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Assessing the energetic and environmental sustainability of organic borazines preparation: A comprehensive life cycle assessment and uncertainty analysis

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ABSTRACT

Since its inception, organic synthesis has played a fundamental role in the development of society, as its efficiency is essential for the preparation of materials in several strategic sectors such as pharmaceuticals, transportation and energy. In this context, organic borazines have emerged as promising molecules useful both as doping units and organic semiconductors, particularly in the production of photovoltaics and organic transistors. However, like most "fine chemical" products, their engineering is generally complex and harmful to the environment due to the need for dangerous reagents, solvents, and harsh reaction conditions. Recent adopted advancements in the manufacturing process, including continuous-flow synthesis and the use of safer, biomass-derived solvents, have been confirmed through a comprehensive cradle-to-gate life cycle assessment (LCA). The study, compared to four batch processes from the literature, identified electricity consumption as the primary contributor to environmental and human health impacts. Additionally, it was demonstrated that adopting a continuous-flow approach, which reduces electricity consumption and leverages safer reaction media such as 2-MeTHF, characterized by an exceptional recovery rate (90%), proved to be an effective strategy, resulting in a notable 11% reduction in emissions. Furthermore, an uncertainty analysis using the Monte Carlo method revealed that energy mixes reliant on fossil fuels increase the impacts across all categories related to human health damage.

1. Introduction

The Circular Economy Action Plan (CEAP) [1], issued by the European Union, is a key element of the European Green Deal, a set of strategies aimed at driving Europe's transition to a sustainable, low-carbon economy. The plan seeks to achieve net-zero greenhouse gas emissions by 2050 and halt biodiversity loss [2]. A central focus of the CEAP is the promotion of safer, more sustainable chemicals through

Abbreviations: 2-MeTHF, 2-Methyltetrahydrofuran; 4-*t*Bu aniline, 4-*tert*-Butylaniline; AE, Atom economy; Ar, Argon; Ar-Li, Aryl-Lithium; B-trichloro-N-triphenylborazole, 2,4,6-Trichloro-1,3,5-triphenylborazine; BCl_3, Trichloroborane; BPR, Back pressure regulator; Br-Li, Bromine-Lithium; $CaCl_2$, Calcium chloride; $CaCO_3$, Calcium carbonate; CEAP, Circular Economy Action Plan; CF, Continuous flow; $CHCl_3$, Trichloromethane; CH_3CN, Acetonitrile; CHX, Cyclohexane; EF, Environmental footprint; Et_2O, Diethyl ether; EtOAc, Ethyl acetate; g, Gram; HAB, B,B′,B″-tri(2,4,6-trimethylbenzene)-N,N′,N″-tris(4-*tert*-butylphenyl)-borazine; HCl, Hydrochloric acid; Hexaphenylborazine, 1,2,3,4,5,6-Hexaphenyl-1,3,5,2,4,6-triazatriborinane; HPLC, High performance liquid chromatography; IC, Impact category; ID, Inner diameter; LCA, Life cycle assessment; LCIA, Life cycle impact assessment; M, Molar concentration; mPts, Millipoints; mbar, Millibar; m.p., Melting point; MeOH, Methanol; MesBr, 2-Bromomesitylene; $MgSO_4$, Magnesium sulphate; mL, Milliliter; mmol, Millimole; *n*-BuLi, *n*-Butyllithium; Na_2SO_4, Sodium sulphate; OSCs, Organic semiconductors; OPV, Organic photovoltaic; OTFTs, Organic thin-film transistors; PTFE, Polytetrafluoroethylene; Rf, Retention factor; RME, Reaction mass efficiency; rt, Room temperature; *t*-BuLi, *tert*-Butyllithium; TCB, Trichloroborazole intermediate; THF, Tetrahydrofuran.

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development practices that meet current needs without compromising the ability of future generations to meet theirs [3].

The concept of chemical sustainability emerged from the identification of the environmental and health risks associated with chemical processes. This led to the development of the twelve milestones, which guide researchers towards more environmentally responsible practices. For example, these guidelines emphasize reducing energy consumption and minimizing the use of oil-derived solvents, since both of them induce a negative impact on the environment by increasing the carbon footprint and contributing to climate change [4]. In contrast, adopting alternative synthetic methods that are less energy-intensive and using biomass-derived reaction and purification solvents, characterized by a closed carbon cycle, can significantly reduce CO_2 emissions and help mitigate global warming.

This research area has become critical globally, as it focuses on preventing or at least minimizing the adverse effects of chemical products on both human and environmental health across their entire life cycle—from production to disposal. Chemicals, used in several strategic sectors, including pharmaceuticals, energy, mobility, and housing, are essential for modern society's well-being despite many of them presenting hazardous properties that can harm the whole ecosystem. In fact, given their significant role, it is imperative to strive for a safer production while adopting greener and more respectful synthetic strategies.

In this context, in the last decades, pushed by the increased energy demand, particular emphasis has been given to the organic semiconductors (OSCs) field [5]. These are polymers or small molecules with π- conjugated systems, which show outstanding electronic properties that make them suitable for the setup of OSC-based devices such as organic photovoltaic (OPV) and organic thin-film transistors (OTFTs). Moreover, they hold special features such as high flexibility and cheap production costs, and they can also be adopted for the manufacturing of e-skin, e-papers, e-textiles, and health monitoring [6].

Borazines have emerged as suitable candidates in organic semiconductors because of their inorganic "benzene" structure, where the C–C bonds are supplanted by B–N bonds [7–10]. This particular molecular structure, in addition to the higher polarity and the weaker cyclic π-electron delocalization, enables a wider HOMO-LUMO gap that makes this class of molecules attractive as inorganic core dopants [11]. In fact, by boosting or simplifying the nature of the organic borazine substituents or enlarging the B_xN_y domains, it is possible to tune their dopant capabilities further, and so the final properties of the carbon-based materials [12–17].

Due to the increasing interest in organic borazines, their synthesis is an object of several investigations starting from the original synthesis that was proposed more than fifty years ago. Groszos and Stafiej were the first to explore the production of 1,2,3,4,5,6-hexaphenyl-1,3,5,2,4,6-triazatriborinane (hexaphenylborazine) adopting a two-pot method based on the cyclocondensation of BCl_3 with aniline in toluene, affording the intermediate 2,4,6-trichloro-1,3,5-triphenylborazine (B-trichloro-N-triphenylborazole) [18]. Successively, other synthetic methods were developed for the preparation of borazines to improve the efficiency and access more complex molecular architectures [7]. In 2005, Wakamiya et al. devised a one-pot protocol where the intermediate, in this case N,N′,N″-tris(4-hexyl phenyl)-B,B′,B″-trichloro borazine, was not isolated form the reaction crude [19]. Further improvements were provided by Kervyn et al. [20] and Renaud et al. [21], which removed HCl, the main reaction by-product, via freeze–pump–thaw.

Although these last-discussed approaches improved both the quality and benignity of the initial method, many issues hamper the definition of a sustainable procedure. The reaction conditions currently required are harsh, involving long reaction times and complex procedures. Additionally, large quantities of flammable and highly toxic solvents such as toluene, pentane, tetrahydrofuran (THF), hexane, cyclohexane, chloroform, and diethyl ether [22] are still necessary either as reaction media and/or as purification solvents.

