Green Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal

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Cite this: DOI: 10.1039/d6gc01508e

Clicking the sustainability: Nobel-awarded copper catalysed azide-alkyne cycloadditions (CuAAC) through Life Cycle Assessments analysis

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Received 11th March 2026,
Accepted 22nd May 2026

DOI: 10.1039/d6gc01508e

rsc.li/greenchem

Copper-catalysed azide–alkyne cycloaddition (CuAAC) reactions represent a class of chemical tranformations belonging to the broader group of so-called "click reactions." CuAAC, which contributed to Sharpless being awarded his second Nobel Prize in 2022, has emerged as a key tool in synthetic chemistry. It is widely recognised as a privileged method for preparing triazole moieties, which are important scaffolds, particularly in the synthesis of active pharmaceutical ingredients (APIs). CuAAC reactions are characterised by high regio- and stereoselectivity, as well as 100% atom economy, resulting in minimal waste generation. This advantage is often highlighted by evaluating green chemistry metrics. However, such metrics do not always provide a fully comprehensive assessment of the advantages and drawbacks of a specific synthetic pathway, as they mainly focus on the amount of waste generated relative to the amount of product synthesised. Under these circumstances, life cycle assessment (LCA) emerges as a powerful tool capable of evaluating the overall environmental impact of a chemical process. In this study, the sustainability characteristics of a series of CuAAC procedures have been investigated using LCA, and the data have been validated through uncertainty analysis. This approach enables identification of the most environmentally friendly procedures among those examined, as well as identification of the critical process stages that limit overall sustainability.

Green foundation

1. By integrating a cradle-to-gate life cycle assessment into the evaluation of CuAAC transformations, this study provides a holistic quantification of human health and environmental impacts, supporting the identification of factors that can enhance process sustainability.
2. We demonstrated that optimised solvent selection and catalyst/solvent recycling lowered the carbon footprint to 0.362 kg CO_2 eq. per g (5–21% lower than alternatives) and reduced Endpoint damage by up to 28%, and that eliminating non-essential ligands cut emissions by 14.5%
3. Further greening could arise from replacing phenyl acetylene, the main environmental hotspot, developing alternative feedstock or synthetic routes, and minimising post-processing solvents through improved isolation and circular solvent recovery strategies.

1. Introduction

As announced by The Royal Swedish Academy of Sciences, on the 5th of October 2022, M. Meldal and B. Sharpless (together with C. Bertozzi for bio-orthogonal click chemistry) were awarded the Nobel Prize in Chemistry because they "*presented what is now the crown jewel of click chemistry: the copper-catalysed azide–alkyne cycloaddition (CuAAC). This is an elegant and efficient chemical reaction that is now in widespread use. Among many other uses, it is utilised in the development of pharmaceuticals, for mapping DNA and creating materials that are more fit for purpose*".[1]

The philosophy of click chemistry was initially introduced by Sharpless and co-workers to describe a synthetic methodology based on a small set of highly efficient, selective, and reliable reactions that enable the rapid assembly of simple molecular moieties into more complex entities. Click chemistry is, in fact, defined as a collection of powerful and modular reactions for the fast synthesis of useful new compounds and combinatorial libraries, typically through the formation of heteroatom-linked connections, and it is characterised by mild reaction conditions, high yields, high degrees of regioselectivity and stereospecificity, and the limited generation of easily removable and inoffensive side products.[2,3] Among click reactions, CuAAC is definitely the most investigated one, particularly because of the relevant utilization of

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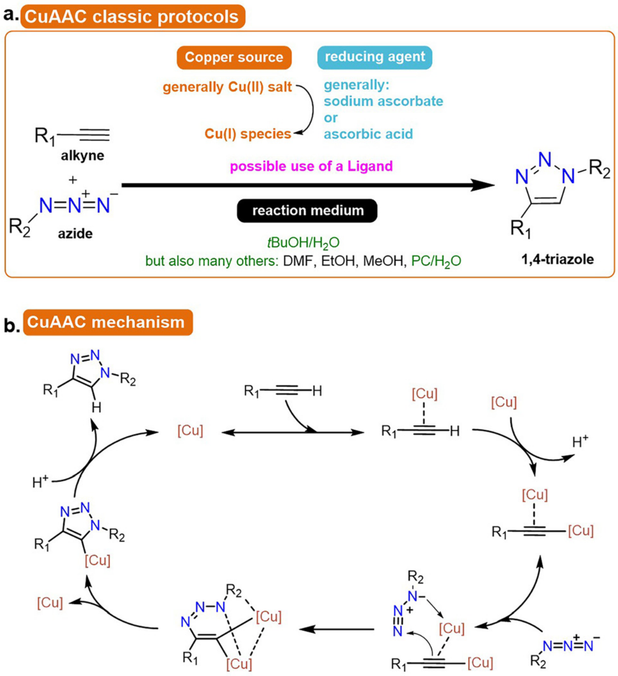
the derived products, *i.e.*, 1,4-disubstituted-1,2,3-triazoles. This family of heterocyclic compounds has attracted sustained attention because of its pronounced biological activity. Numerous studies have demonstrated that members of this class display significant antibacterial and antiviral properties, making them valuable motifs in the development of therapeutic agents and pharmacologically relevant molecules.[4]

In recent decades, however, the relevance of the triazole scaffold has expanded well beyond medicinal chemistry. Owing to its efficiency, selectivity, and tolerance toward many functional groups, this reaction has become a cornerstone in modern synthetic methodology. It is now routinely employed in materials science to assemble complex macromolecular architectures, including dendrimers[5] and functional polymers,[6–8] where the triazole ring serves as a robust and reliable linkage that imparts structural stability and tunable physicochemical properties. Furthermore, the incorporation of azide and alkyne moieties into biological molecules has been successfully applied in bioconjugation.[9]

Chemically, CuAAC is defined as a [3 + 2] dipolar cycloaddition catalysed, as suggested by its name, by Cu(I) species. These are typically generated *in situ* by the reduction of copper(II) salts, such as copper sulfate ($CuSO_4$), using suitable reducing agents (sodium ascorbate or ascorbic acid), or by the oxidation of metallic Cu(0) (Scheme 1). Alternatively, Cu(I) salts may be directly employed; however, due to their thermodynamic instability, they can be readily oxidised to the inactive Cu(II) form.[10,11]

From a mechanistic point of view, the generally accepted mechanism is that proposed by Worrell and colleagues,[12] requiring the involvement of two copper atoms binding the alkyne to form the acetylide complex, which is further attacked by the nucleophilic azide to form a six-membered ring, which, after the formation of the new C–N bond, affords the desired triazole.



Scheme 1 (a) Common protocols for CuAAC reactions. The text in green highlights the solvent mixtures considered in this assessment. (b) The mechanism of CuAAC.

