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PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/d5su00636h

Automating and improving GHG emissions calculation in pharma/fine chemicals synthesis R&D: GreenSpeed as a digital tool to navigate complex value chains

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As the pharmaceutical and fine chemicals industries strive to meet climate goals, optimizing the environmental impact of chemical synthesis during the research and development (R&D) phase becomes crucial. This paper demonstrates the challenges involved in evaluating climate change impacts due to lack of harmonization in calculation standards, missing raw material data in environmental footprint (EF) databases, and common mistakes to choose proxy data when closing data-gaps in manual calculations. As one approach to mitigate this situation, we introduce GreenSpeed, a digital tool developed by Merck KGaA, Darmstadt, Germany, that automates the assessment of greenhouse gas (GHG) emissions and resource consumption metrics, such as Product Carbon Footprint (PCF) and Process Mass Intensity (PMI). By integrating with Electronic Laboratory Notebooks (ELNs) and automatically matching environmental footprints based on chemical structure and molecular complexity, GreenSpeed enhances data accuracy and accessibility, empowering researchers to make informed decisions that promote sustainability aspects. The tool provides an overview of the three main contributions to climate change impacts relevant to R&D and process chemists: raw materials, waste treatment, and energy consumption. In addition, GreenSpeed features functionalities for direct route comparisons, scenario modeling, and recycling assessments, enabling a fit-for-purpose evaluation of environmental impacts across complex value chains. This approach addresses the intricacies of complex molecule manufacturing, where multiple synthesis pathways can lead to varying environmental footprints. Through a detailed case study focused on an API precursor synthesis as well as the underlying chemical building blocks used as raw materials, this work demonstrates GreenSpeed's capability to improve accuracy in PCF calculations. Potentials for GHG emissions reduction are presented as well, considering the complexities of pharma and fine chemicals supply chains. The study highlights the complexity to perform such assessments and the necessity of digital solutions in advancing emissions reduction initiatives within the pharmaceutical and fine chemicals sector. Guidance on how to create datasets for PCF calculations with reasonable quality and how to close data-gaps is presented as well.

Received 31st July 2025
Accepted 6th January 2026

DOI: 10.1039/d5su00636h

rsc.li/rscsus

Sustainability spotlight

This work showcases a significant advancement in sustainable practices within pharmaceutical and fine chemicals synthesis R&D by automating the assessment of greenhouse gas emissions and resource consumption through a digital tool, GreenSpeed. In addition, guidance on how to improve the quality of such environmental footprinting evaluations is provided for process chemists as well as life cycle assessment practitioners. The work aligns with the UN's Sustainable Development Goals (SDGs) by contributing to sustainable innovation and industry (SDG 9), promoting responsible consumption and production (SDG 12) by enabling informed decision-making in chemical synthesis, and combating climate change (SDG 13) by identifying pathways for GHG emissions reduction.

Introduction

In the quest to achieve climate goals and reduce resource consumption, the pharmaceutical and fine chemicals industries face significant challenges: due to the material intensive

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manufacturing of Active Pharmaceutical Ingredients (APIs) and other complex functional molecules, the environmental impact of these industries is predominantly product-related.[1–3] It is commonly proposed, that over 80% of a product's environmental impact is determined during the research and development (R&D) phase.[4–6] This underscores the critical need for informed decision-making early in the development process regarding synthesis routes, raw material selection, and solvent choices. In this article we present:

- GreenSpeed, a digital design tool that automates calculation of resource intensity metrics and climate change impacts (GHG emissions) in chemical R&D and process development.
- Challenges resulting from the high complexity of pharma and fine chemicals value chains, showcased in an illustrative example of an API precursor synthesis.
- Perspectives on GHG emissions reduction in pharmaceutical manufacturing and allied (fine chemicals) industries.

Process Mass Intensity (PMI) has emerged as a widely used and reliable metric for assessing the environmental impact of chemical processes during the design phase.[7–11] It focuses on resource efficiency and is championed in the industry by *e.g.* the ACS Green Chemistry Institute Pharmaceutical Roundtable (ACS GCI PR) and its member companies through its guidelines for green chemistry.[12,13]

In addition, a rising number of customers and the general public request information on and reduction of greenhouse gas (GHG) emissions incurred by products.[14,15] Regulatory frameworks, such as the EU's Corporate Sustainability Reporting Directive (CSRD),[16] are increasingly demanding transparency in carbon footprint reporting, including Scope 3 emissions which account for the majority of a product's life cycle emissions.[17] This has led to the situation that many companies have set ambitious net-zero targets, and the products currently in development will have to play a pivotal role in achieving these goals.

