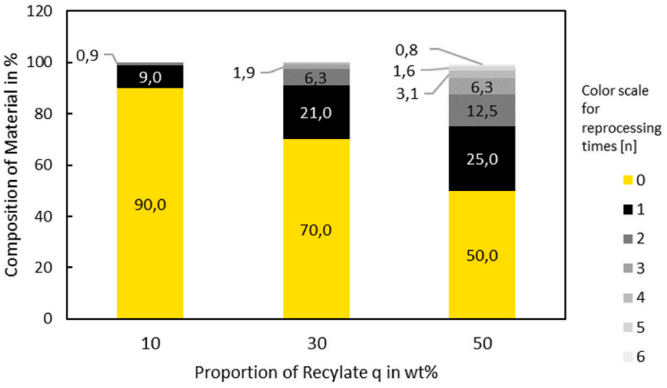

Fig. 11. Composition of recycled plastics material after n reprocessing steps for 10 %, 20 %, and 50 % recycled material.

the linear scenario. In open-loop scenarios, the benefits to "Climate Change – total" are due to the polycarbonate being sent for recycling, which avoids the impacts associated with polycarbonate incineration at the end-of-life when considering a 100% return rate, or reduces the end-of-life impacts when considering a lower return rate.

To discuss and verify the robustness of the statement "all the recycling scenarios showed a positive impact on the "Climate Change – total" impact" it was decided to expand the options and examine the effect of the return rate of post-used products on the ideal model of 100% close-loop recycling (Table 4 and Fig. 12). When assuming a 15% return rate (the upper value for Returpen™) for 100% recycled content in a closed-loop, with the remaining required polycarbonate coming from another recycling stream but same application, the positive impact on reducing the "Climate Change – total" impact drops from 34% to 18% compared to the baseline. This reduction is very close to the impact of an open-loop approach with a 100% returning rate.

Considering a 15% return rate of products in an open-loop scenario would lead to a 3% positive impact when compared to the linear scenario, which, although limited, is still positive. However, many different scenarios could be modelled, and various assumptions could change these trends, especially with the use of real data.

As demonstrated here, the benefit of recycling for the product owner, when looking only at "Climate Change – total" impact is lower when post used products are recycled in an open-loop compared to a closed-loop. Within the boundaries defined in this study, the only benefit comes from the end-of-life, i.e., savings on incineration emission. The plastic is recycled into another product and the aim of the life cycle assessment is to quantify the environmental impacts of a single product, which complicates the valorization of recycling (Ekvall et al., 2020).

Table 4
Relative effect of closed-loop versus open-loop recycling at 100% and 15% used products return rate (NA means here not applicable) with a linear model as a reference, (1) remaining 85% comes from recycled polycarbonate, different product, same application.

Scenario	Recycled content	Return rate	Climate Change Total Impact	% Positive Impact Versus Reference
Linear	NA	NA	100%	NA (Reference)
Closed-loop	100%	100%	66%	34%
Closed-loop	20%	100%	93%	7%
Closed-loop	100%(1)	15%	82%	18%
Open-loop	0%	100%	80%	20%
Open-loop	0%	15%	97%	3%

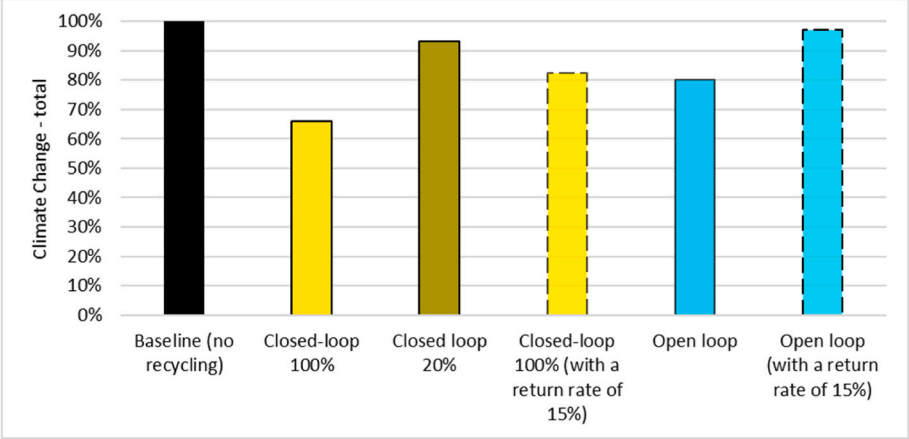

Fig. 12. Impact of an open-loop recycling on "Climate Change – total" compared to base line and closed-loop scenario.