If the characteristics of CuAAC and the revolutionary twelve principles of green chemistry developed a few years earlier are considered, it is evident that the two are closely connected, with the former representing the implementation of the more general principles listed by Warner and Anastas.[13] Indeed, one of the defining features of click chemistry, especially CuAAC, is its quantitative atom economy,[14] a core concept of green chemistry, ensuring the incorporation of all atoms from the starting materials into the final product. Furthermore, the close connection between these two philosophies is reinforced by the use of catalysts, which enhance reaction efficiency by lowering the activation energy barrier, thereby saving energy.[15]

Click chemistry methodologies also incorporate green chemistry principles, notably reducing waste through alternative, less-material-intensive purification strategies (such as precipitation and crystallization rather than column chromatography) and avoiding or replacing hazardous solvents with safer, more sustainable options. These are widely recognised as critical determinants of the environmental sustainability of chemical processes, as they generally constitute the largest mass fraction in most transformations and are extensively used in product purification and isolation.[16] The adoption of renewable and less toxic media, as well as the careful selection and development of efficient solvent recovery and recycling strategies, can significantly reduce the environmental concerns associated with a given process.[17–20]

To date, chemists have several options at their disposal for evaluating, both quantitatively and qualitatively, the actual footprint associated with a specific procedure and, moreover, the improvements introduced. Mass metrics, such as the *E*-factor,[21] introduced by Sheldon in 1994, and process mass intensity (PMI),[22] are among the most widely used tools for evaluating a process's sustainability. The *E*-factor, representing the mass of waste generated with respect to the mass of the final product, offers a straightforward quantitative indication of the waste generated per kilogram of product. Despite their usefulness, both the *E*-factor and PMI exhibit significant limitations. In particular, without differentiating between safe and dangerous by-products, they treat all waste as equivalent, failing to account for toxicological or environmental consequences. To address this shortcoming, the environmental quotient (EQ) was proposed as an empirically derived weighting factor that reflects and differentiates the hazards associated with each waste type, thereby enabling a more appropriate evaluation.

At this stage, to properly and comprehensively assess the environmental and human-health sustainability associated with chemical transformations and synthesis procedures, life cycle assessment (LCA) is the most appropriate method (Fig. 1).

This is a specific computational analysis process that considers all life stages of the procedure under investigation, from

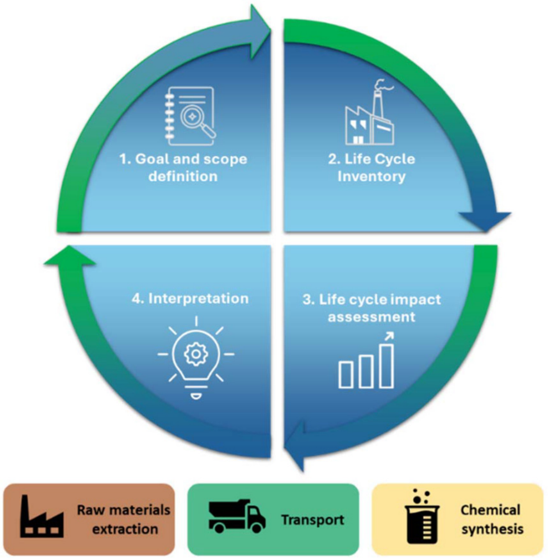


Fig. 1 LCA analysis stages applied to cradle-to-gate chemical processes.

raw material extraction to product use and disposal/recycling.[23]

In contrast to mass-based metrics, LCA considers not only the impacts associated with a given process but also the related human health and environmental consequences,[24] making it a more precise and faithful-to-reality evaluation.

In this context, over the past decades, LCA has been increasingly adopted to evaluate the environmental impact of chemical synthesis procedures. Very recently, Folkerts and co-workers reported an integrated LCA-guided approach for the synthesis of Letermovir, showing how iterative sustainability assessment can identify environmental hotspots and support route optimisation beyond conventional metrics.[25] Similarly, Tannert *et al.* applied LCA to compare petrochemical and enzymatic epoxidation routes for the synthesis of a bio-based diepoxy monomer. The enzymatic pathway showed generally lower environmental impact, while highlighting the strong influence of yield, solvent recycling, and waste generation on process sustainability. Their work also emphasised the importance of comprehensive LCA analyses beyond conventional green chemistry metrics.[26] More recently, LCA has also been employed to assess greener amidation methodologies for pharmaceutical synthesis, demonstrating that saccharin-based routes combined with solvent and reagent recycling strategies can significantly reduce greenhouse gas emissions and overall environmental impact in the production of active pharmaceutical ingredients (APIs).[27]

Accordingly, the work presented here investigates the environmental burdens associated with CuAAC by evaluating a series of strategies previously employed for the synthesis of triazole moieties.

Because our principal objective was to investigate the synthetic process solely through a cradle-to-gate analysis, all procedures considered were assumed to yield the same benchmark compound, *i.e.*, 1-benzyl-4-phenyl-1*H*-1,2,3-triazole, obtained from the reaction between phenyl acetylene and benzyl azide. Several aspects of the selected procedures have been analysed, including the effects of previously cited starting materials, copper-based catalysts such as copper sulfate, copper metal and $CuBr(PPh_3)_3$ (*vide infra*), ligands and solvents (*tert*-butanol and Polarclean®), revealing that the proper choice of all these components can significantly reduce the impact associated with CuAAC methodologies.

2. Methods

This study adhered to the four phases outlined in LCA methodology.[28,29] Initially, the goal and scope were defined, as was the study typology. Next, the procedures for constructing material inventories were detailed for each synthetic process, along with the assumptions underlying them. Ultimately, the impact assessment approach and method were outlined.

2.1 Goal and scope definition

The main aim of the LCA study conducted herein is to evaluate the environmental profiles of a series of synthetic procedures used to prepare 1,4-triazoles *via* CuAAC and to identify which components or procedures most hinder their sustainability.

Experimental procedures for the synthesis of the benchmark triazole 1-benzyl-4-phenyl-1*H*-1,2,3-triazole were extracted from the literature. The five most notable examples, in terms of providing excellent yields, selectivity, and a variety of catalysts and conditions, were chosen for evaluating their impact through an LCA study (Table 1).[30–34]

The system boundary was defined following a cradle-to-gate approach, and the functional unit was established as 1 g of the target product (Fig. 2). As all the investigated procedures were carried out at laboratory scale, this amount was considered an appropriate and representative reference unit for evaluating and comparing their environmental impact.

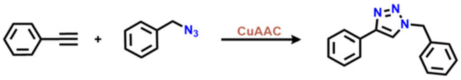
Resource exploitation and water, air, and soil emissions were shaped by both the extraction and manufacturing of all materials, thereby framing the environmental profile and subsequent human-health impact for each chemical route analysed.[35,36]

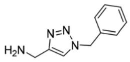
It was assumed that all processes were conducted at a single site. The environmental impact of raw material transportation was accounted for, based on transport distances of 100 km by lorry (>16 t) and 600 km by train. Additionally, the impact associated with chemical plant infrastructure, including manufacturing facilities and equipment, was incorporated as 4.00×10^{-13} p (where "p" represent the fractional share of the whole facility allocated per functional unit).

2.2 Inventory analysis

While setting up the LCA analysis, adopting a retrosynthetic strategy, new inventories for several chemicals have been prepared to be utilised in the evaluation. When an existing inven-

Table 1 Details of the literature procedures investigated[a]



Ref.	Catalyst	Ligand	Reductant	Solvent	T (°C)	Time (h)
30	$CuSO_4$ (1 mol%)		Na-Asc. (4 mol%)	tBuOH/H_2O (2 : 1)	Not specified	24
31	Cu turnings [Cu(0)]	None	None	tBuOH/H_2O (1 : 1)	RT	12–24
32	$CuSO_4$ (1 mol%)	None	Na-Asc. (10 mol%)	tBuOH/H_2O (1 : 1)	RT	6–12
33	$CuSO_4$ (2 mol%)	None	Na-Asc. (10 mol%)	PC/H_2O (4 : 1)	50	24
34	$CuBr(PPh_3)_3$ (0.5 mol%)	None	None	Neat	RT	7–24

[a] For all procedures, a 95% isolated yield was assumed to minimise the effect of small yield variations on the comparative LCA results and enable a more objective assessment of the environmental impact of reagents, solvents, and process conditions; Na-Asc.: sodium ascorbate; tBuOH: *tert*-butanol; PC: Polarclean®; ligand: (1-benzyl-1*H*-1,2,3-triazol-4-yl)methanamine; reaction scale: 0.5–3 millimoles.