Consequently, the present shortcomings pushed us to design an innovative method for the greener and more effective production of hexaarylborazines, exploiting the green chemistry precepts, including the use of biobased derived solvents such as 2-methyltetrahydrofuran (2-MeTHF) [23] and the set-up of a continuous flow (CF) procedure, able to increase both the efficiency and safety of the investigated protocol while minimizing energy consumption and waste generation [24].

Setting aside the "green principles" that form the foundation of the sustainable continuous flow synthesis of borazine, a comprehensive study to assess the actual benignity and environmental impact of all the available procedures is needed to direct future larger scale access to this intriguing class of materials.

Most common green chemistry metrics such as E-factor, atom economy (AE), reaction mass efficiency (RME), and carbon mass efficiency focus on the mass involved in the process and are based solely on materials' efficiency, i.e., the amount of raw waste produced. Intrinsically, they do not consider the 'benignity' of a process in terms of energy cost, toxicity of the materials and so on. This means that using classic "mass" green metrics, both hazardous and benign waste are treated equally. The "Benign Index" and "Safety Hazard Index" developed by Andraos represent [25,26], when combined, a more holistic sustainability evaluation method that considers both materials consumption and the weighted environmental impacts of both inputs and outputs. In this case, energy consumption and emissions are not considered as two essential elements that significantly contribute to environmental well-being, thus limiting the overall environmental footprint assessment.

To comprehensively evaluate the environmental impact and sustainability of the proposed CF method, an exhaustive life cycle assessment (LCA) study is conducted. This study compares the CF approach with traditional batch processes on both small and large scales, quantifying their contributions to environmental damage areas and highlighting the trade-offs between materials efficiency, energy consumption, and emissions. By providing a holistic assessment, this work establishes a roadmap for achieving safer, more sustainable production of borazines and contributes to advancing the field of green chemistry. In particular, the study is focused on the small and large-scale synthesis of B,B′,B″-tri(2,4,6-trimethylbenzene)-N,N′,N″-tris(4-*tert*-butylphenyl)-borazine (HAB) under continuous flow regime, adopting 2-MeTHF as green reaction media (Fig. 1) [24–27].

The CF-mediated transformation offers several advantages compared to the same reaction in a batch. The improved control of both reaction conditions (temperature and pressure) and variables, such as mass and heat transfer, as well as reactants mixing, intrinsic safety, higher contact between phases, and easier reproducibility and scalability, affords opportunities to explore novel transformations, while earning a central role as a trailer toward sustainability [28,29] Notably, in addition to the new technology adopted (CF vs. batch), fundamental improvements compared to the benchmark procedures, have been made in the purification step: first of all, the freeze–pump–thaw usually adopted to remove the HCl excess generated after the preparation of HAB was successfully substituted using a $CaCO_3$ packed Omnifit column working as a solid scavenger. Moreover, while isolating the target borazine, around 90.00 % of 2-MeTHF was distilled and recovered, severely diminishing its impact on the ecosystem. Such advancements, already stated by the results obtained when calculating the E-factor, benign and safety hazard index need to be confirmed through LCA [30] addressing the environmental impact of the production process in different damage areas such as *Human health*, *Ecosystems*, and *Resources*. It considers both the environmental and toxicological outcomes, starting from the raw materials obtainment, the energy consumed for their transformation, and the further process emissions.

2. Methods

The present work follows the four phases characterizing the LCA methodology, which are the goal and scope definition, inventory analysis, impact assessment, and finally, the interpretation of the results

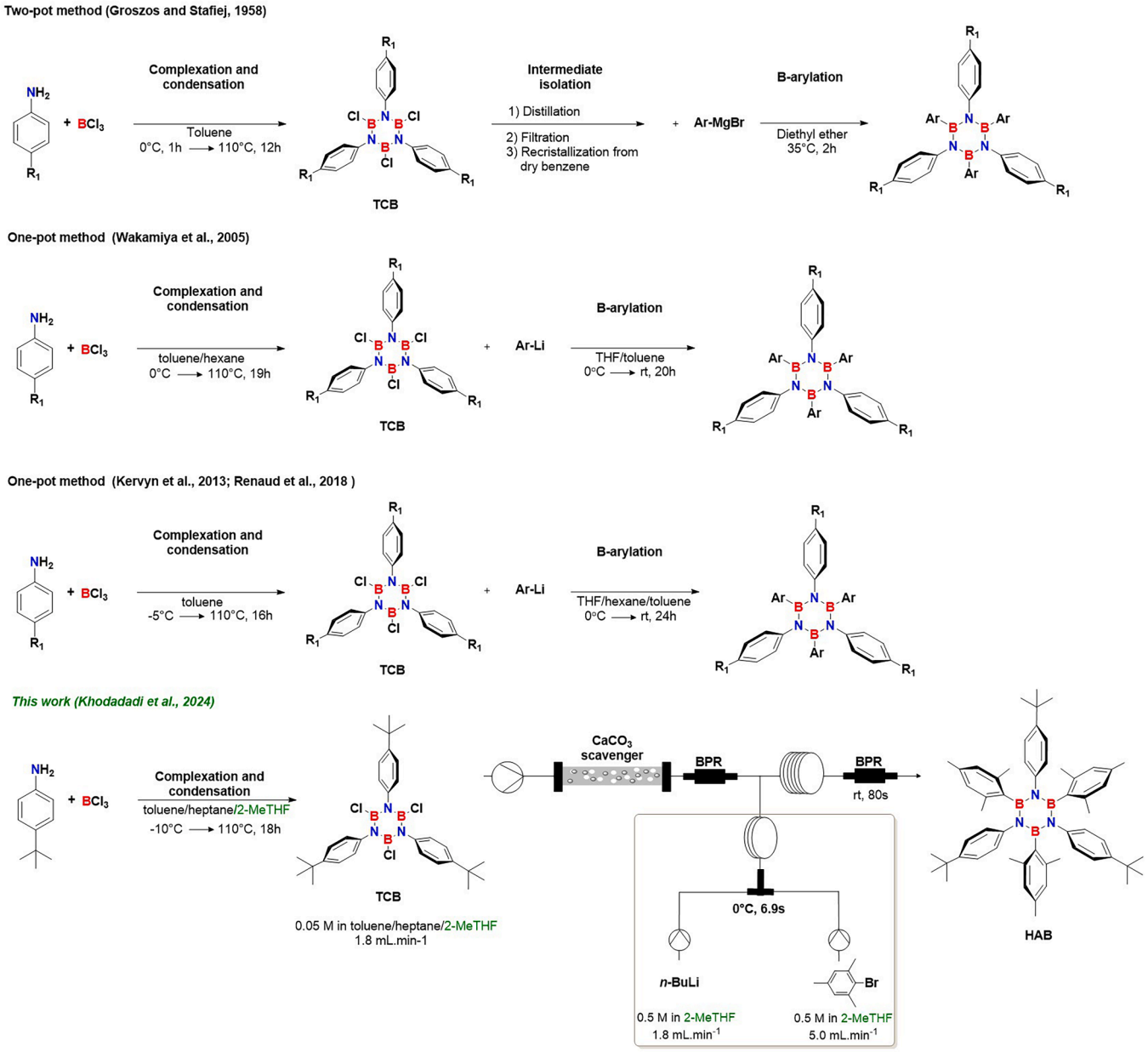

Fig. 1. Representative literature and continuous flow (CF) synthesis of borazines.

