Anticipatory Life Cycle Assessment of Gold Nanoparticles Production: Comparison of Milli-Continuous Flow and Batch Synthesis

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ABSTRACT

The demand of gold nanoparticles (AuNPs) is growing steeply as a result of the remarkable advances in the applications of this product in the healthcare and diagnostics sectors. To this end, having an efficient and sustainable production system is of paramount importance for achieving low environmental impacts and avoiding depletion of capitals. In this respect, the present work gives insights on the environmental impact and costs of the production of AuNPs for nano-enabled medical applications, by looking at two production technologies: the conventional batch production and an innovative milli-continuous flow production, currently at lab scale. Life Cycle Assessment (LCA) and cost assessment are used to evaluate the sustainability and economics of the continuous-flow technology in an anticipatory fashion; this means capturing the environmental impacts and production costs of the emerging technology before it reaches full-scale and is deployed. The aim is to prevent waste of resources in the process development and avoid having a non-optimized final system, which would lead to high costs and reduce competitiveness. The milli-continuous flow production was subjected to a scale up/out-analysis enabling the comparison with the batch production, already established at large scale. The life cycle of both production systems is described, and the results of the assessment comprise a normalisation analysis, which frames the environmental impacts of the gold nanoparticles production in the European context, a scenario analysis, a comparative analysis and a hotspot analysis. The results show that significant advantages can be gained from the adoption of the continuous-flow production in place of the batch system, both in terms of environmental impact and production costs. Specifically, the environmental impact is reduced in terms of human toxicity (cancer effect), ecotoxicity of freshwater and depletion of gold resources; these impact categories were identified as the main carrier of the environmental impact in the conventional production. The main contributors to savings for the flow production are primarily milder cleaning procedures, reduction of hazardous wastes produced, and less labour required for the operation and control of the process. Finally, the depletion of gold resources associated to the production of AuNPs emerges as a major issue. It is hardly addressable by using second-hand gold, and this calls for the necessity of recycling the product at the end of its life cycle or complementing AuNPs with alternative nano-products.

KEYWORDS: Life Cycle Assessment; Anticipatory assessment; Sustainability; Gold nanoparticles; Continuous flow production; Tumour targeting

HIGHLIGHTS:

- The sustainability and economics of gold nanoparticles production is assessed
- Main impacts concern depletion of gold, freshwater ecotoxicity and human toxicity
- Continuous flow synthesis has better environmental performance than batch synthesis
- In the flow system OPEX is reduced by 42%, and offers a faster return on investment
- Process development shall prioritize anticipatory assessments at early stages

1 INTRODUCTION

In the last two decades, gold nanoparticles (AuNPs) have captured the attention of academic researchers and industries. The number of AuNPs related papers published since 2000 has reached the astonishing number of 50,415 and half of these have been published during the last 5 years (according to Thomson Reuters' Web of Science database; search conducted in March 2020). The area of interest spans from electronics to medicine. Several publications have reviewed the advances and perspectives of AuNPs in these fields by summarising their immunological properties (Dykman and Khlebtsov, 2012) and their use in biomedicine (Yang et al., 2015), by focusing on synthesis methods (Elahi et al., 2018), or by exploring their use in drug delivery (Kumar et al., 2013) and sensing applications (Qin et al., 2018). With their unique chemicophysical properties, either optical (Eustis and El-Sayed, 2006) or unexpected magnetism (Trudel, 2011), AuNPs are suitable candidates for being used in healthcare fields such as in diagnostics (Beik et al., 2017; Kircher et al., 2012) and cancer treatment (Govindaraju and Yun, 2018). To this end, AuNPs have been widely implemented as one of the leading nanomaterials for combinatorial cancer therapy (Beik et al., 2019). For instance, AuNPs emerge as a particularly promising platform to combine photothermal and chemotherapy by co-incorporating AuNPs as photothermal agent, with cisplatin as anticancer drug, into alginate hydrogel (Alamzadeh et al., 2019; Mirrahimi et al., 2019), or by amplifying the effectiveness of chemotherapy and chemoradiation with plasmonic nanobubbles (Lukianova-Hleb et al., 2014).

Accordingly, the global market for nanoparticles in the life sciences is forecast to reach USD 97.4 x 10^9 by the end of 2020 registering a healthy compound annual growth rate (CAGR) of 22% (James et al., 2014). The biggest increase is expected to come in the area of drug delivery: AuNPs based applications are estimated to represent a 21% share of the total market of nano-drug delivery applications by 2021 (Sezer, 2014). As a consequence of the this, gold nanoparticle production has been increasing at a sustained rate to match the fast-growing demand of the product. In 2015, on the basis of both nano-enabled medical applications that either were on the market or had the potential to be introduced in the market, the annual mean prospective use of AuNPs for the UK and US was estimated to be around 540 kg and 2700 kg respectively, with tumour targeting and drug delivery being the main contributors (75% and 24% respectively) (Mahapatra et al., 2015). According to WHO's prediction, annual cancer cases are expected to increase from 16.4 M in 2018 to 22 M in 2032 (GCO, 2018; WHO, 2018). Considering an average amount of 5000 mg/person for the whole treatment cycle (Mahapatra et al., 2015), the employment of gold nanoparticles could potentially reach 110 t/y in 2032.

Each year approximately 2,500-3000 t of gold are extracted. At present the total amount of above ground gold stocks is 190,040 t being divided among: jewellery (47.7%), private investment (21.1%), official sector (central banks) (17.1%) and other (14.1%) (World Gold Council, 2018). Below ground gold reserves are estimated to be around 54,000 t (Ed Prior (BBC), 2013; O'Connell et al., 2018). Should the gold stocks above ground be represented visually, they would appear as a 15-floor building, with below ground reserves being equivalent to an extension of mere four additional floors (Figure 1).

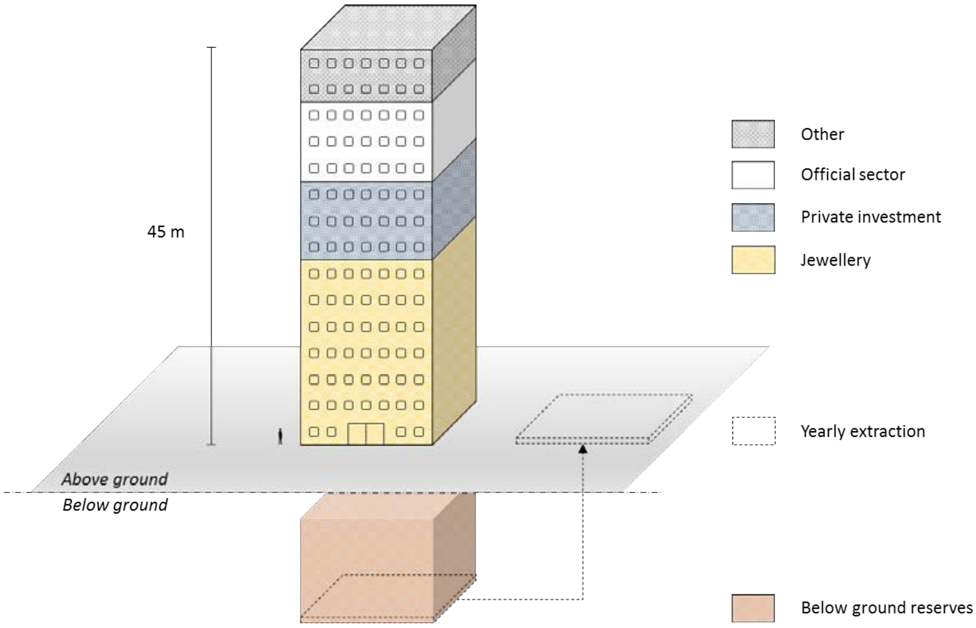


Figure 1 – Gold stocks distribution: visual representation of above and below ground gold stocks

The extraction costs are increasing (Mudd, 2007), ore grade have been decreasing over the last decade (Schodde, 2011) and there are thoughts of having surpassed the peak gold: date at which the maximum rate of gold extraction is reached (Kerr, 2012). Furthermore, the volumes required to sustain the gold nanoparticles industry are limited (Starr and Tran, 2008), even though the demand is steeply going up (Roco, 2011).

In the light of current and potential applications, growing markets and gold availability, a rigorous analysis of the production routes of AuNPs is needed. To this end, a holistic method such as Life Cycle Assessment (LCA), complemented with a cost analysis, serve this purpose by covering most of the critical aspects of a production cycle. LCA is a methodology - regulated by the International Standard Organization through ISO 14040 (International Organization for Standardization, 2016) and ISO 14044 (International Organization for Standardization, 2006) - that enables the qualification and quantification of environmental impacts and identifies improvement options throughout the life cycle of a product, process or activity. In this paper, the LCA methodology is applied to an emerging technology, namely a milli-continuous flow production of AuNPs via the Turkevich method with the aim of providing a prospective assessment of such production technology at large scale and hence understanding the consequences of its full exploitation. The conventional method of gold nanoparticle production is batch-type. On the other hand, micro/milli-continuous flow (CF) technologies are innovative solutions in the synthesis of nanoparticles (Huang et al., 2018; Zhao et al., 2011), and more generally in the intensified synthesis of chemicals (Elvira et al., 2013). These type of CF technologies are largely investigated because of their attractive features, such as high controllability of the product quality, ease of operation and scalability (Zhang et al., 2017), and efficiency in the recovery of energy and in the reduction of wastes (Kralisch and Kreisel, 2007). To this end, the transition from batch to CF production is a process intensification step that is currently being looked at in great detail by many academic and industrial sectors (i.e. COSMIC project as part of the Horizon 2020 programme (European Union's EU Framework Programme for Research and Innovation Horizon 2020, 2016)).