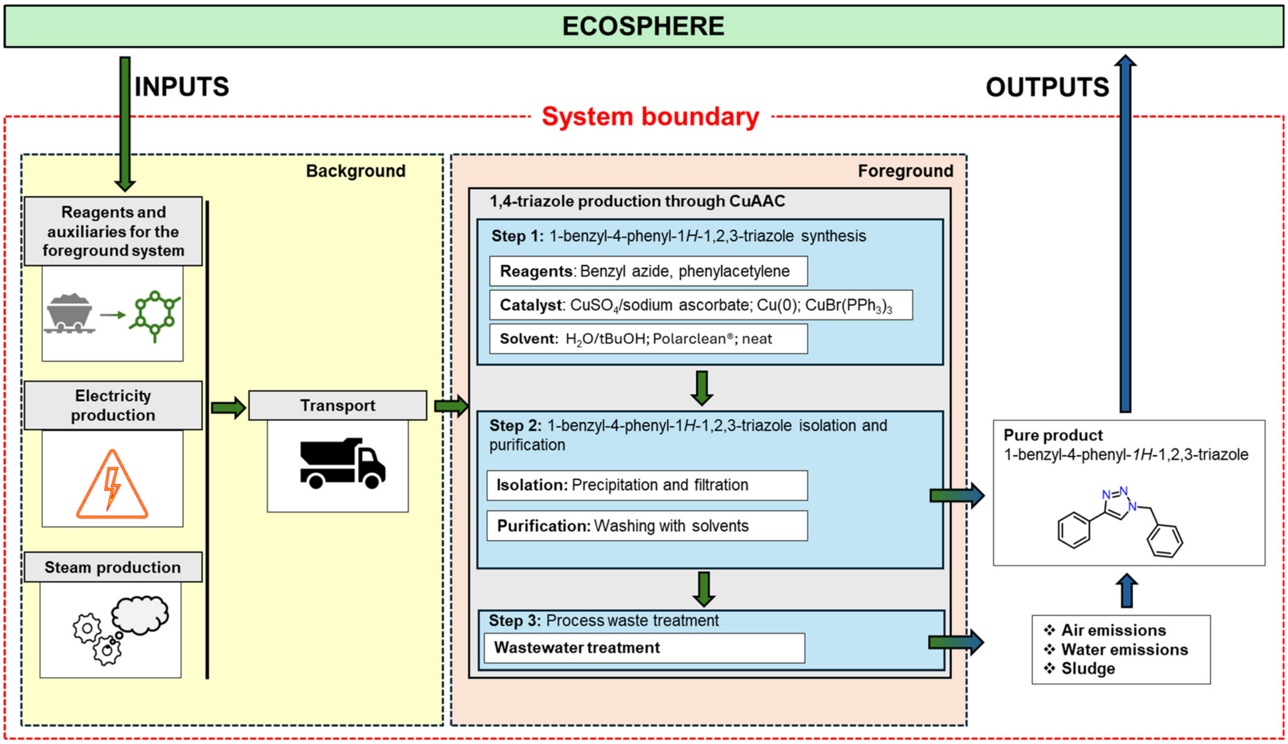


Fig. 2 The cradle-to-gate system boundary employed for the present LCA study, encompassing the synthesis of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole.

tory dataset was available in the literature, it was considered, adjusted according to the assumptions provided, and used for constructing other inventories.

General assumptions were made regarding process energy (0.0002 MJ per gram of compound) and electricity consumption (0.000333 kWh per gram of compound) for all unavailable compounds that required specific modeling.

Given the European Union's statements that energy production and use account for over 75% of greenhouse gas emissions across Europe,[37] the contribution of electricity to the final synthetic steps that afford the desired molecule has been intentionally omitted, as it is nearly identical across all the procedures studied.

This exclusion from the system boundary has been further motivated by different factors. First, because the reactions are carried out at near-room temperature, the energy demand associated with stirring can be considered negligible. In addition, DFT calculations reported by Himo and colleagues demonstrated that azide–alkyne cycloaddition is a highly exothermic reaction, releasing approximately 60.8 kcal mol^{-1}.[32] Under these conditions, the intrinsic chemical energy of the reactants represents the main driving force of the process, while external energy inputs play only a marginal role compared with the need to control the spontaneous heat release for safety purposes.

Accordingly, the present analysis, primarily focused on atomic efficiency, emphasises the impact of the chemicals involved, with particular attention to the environmental and human-health implications associated with the selection of catalysts, reducing agents, and, most importantly, solvents, whose significant contribution to the environmental footprint of chemical processes is widely recognised.

Particularly, the emissions considered, consistent with LCA studies of chemical processes and representing primary contributors to the associated impacts, were calculated with the following assumptions:[23]

- 0.20% of volatile input materials was considered to be emitted into the atmosphere as a consequence of the procedural operations;
- 24.50% of the wastewater treatment was presumed to be oxidised and released into the air as CO_2 (in the case of organic materials);
- 65.80% of the organic compounds was retained in the sludge;
- 9.70% was modeled to be discharged into rivers;
- no emission into the soil was determined, as no agricultural destination for the digested sludge was considered.

Assumptions regarding data gaps, such as the amount of ethyl acetate used in the Lal *et al.*[34] procedure, were based on our expertise and are clearly outlined in the corresponding inventory tables. When specific chemical inventories were not available, proxy data were used, with substitutions made using chemically similar alternatives. For example, the isobutanol ecoinvent inventory was used instead of *t*BuOH. To provide further insight, the present limitations are listed in SI Table S23.

Specifically, the inventory for Polarclean® was not newly developed, as an existing one from the literature (see the SI) was used.

Finally, to evaluate the absolute impact of each chemical synthesis process, the yields of all procedures were standardised to 95%.

2.3 Impact assessment

The impact assessment was performed using SimaPro 9.6 software and the ReCiPe 2016 method, considering 18 impact categories (*Global warming*; *Stratospheric ozone depletion*; *Ionizing radiation*; *Ozone formation: Human health*; *Fine particulate matter formation*; *Ozone formation: Terrestrial ecosystems*; *Terrestrial acidification*; *Freshwater eutrophication*; *Marine eutrophication*; *Terrestrial ecotoxicity*; *Freshwater ecotoxicity*; *Marine ecotoxicity*; *Human carcinogenic toxicity*; *Human non-carcinogenic toxicity*; *Land use*; *Mineral resource scarcity*; *Fossil resource scarcity*; and *Water consumption*).[38]

Midpoint impact categories and Endpoint damage areas (*Human health*, *Ecosystems*, and *Resources*) were analysed hierarchically over 100 years. Long-term emissions, which affect scenarios beyond 100 years, were excluded. The results from the various protocols examined are presented and analysed in Midpoint form, with outcomes further converted in Endpoint damage areas. This enables a comparison of our approach with others using a single indicator as a benchmark for global environmental impact. During this process, Midpoint characterization results are transformed into intermediate units, which are then weighted and normalised to represent the relative impact in millipoints (mPts), reflecting the severity within a global context.