[31]. Raw materials and consumed energy inventories for all the procedures considered in the study are described, as well as the detailed synthetic procedures (see Supporting Information), assumptions, software, and methods adopted.

2.1. Goal and scope definition

The main aim of the herein presented LCA is to assess the potential environmental impact of the continuous flow synthesis of HAB, comparing it with four known batch literature procedures [18–21]. The functional unit was defined as 1 g of the desired target product. The system boundary was explicitly defined as cradle-to-gate, encompassing upstream processes such as raw material extraction, energy production, and emissions related to the manufacturing of all materials. This boundary ensures a comprehensive assessment of environmental impacts associated with the synthesis phase while excluding downstream processes such as product usage and disposal, which are beyond the study's scope. The choice of this boundary reflects the primary goal of evaluating the production phase's sustainability and identifying improvement opportunities within this domain. Moreover, it was assumed that all the processes analyzed were performed at one location and that the synthesis proposals were set only to produce borazines without by-products. The environmental effects caused by the production of raw materials have been included, while the impacts of transportation and chemical factories have not been considered. The system boundary for LCA of borazines preparation is shown in Fig. 2.

2.2. Inventory analysis

While setting up the life cycle impact assessment (LCIA), new inventories for different materials had to be created (see ESI for further details) to be included in the model. Given the presence of many data gaps, both in the reference procedures and literature, some assumptions were adopted to construct the inventories. Generally, for the inventories' construction, a retrosynthetic approach was used, and when not possible because of missing database data or too uncertain

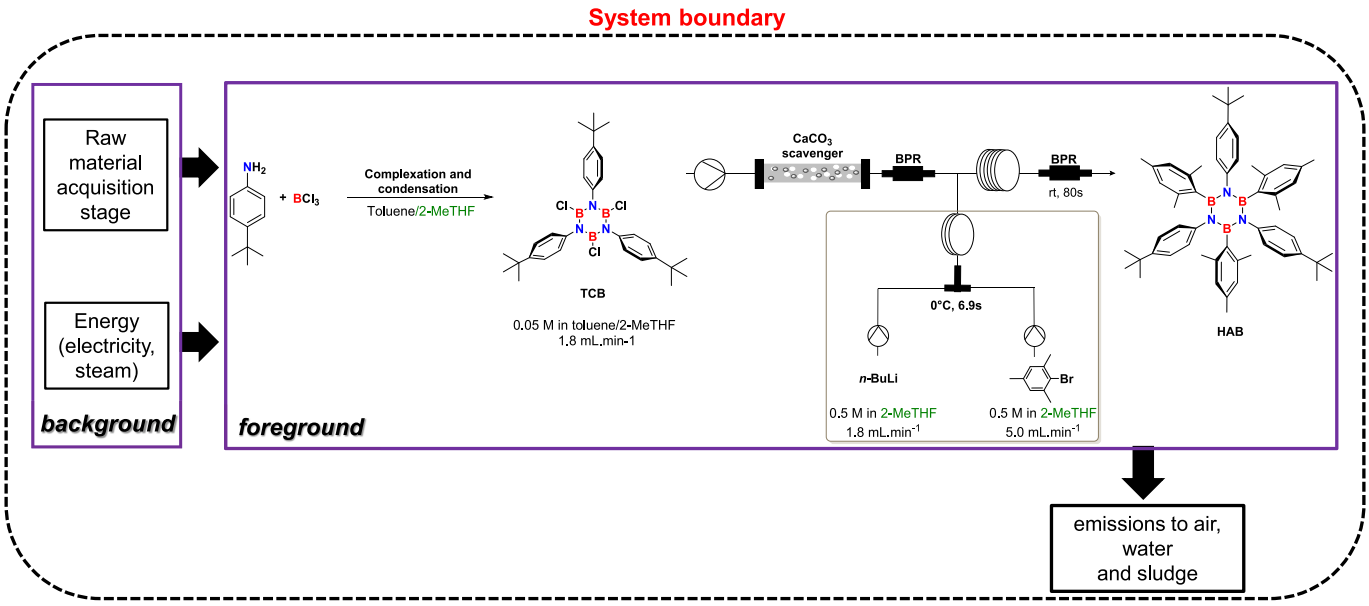

Fig. 2. System boundary for the HAB synthesis under continuous-flow regime.

secondary data, similar compounds were adopted (e.g., 4-pentylaniline instead of 4-hexylaniline or 4-*tert*-butylaniline, *n*-BuLi instead of *t*-BuLi, silica sand instead of quartz beads, $CaCl_2$ instead of Mg_2SO_4 or Na_2SO_4, *n*-heptane instead of *n*-hexane or *n*-pentane).

The energy utilized in the procedures under investigation for heating, cooling, stirring, evaporating, and pumping is not measured or documented. For these reasons, thermodynamics assumptions considering a proportional watt (W) absorption per hour of heating plates (for T > 25 °C procedures such as reactions and distillations or stirring), chiller (for T < 25 °C reactions), heating bath (fixed temperature of 50 °C) and vacuum pump were taken into account. When using secondary data to create inventories, if the isolated product yield is missing, a 95.00 % value is assumed. General assumptions were made regarding process energy (0.0002 MJ per g of the compound) and electricity consumption (0.000333 KWh per g of the compound) for all unavailable compounds that had to be specifically modeled [32]. Moreover, when solvent or additive amounts for liquid–liquid extractions, continuous extraction procedures, or purification steps (such as drying to remove water or freeze pump thaw to remove acid excess) were missing, different scenarios were designed considering our expertise. The same was done for column chromatography, where a fixed amount of activated silica (25 g) was considered to afford 1 g of product. Materials reclaim was only considered if specified in the synthetic steps considered (both primary and secondary). For 2-MeTHF inventory, a total reclaim of the catalyst (Pd/C) was considered, while a 90.00 % 2-MeTHF recovery was included in both the small- and large-scale CF procedures. The emissions to air during the synthetic processes (0.20 % volatile input materials) and air (CO_2), water (river), and sludge emissions after wastewater treatment were calculated as well. No emissions to the soil were determined since no agricultural destination of the digested sludge was considered. In the wastewater treatment, 65.80 % of the organic compounds were retained in the sludge, 24.50 % were oxidized and emitted to air in the form of CO_2, and the remaining 9.70 % were released into the river [33,34].

2.3. Impact assessment

The impact assessment was performed using SimaPro 9.5 and GaBi 10.7.1.28 software and the ReCiPe 2016 [35] and EF 3.1[36] LCIA methods. Precisely, 16 impact categories (IC) were selected when EF 3.1 method was chosen, while 18 impact categories were considered when ReCiPe 2016 method was used (see Table S26 and Fig. S1) [35,36]. Midpoint impact categories and endpoint damage areas (*Human health*, *Ecosystems*, and *Resources*) were analyzed from a hierarchical perspective over a 100-year period. Long-term emissions, which affect scenarios beyond 100 years, were excluded due to their high uncertainties and their relationship to heavy metal toxicity. Therefore, they are not particularly relevant in organic chemical processing. The results for the CF protocols are presented and analyzed in midpoints, and the results are weighted and normalized in endpoint damage areas to compare our approach against others by a single indicator as a benchmark of the global environmental impact. In this process, midpoint characterization results are converted to intermediate units to be weighted and normalized to represent, in millipoints (mPts), the relative impact of the results according to their severity in a global context.