With regards to the synthesis method, the Turkevich method has been one of the main routes of synthesis of AuNPs for many years (Turkevich, 1985). Recently, as result of the growing application of AuNPs, this synthesis method has received renewed attention with the aim of investigating more in depth on the role of pH in the synthesis (Ji et al., 2007; Kettemann et al., 2016) and on the growth-mechanism (Wuithschick et al., 2015), exploring the possibility of in-situ characterisation (Polte et al., 2010), and intensifying the synthesis through continuous-flow systems (Bayazit et al., 2016) as opposed to conventional batch systems. To this end, the sustainability of new intensified systems needs to be assessed in order to capture the future potentiality of these systems. In research-intensive industries (i.e. healthcare), it is paramount to filter emerging technologies at early stages to prevent waste of resources, which leads to high costs and reduce competitiveness. Not all processes reach in fact commercial scale, and this turns into loss of human and capital resources. Furthermore, early assessments can grasp the consequences of adopting such systems after the scale up/out to commercial scale, in place of conventional production systems.

LCA can be used in this respect to provide a faithful evaluation of the environmental impact of innovative production systems in an anticipatory fashion (Cucurachi et al., 2018; Grimaldi et al., 2020), at the early stages of the process development. To the best of the authors' knowledge, no LCA and cost assessment on gold nanoparticles production systems at large scale have been published yet. Currently available publications consider only syntheses at lab scale (Leng et al., 2015) either focusing on different recipes (Pati et al., 2014; Virkutyte and Varma, 2011) or nano-waste recovery (Dei et al., 2017), but without investigating a full scale production inclusive of high impacting peripheral steps such as cleaning or waste disposal (Bhattarai et al., 2018), or offering a comparison with conventional production systems. Therefore, the whole life cycle of the production of gold nanoparticles needs to be properly assessed prior to its large-scale deployment in consequence of the imminent growth of gold nanoparticles demand. This anticipatory assessment would help establishing optimized production plants (Falsini et al., 2018) and hence prevent waste of resources which is usually synonymous of high costs and high environmental impacts.

LCA and cost assessments are used in this work to interlace three macro topics, namely sustainable development, process intensification and scale-up of emerging technologies. The synthesis of AuNPs is investigated by taking into consideration two production systems, batch and milli-CF. The batch system mirrors a standard industrial production, hence it is taken as the reference case, while the continuous flow system is extrapolated from the lab scale, scaled up/out and benchmarked against the batch production at large scale. Both production systems refer to the synthesis of 10 nm gold nanoparticles- of Optical Density 1 (OD1), produced via the Turkevich method- a product that is used intensively in nano-enabled medical applications. The whole set of operations typically involved in an industrial plant are considered: cleaning, separation, energy and material recovery. In addition, the modelling of the life cycle of the production systems comprises all the peripheral activities supporting the synthesis of gold nanoparticles, such as the production of chemicals, energy generation, raw material extraction and waste treatment.

On the whole, the primary goal of the present study is to give insights on the environmental impact and cost of batch and CF production at large scale, and investigate on how sustainable the full exploitation of AuNPs products in nano-enabled medical applications would be in the near future.

2 MATERIAL AND METHODS

2.1 Framework

The basic structure of this work is represented in Figure 2. It consists of three main phases: system definition, assessment, comparative analysis.

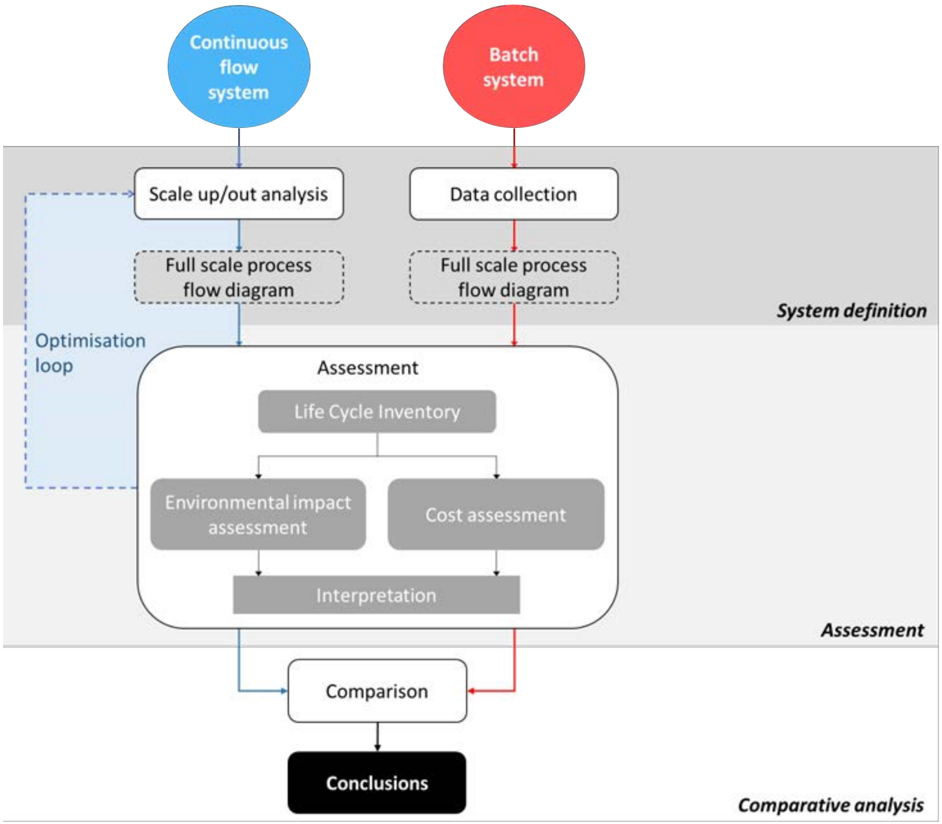


Figure 2 – Framework: system definition, assessment and comparative analysis

- **System definition**

  In this phase the process flow diagrams (PFD), material and energy flows are defined for both the continuous flow and batch system. The batch system is designed to represent a typical commercial production scale (approximately 45 m^3 of AuNPs product, OD1 namely $5.76x10^{-2}$ mg/ml, with a maximum coefficient of variation of 10%, equivalent to 2.5 kg of dry gold nanoparticles per year) and its scale is used as the reference to which the continuous flow system is based on. With regards to the latter, the construction of the PFD originates from a lab scale and brought, through a scale up/out study, up to a commercial scale matching the reference (batch) productivity. Continuous-flow synthesis of AuNPs is a novel, under-development technology and hence LCA and cost analysis serve the purpose here of optimizing the projected full-scale PFD through a loop-system, by performing an anticipatory assessment of the interim system and providing feedbacks on the inputs used in the PFD definition. These inputs - coming from the first iteration of assessment - enable the optimisation of the continuous flow system. The modified system is then re-assessed and used as basis for the successive iterations. After a sufficient number of iterations, the iterative loop is ended, and the results of the assessment are further benchmarked in the comparative analysis step. The goal of the explained approach is to take the system to its optimum point in terms of costs and environmental impact, keeping the product quality unvaried. Subsequently, the defined continuous flow system and the reference batch system are compared. The full set of operations involved in a full-scale PFD is taken into account, namely, the precursors' preparation, pumping, synthesis, heating and mixing, cleaning, separation and waste disposal.

- **Assessment phase**

  The assessment phase is composed of three main steps: Life cycle inventory (LCI), environmental impact assessment and cost assessment.

  Life Cycle Inventory

  This is an inventory analysis in which all the relevant inputs and outputs of the product system are quantified by means of data collection and calculation procedures (indicated by the ISO 14040 (International Organization for Standardization, 2016)). This step serves the purpose of qualifying and quantifying material and energy streams throughout the life cycle of the production and is the basis from which the environmental impacts and costs are calculated.

  At the basis of the inventory analysis there is the definition of the Functional Unit (FU), that quantifies the function of the product under study and serves the purpose of providing a reference to which input and output data are normalized. Specifically, the chosen FU for this study is 1 litre of AuNPs product (OD1, 10 nm).

  The data for the LCI are quantified for each unit process included into the defined system boundaries (Figure 3). System boundaries are subdivided into two macro systems: foreground and background systems. The foreground system is composed of the array of operations occurring in the production phase, separation, cleaning and waste processing. The background system is composed of the set of operations and services that revolve around the synthesis, and whose impacts were taken into account in the assessment: electricity production, raw materials extraction, chemical production and waste disposal.

  Each process has been built into the model by compiling the material and energy balance occurring in them (see supporting information) through the standardised approach indicated in the ISO 14040 (International Organization for Standardization, 2016) and these include:

  - Energy inputs, raw materials, ancillary inputs, other physical inputs,

- Products, co-products and waste,
- Emissions to air, discharges to water and soil, and other environmental aspects

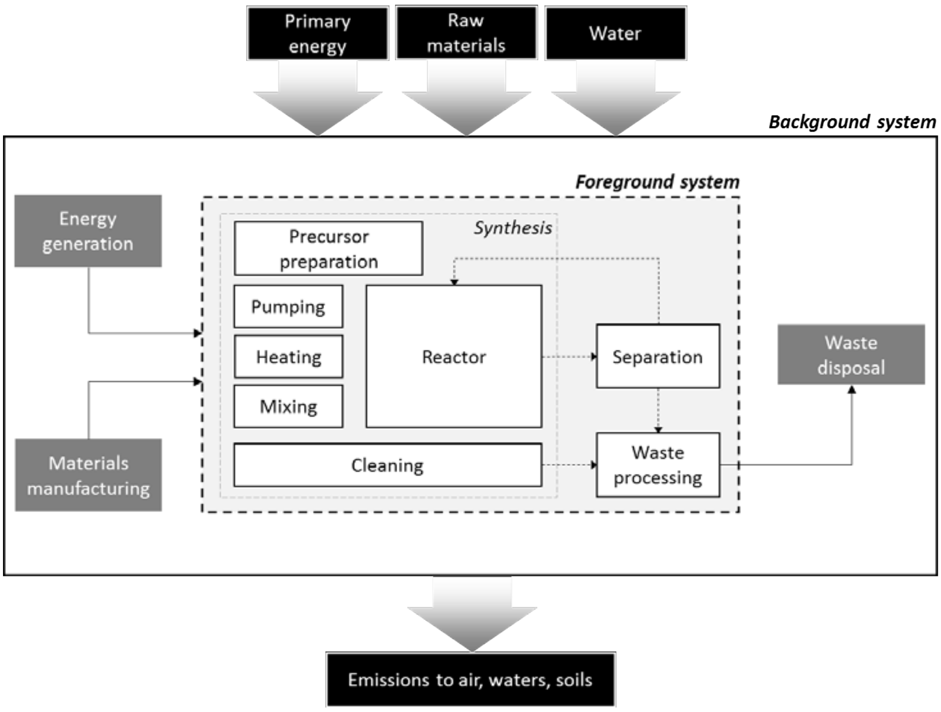


Figure 3 – System boundaries: foreground and background systems

The functional unit and the system boundaries defined are the same for both continuous flow system and batch system, this is a *sine qua non* condition for a coherent comparison.