3. Results and discussion

Before describing the methodologies and their overall impacts, we first examined the limitations and advantages of selecting and using one catalyst over another, as well as one solvent over another.

The catalysts adopted in the reference procedures are $CuSO_4$, copper turnings [Cu(0)], and tris(triphenylphosphine) copper(I) bromide [$CuBr(PPh)_3$], as reported in Table 1.

$CuBr(PPh_3)_3$ (Fig. 3) is usually the most impactful catalyst, mainly because of its multistep production route, which requires the depletion of significant amounts of fossil-derived components.

In contrast, $CuSO_4$ exhibits the most benign profile, even less impactful than metallic copper, despite being produced from it. In fact, given the amount of Cu in $CuSO_4$, the impact of the extraction and purification of the pure metal is significantly reduced. This is also reflected in the *Human carcinogenic toxicity*, *Human non-carcinogenic toxicity*, and *Mineral resource scarcity* impact categories, where the mining process significantly influences the final product's human-health footprint. In contrast, $CuSO_4$ is more sensitive in terms of *Freshwater ecotoxicity* than metallic copper because its high water solubility leads to the more rapid release and bioavailability of Cu^{2+} ions. Besides reagents and catalysts, another component that

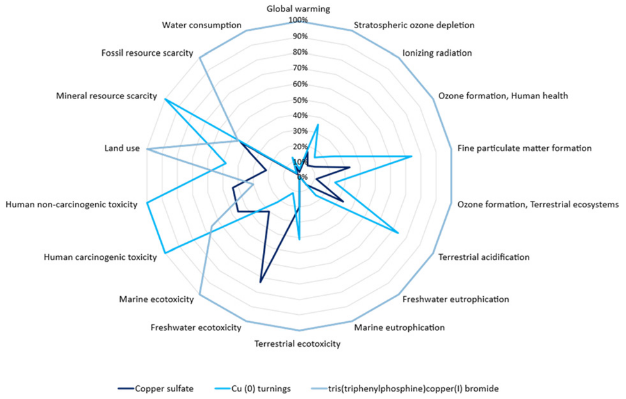


Fig. 3 A midpoint analysis comparison among the different catalysts adopted in the investigated procedures (ReCiPe 2016).

shapes the sustainability of a synthetic route is undoubtedly the solvents used. They, in fact, are used not only to solubilize reactants, stabilise transition states, and transfer mass and heat, but they are also used in the post-processing and purification phases to isolate the pure product.[39,40]

Among the solvents used in the procedures analysed, *t*BuOH and Polarclean® are reported. The first one is a tertiary alcohol industrially produced through isobutene hydration.[41] The second one is a mixture of two components, the major one being methyl 5-(dimethylamino)-2-methyl-5-oxopentanoate, which is produced from methyleneglutarodinitrile (MGN), a by-product of nylon 6,6 production.[42] In the last few decades, Polarclean® has been used for several purposes, including polymerisation,[43] membrane fabrication,[18] solid-phase peptide production[44] and, obviously, organic chemical synthesis, such as radical-mediated cyclization promoted by metal catalysts,[45] the oxidation and rearrangement of carbonyl groups,[46] and copper-mediated 1,3-dipolar cycloadditions.[33]

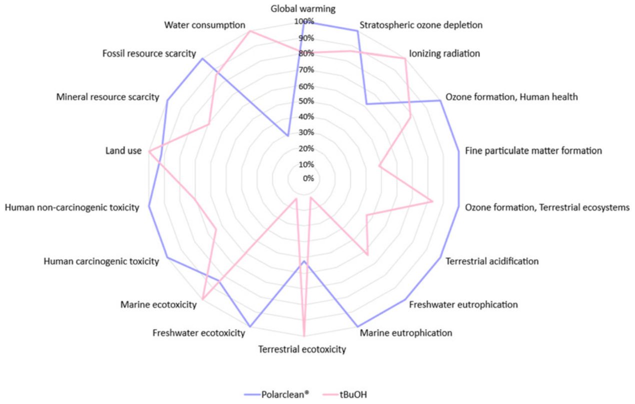


Fig. 4 Midpoint characterization of Polarclean® and *t*BuOH (ReCiPe 2016).

From an environmental point of view, generally Polarclean® shows a worse ecological profile compared to *t*BuOH because of the multistep synthesis process necessary for its production (Fig. 4).[47]

Some exceptions can nevertheless be identified, especially in the categories of *Water consumption* and *Terrestrial ecotoxicity*. This is because PolarClean® is produced from recycled starting materials, whereas *t*BuOH is derived from isobutene obtained directly from crude oil refining.

Following analysis of the key components that influence the environmental footprint of the selected CuAAC procedures, an overall evaluation was conducted.

Firstly, focusing on the procedure developed by Chan *et al.*[30] (Fig. 5), we observed that phenyl acetylene is the major contributor with an impact accounting for an average of 56.4% across the 18 categories, followed by the additive (18.5%) and finally benzyl azide (17.1%). Although phenyl acetylene and benzyl azide are necessary partners for the CuAAC transformation, (1-benzyl-1*H*-1,2,3-triazol-4-yl)methanamine is used as a ligand to enhance the reaction rate, thereby stabilising the Cu (I) species formed upon $CuSO_4$ reduction by sodium ascorbate. This means that the role of the ligand is beneficial but not essential to the reaction course, and from an environmental point of view, it can be avoided, greatly boosting the procedure's sustainability.

The possibility of avoiding the use of a ligand in the synthesis of triazole moieties has already been demonstrated by

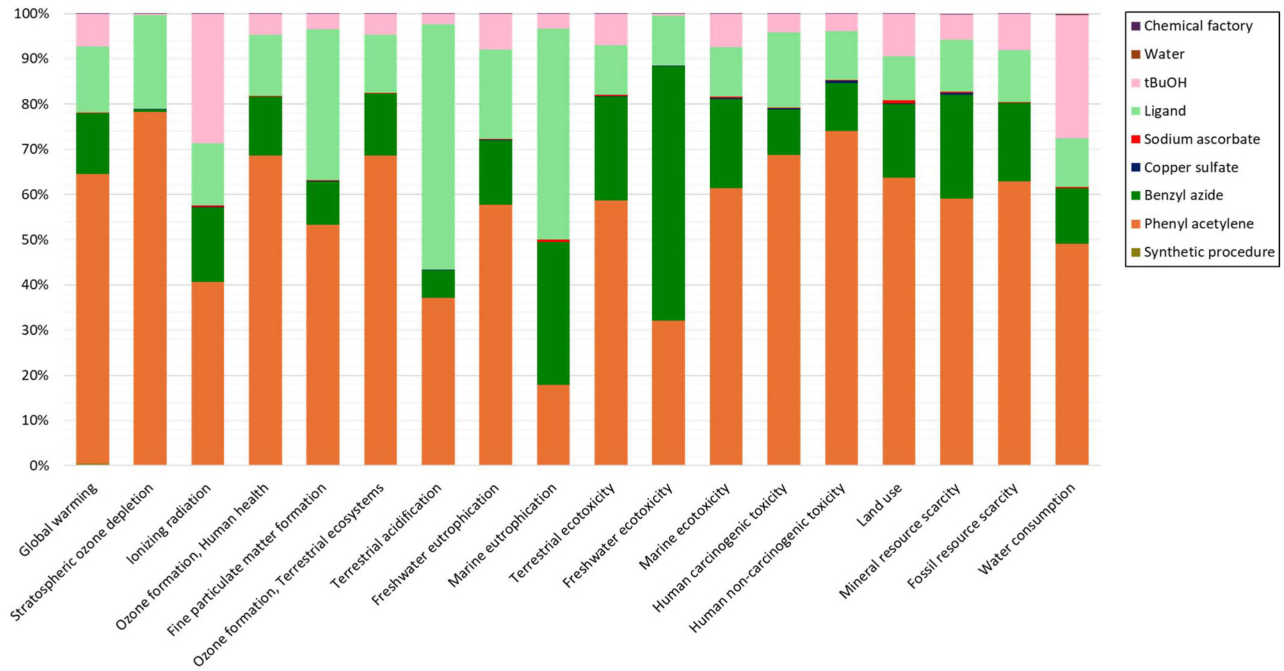


Fig. 5 Midpoint characterisation of the Chan *et al.*[30] procedure (ReCiPe 2016).