3. Results and discussion

3.1. LCA of CF and batch methods

To ascertain which inputs of the developed continuous flow synthetic protocols mostly impact the environment and health, CF small-scale and CF large-scale approaches affording HAB were examined. The present investigation first started by analyzing the small-scale continuous flow method (Fig. 3a). The production of 1 g of HAB is associated with 4.55 kg of CO_2 emissions, whose approximately 57.50 % is generated as a consequence of the electricity required for the reaction itself and solvents evaporation. Furthermore, the contribution of 2-bromomesitylene to the same emissions accounts for a non-negligible 30.70 %. In general, the energy expended for heating, cooling, stirring, and evaporation has a profound influence on the majority of the impact categories taken into account.

Besides *Climate change*, the energy spent in the whole process significantly conditions many other categories such as *Ozone depletion; Human toxicity: Cancer; Human toxicity: Non-cancer; Fine particulate matter formation; Ionizing radiation; Photochemical oxidant formation: Human health; Terrestrial acidification; Freshwater eutrophication; Water use; Land use and Terrestrial ecotoxicity,* where accounts for more than 50.00 % of the impact. Noticeably, the impact on *Ionizing radiation* and *Human toxicity: Non-cancer* reaches 90.00 % and 70.00 %, respectively. Moreover, the utilization of 2-bromomesitylene was shown to be the predominant factor contributing to *Marine eutrophication*, *Fossil resource*

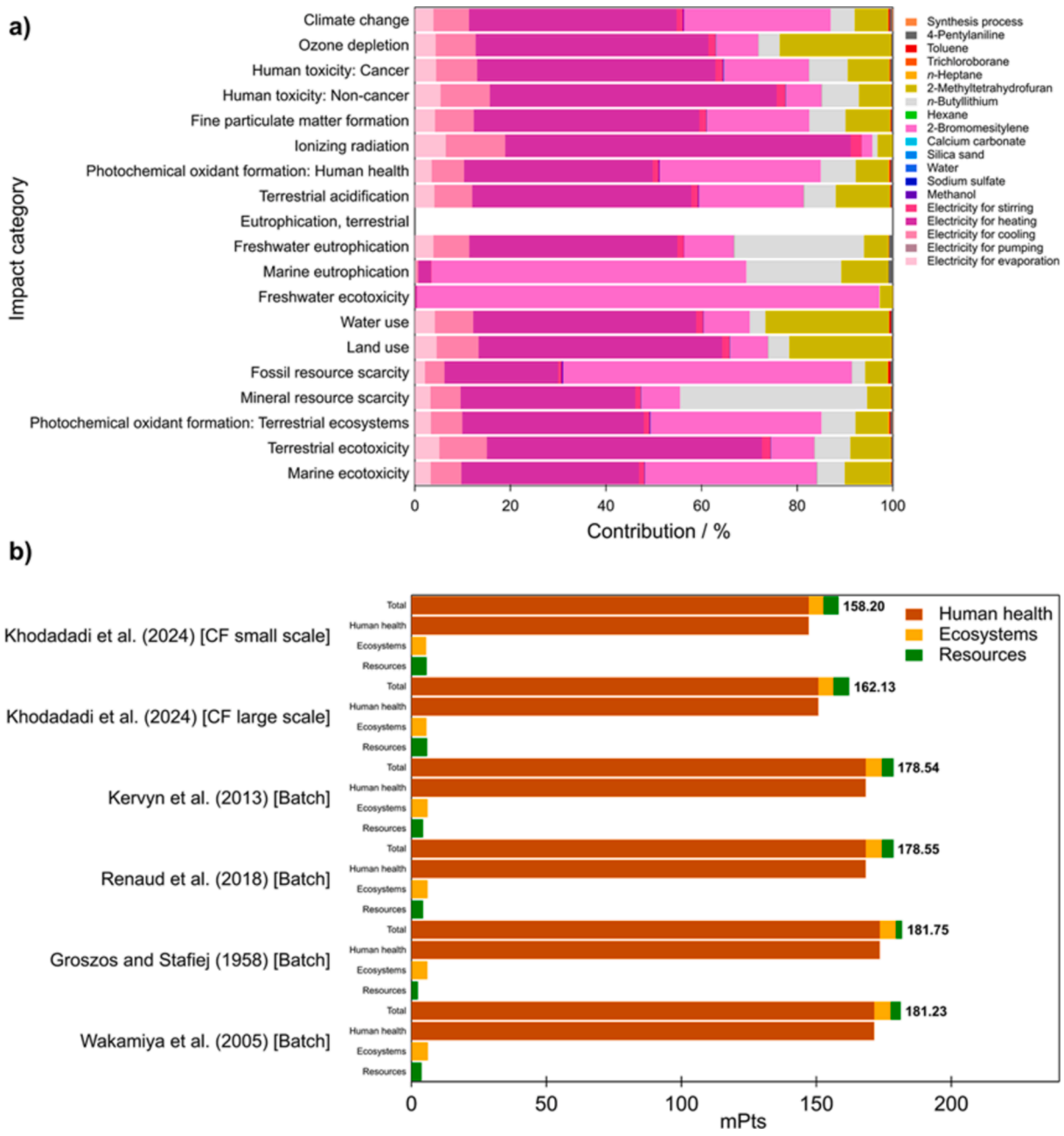

Fig. 3. Overview of life cycle assessment [SimaPro, ReCiPe 2016 method]. (a) Percentage contribution of each input in midpoint impact categories for Khodadadi et al. [CF small scale] process. (b) Endpoint single score comparison for the synthesis of 1 g of borazine among the synthetic routes considered.

scarcity, and *Freshwater ecotoxicity* categories, accounting for 65.80 %, 60.40 %, and 96.70 %, respectively, and, in general, contributing $\gtrsim$ 5.00 % in all the categories. A similar behaviour is also observed in the production of *n*-Butyllithium, which significantly contributes to the *Mineral resource scarcity* and *Freshwater eutrophication* categories, accounting for 39.10 % and 27.10 %, respectively. Because of its fairly low boiling point and the synthetic procedure required for its manufacturing starting from glucose, 2-MeTHF accounted for 23.30 % of the *Ozone depletion*, 21.30 % of the *Land use*, and 25.80 % of the *Water use* categories. Despite the previously cited contributions and the large amount used in the CF small scale method, 2-MeTHF was among the least impacting materials, accounting for around 5.00–25.00 %. The use of 2-MeTHF, a bio-based solvent, contributes to the improved environmental performance of the CF synthesis method, primarily due to its lower environmental footprint and high recovery rate (90.00 %).