Environmental impact assessment

The environmental impacts of the batch and continuous flow production systems are calculated. This step is called Life Cycle Impact Assessment (LCIA) and aims at translating the elementary flows described in the life cycle inventory into environmental impacts. It assigns to each flow (i.e. emissions or resource use of a product system) an impact on the environment. This is achieved by means of impact categories: an impact category covers a specific aspect of the environmental consequences of the emissions arising from the production system. The environmental impacts are expressed on the basis of the declared FU.

An environmental impact can be defined as a set of environmental changes due to causes originating in human activities. These impacts are generally calculated by means of a Characterisation Factor (CF), namely the impact contribution per unit of elementary flow, to a specific environmental issue (Impact category): $Impact_i = \sum_j (CF_j * E_j)$ where, i is the considered impact category and j is a given emission or resource extraction (E_j).

The impact is then obtained as the sum over all interventions j, of the elementary flows, classified within a specific impact category i, multiplied by their respective CF. The unit is given by the characterisation factor and it is equal for all elementary flows classified under the same impact category. CF is calculated using quantitative models based on the cause-effect chain of events leading to the impact on the environment (adverse effects). For instance, 1 kg of methane emitted into air does not have the same impact on climate change as 1 kg of CO_2, even though their emitted quantities are the same since methane is a stronger greenhouse gas (GHG). LCIA characterisation methods essentially model the environmental mechanism that underlies each of the impact categories as a cause-effect chain starting from the environmental intervention (emission or physical interaction) all the way to its impact. To this end, the impact can be expressed throughout midpoint and endpoint methods, depending on the type of output the analysis is meant to provide (i.e. increased chemical concentration in a lake vs extinction of species). As a general rule, the further the outcome of the assessment is expressed in the cause-effect chain, the more the results can be biased. In the present study, the chosen LCIA method implies a midpoint level assessment in order to minimize errors.

Cost assessment

This provides a detailed breakdown of all the costs involved in the production of AuNPs. The production cost is calculated for both batch and continuous flow system on the basis of the inventorial information defined through the LCI. Each chemical, activity or service involved in the production phase is included in the cost assessment. It hence enables a comparison between the two systems analysed in terms of cost efficiency.

- **Comparative analysis**

  The results of the LCIA and cost assessment are organised, and an uncertainty analysis is performed. With regards to the LCIA, the environmental impacts are further examined through normalisation and a scenario analysis is undertaken. This contextualises the environmental impacts of the production of gold nanoparticles in the broader context of European emissions. It also provides a projection of the environmental impacts of the AuNPs production in the scenario in which gold nanoparticles are fully adopted in nano-enabled medical applications.

  A hotspot analysis is also performed with the aim of identifying the steps in the production process that cause most of the environmental impacts.

  Finally, the output of these analysis, for the batch and CF systems, are compared and discussed.

2.2 System definition

The full-scale process flow diagrams are presented in this section for the batch and the CF systems, describing the production phase of AuNPs in detail. The definition of these systems provides all the inventorial information for the LCI. The production phase is highly important for the description of the life cycle of AuNPs product. In fact, it determines all the peripheral activities that orbit around it, such as electricity production, waste disposal and production of chemicals, which are considered in the assessment.

In the assessed systems, the synthesis of AuNPs follows the Turkevich method. This has been one of the main routes of synthesis of gold nanoparticles for many years (Turkevich, 1985) and hence a large amount of data and knowledge on it is available in literature. This literature-based information was used to complement the data from the lab experiments and from the industrial practice, in order to fully describe a full-scale production system for both batch and CF. In fact, on one side, the batch production is conventionally adopted for the production of gold nanoparticles at commercial scale, and the description of this system has been achieved mainly by means of data collection and only partly integrated with literature data to cover missing details. On the other side, the CF production system is an emerging technology and it has not been scaled up yet. The full-scale CF system described in this section is a projection, and therefore its definition required a lot of information based on lab experiments and on information available in literature. The maturity of the continuous flow production system developed in the lab and complemented with the data coming from literature (Kettemann et al., 2016; Polte et al., 2010; Wuithschick et al., 2015) was adequate to enable a scale up/out analysis.

With regards to the details of the Turkevich method, the synthesis of gold nanoparticles occurs via reduction of tetrachloroauric acid trihydrate ($HAuCl_4$) by trisodium citrate (Na_3Cit). The target product is 10 nm gold nanoparticles suspended in water with optical density OD1, equal to 5.76×10^{-5} g_{gold}/l, and maximum coefficient of variability (CV, calculated by dividing the standard deviation of the nanoparticle size by the mean nanoparticle size) of 10%. The recipe adopted for both batch and CF synthesis is the same: $[HAuCl_4] = 0.5\ mM;\ \frac{mol\ Na_3Cit}{mol\ HAuCl_4} = 6$.

A schematic representation of the PFD of the two system is shown in Figure 4.

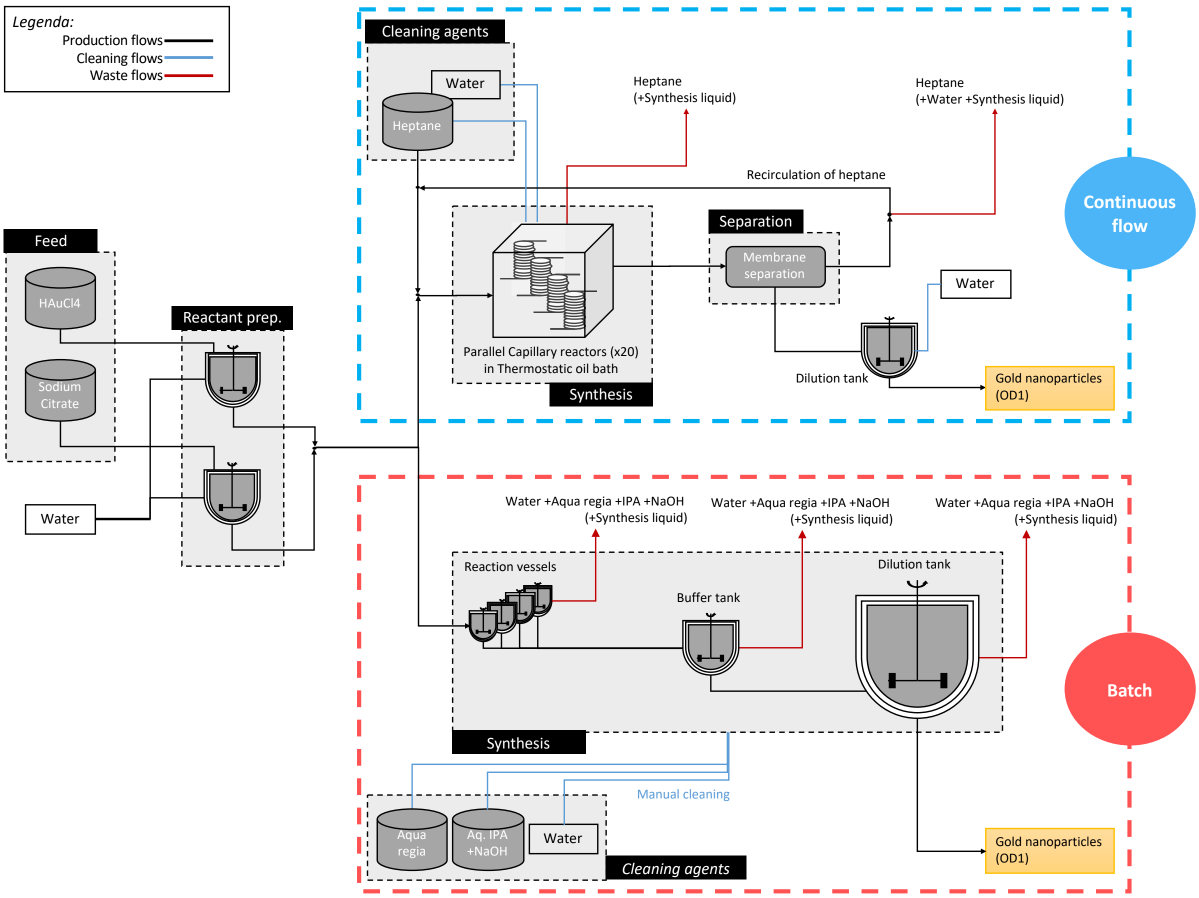


Figure 4 – Schematic representation of the process flow diagram of batch and continuous flow system

There are a number of substantial differences in the PFD of the two systems. The CF setup involves a segmenting fluid, heptane, to achieve a Taylor flow in the reaction step. This is necessary in order to improve residence time distribution and avoid fouling that can affect product quality. Furthermore, a separation step is included in the CF system for the separation of the product from the segmenting fluid and the recirculation of the latter. The cleaning of the two systems also follows different procedures.

The summary of the LCI information regarding the batch and CF systems is reported in Table 1.