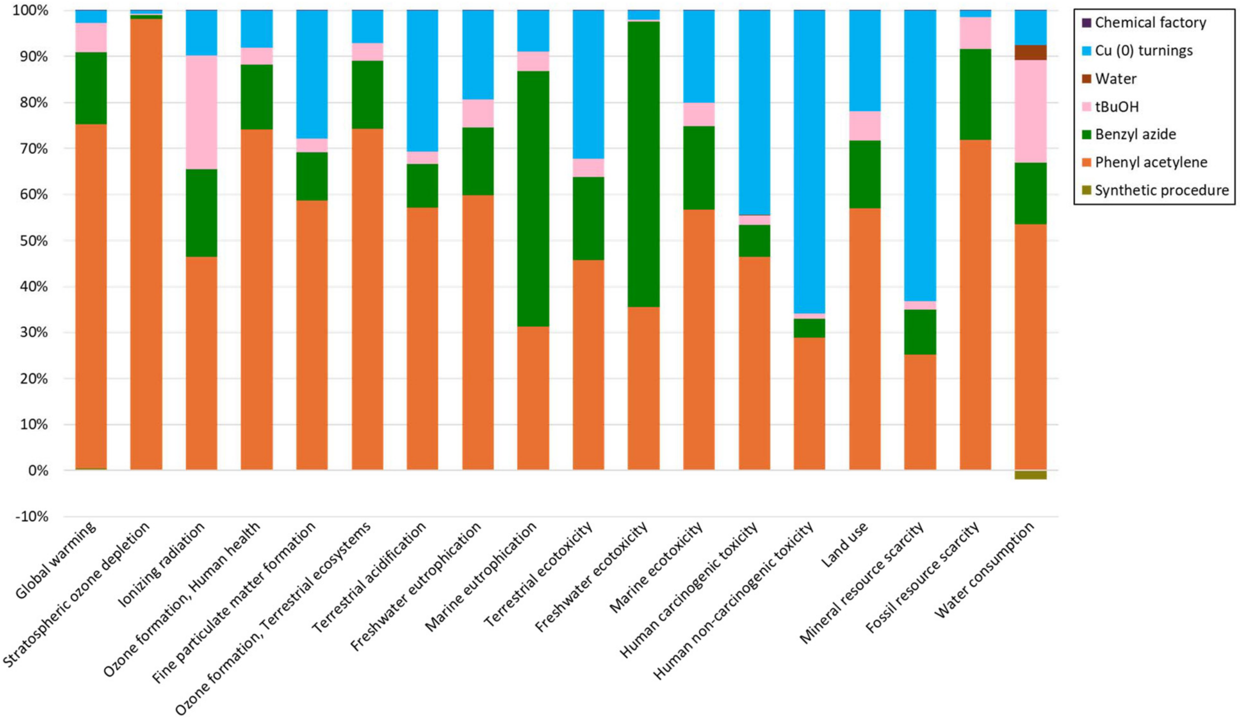


Fig. 6 Midpoint characterization of the Rostovtsev *et al.*[31] procedure.

Rostovtsev *et al.*,[31] including the possibility of catalysing the reaction using Cu(0) turnings (Fig. 6).

For this procedure, the Midpoint analysis highlighted that phenyl acetylene remains the most impactful component across most categories, whereas metallic copper turnings have a highly impactful effect on the *Human carcinogenic toxicity*, *Human non-carcinogenic toxicity*, and *Mineral resource scarcity* categories.

Generally, avoiding the use of the ligand is the key factor contributing to the lower environmental impact, resulting in a reduced global warming potential (GWP).

Specifically, while the procedure including the ligand[30] showed an impact of 0.456 kg CO_2 eq. per g, the one that avoided its use[31] showed a 14.5% reduction to 0.390 kg CO_2 eq. per g. Further environmental improvements were reported by Himo *et al.*[32] by avoiding the use of the ligand and adopting a catalytic system based on $CuSO_4$ with sodium ascorbate as the reductant.

These experimental conditions enabled an additional reduction in the carbon footprint (0.382 kg CO_2 eq. per g) compared with the previously discussed strategies.

This improvement primarily resulted from using a copper salt rather than metallic copper as the catalyst.

Indeed, although $CuSO_4$ requires a synthetic step for its production, its significantly lower copper content by weight reduces the overall mining and extractive impact associated with the metal (Fig. 7).

Once the optimal catalyst has been identified and superfluous components removed, *t*BuOH and, most notably, phenylacetylene and benzyl azide remain the principal contributors to the overall impact. Further improvements in sustainability could nonetheless be achieved by adopting an alternative solvent that facilitates product precipitation, thereby enabling straightforward recovery and reuse. This is the case for Polarclean®, which, when combined with water in a 4 : 1 (v/v) ratio, ensures good solubility of the reagents and allows straightforward isolation by simple under-vacuum filtration of the insoluble product, without the need for additional water to promote product precipitation.

As reported in the procedure developed in 2018 by Luciani *et al.*,[33] when this commercial ester–amide reaction medium is used, the environmental footprint is clearly dominated by the reactants phenylacetylene and benzyl azide (Fig. 8), while the contributions of both the solvent, the reducing agent and the catalyst are negligible since they are recovered and reused for 5 consecutive runs.

Using this green approach, the procedure discussed earlier reduced the carbon footprint to a minimum of 0.362 kg CO_2 eq. per g.

The pivotal environmental role of the solvent is further highlighted when the same procedure is analysed without considering solvent and catalyst recovery.

In this case, the environmental impact is 0.390 kg CO_2 eq. per g, which is 7.73% higher than that of the procedure that entails recovery.