Even though Fig. 3a provides a detailed view of the contributing factors that define the CF small-scale methodology, the best way to determine the most sustainable route is to perform an endpoint single-score analysis comparing the flow process with the literature taken as references. This is a particular evaluation that categorizes all impact categories inside macro damage area, offering a final score, expressed in mPts, that defines the greener method considering its impact on *Human health*, *Ecosystems*, and *Resources* damage areas. As illustrated in Fig. 3b, the *Human health* category dominates the three endpoints for all the processes analyzed, accounting for 93.00 % to 95.50 % of the overall damage. The *Ecosystems* and *Resources* damage areas follow, accounting for 3.20 % to 3.40 % and 1.30 % to 3.60 % of the overall damage, respectively. All batch approaches resulted in the most impactful procedures. Among these, the one-pot approach developed by Wakamiya et al. [19] had among the highest environmental score (181.23 mPts). This is primarily due to the methodology's intrinsic nature, which requires long reaction times (19 and 20 h) and several additional steps at

low temperatures, leading to high energy consumption accounting for approximately 76.50 % of the *Climate change* category, which in turn contributes 44.50 % to the final environmental score. Additionally, the significant volumes of hazardous and non-renewable solvents (THF, $CHCl_3$, hexane, and toluene) used as reaction media and for purification to isolate the product significantly affect the final evaluation.

The overall sustainability is strongly influenced when using a two-pot method, which involves the isolation of the final target intermediate. This is the case of the first developed process by Groszos and Stafiej [18]. Despite the multiple isolation steps required and the large volume of solvents used, this procedure resulted in a similar score (181.75 mPts) to the Wakamiya et al. protocol. From our point of view, this behaviour depends on the several data gaps present in the published procedure, such as the solvent volumes adopted for the liquid–liquid and continuous extraction. Consequently, we were prompted to provide many assumptions based on our expertise that could heavily underestimate the final footprint. Kervyn et al. and Renaud et al. [20,21] further optimized the synthesis of B,B′,B″-tri(1,3,5-trimethylbenzene)-N,N′,N″-

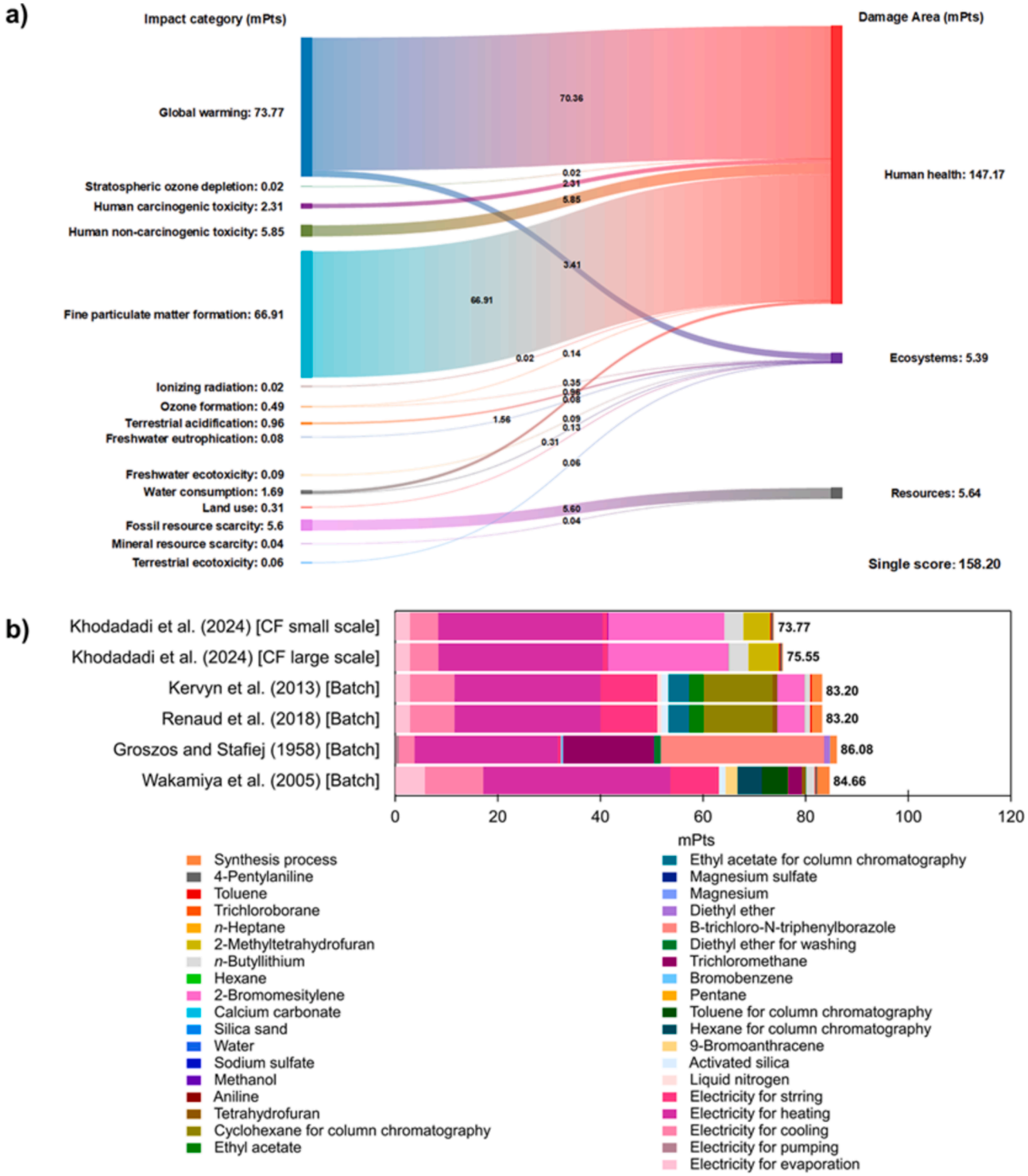

Fig. 4. Snapshots of life cycle assessment [SimaPro, ReCiPe 2016 method]. (a) Midpoint to endpoint single score for the Khodadadi et al. [CF small scale] synthesis route. (b) Endpoint single score comparison among the different routes considered in the *Climate change* impact category.

trisphenylborazine, obtaining 40.00 % and 78.00 % yields, respectively, with the same protocol. A detailed analysis of the synthetic procedure reveals their strong resemblance to the Wakamiya et al. method. The primary distinction is using different solvents for borazine isolation: ethyl acetate replaces chloroform, and an ethyl acetate/cyclohexane mixture is used instead of a hexane/toluene mixture. This enhancement, could induce a general sustainability upgrade at first sight, did not affect the overall substantially because of the large volume employed, especially in column chromatography. Actually, the real enhancement provided in both the Kervyn et al. and Renaud et al. procedures come from the process itself, conducted on a smaller scale, which results in limited material consumption.

Finally, the CF synthesis showed to be the greener choice [24]. In particular, CF small scale protocol resulted in the best option, obtaining an environmental score of 158.20 mPts. This achievement is mainly due to the continuous flow technology adopted, using low-energy consumption syringe pumps to flush the reaction mixtures inside the reactors, reducing the strain on energy supplies. Moreover, a significant contribution to the overall sustainability of the present method was achieved through the limited use and subsequent recovery of solvents. Specifically, recovering approximately 90 % of the 2-MeTHF used drastically reduced the solvent's impact on the final score. To put this into perspective, in the Renaud et al. process, where large amounts of solvents were used, particularly in the purification step, and not recovered, solvents accounted for about 25.40 % of the final assessment. In contrast, their influence was reduced to 8.70 % in the CF small-scale method.