Table 1 – Inventory list for the batch and continuous flow system: materials, energy consumption and labour

		Quantity		
		Continuous Flow system	Batch system	
Chemicals	$HAuCl_4$ trihydrate	4.33	4.33	*kg*
	Trisodium citrate	19.7	19.7	
	Water	44000	44000	
	Heptane	134.4	0	
Cleaning	Water	23010	289575	*kg*
	Aqua regia	0	223	
	IPA	0	43018	
	NaOH	0	7596	
	Heptane	95.7	0	
Reactor equipment and service fluids	Teflon capillary	120	0	*m*
	Silicone oil	3880	100	*kg*
Peripheral equipment	Membrane separator	1	0	*unit*
	Pumps	27	16	
Energy consumption	Electricity (Heating)	21609	1686	*kWh*
	Electricity (Mixing)	171	5081	
	Electricity (Pumping)	97306	20167	
Labour	Technicians	2920	5072	*person*h*
Waste disposal	Water treatment	1500	1500	m^3
	Hazardous waste	230	340	*kg*

The full description of the PFD of the batch and CF system is reported in the 'Supporting Information'. This includes a quantitative and qualitative report of the procedure of cleaning and maintenance observed in the production systems, along with the full list of the material and energy inputs used in the LCI.

3 CALCULATIONS

This section reports the approach followed for the calculation of environmental impacts and costs. A more detailed explanation is presented in the 'Supporting Information' along with the calculation of the uncertainties associated to the results of the assessment.

3.1 Environmental impact assessment

ILCD/PEF recommendation 1.09 (Hauschild et al., 2011) is the chosen method for the LCIA. This method fixes the quantitative modelling to early stages in the cause-effect chain to limit uncertainties. Results are grouped in midpoint categories. The database used for the model is GaBi ts 8.7 (SP36) professional + extensions (II, VI, IX, XVII) and Ecoinvent 3.5 (integrated SP36): the datasets are in compliance with the ISO 14044 (International Organization for Standardization, 2006), ISO 14064 (International Organization for Standardization, 2018) and ISO 14025 (International Organization for Standardization, 2015) standards. The LCIA results are expressed on the basis of the functional unit - by standard defined in ISO 14044 (International Organization for Standardization, 2006) as the "quantified performance of a product system for use as a reference unit" – specifically 1 litre of

AuNPs product (OD1, 10 nm) obtained from a yearly production of around 45 m^3 of product. In accordance to the ISO 14044, with regards to a comparative analysis, the functional unit is set to be the same for all the compared product systems. In general, environmental impacts were estimated using a cradle-to-gate boundary for European production: in other words, the activities that compose the life cycle (e.g electricity production) are region-specific and are modelled on the basis of European activities. The environmental impacts of the batch and CF systems are expressed for different impact categories; each impact category covers a specific aspect of the environmental consequences associated to the emissions arising from the production system. These impact categories are selected from the LCIA method 'ILCD/PEF recommendation 1.09' (Hauschild et al., 2011) and they are reported in Table 2.

Table 2 – Impact categories used for the LCIA and description: the impact categories are selected from the LCIA method 'ILCD/PEF recommendation 1.09'

Impact category	Description	Unit	Abbreviation
Acidification	It is mainly caused by air emissions of NH_3, NO_2 and SO_x.	[mole H^+ eq.]	A
Climate change, excluding biogenic carbon	Contributions of the greenhouse gases to the global warming and climate change	[kg CO_2 eq.]	CC
Ecotoxicity freshwater midpoint	Toxic effect on aquatic freshwater species in the water ecosystems.	[CTUe]	EcoTOX
Eutrophication freshwater midpoint	Eutrophication effects in the freshwater compartment.	[kg P eq.]	E fw
Eutrophication marine midpoint	Eutrophication effects in the marine compartment.	[kg N eq.]	E mw
Eutrophication terrestrial midpoint	Eutrophication effects in the terrestrial compartment.	[mole N eq.]	E t
Human toxicity midpoint, cancer effects	Toxic effect on humans referring to potential cancer effects.	[CTUh]	HT c
Human toxicity midpoint, non-cancer effects	Toxic effect on humans referring to potential non-cancer effects.	[CTUh]	HT non-c
Ionising radiation	Human exposure to ionizing radiation with potential alterations in the DNA	[kBq U235 eq.]	IR
Ozone depletion	Depletion of the ozone layer at the stratosphere level.	[kg CFC-11 eq.]	OD
Particulate matter	Direct and indirect contribution to particulate matter formation	[kg PM2.5 eq.]	PM
Photochemical ozone formation midpoint	Contributions of VOC (volatile organic compounds) and non-VOC to the formation of ozone at troposphere level.	[kg NMVOC eq.]	POF
Resource depletion, water	Water resource depletion.	[m^3]	RD water
Resource depletion, minerals, fossils and renewables	Depletion of mineral and fossil resources.	[kg Sb eq.]	RD m, f, ren

Normalisation

Through the normalisation, the environmental impacts of the LCIA results are compared to the environmental impacts arising from a defined geographical region or sector, for each impact categories. This step also enables the comparison of the environmental impacts across different impact categories. The normalised impact (*NI)* is calculated by multiplying the impact of the product by the normalisation factor (*NF*):

$$NI_i = Impact_{i,tot} * NF_i \quad (10)$$

Where, *i* is the considered impact category.

The chosen normalisation method is ILCD/PEF recommendation 1.09 (Benini et al., 2014): the normalisation factor is expressed in impact per person equivalents (*P,* representing the reference region, EUROPE) per year:

$$NF_i = \left(\frac{Impact_{i,EU}}{P}\right)^{-1} \quad (11)$$

Where, i is the considered impact category, P is the European (EU-27) population equal to 499M inhabitants (Benini et al., 2014).

3.2 Cost assessment

The production cost is calculated for both batch and continuous flow system on the basis of the inventory information defined through the LCI. Each chemical, activity or service involved in the production phase is included in the cost assessment. The list of the prices related to these elements is reported in the 'Supporting Information'. The source of data is mainly Sigma-Aldrich (for chemicals) and EUROSTAT (for electricity and labour cost). With regards to the cost of the chemicals, a correction factor is applied to the prices. This is done with the aim of taking into account the favourable quotations that can be obtained in the case of large bulk orders or in the case of tailored agreements with suppliers for large scale productions (see 'Supporting Information'). The evaluation of the economics of the production systems is based on Operational Expenses (OPEX), Capital Expenses (CAPEX), and Payback Period (PBP).

Specifically, OPEX comprises the cost of chemicals and cleaning agents involved in the syntheses, labour, energy consumption and waste management. The cost associated with a generic chemical i, for a year of production, is expressed as $cost_i = \left(\frac{£}{kg}\right)_i * kg\ of\ chemical\ i\ used\ in\ a\ year\ of\ production.$

CAPEX is estimated in accordance with the following methods, and the obtained values are subsequently averaged:

- Lang's correlation (Lang, 1948); $C_T = F_{Lang} \sum_{i=1}^{n} C_{p,i}$, where C_T is the capital cost of the plant, $C_{p,i}$ is the purchased cost for the major equipment units, *n* is the total number of units, and F_{Lang} is the Lang factor.
- Percentage of Fixed capital Investment (Peters et al., 2003)

With regards to the PBP, this is calculated as $PBP_i = \left(\frac{(A_{NCI} - OPEX_i)(1-TAX)}{CAPEX_i}\right)$, where i is the production system considered, A_{NCI} is the annual revenue, and TAX is the applied tax rate. For the comparison of the PBP of batch and CF process, the ratio of their PBPs is calculated as follow:

$$\frac{PBP_{Batch}}{PBP_{Continuous\ flow}} = A_{NCI}\left(\frac{1 - OPEX_{Batch}}{1 - OPEX_{Continuous\ flow}}\right)\left(\frac{CAPEX_{Continuous\ flow}}{CAPEX_{Batch}}\right) \quad (12)$$

This indicator gives an idea of the relative amount of time needed to recover the investment, and it is used for the comparison of the economic performances of the two production systems.

4 RESULTS AND DISCUSSION

Results are organised into two sections: environmental impact assessment and cost assessment. Each section offers an analysis on the results related to the single production systems, as well as a comparative analysis.

4.1 Environmental impact assessment

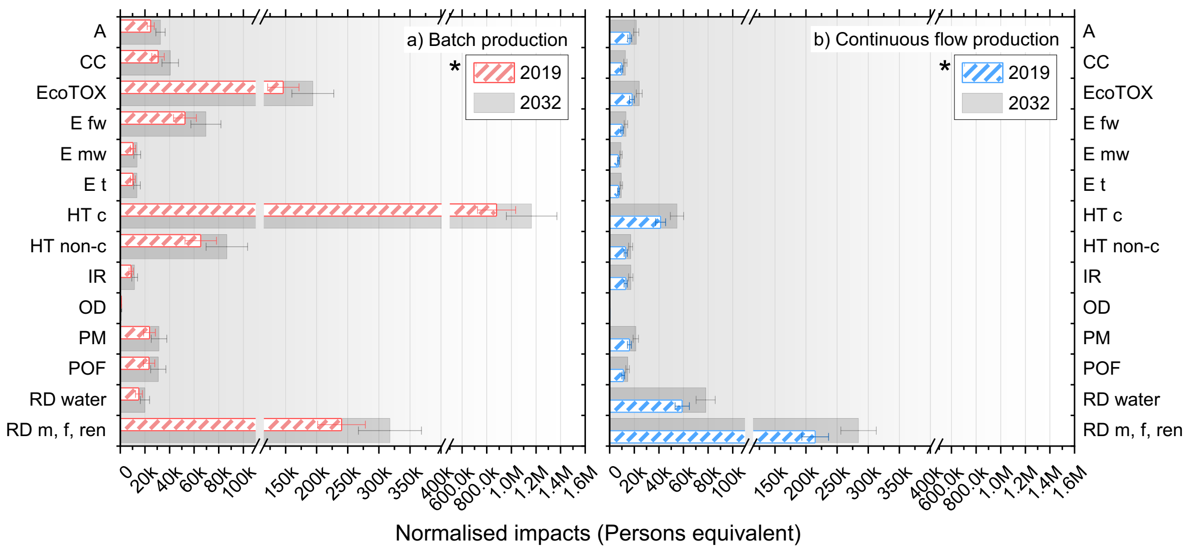
The results of the LCA are divided into three sections, each one offering a different perspective on the environmental impact of the AuNPs production systems:

- **Normalisation and scenario analysis**
  This section contextualises the environmental impacts of the AuNPs production in the broader context of European emissions. It also provides a projection of the environmental impacts of the AuNPs production in the scenario in which gold nanoparticles are fully adopted in nano-enabled medical applications.
- **Technology comparison**
  The absolute environmental impacts of the batch and continuous flow production technologies are compared and discussed.
- **Hotspot analysis**
  A hotspot analysis is undertaken. The goal of this section is identifying the causes of the environmental impacts of the AuNPs production systems.