In the context of CuAAC, solvent-free procedures have also been developed. This is the case for the methodology reported by Lal *et al.*,[34] which achieved excellent yields

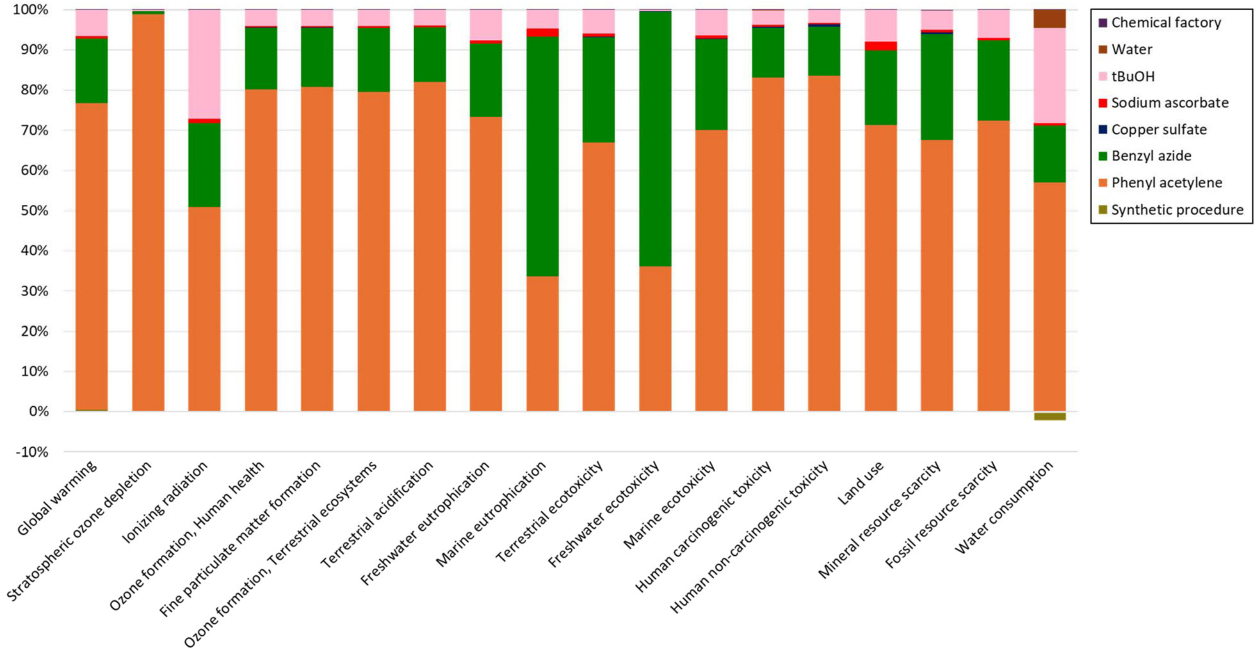


Fig. 7 Midpoint analysis of the Himo *et al.*[32] synthetic route (ReCiPe 2016).

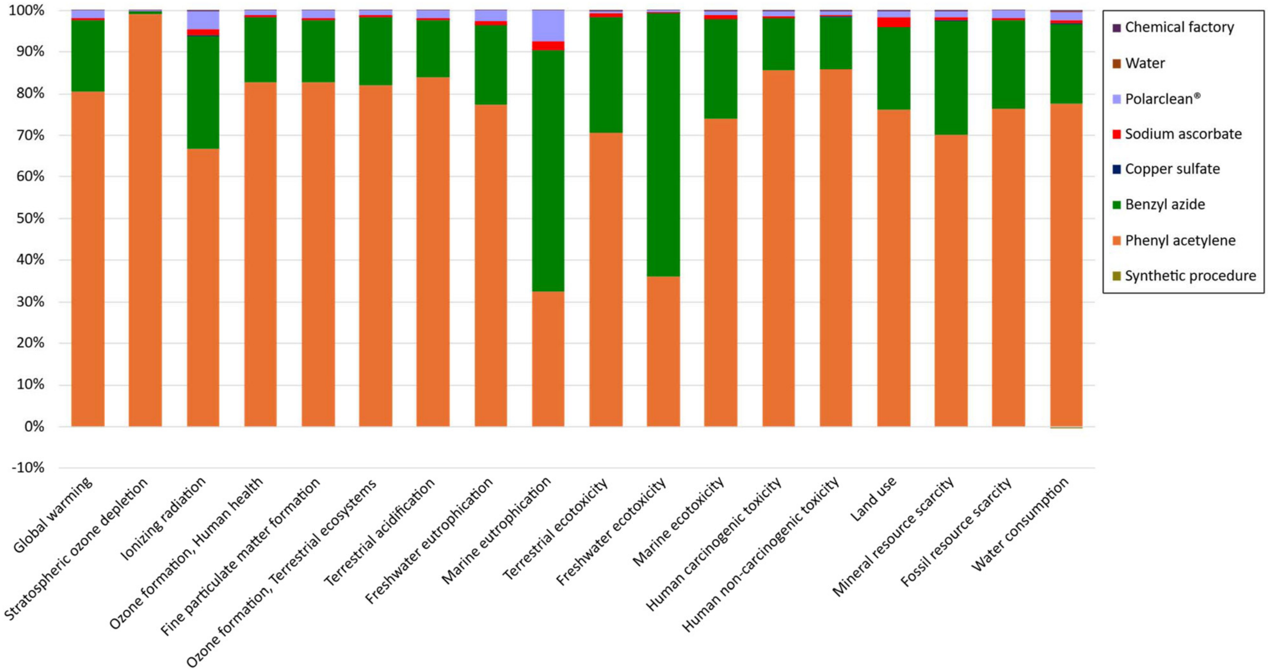


Fig. 8 The Luciani *et al.*[33] CuAAC method (solvent and catalyst recovery and reuse) analysed through Midpoint characterisation (ReCiPe 2016).

under neat conditions by adopting a tailor-made copper catalyst, namely tris(triphenylphosphine)copper(I) bromide [$CuBr(PPh_3)_3$].

Here, despite the complexity of the catalyst synthesis, the overall environmental impact remains limited, even though it is higher than that reported by Luciani *et al.* (0.429 *vs.* 0.362 kg CO_2 eq. per g, respectively).[33]

Indeed, while in the latter method, the contribution of the solvent mixture to the total carbon footprint is negligible, accounting for only 1.78% of the overall impact, in this instance, solvents contribute 16% of the total footprint. This increase is mainly due to the need to use a non-negligible volume of an extractive medium, namely ethyl acetate, to isolate the pure product.