Interestingly, CF small-scale method was slightly better than the CF large scale one method (162.13 mPts). In this case, as well, the reason behind these results lies in the lower amount of materials used (reagents, solvents, and additives), which reflects lower emissions and energy consumption (7.04 vs. 7.23 KWh). As stated above, this is the most impactful parameter affecting the assessment. This consideration suggests that the use of cleaner energy, characterized by a lower percentage of fossil-based sources, will be able to decrease the environmental footprint further [37].

Fig. 4a shows how the different impact categories influence the three damage areas in more detail. In the Sankey diagram, it is clearly possible to notice how two main categories, *Climate change* and *Particulate matter formation*, mostly contribute (44.00 % and 42.20 %, respectively) to the total damage, especially in *Human health*, which alone contributes to 93.00 % of the total footprint. This considerable contribution is because global warming, caused mainly by CO_2 emissions and considered in the *Climate change* category, can induce severe consequences on human health, such as malnutrition, malaria, and natural disasters [38,39]. The formation and spreading of fine particulate aerosols, primarily responsible for cardiopulmonary and lung diseases, influence the same damaged area [40]. Because *Climate change* is the most significant contributor to the global environmental impact, it is reasonable to extrapolate those factors that, in this precise category, mainly shape it.

As depicted in Fig. 4b, the main difference between CF small and large-scale protocols lies in the larger amount of 2-bromomesytilene and 2-MeTHF adopted in the large-scale approach. In fact, while for the CF small-scale method, in the *Climate change* endpoint score, they account for 30.70 % and 7.00 %, respectively, for the large-scale method, a little increment in their impact is noticed (31.13 % and 7.80 %). In addition, energy consumption had higher scores in the *Climate change* category for all methods, with CF small-scale method having an environmental score of 41.50 and Wakamiya method having an environmental score of 62.50, which is attributed to shorter reaction times and more efficient heat transfer in continuous systems. Analyzing the other procedures considered in the present work, besides the contribution given by the electricity consumption, an important effect is brought by solvents. In the batch approaches, where several purification steps such as liquid–liquid extraction and/or column chromatography are required, solvents play a central role in the final impact, accounting for between 15.00 % and 24.50 %, confirming their negligible effect on ecosystem well-being [41]. To understand the improvements introduced over time, it is essential to emphasize the contribution of B-trichloro-N-triphenylborazole in the Groszos and Stafiej procedure. In this method, since this intermediate is isolated (two-step method) before accessing the final products, its synthesis and isolation steps significantly impact the final value, accounting for around 37.00 %.

3.2. Comparison of different software and methods

Like most environmental assessment methods, the life cycle analysis is based on different assumptions that can be integrated within different software, each of them characterized by specific features that can influence the final evaluation. For this reason, we studied next two of the strategies discussed here, the Khodadadi et al. [CF large scale] and Groszos and Stafiej [Batch], both with SimaPro and GaBi software, adopting two different calculation methods, ReCiPe 2016 and EF 3.1, to evaluate the differences in various LCA implementations (Fig. 5).

First of all, by analyzing Fig. 5a and 5c, it can be noticed that when the impact is calculated for the Khodadadi et al. [CF large scale] process, using ReCiPe 2016 or EF 3.1, some apparent differences are present. In fact, in the *Ozone depletion* category calculated with the ReCiPe 2016 method, the impact of 2-bromomesitylene and *n*-BuLi is almost half compared to the EF 3.1 method. This is due to an increased impact consideration attributed to 2-MeTHF, which, on the contrary, is overestimated when using EF 3.1 as opposed to ReCiPe 2016 in the *Freshwater ecotoxicity* (or *Ecotoxicity, freshwater*) and *Water use* categories. Interestingly, there is also a different weight given to *n*-BuLi in the *Mineral resource scarcity* (or *Resource use, minerals, and metals*), accounting for 39.55 % when using ReCiPe 2016 and just for 8.46 % in EF 3.1. This behavior is supposed to depend on the reference unit adopted in the two methods, that is, kg Cu-eq for the ReCiPe 2016 [42] method and kg Sb-eq For EF 3.1 [43]. Indeed, considering that the abundance of Cu in the bulk continental Earth's crust is around 60 ppm while that of Sb is 0.2 ppm [44], it is evident that its impact on the ReCiPe 2016 method is considerably higher.

Moreover, when the same procedure is analyzed with GaBi software (Fig. 5e) using ReCiPe 2016 method, the results for the first eight categories are pretty similar to the same analysis performed with SimaPro, even if the impact of 2-MeTHF is slightly lower as well as that of the electricity used for heating processes, while that of 2-bromomesitylene is considerably higher. A significant deviation is observed in the *Freshwater eutrophication, Marine eutrophication,* and *Mineral resource scarcity*. While in the first two categories, the impact *n*-BuLi when SimaPro is used is between 27.50 % and 19.60 %, analyzing the process with GaBi, its contribution is almost negligible because of a neat increase in the 2-MeTHF consideration. The same outcome is noted for 2-bromomesitylene in *Marine eutrophication* as well. Above all, the most interesting data is that revealed by the *Mineral resource scarcity* category. If the *n*-BuLi contribution in SimaPro (ReCiPe 2016) is around 40.00 %, the *n*-BuLi contribution in GaBi (ReCiPe 2016) is almost 90.00 %. Considering that the reference unit is the same in this case, the discrepancy lies in the different calculation methods adopted by the two software.

As expected, variations are detectable also when using the EF 3.1 method with different software. Looking at Fig. 5g, it is clear that the impact of 2-MeTHF in the *Ecotoxicity, freshwater*, and *Water use* categories while calculating the impact employing GaBi and EF 3.1 method is significantly lower than the counterpart using SimaPro. The same material shows, on the contrary, an opposite behavior in the *Eutrophication, freshwater,* and in *Human toxicity, non-cancer* categories. Finally, similar disagreements have occurred for ReCiPe 2016 and EF 3.1 in SimaPro, which can be pointed out by utilizing GaBi.

The different consequences clarified in the Khodadadi et al. [CF large scale] protocol are less pronounced while studying the Groszos and Stiafej [Batch] procedure. As shown in Fig. 5b, 5d, 5f, and 5 h, the main differences lie between the two software and not between the methods.