4.1.1 Normalisation and scenario analysis

Through the normalisation, the environmental impacts are expressed in "persons equivalent". It is a way of expressing the weight of the environmental impact of the production system considered on the total environmental impact arising from a geographical region, which in this case is Europe.

The results of the normalisation are showed in Figure 5 for batch and CF production systems. The figure refers to the case in which gold nanoparticles are fully adopted in nano-enabled medical applications in UK.



* The estimated demand of gold nanoparticles in 2019 is 594 kg – on the basis of the nano-enabled medical applications already on the market or that have the potential to be introduced in the market (Mahapatra et al., 2015). In 2032, the demand of gold nanoparticles in UK is estimated to increase and reach 770 kg. This value is obtained on the basis of World Health Organisation's prediction of cancer cases in 2032 (GCO, 2018; WHO, 2018); tumour targeting is in fact the main medical application of AuNPs and hence the demand of AuNPs is expected to grow accordingly with cancer cases.

Figure 5 – Normalised LCIA results for a) batch production and b) continuous flow production: each graph refers to the scenario in which gold nanoparticles are fully adopted in nano-enabled medical applications in UK, for two time horizons.

In the analysis, two scenarios are outlined: a present situation and a projection of the impacts in the future. With regards to the 2032 scenario, this takes into account the growth of cancer-cases estimated by the WHO; the latter could eventually reflect in an additional demand of AuNPs and consequently increased production. As mentioned in the Introduction, it is paramount to consider the potential evolution of the market in order to grasp anticipately the consequences of a burdened production system in relation to issues such as the availability of gold resources. Evidently, by looking at Figure 5a, the batch production system has high environmental impacts, primarily with respect to Human Toxicity (cancer effects). In this impact category, the normalised impact is equal to nearly one million persons equivalent in 2019 and exceeds 1 M persons equivalent in 2032. As explained previously, each bar of the graphs in Figure 5 is obtained by dividing the environmental impact of the production system in a specific impact category by the environmental impact of all European activities; the number obtained –that is the share of the total environmental impact arising from Europe – is then multiplied by the European population (see section 3.1 for detailed information on the Normalisation). Therefore, this means that the environmental impact of the batch production system in Human Toxicity (cancer effects) in 2019 is equal to the 0.2% of the environmental impact arising from Europe in the same impact category. This percentage share may seem small, but instead is particularly high considering that: firstly, it refers only to a specific industrial field of application (gold nanoparticles for nano-medical applications); secondly, it refers only to a specific region (UK) and not to the demand of gold nanoparticles in Europe.

The first main output of the normalisation is hence that the full exploitation of gold nanoparticles in nano-enabled medical applications can have a magnitude of environmental impact of continental scale, and therefore, the production system of gold nanoparticles needs to be properly considered before its large scale-deployment. To this end, it is also worth noting that the projected environmental impact of the AuNPs production systems is expected to increase - by 33% circa in 2032 (grey bars in Figure 5). This additional environmental impact is a consequence of the increase of lung and neck cancer cases expected in the next years. This will therefore lead to an increase of cancer treatments, which is the main medical application of gold nanoparticles.

Figure 5b offers a different perspective on the same matter by reporting the environmental impact of the production of gold nanoparticles in the case in which the innovative continuous flow technology is adopted in place of the conventional batch technology. The scenario considered is the same, namely the full exploitation of gold nanoparticles applications in UK. In this case, however, the results show that the normalised environmental impact of the CF production systems is on average lower than the batch production systems, in all the impact categories considered. For example, Resource Depletion (minerals, fossils, renewables) is the impact category showing the highest impact for the CF system; however, this impact is equal to 200k persons equivalent circa, which translates into a mere 0.04% of the total European environmental impact in the same impact category. This is circa one order of magnitude lower compared to the highest normalised impact of the batch system (0.2% in HT, cancer effects).

In light of the above, it is clear that an enhanced production technology, such as the continuous flow, could significantly reduce the emissions related to the production of gold nanoparticles. This is especially crucial when we consider the large scale-deployment of this production system that is needed for fulfilling the potential demand of gold nanoparticles. In this respect, a detailed comparison of batch and CF production technologies is reported in the following section 'Technology comparison'.

Another major output of the normalisation is that it enables a comparison of the environmental impacts across different impact categories and hence it is possible to have a criterion of selection of the impact categories of major relevance. In order to enable such selection, it is necessary to look at the shares of the total impact of batch and CF production for each impact category considered in the analysis. The total impact of a production system is the sum of the normalised impacts of all the impact categories. The total impacts of batch and CF production are respectively 1.29 M and 0.22 M persons equivalent. Consequently, the share of the total impact for each impact categories is obtained by dividing the normalised impact of a given impact category by the total impact of the production system considered. For example, the normalised impact for Human Toxicity (cancer effects) in the batch system is 0.88 M persons equivalent and hence the share of the total impact is 57%. The same procedure is followed for the rest of the impact categories and the results are reported in Table 3.

Table 3 –Share of the total impact for batch and continuous flow production for the impact categories considered in the normalisation

	Share of the total impact*		Relevance
	Batch	Continuous flow	
Human toxicity, cancer effects	57%	9%	HIGH
Resource depletion, mineral, fossils and renewables	16%	49%	
Ecotoxicity freshwater	10%	4%	
Human toxicity, non-cancer effects	4%	3%	MODERATE
Eutrophication freshwater	3%	2%	
Acidification	2%	4%	
Climate change	2%	2%	
Particulate matter	2%	4%	
Photochemical ozone formation, human health	2%	3%	
Resource depletion, water	1%	13%	
Eutrophication marine	1%	2%	LOW
Eutrophication terrestrial	1%	2%	
Ionizing radiation	1%	3%	
Ozone depletion	<1%		

*Total impact is the sum of the normalised impact of all the impact categories and is equal to: 1.29 M persons equivalent for the batch system and 0.88 M persons for the continuous flow system

As it emerges from Table 3, the highest shares are those related to Human Toxicity (cancer effects), Ecotoxicity and Resource depletion (minerals, fossils and renewables) whilst Eutrophication marine water and terrestrial, Ozone depletion and Ionising radiation contribute only marginally to the overall impact of the system. Therefore, these impact categories are excluded from the following analyses ('Technology comparison' and 'Hotspot analysis') with the aim of narrowing down the scope of such analyses to the most critical environmental consequences. It is worth noting that the order of relevance of the impact categories listed in Table 3 changes significantly for the CF system compared to the batch system. For example, Human toxicity (cancer effects) and Resource depletion (minerals, fossils and renewable) showed the highest contribution (57% and 16% respectively) in the batch production system, while the result is inverted for the CF system. On the other hand, the impact related to Resource Depletion (mineral, fossils and renewables) takes 49% of the total impact of the CF production. This share is increased with respect to the batch system (16%) and hence this may suggest an increase of the impact; on the contrary the impact is reduced. The reason behind this lies that the total environmental impact of the continuous flow system is lower than the batch system: 0.22 M and 1.29 M persons equivalent respectively, as reported before.

In order to capture the factors that make the continuous flow system have a reduced environmental impact compared to the batch system, it is necessary to complement the results of the normalisation analysis with the direct comparison of the absolute environmental impacts of the two production systems. Such comparison is offered in the next section and it shows that the different shares of the total impact highlighted in Table 3 are generally attributable to drastic reductions of the environmental impacts of the CF production with respect to the batch production in certain impact categories.

4.1.2 Technology comparison

The comparison of the absolute environmental impacts of the batch and continuous flow production technologies is shown in Figure 6: the graph refers to 1 l of product obtained from the yearly production of gold nanoparticles. In this section the environmental impacts are expressed through absolute units instead of the normalised unit (persons equivalent) adopted in the normalisation. Therefore, it is no longer possible to compare the environmental impacts across different impact categories and the columns in Figure 6 must be compared only within the same impact category. The columns are equalised for sake of readability: every columns' value needs to be multiplied by the factor reported on the inside top of the graph's area. The boxes report the percentage change of the environmental impact of the CF production with respect to the batch production.

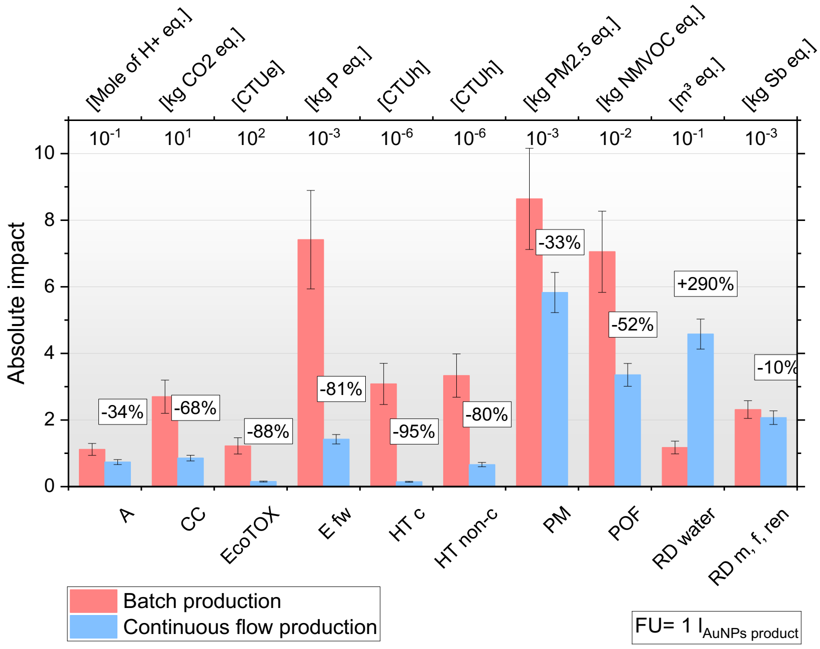


Figure 6 – Absolute LCIA results and comparison: absolute impacts per 1 l of AuNPs product for batch and continuous flow system

The continuous flow production achieves significantly lower environmental impacts compared to the batch production in every impact category with the exception of Resource Depletion (water). The percentage reduction of environmental impact span from -10% (in RD minerals, fossils, renewables) to -95% (in HT cancer effects) with the major savings being in the impact categories: Climate Change, Ecotoxicity of freshwater, Eutrophication of freshwater, Human Toxicity (cancer and non-cancer effects) and Photochemical Ozone Formation.