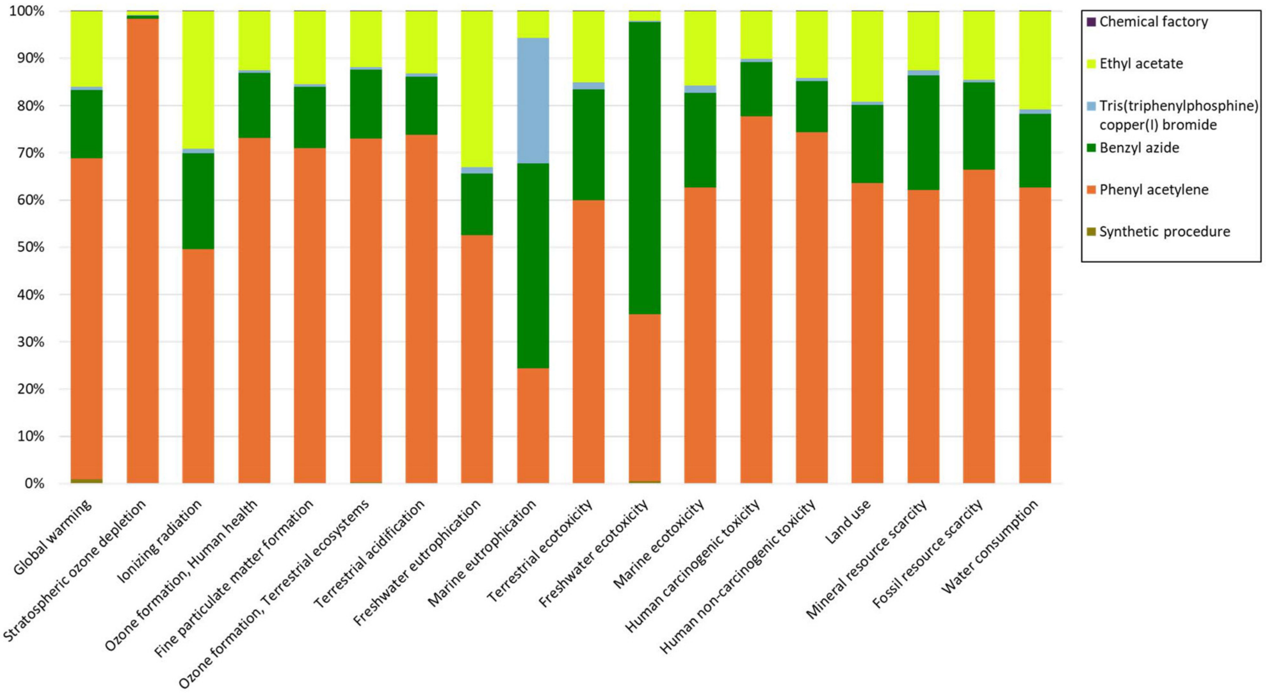


Fig. 9 Midpoint analysis of the Lal *et al.*[34] synthetic CuAAC procedure (ReCiPe 2016).

In principle, this impact could be further reduced by developing an alternative isolation strategy that minimises the use of post-processing solvents (Fig. 9).

In the first part of the analysis, we evaluated the different methods focusing on their Midpoint characterization, *i.e.*, quantifying the "potential" environmental impact at the intermediate stage of the cause-effect chain. During this stage, we compared the various routes, highlighting their impact in terms of GWP, expressed as equivalent kilograms of CO_2, for their carbon footprints. As is well known, comparing two or more synthetic methodologies solely by their GWP is not entirely accurate, as environmental and human health sustainability depend on multiple factors across different categories. For this reason, we also performed an Endpoint characterization to enable a comprehensive comparison of all the evaluated methodologies. The Endpoint assessment quantifies the ultimate effects on the areas of protection, *Human health*, *Ecosystems*, and *Resources,* by translating the impacts calculated at the Midpoint level using specific "damage factors". This approach is particularly important in chemical transformations, where certain environmental flows may appear minor or negligible within the non-comparable scales of a Midpoint profile. However, when integrated through category-specific damage factors and aggregated at the Endpoint level, these underlying indicators can become dominant, significantly reshaping our understanding of the overall environmental burden.

With this strategy, we were able to quantify the overall impact of the methodologies using a numerical value (namely single score) expressed in mPts, enabling a clearer, more comprehensive "sustainability rank".

As shown in Table 2, the details specified confirm that the impact is not dominated by GWP alone but by a mediated combination of all impact categories. For example, while the Lal *et al.*[34] methodology is the second most impactful from a GWP perspective, at the Endpoint level, it ranks third, indicating that all Midpoint categories influence the final Endpoint level and the global impact. As shown in Fig. 10, Global warming is clearly highlighted as a fundamental contributor to the global footprint, which is also mediated by *Fine particulate matter formation* (FPMF), that significantly affects human health. This conclusion relies on the methodology's components, above all, copper metal, whose derived

Table 2 GWP, mPt score, and Endpoint unit values of the procedures considered (ReCiPe 2016)

Procedure	GWP (kg CO_2 eq. per g)	mPts	DALY	Species.yr	USD2013
Chan *et al.* (2004)[30]	0.456	17.2	9.59×10^{-7}	2.31×10^{-9}	0.0853
Rostovtsev *et al.* (2002)[31]	0.390	16.1	9.0×10^{-7}	1.9×10^{-9}	0.0756
Himo *et al.* (2005)[32]	0.382	13	7.18×10^{-7}	1.7×10^{-9}	0.0748
Lal *et al.* (2011)[34]	0.429	14.6	8.09×10^{-7}	1.89×10^{-9}	0.0796
Luciani *et al.* (2018)[33]	**0.362**	**12.4**	$\mathbf{6.89 \times 10^{-7}}$	$\mathbf{1.62 \times 10^{-9}}$	**0.0709**

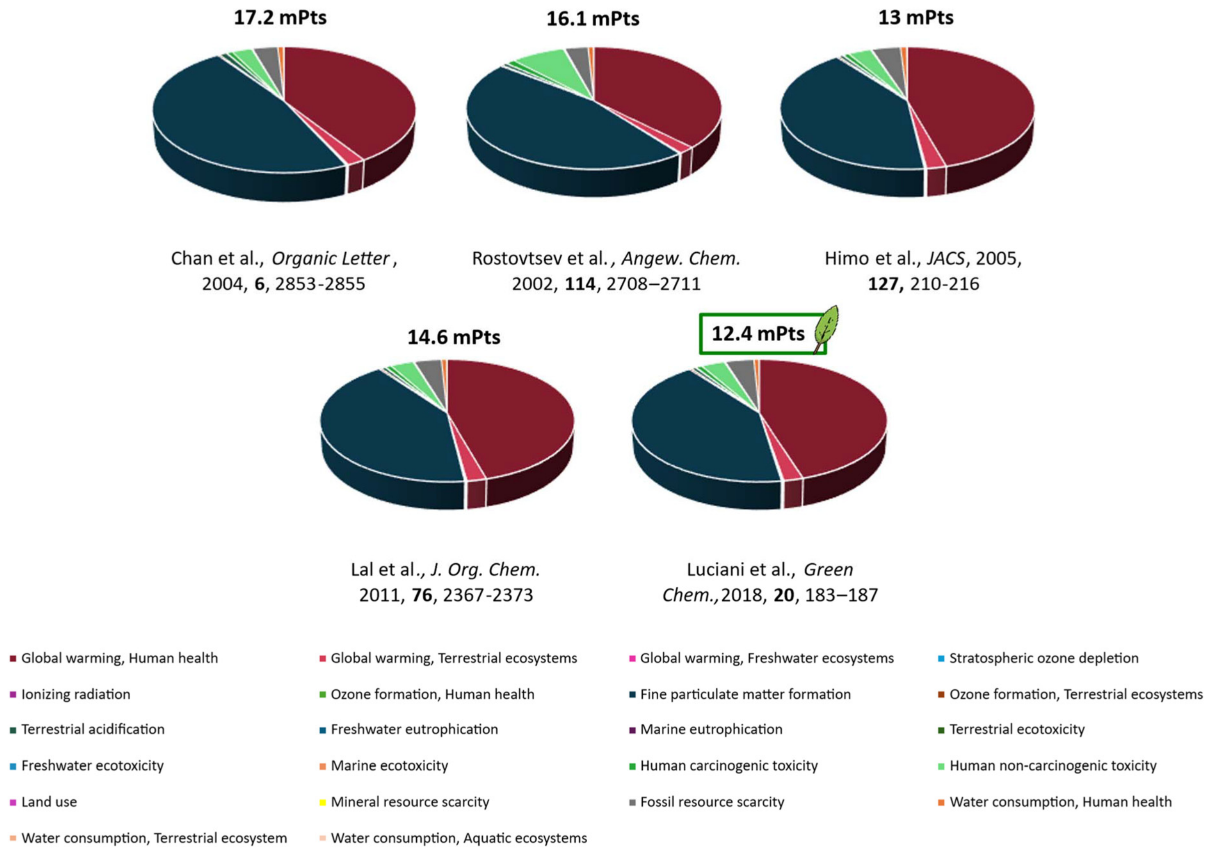


Fig. 10 An Endpoint comparison of the investigated methodologies (ReCiPe 2016, influence of the impact categories on the single score).

extraction and utilization impacts are similar to those of PM2.5.