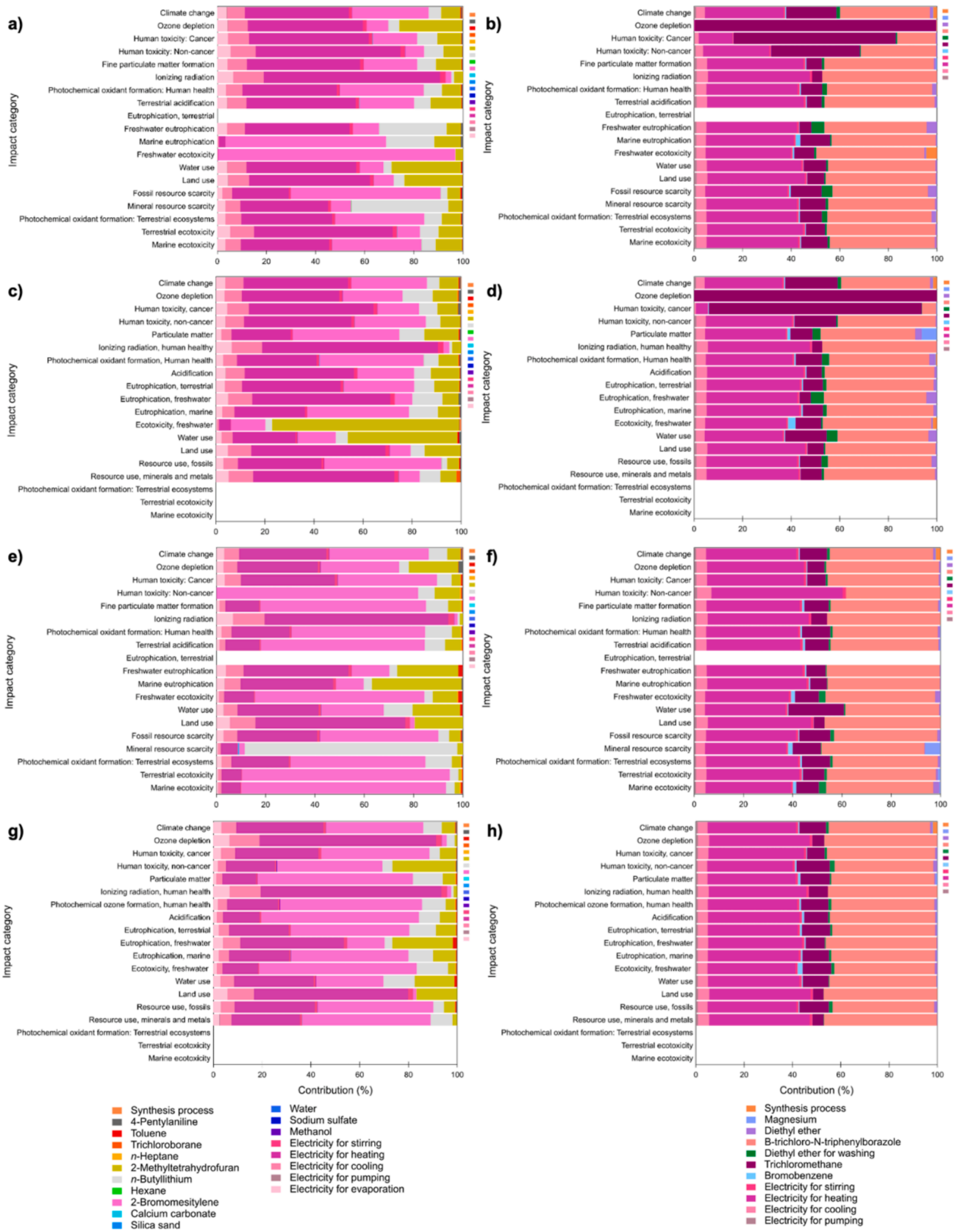

Fig. 5. Midpoint characterization of the Khodadadi et al. [CF large scale] and Groszos and Stafiej [Batch] processes using different software and methods. (a) Khodadadi et al., SimaPro, ReCiPe 2016. (b) Groszos and Stafiej, SimaPro, ReCiPe 2016. (c) Khodadadi et al., SimaPro, EF 3.1. (d) Groszos and Stafiej, SimaPro, EF 3.1. (e) Khodadadi et al., GaBi, ReCiPe 2016. (f) Groszos and Stafiej, GaBi, ReCiPe 2016. (g) Khodadadi et al., GaBi, EF 3.1. (h) Groszos and Stafiej, GaBi, EF 3.1.

This is because the most varying categories in both the methods adopted (i.e., *Ozone depletion, Human toxicity, cancer*, and *Human toxicity, non-cancer*) utilize the same or similar units (kg CFC-11 eq for *Ozone depletion*, Comparative Toxic Unit for Humans for *Human toxicity, cancer*, and *Human toxicity, non-cancer* in EF 3.1, and Human Toxicity Potential for *Human toxicity, Cancer*, and *Human toxicity, Non-cancer* in ReCiPe 2016).

3.3. Uncertainty analysis

By its nature, LCA is based on both primary data from experimental works and secondary data sourced from literature or the authors' expertise. This means that the study results can be influenced by an inherent variability, making them potentially misleading [45]. Regarding the preceding, an uncertainty analysis exploiting the Monte Carlo method has been carried out, using GaBi software, on the Khodadadi et al. [CF large scale] and Groszos and Stafiej [Batch] methods (Fig. 6), while adopting both the ReCiPe 2016 and EF 3.1 methods.

For the uncertainty analysis of the Khodadadi et al. synthetic process, 2-bromomesitylene and electricity for heating have been taken as random variables due to their substantial impact on the LCA analysis. In addition, the energy sources with the highest percentage contribution to European electricity generation are used as variables. The results show that when analyzing the impact of the variation of 2-bromomesitylene (group 1), the median and uncertainty are similar in most indicators. On the contrary, when considering the influence of uncertainty in nuclear power and natural gas sources belonging to group 2 (including 2-bromomesitylene), the median of the indicators tends to be lower. This suggests that using preponderantly these types of energy reduces the environmental impact. At the same time, when the rest of the energy sources belonging to group 3 are included, a significant increase in the median of indicators related to those categories influencing damage areas such as *Human health* and *Ecosystems* is revealed. The *Water use* category is remarkable. In fact, no variation occurs when considering groups 1 and 2 solely, while significant uncertainty is pointed out by looking at group 3, where electricity from hydropower is included. Generally, no net discrepancy is observed when switching from one method to another, confirming the analysis consistency.

Because of their marked impact, B-trichloro-N-triphenylborazole and electricity for heating have been taken as random variables to evaluate the uncertainty analysis in the Groszos and Stafiej process. The Monte Carlo analysis shows that when analyzing the impact of the variation of B-trichloro-N-triphenylborazole (group 1), the median and uncertainty are similar in all indicators, both using ReCiPe 2016 and EF 3.1. When analyzing the influence of uncertainty in nuclear power and natural gas sources belonging to group 2 (including B-trichloro-N-triphenylborazole), it is observed that, in general, the median of the indicators tends to be lower, corroborating the results obtained for the investigated Khodadadi et al. synthetic process. This observation is particularly

a)

Scenarios group	Variable	Reference value	Standard deviation
Group 1	2-Bromomesitylene	3.64 g	± 5 %
Group 2	Electricity from nuclear power	25.3 %	± 5 %
	Electricity from natural gas	19.1 %	± 5 %
Group 3	Electricity from wind power	11.6 %	± 5 %
	Electricity from hydro power	11.6 %	± 5 %
	Electricity from hard coal	9.7 %	± 5 %
	Electricity from lignite	9.1 %	± 5 %

b)

Scenarios group	Variable	Reference value	Standard deviation
Group 1	B-Trichloro-N-triphenylborazole	1.18 g	± 5 %
Group 2	Electricity from nuclear power	25.3 %	± 5 %
	Electricity from natural gas	19.1 %	± 5 %
Group 3	Electricity from wind power	11.6 %	± 5 %
	Electricity from hydro power	11.6 %	± 5 %
	Electricity from hard coal	9.7 %	± 5 %
	Electricity from lignite	9.1 %	± 5 %