The relative importance of the percentage changes shown in Figure 6 is appreciable relating these percentage changes to the values reported in Table 3 that highlights the relative weight of each impact category with respect to the total impact of the production system. For example, Figure 6 may give the impression that Resource Depletion (Water) is the category with the most relevant impact change when comparing batch to CF production. However, this change (+290%) must be looked at also considering the normalised analysis (Table 3); this showed that the impact of Resource Depletion (Water) is marginal when compared to the total impact of the batch production (1% of the total environmental impact). Therefore, the percentage change of the impact in Resource Depletion (water), in Figure 6, is negligible when compared to the percentage change in those impact categories that have a higher share of the total impact of the production systems. These impact categories are highlighted in Table 3 and are, in order of importance, Human Toxicity (cancer effects), Resource depletion (mineral, fossils and renewables) and Ecotoxicity of freshwater.

It is worth noting that the CF production showed a reduction of the environmental impact in all of these impact categories compared to the batch production. Specifically, the impacts of the CF production are reduced by 95% in Human Toxicity (cancer effects), by 88% in Ecotoxicity of freshwater and by 10% in Resource Depletion (mineral, fossils and renewables). The latter is the lowest percentage reduction compared to other impact categories. This suggests that the primary causes of the impact in RD (mineral, fossils and renewables) might be elements in common between the batch and CF systems, such as the synthesis method. In fact, Resource Depletion (mineral, fossils and renewables) takes into account the depletion of gold, which is used as the main raw material for the production of the gold precursor ($HAuCl_4$) for both the batch and the continuous flow production systems. More insight on the causes of the environmental impact of the two systems are presented in the next section through the hotspot analysis.

4.1.3 Hotspot analysis

The previous sections profile that the batch and continuous flow production systems have a radically different environmental impact. In this section, the causes of the different environmental impacts are identified through a hotspot analysis. The latter was performed by following two approaches:

- By groups (Figure 7); the environmental impacts are sorted on the basis of the inventory group that caused the impact. These groups are the same groups defined during the Life Cycle Inventory, namely, chemicals, energy consumption, reactor equipment and service fluids, cleaning and waste disposal. Through this approach, it is possible to localise the generic source of the impact in the production system
- by activity (Figure 8); the environmental impacts are sorted on the basis of the activity that caused the impact (i.e. incineration, sodium citrate production, etc.). It is worth remembering that each activity belongs to a specific group (see Table 4); thus, the sum of all the environmental impacts or costs of the activities in a given group is equal to the environmental impact of that group. For example, the environmental impact of the group 'Chemicals' is the sum of the environmental impacts of the activities belonging to 'Chemicals', namely: $HAuCl_4$ production, sodium citrate production, heptane production and water use.

Table 4 – List of the inventorial groups and related activities

Groups	Activities*
Chemicals	$HAuCl_4$ trihydrate production
	Sodium citrate production
	Water use
	(CF) Heptane
Cleaning	(B) Aqua regia production
	(B) IPA production
	(B) NaOH production
	(CF) Heptane
	Water use
Reactor equipment and service fluids	(B) Borosilicate reactor manufacturing
	(CF) Teflon capillaries manufacturing
	Silicone oil production
Energy consumption	Electricity production, heating
	Electricity production, mixing
	Electricity production, pumping
Waste disposal	Wastewater treatment
	(B) Hazardous treatment incineration

*the activities that are specific only to a production system are preceded by brackets: (B) batch production system, (CF) continuous flow production system

This approach to the hotspot analysis brings out a higher level of information than the hotspot analysis sorted by groups, and hence it is possible to trace the primary causes of the environmental impacts.

The results of the hotspot analysis, sorted by groups, are reported in Figure 7.

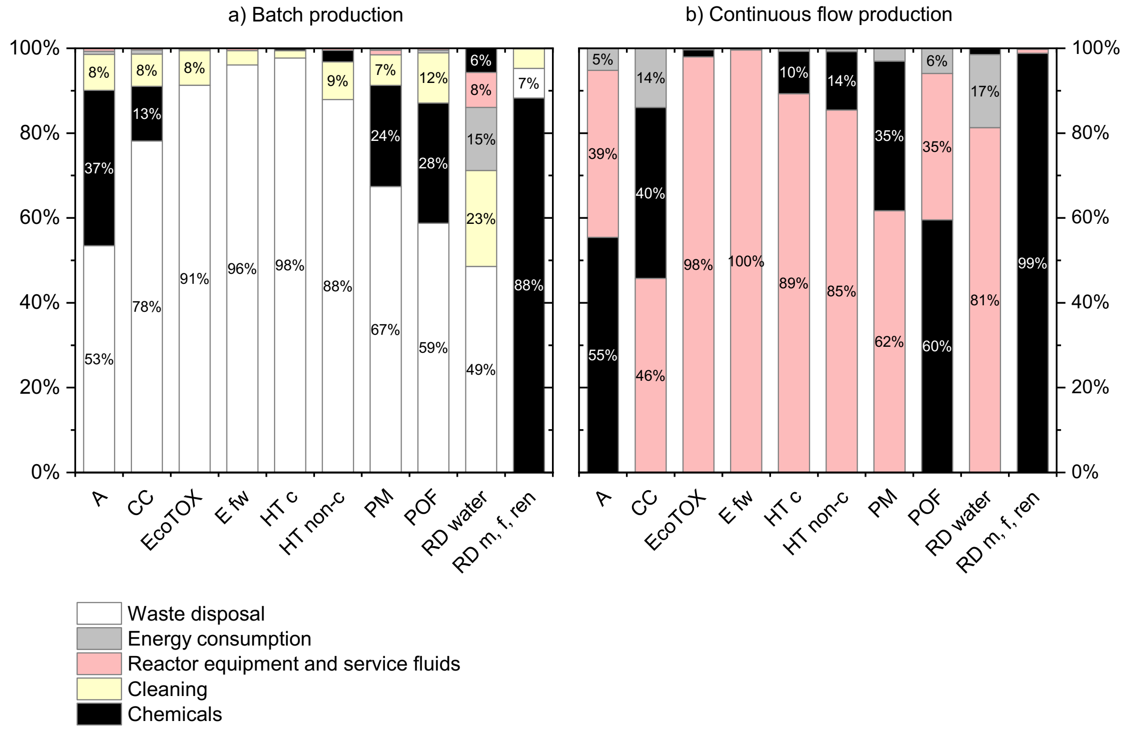


Figure 7 –Hotspot analysis (sorted by group) for: a) Batch system, b) Continuous flow system

On one hand, the main contributors to the environmental impact of the batch system (Figure 7a) are waste disposal, chemicals and cleaning. Energy consumption and reactor equipment and service fluids contribute only marginally to the overall environmental impact. Their contributions is negligible (<2% of the total impact of the batch production) in every impact category exception made for Resource Depletion (water) but, as seen before, the latter is an impact category of minor relevance (Table 3).

On the other hand, the largest share of the environmental impact of the CF system (Figure 7b) is associated to reactor equipment and service fluids, chemicals and, in minor part, energy consumption. Waste disposal and cleaning contribute to less than 1% of the total the total impact of the CF production in all the impact categories.

By cross comparing the results of the hotspot analysis with the absolute impacts reported in the previous section, it is clear that the reduced environmental impact of the CF system compared to the batch system is mainly attributable to the differences in the cleaning procedures and treatment of wastes. To capture this, it is necessary to consider three factors:

- the largest share of the total environmental impact of the batch production is associated to the impact categories of Human Toxicity (cancer effects), Resource depletion (mineral, fossils and renewables) and Ecotoxicity of freshwater, as emerged from the normalisation in Table 3.
- In these impact categories, the continuous flow production showed major percentage reductions of the impact (Figure 6): respectively, -95%, -10% and -88% compared to the batch production.
- The hotspot analysis showed that, in these impact categories, the main differences between batch and CF production are due to waste disposal and cleaning. Specifically, this is shown in Figure 7a (HT c.,

EcoTOX and RD m., f., ren.) where waste disposal and cleaning are the "hotspots" of the batch production whilst they are practically untraceable in the CF system, see Figure 7b.

The second part of the hotspot analysis investigates into the causes of the environmental impact in more depth by looking at the single activities -composing the life cycle of the production systems- responsible for the impacts. Each activity belongs to a specific group (see Table 4); thus, the sum of all the environmental impacts or costs of the activities in a given group is equal to the environmental impact of that group. For simplicity, the group to which each activity belongs is indicated after the name of the activity, in brackets (i.e $HAuCl_4$ production (Chemicals), electricity production, mixing (Energy consumption), etc.).

The results of the hotspot analysis, sorted by activity, is reported in Figure 8.