In particular, the procedures proposed by Chan *et al.*[30] and Rostovtsev *et al.*[31] proved to be the least favorable, primarily due to the substantial contribution of the FPMF category. In the former case, it accounts for 47.38% (8.15 mPts) of the total impact, whereas in the latter, it accounts for 45.96% (7.40 mPts). Notably, in the procedure by Chan *et al.*,[30] the substantial FPMF contribution arises primarily from phenylacetylene (53.3%) and the ligand (33.4%). Conversely, in the Rostovtsev *et al.*[31] method, in addition to phenylacetylene, a major portion of the impact comes from the use of Cu(0) turnings as the catalyst (27.8%). Among the remaining routes, the procedure reported by Luciani *et al.*[33] is confirmed to be the most environmentally friendly.

This result is mainly attributed to the recyclability of both the solvent mixture and the catalytic system, which, by reducing toxic emissions and climate-change-related impacts, improves the overall sustainability of the process. With respect to the methodologies proposed by Himo *et al.*[32] and Lal *et al.*,[34] the main impact in the former is associated with the *t*BuOH : H_2O solvent mixture, whereas in the latter, it is driven primarily by using $CuBr(PPh_3)_3$ as catalyst and the large amount of ethyl acetate required for product isolation.

3.1 Uncertainty analysis

To assess the reliability of comparative LCA regarding the five triazole synthesis procedures, a stochastic uncertainty analysis was performed using Monte Carlo simulations (1000 runs). The uncertainty parameters for the inventory data were defined through Pedigree analysis, evaluating five quality criteria: reliability, completeness, temporal correlation, geographical correlation, and further technological correlation. This assessment focused specifically on the *Global warming* and *Fine particulate matter formation* categories, using the ReCiPe 2016 Midpoint (H) method. The results, summarised in Table 3, show that the coefficient of variation (CV) ranges from 9.4% to 19.2%, indicating the high overall stability of the LCA model. The analysis highlights a clear distinction between procedures based on data quality and those based on inventory specificity. The most recent methodologies, specifically those by Luciani *et al.*[33] and Lal *et al.*,[34] exhibit the highest statistical robustness, with CV values below 10%. These low uncertainty levels reflect the use of specific and updated datasets from the Ecoinvent database, confirming the scientific reliability of these strategies. In contrast, the procedures by Himo *et al.*,[32] Rostovtsev *et al.*,[31] and Chan *et al.*[30] show higher uncertainty (CV between 14% and 19%). This increased variability is a result of increased temporal distance and, because of a delib-

Table 3 Monte Carlo uncertainty analysis results (1000 runs, 95% confidence interval) for the global warming and fine particulate matter formation impact categories using the ReCiPe 2016 Midpoint (H) method

References	Impact category	CV (%)	95% Confidence interval
Chan *et al.* (2004)[30]	*Global warming* (kg CO_2 eq. per g)	15.6	0.336–0.607
	Fine particulate matter formation (kg PM2.5 eq.)	15.1	0.00057–0.00103
Rostovtsev *et al.* (2002)[31]	*Global warming* (kg CO_2 eq.)	16.5	0.274–0.529
	Fine particulate matter formation (kg PM2.5 eq.)	14.2	0.000529–0.000923
Himo *et al.* (2005)[32]	*Global warming* (kg CO_2 eq.)	18.4	0.273–0.561
	Fine particulate matter formation (kg PM 2.5 eq.)	19.2	0.000363–0.000762
Lal *et al.* (2011)[34]	*Global warming* (kg CO_2 eq.)	9.61	0.357–0.521
	Fine particulate matter formation (kg PM 2.5 eq.)	9.98	0.000481–0.00071
Luciani *et al.* (2018)[33]	*Global warming* (kg CO_2 eq.)	9.4	0.302–0.433
	Fine particulate matter formation (kg PM 2.5 eq.)	9.64	0.000416–0.000603

erate and transparent methodological choice, due to the absence of *t*BuOH in the ecoinvent 3.11 database, isobutanol was adopted as a conservative technological proxy. To rigorously account for the uncertainty introduced by this substitution, a maximum Pedigree score (technological correlation = 5) was assigned, resulting in a geometric standard deviation (SD2) of 2.29 for this input. Consequently, the higher CV values for these procedures do not represent a flaw in the chemical synthesis itself, but rather an honest quantification of the uncertainty inherent in the available literature data.

Despite the variability introduced by proxies, the comparative hierarchy remains statistically significant. Regarding GWP, the procedure by Luciani *et al.*[33] emerged as the most efficient and robust solution. Its 95% confidence interval (0.302–0.433 kg CO_2 eq.) is the narrowest among the studied examples and remains consistently below the upper uncertainty limits of the competing procedures. A similar trend was observed for *Fine particulate matter formation*, where the procedure reported by Luciani *et al.*[33] provides the most favourable balance between low environmental impact and statistical certainty.

4. Conclusions

In this work, a cradle-to-gate LCA approach has been used to investigate the sustainability characteristics of copper-catalysed azide–alkyne cycloaddition using a series of benchmark methodologies.

In this study, it has been demonstrated that reaction and work-up solvents significantly influence the impact on both human health and environmental sustainability. Accordingly, a proper reaction design that utilises more benign solvents, along with an appropriate recovery and reuse strategy, can undoubtedly enhance the overall ecological profile. In this regard, Polarclean® has been confirmed as an effective solvent that, in addition to enabling excellent reaction yields, can significantly reduce a process's environmental impact due to its recyclability. Indeed, this type of process exhibits a lower carbon footprint (0.362 kg CO_2 eq. per g), being 5.24–20.62% less carbon-intensive and reducing the impact on human health, ecosystems, and resource depletion by 4.62–27.91% compared to the other methodologies evaluated; moreover, Pedigree analysis combined with Monte Carlo simulations confirms the environmental superiority of the procedure proposed by Luciani *et al.*,[33] even under the most conservative probabilistic scenarios.

Despite considerable efforts to improve CuAAC transformations, several drawbacks remain, hindering these processes from achieving full greenness. As demonstrated throughout this work, phenylacetylene constitutes the main environmental hotspot, as it is industrially produced from styrene or from halogenated (mono- or dihalogenated) styrene derivatives. For this reason, further investigation aimed at identifying alternative renewable raw materials and more sustainable synthetic routes for its production represents the keystone to effectively and sharply cutting the overall environmental footprint of CuAAC.

Author contributions

F. C.: investigation, methodology, inventory construction, data analysis, writing, review, editing; D. L.: investigation, methodology, inventory construction, data analysis, writing, review, editing; L. V.: conceptualization, project administration, and manuscript review/editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

Supplementary information (SI): material life cycle inventories and LCA impact assessment datasets. See DOI: https://doi.org/10.1039/d6gc01508e.

Acknowledgements

This work has been funded by the European Union – NextGenerationEU under the Italian Ministry of University and Research (MUR) National Innovation Ecosystem grant

ECS00000041 – VITALITY. We acknowledge Università degli Studi di Perugia and MUR for support within the project Vitality. The University of Perugia is acknowledged for financial support to the university project "Fondo Ricerca di Ateneo, edizione 2022". MUR is also thanked for PRIN-PNRR 2022 project "20223ARWAY – REWIND" and for the PRIN project no. 20207CNBE4 "FAITH".

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