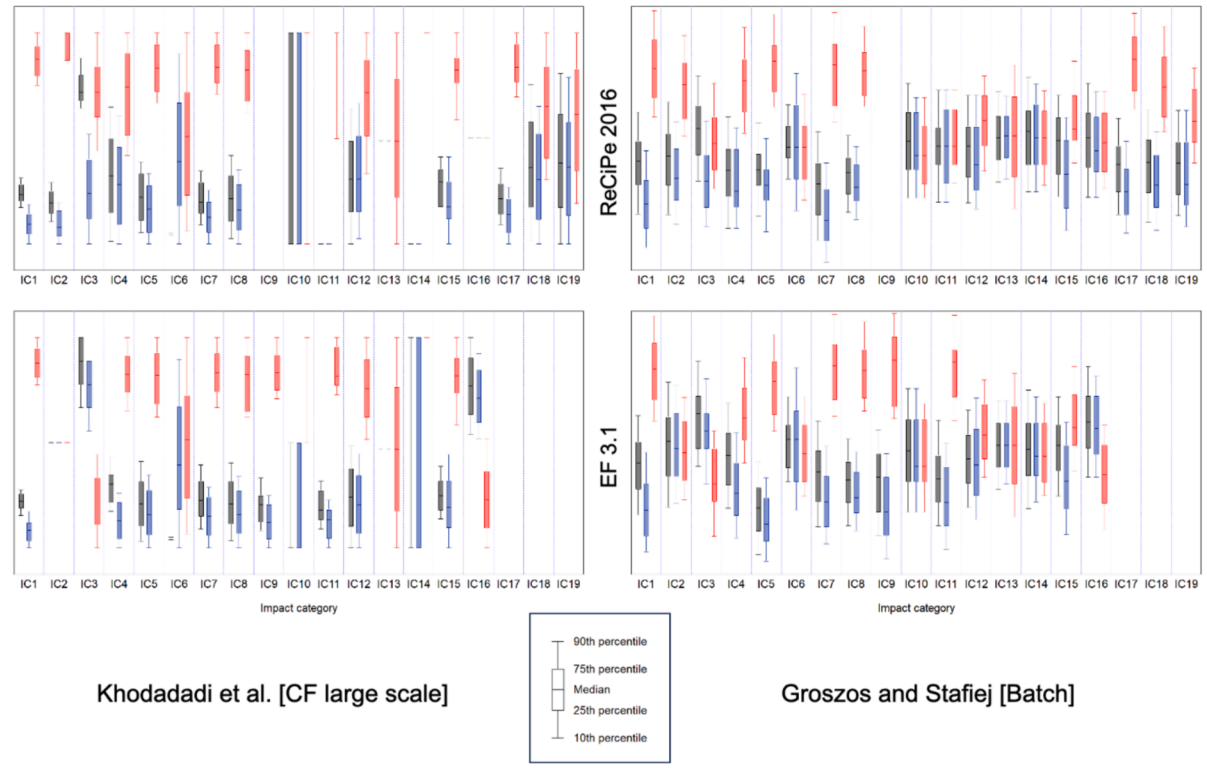

Fig. 6. Scenarios and uncertainty analysis by Monte Carlo method, GaBi, ReCiPe 2016 (top panels) and EF 3.1 (bottom panels) methods. Simulations considered normal distribution type for input quantities and 100 iterations. (a) Khodadadi et al. [CF large scale]. (b) Groszos and Stafiej [Batch].

attractive because it suggests that nuclear energy can be considered a green source of energy, at least in this study.

Finally, the results of the Monte Carlo analysis indicate that energy consumption is the most sensitive parameter influencing the environmental performance of the Khodadadi et al. synthetic process and the Groszos and Stafiej synthetic process. The uncertainty associated with modelling fossil energy sources, such as coal, had a significantly higher impact on the median metrics associated with human health and ecosystem damage. This demonstrates the overall negative impact of fossil fuel-based energy mixes. The incorporation of renewable energy sources reduces the variability of results and increases the sustainability of the CF synthesis process.

4. Conclusions

In this manuscript, a comprehensive cradle-to-gate LCA analysis was conducted using two software tools, SimaPro 9.5 and GaBi 10.7.1.28, and methods including ReCiPe 2016 and EF 3.1. The study aimed at comparing the CF synthesis of HAB with the batch production of different hexarylborazines. It confirmed that applying green chemistry principles and practices is valuable for ensuring more sustainable procedures without compromising process efficiency. The results highlight the environmental benefits of the CF synthesis, such as significant reductions in energy consumption and solvent waste generation compared to traditional batch processes. These findings, perfectly fit and support the results obtained in the evaluation of different green metrics such as E-factor, Bening index and Safety-Hazard index, as calculated and reported in Khodadadi et al. [24], where the synergy between process efficiency and environmental performance was highlighted. Specifically, the use of a bio-based solvent like 2-MeTHF, characterized by an intrinsically lower environmental impact and an excellent recovery rate (90 %), enabled the development of a greener procedure with a significantly 11 % reduced emissions compared to the best batch method, resulting in a lower environmental score (158.20 mPts). These findings are also prompted by continuous flow technology, which played a fundamental role in permitting high isolated product yields, limiting the purification step to a simple distillation and electricity consumption. Indeed, it has emerged as the most impactful factor, accounting for between 40.00 % and 76.50 % of the total environmental footprint. This is corroborated by a Monte Carlo analysis which elucidates the pivotal influence of energy sources on the environmental performance of boron and nitrogen synthesis. The utilisation of renewable energy sources has the potential to significantly reduce the environmental impact and greenhouse gas emissions in comparison to those derived from fossil energy sources. These findings emphasise the necessity of incorporating cleaner energy sources into CF systems in order to optimise their sustainability potential.

This study, which represents the inaugural application of LCA to borazines production, establishes a benchmark for future research. The combination of CF technology with bio-based solvents and efficient purification strategies has resulted in notable advancements in process sustainability and scalability. Our findings provide valuable insights into developing more environmentally conscious chemical processes, with future research focused on integrating renewable energy solutions for continuous flow setups and evaluating the scalability of such approaches for industrial applications. These strategies offer promising pathways for further reducing the ecological footprint of advanced chemical synthesis technologies.

In particular, scaling up the continuous flow procedure and incorporating more efficient heating systems, such as microwave irradiation, could significantly reduce energy consumption and improve sustainability. This would also enhance solvent recovery rates, especially in processes like the preparation of trichloroborazole intermediates. Moreover, exploring emerging solvent systems, such as those derived from residual biomass or industrial waste valorization (e.g., Polarclean® or Cyrene®), could further contribute to the sustainability of hexaaryl borazines synthesis. These efforts collectively promise to reduce the overall environmental impact of chemical synthesis, advancing both efficiency and sustainability in the field.

CRediT authorship contribution statement

Filippo Campana: Writing – review & editing, Writing – original draft, Methodology, Data curation. **Kejie Zhou:** Writing – review & editing, Writing – original draft, Software. **Jhonny A. Yunda:** Writing – review & editing, Writing – original draft, Data curation. **Alireza Nazari Khodadadi:** Resources, Methodology, Data curation. **Davide Bonifazi:** Resources, Methodology, Data curation. **Sorin Melinte:** Writing – review & editing, Writing – original draft, Funding acquisition, Data curation, Conceptualization. **Luigi Vaccaro:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cej.2024.158822.

Data availability

No data was used for the research described in the article.

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