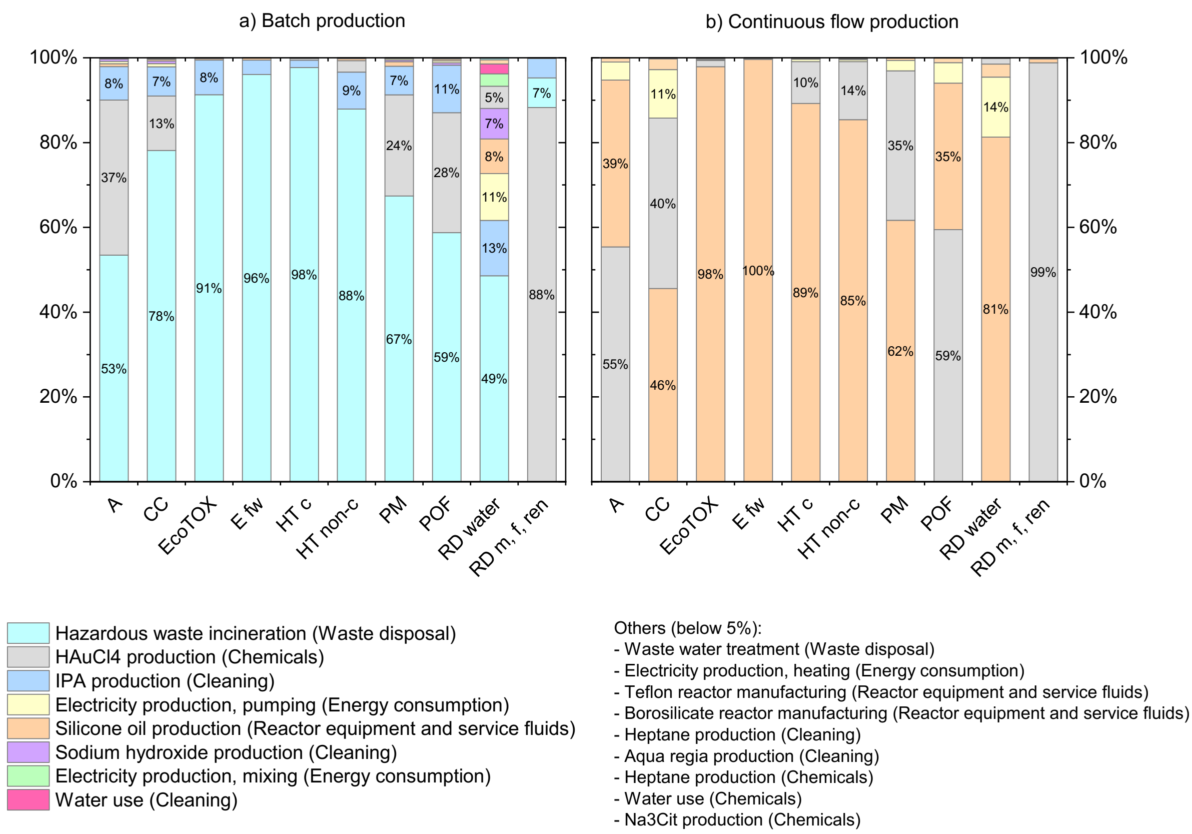


Figure 8 - Hotspot analysis (sorted by activity) for: a) Batch system, b) Continuous flow system

The activities that take most of the share of the environmental impact of the production of gold nanoparticles are:

- Hazardous waste incineration (Waste disposal), $HAuCl_4$ production (Chemicals), IPA production (Cleaning) and Sodium hydroxide production (Cleaning) for the batch system (Figure 8a)
- Silicon oil production (Reactor equipment and service fluids), $HAuCl_4$ production (Chemicals) and Electricity production, pumping (Energy consumption) for the continuous flow production (Figure 8b)

It is worth noting that each one of these activities is the main cause for the environmental impact of the group to which they belong (indicated in brackets). This is appreciated by looking at the percentage share of these activities in Figure 8 in comparison with the percentage share of the related groups in Figure 7: these activities take nearly the whole share of the environmental impact of the group to which they belong.

The hotspot analysis is particularly useful for identifying the causes of the environmental impact in those impact categories that, through the normalisation, were found to be the most relevant for the LCA: Human Toxicity (cancer effects), Resource depletion (mineral, fossils and renewables) and Ecotoxicity of freshwater. It must be stressed that the total environmental impact of the two production systems is coming for the major part from these impact categories. Therefore, the activities that contribute the most to the environmental impact in these impact categories are the mere primary causes of the total environmental impact of the two systems: hazardous waste incineration and production of $HAuCl_4$.

It must be also noted that the CF system showed a significant percentage reduction of the environmental impact compared to the batch system in each of these highly relevant impact categories. This must be taken into account when looking at the results of the hotpots analysis of the continuous flow system (Figure 8b). For example, the fact that silicone oil production is barely present in Figure 8a (batch hotspot) whilst being a predominant contributor in Figure 8b (CF hotspot), does not indicate an increase of the environmental impact of the production of silicone oil in the CF system. This effect is the result of the absence or strong reduction, in the life cycle of the CF system, of those ‘high impacting’ activities that are present in the life cycle of the batch production, namely, hazardous waste disposal, IPA production and sodium hydroxide production. Therefore, some ‘low impacting’ activities, such as silicone oil production, that were out of the radar of the hotspot analysis of the batch system, emerge in the hotspot of the CF system: their relative share of the impact increases compared to the batch system even though their absolute environmental impact does not change.

In consequence of the previous considerations, the rest of the activities investigated through the hotspot analysis have negligible effects on the total environmental impact of the production systems. These ‘low impacting’ activities are listed in the legend of Figure 8 but are not easily traceable in the graphs as their share of the environmental impact was found to be below 5% in every impact category.

Lastly, further insight is offered with regards to the two activities that emerged from the hotspot analysis as the major causes to the environmental impact of the production of gold nanoparticles, namely hazardous waste incineration and production of $HAuCl_4$.

- **Hazardous waste incineration**

  Hazardous waste incineration is the main contributor to the life cycle emissions of the batch system: it takes 96% and 98% of the environmental impact in Human Toxicity (cancer effects) and Ecotoxicity of freshwater (Figure 8a). The wastes of the batch system are composed for the major part by the high volumes of aggressive cleaning agents arising from the cleaning procedures. The cleaning of the batch reactors requires, in fact, abundant quantities of IPA, aqua regia and sodium hydroxide that are disposed after the cleaning phase. The resulting waste stream has to be treated as hazardous waste, according to the SDS of these compounds, via incineration. The environmental impact of the incineration is mainly attributable to emissions of compounds that contain sulphur, nitrogen, halogens (such as chlorine), and toxic metals. These emissions are of primary concern, owing to their potential effects on human health and the ecosystem.

On the other side, the CF system produces primarily a non-hazardous waste stream and hence has a much lower environmental impact associated with waste disposal. The wastes of the CF production are in fact principally composed by mild cleaning agents used in the cleaning procedures (only small quantities of heptane are used, around 230 kg/y). Consequently, the impact of the hazardous waste incineration is negligible: virtually the entire waste stream is processed into wastewater treatment facilities whose resulting impact takes less than 1% of the total environmental impact of the CF system in all the impact categories considered in the analysis (see Figure 8b).

- **$HAuCl_4$ production**

  $HAuCl_4$ is used as the gold precursor in the synthesis of gold nanoparticles. Its production strongly affects the environmental impact of the batch and continuous flow production systems.

  The high environmental impact of the production of $HAuCl_4$ is caused predominantly by the extraction of the gold needed for its production. The gold extraction activities are, in fact, highly energy-demanding and resource consuming, and have a high impact on acidification, climate change and resource depletion. The standard method of gold extraction worldwide is the cyanide method (Karahan et al., 2006). The mining, comminution (crushing and grinding) and cyanidation stages make the greatest contribution to the environmental impact of this process, with electricity being responsible for just over half of the greenhouse gas footprint (Norgate and Haque, 2012). It is worth noting that the environmental footprint of the extraction of gold is expected to increase in the next years in consequence of falling gold ore grades.

  With regards to how this affects the comparison of the two production technologies, it is firstly necessary to recall that the LCA emphasized the lower environmental impact of the continuous flow system, compared to the batch system, in nearly all the impact categories considered. Among these, the percentage reduction of the impact in Resource Depletion (mineral, fossil, renewables) was the lowest reduction of impact achieved by the continuous flow production (-10%, Figure 6). This impact category emerged from the hotspot analysis as strongly dependant on the environmental impact of $HAuCl_4$ production (between 88% and 99%, Figure 8). However, it is impossible to reduce the environmental impact associated to $HAuCl_4$, and hence further reduce the total environmental impact of the CF system, without either changing the synthesis method or the source of gold as its use is a direct consequence of the synthesis method.

  To this end, second-hand gold could theoretically be used to manufacture $HAuCl_4$ and consequently reduce the depletion of gold. It has been estimated that about 15% of all gold ever mined was used in dissipative industrial applications or is unaccounted for or unrecoverable, leaving about 85% (between 133,000 and 153,000 t) still in use and available for recycling (Muller and Frimmel, 2010). However, the use of recycled gold would imply a redistribution of these gold stocks, today distributed in major part in the investment and jewellery sector. Therefore, this would eventually lead to increase the gold demand in those sectors deprived of the gold resource in consequence of the redistribution; thus, resource depletion would be only shifted and not reduced. The last viable option could finally be the recycling of gold nanoparticles products at the end of their cycle of use but the feasibility of this option needs to be further investigated (Pati et al., 2016).

4.2 Cost assessment

Figure 9 reports the capital and operating expenses for the batch and continuous flow systems.