This might hinder the motivation to recycle product in an open loop system, which also requires logistical effort to maintain the value of the plastic, especially when the priority is given to carbon emission savings. Nonetheless recycling even in an open-loop is commonly considered an environmental benefit.

This study aimed to assess the technical feasibility of a close-loop recycling in a life science application, excluding the logistics and business considerations. To advance the recycling of the small-scale polycarbonate bioreactor after use, these aspects must be addressed. The trials in this study were conducted under ideal sorting conditions and all recycling process steps performed by experts. Costs were not assessed, and the value of the recycled polycarbonate, will depend on the cost associated with collection and sorting process (Nzihou et al., 2022).

One anticipated barrier is the need to establish a specific flow for used small-scale bioreactor. Ideally, these products should be separated from other waste at the point of use. although disconnecting, the 250 mL bioreactor was proven to be easy, the effort to disconnect and recover polycarbonate from the 15- and 250-mL bioreactor needs to be quantified. Another challenge is the overall mass of collected used small-scale bioreactors required for recycling, which might require long storage time to reach is the usual recycling flow expectations, usually above 1 ton, especially in a close-loop process where a complete traceability is required to limit variability and risk of contamination by a non-controlled flow of material.

The open-loop recycling could serve as an intermediate step, but the return rate must be significantly higher than current literature reports to achieve a significant carbon footprint reduction, which is currently the primary driver for circularity in the industry. However, the European Commission directive on plastic packaging (Directive on packaging and packaging, 1994) requires Member States to establish systems for the return, collection, reuse, and recycling of used packaging to meet the recycling targets. It also mandates Extended Producer Responsibility schemes for packaging. This directive is expected to create demand for recycled plastic, trigger new technology development and foster new business models, making open-loop recycling more attractive and expanding the opportunities for close-loop recycling in life-science and healthcare applications.

5. Conclusions

The study highlighted that the mechanically recycled polycarbonate from a small-scale single-use bioreactor used in life-science and bioprocessing could technically be used in the same application. Under these testing conditions, using a single-use small-scale bioreactor vessel containing 100% of recycled polycarbonate (from the same product) didn't impact cell compatibility or cell culture results, despite some changes in plastic properties and a visible change in the color.

The comparative life cycle assessment, based on a theoretical framework and within the boundaries of this study, shows that all the small-scale single use bioreactor polycarbonate recycling scenario included here, results in a positive change on the "Climate Change - total" impact, when compared to the current linear baseline. The highest positive reduction would be 35%, with the ideal 100% close-loop recycling with a 100% return rate. However, with a more realistic return rate, the positive impact would drop below 10%. Due to the limited benefit of this latest option, an open-loop recycling approach, where the polycarbonate of post-use vessels is recycled and used for a different application, with a realistic return rate was considered. Although, the positive impact of this scenario when compared to the baseline is quite low, this opportunity could represent an intermediate milestone toward circularity. Joining an existing high-value polycarbonate recycling stream would allow for faster implementation and contribute to waste reduction in the life-science and bioprocessing sectors.

These encouraging results are the first milestones toward greater circularity in the life-science and bioprocessing sectors. However, several questions remain and need to be addressed before this concept can be implemented on a commercial scale.

From a quality perspective, the impact of cell biomass contained in post-used vessels, potential chemical decontaminants, and the cell lines must be further assessed. The process parameters for both recycling and injection molding must be optimized to minimize changes. Specifications for the recycled plastic must be defined, as well as the proportion of recycled content. The consistency of quality must be proven and supported by further biocompatibility data relevant to the market applications for the product, in this case the small-scale single-use bioreactor.

From an environmental impact perspective, running a full cradle-to-cradle life cycle assessment with primary and more accurate data at industrial scale (including raw materials, production, location, use, waste treatment streams etc.) could alter the results observed here.

From a logistic perspective, establishing an open-loop recycling as an intermediate step could allow for faster implementation and contribute to the waste reduction in the life-science and bioprocessing sector, provided that reducing carbon footprint is not the sole driver for recycling. Regardless of whether the loop is open or closed, the recycling flow - from the collection of used products to the injection into new products at a commercial scale - must be created and implemented. This is currently a challenge for the entire plastics industry, which anticipates challenging recycling targets from policymakers to trigger innovation investments and new business models for sustainable recycling.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Magali Barbaroux: Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Alena Rosskamp:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology. **Jannik Dippel:** Writing – original draft, Validation, Supervision, Methodology. **Alison Rees-Manley:** Writing – review & editing, Writing – original draft. **Bernd Garska:** Writing – original draft, Supervision, Methodology. **Roberta Tosato:** Writing – review & editing, Writing – original draft, Validation, Methodology.

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.

Data availability

Data will be made available on request.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclepro.2024.143436.

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