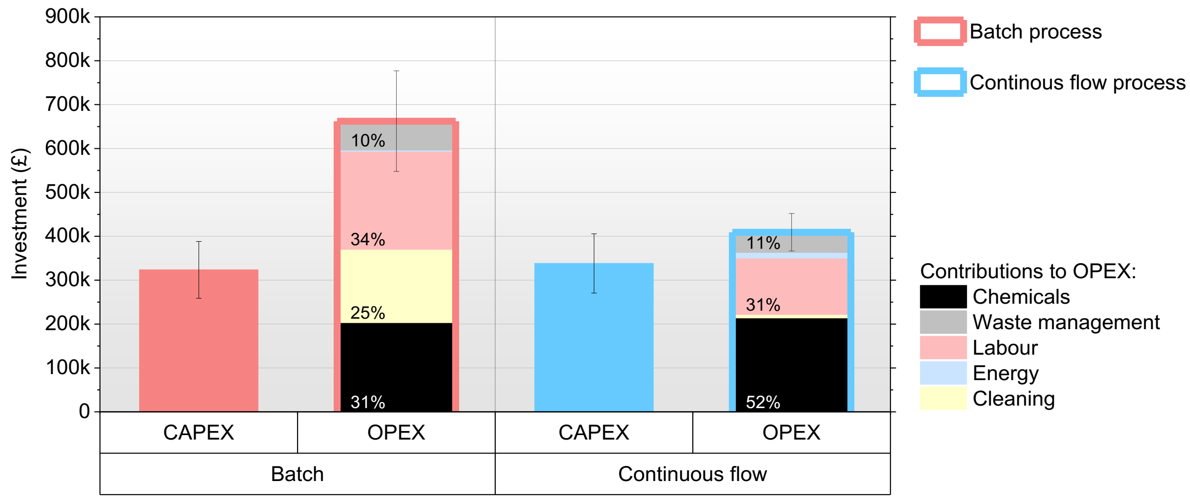


Figure 9 –Comparison of operating expenses (OPEX) with relative contributions, and capital expenses (CAPEX) for batch and continuous flow process

In the CF system, the operating expenses are around 38% lower than the batch production. The main contributors to this significant reduction are the costs associated with cleaning, waste disposal and labour. The cost of the cleaning and waste disposal are closely connected as the waste arising from both production systems is mainly composed of the cleaning agents used up in the synthesis. In the batch system, the sum of the costs associated to cleaning and waste disposal is 4.3 times higher than the CF system. Aqua regia, IPA and NaOH are used in large quantities during the cleaning procedures of the batch system and they are disposed as hazardous wastes. In the continuous flow system, the cleaning is milder and involves water and small volumes of heptane, and the associated cost of disposal is negligible compared to the overall production cost. With regards to the labour cost, this is a major contributor with around 32% of OPEX in both the systems. The easiness of the operations, maintenance and cleaning of the CF system translate into less labour and hence less labour cost (42% lower than the batch system): the production requires only a technician working full time. Furthermore, the cost of chemicals is virtually identical in the two production systems (black bars in Figure 9); the recipe used for the synthesis in the two systems is in fact the same, except for the heptane, used in the CF system as a segmenting fluid. The additional cost of heptane, however, does not impact heavily on the operating costs of the CF system, as it is recirculated for the major part. With regards to the energy cost, energy consumption is slightly higher in the CF system. However, the associated cost is relatively low, less than 5% of the OPEX in the CF system, and hence contribute only marginally to increasing the production cost.

Figure 9 provides a summary of the capital expenses for the batch and CF systems. CAPEX has a similar impact on the economics of both production systems, being respectively around £323 k for the batch system and £338 k for the CF system. The difference is marginal; thus, adopting the CF system in place of the batch system does not have a tangible effect on the capital expenditure. On the other hand, the similar CAPEX but a notably lower OPEX, contribute to reduce the overall expenditures compared to the batch system. This translates into a reduced payback period in the CF system, as outlined in Figure 10.

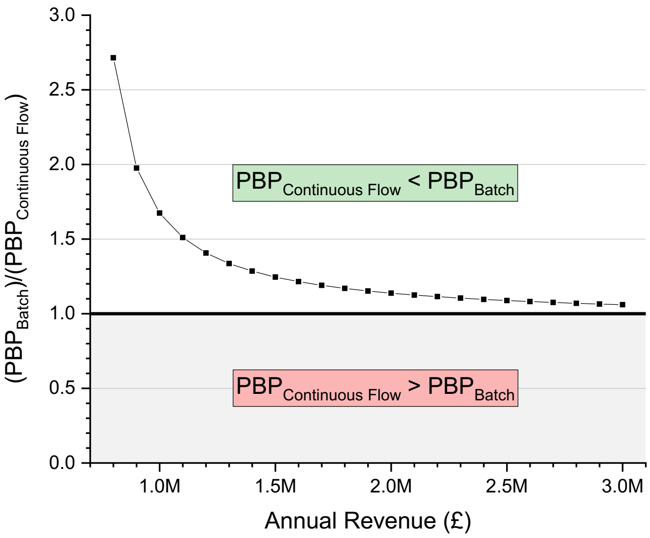


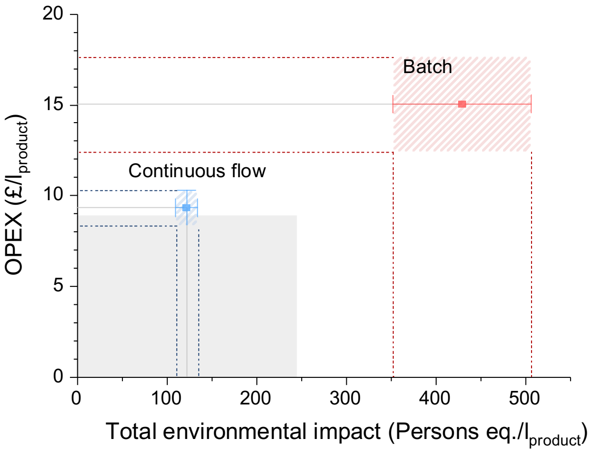
Figure 10 – Comparison of the payback period (PBP) for batch and continuous flow system under variable annual revenue

The PBP of the CF system is in fact shorter than the PBP of the batch system across the whole spectrum of annual revenues. The ratio of PBP_{Batch} to $PBP_{Continuous\ flow}$ decreases with higher annual revenues as a result of a relatively high operating expenses of the two production systems compared to capital expenses. On the whole, the reduction of OPEX is identified in the cost assessment as the main business driver for the CF system. The latter emerges as a financially robust system, having a shorter payback period than the batch system, and hence being more attractive to investments.

5 CONCLUSIONS

We have performed an anticipatory life cycle assessment and a cost assessment on the production of gold nanoparticles. The life cycles of two production technologies were compared, a conventional batch production, used as reference, and an emerging production technology based on milli-continuous flow.

A major trend is clearly visible. Significant advantages can be gained from the adoption of the CF technology in place of the conventional batch technology, both economically and in terms of environmental performances (summary in Figure 11).



Production system	Total environmental impact *Persons eq./$l_{product}$*	Operating expenses (OPEX) *£/$l_{product}$*
Batch	430 ± 77	£15.0 ± £2.6
Continuous flow	123 ± 12	£9.3 ± £1.0

Figure 11 – Summary of the results: comparison of operating expenses and total environmental impact of batch and continuous flow production of AuNPs

With regards to the cost assessment, these advantages consist of a notably lower OPEX (-38%) and a shorter payback period. In the CF system, the lower OPEX stems from milder cleaning procedures and from the reduction of hazardous wastes produced (-32% in mass). Also, less labour is required compared to the batch system, and this translate into reduced expenses in this respect (-42%), thanks also to a more automated process that enables an online control system and involves no manual cleaning operations.

In terms of environmental performances, a number of drawbacks come to light from the LCA of the batch production system, namely, the production of aggressive compounds used intensively as cleaning agents, and the necessity of resorting to incineration to treat the high volumes of hazardous wastes produced in the synthesis. These factors translate into a high environmental impact that primarily concerns the impact categories of Human Toxicity (cancer effects), Ecotoxicity of freshwater and Resource Depletion (minerals, fossil, renewables); these impact categories emerge from the normalisation analysis as the major contributors to the total impact of the batch production, accounting for ca. 83% of the total impact. Furthermore, the scenario analysis highlights that, in the scenario in which gold nanoparticles are fully adopted for nano-enabled medical applications in UK, the large-scale deployment of the conventional batch production technology would be unfavourable compared to the CF production. This is primarily evident with regards to Human Toxicity (cancer effects), Ecotoxicity of freshwater and Resource Depletion (minerals, fossil, renewables), in which the CF production system has an environmental impact respectively 95%, 88%, and 10% lower than the batch system. This significant reduction mainly springs from low volumes of hazardous waste generated during the synthesis, as shown in the hotspot analysis. A special remark should be made for the drop of carcinogenic emissions in the CF production. This is particularly relevant as gold nanoparticles are a product that has the majority of its medical applications in tumour targeting 75% (Mahapatra et al., 2015); thus, this severe reduction of the impact avoids the paradox of having a production system that contributes to an increase in cancer cases and hence hampers the effectiveness of its product.

Amongst the chemicals used in the synthesis of gold nanoparticles, the gold precursor ($HAuCl_4$) is the highest contributor to the environmental impact. Its production strongly hinges on gold extraction activities that have the principal consequence of aggravating the depletion of gold resources; moreover, the impact is expected to further increase in the next years as a consequence of falling ore grades. Unfortunately, mitigating the impact of $HAuCl_4$, is not an easy task. Second-hand gold could theoretically be used to manufacture this gold precursor. However, the use of recycled gold would imply a redistribution of gold resources. The redistribution of gold resources would eventually lead to an increase of gold demand in the sector deprived of its resource; thus, resource depletion would be shifted and not reduced. A potential solution might be the recycling of gold nanoparticles after their use, but the feasibility of this option needs further investigation (Pati et al., 2016).

Finally, it is worth noting that nano-enabled medical applications are growing significantly, and we envisage that gold nanoparticles will be complemented by alternative nano-products. To this end, a number alternatives have been produced, such as selenides and oxides of Pt and Bi (Zhang et al., 2014), Gd (Le Duc et al., 2011) and Fe (Giustini et al., 2011), but have not been subject yet to the same level of scrutiny as gold nanoparticles.

On the whole, the findings of this paper highlight the need for anticipatory assessment on emerging technologies during the early stages of their development. This type of assessment provides insights on their optimisation and on the future consequences of their implementation; thus, this can be used for the screening and the selection of these technologies along process conditions and potential raw materials. We hence envisage the application of this approach to other emerging technologies with the aim of reducing waste of resources and capitals in the process development.

Acknowledgments

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