To enhance the assessment of a product's environmental footprint (EF), PMI should therefore be supplemented with Product Carbon Footprint (PCF) metrics,[18,19] expressed in kg CO_2 equivalents (CO_2e) per kg of product. These metrics account better for the complexities introduced by more intricate building blocks and raw materials, providing a more comprehensive view of a product's sustainability profile. The Together for Sustainability (TfS) initiative, a global industry group formed by the world's largest chemical companies, has developed a PCF Guideline[20] that aligns with international standards such as ISO 14067 [21] and the Greenhouse Gas Protocol,[22] providing a framework for consistent carbon footprint calculations in the chemical industry. An even broader framework focusing on the pharmaceutical industry is the PAS2090 standard that provides product category rules for environmental life cycle assessments. It encompasses impact categories beyond climate change and was published in 2025 under the guidance of the British Standards Institute (BSI).[23]

A variety of manual tools are available for calculating PMI and/or PCF including the streamlined PMI-LCA tool[11,24,25] by the ACS GCI Pharmaceutical Roundtable, among others[26–34]. Other tools like DOZN[35–37] focus on the 12 principles of Green Chemistry[12,38] to assess ecological sustainability. These manual tools, while effective, require expertise and often considerable time for data entry, which can be a barrier for scientists who may not specialize in sustainability. In our experience, asking researchers to manually fill scorecards or spreadsheets has led to very slow adoption and eventually lack of use. In addition, practitioners often only focus on raw materials evaluations without considering emissions from energy consumption and waste treatment, *e.g.* from incineration of solvents. The resulting environmental footprint assessments are then underestimated as was found to be the case in recent studies.[19,39,40]

For these reasons, it is essential to empower chemists with tools that provide accessible, quick and fit-for-purpose evaluations.[41] At the same time, such tools must provide evaluations based on harmonized methods and should allow to explore "what-if" scenarios, such as the implications of selecting alternative raw materials or implementing waste recycling strategies for the intentional design of greener chemical processes.

In response to this need, the Process Development Department of Merck KGaA, Darmstadt, Germany, has collaborated with the company's Corporate Sustainability Group to develop a web-based application for internal use in the R&D process called GreenSpeed. It was built as part of the sustainability program SPEED (Sustainability-focused Process Evaluation, Engineering, and Design). The digital tool facilitates sustainable decision-making by enabling R&D scientists to quickly calculate essential sustainability metrics per mouse-click, including PMI and PCF, which is achieved through automatic data collection from Electronic Laboratory Notebooks (ELNs) and linking to environmental footprint data (Fig. 1). By streamlining the assessment process, GreenSpeed aims to enhance the ability of scientists to intentionally make more sustainable choices during the critical early stages of product development. The automation of the process through integration with the ELNs has been a key component for quick adoption and wide usage among the scientists and researchers.

Automating PCF calculations – core features and key metrics of GreenSpeed

GreenSpeed is a web-based application that automates sustainability assessments of chemical products and supports the design process. One of the key features is that it integrates with our in-house Electronic Laboratory Notebooks (ELN), allowing researchers to connect synthesis information directly with environmental footprint data from both external and internal sources. This integration enables immediate feedback on sustainability metrics upon documenting experiments, with no additional data entry required beyond the experiment IDs from the ELN. These can be entered by simply copy-pasting the respective experiment IDs into the app. The application accommodates both single-step and multi-step, multi-branched syntheses, facilitating relevant sustainability evaluations for chemical processes.

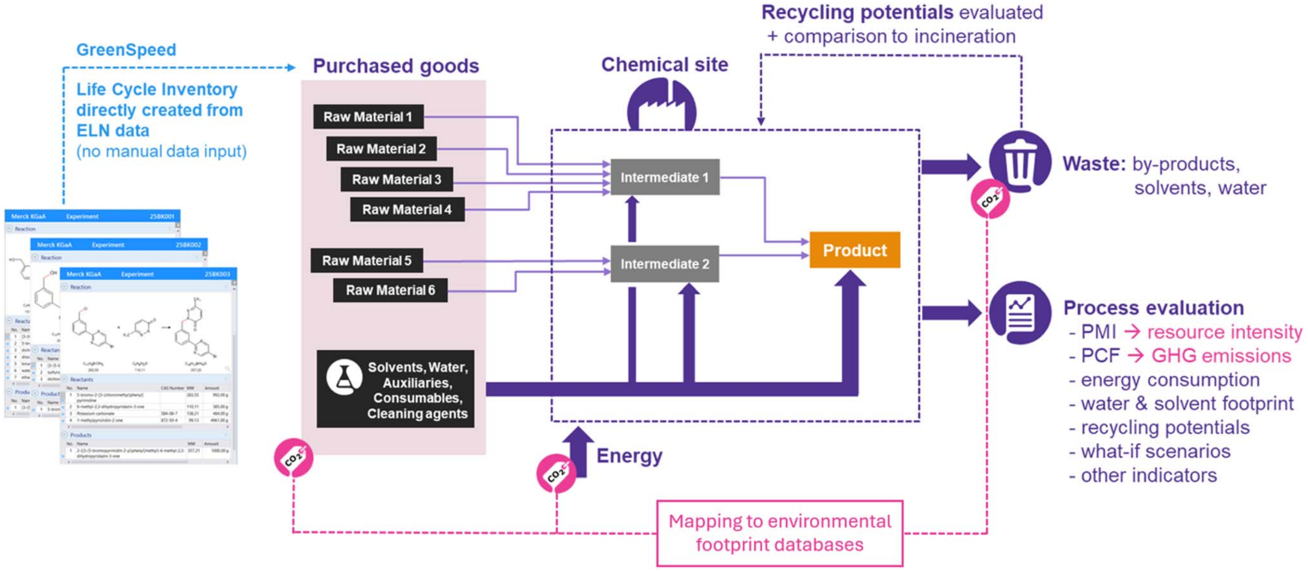
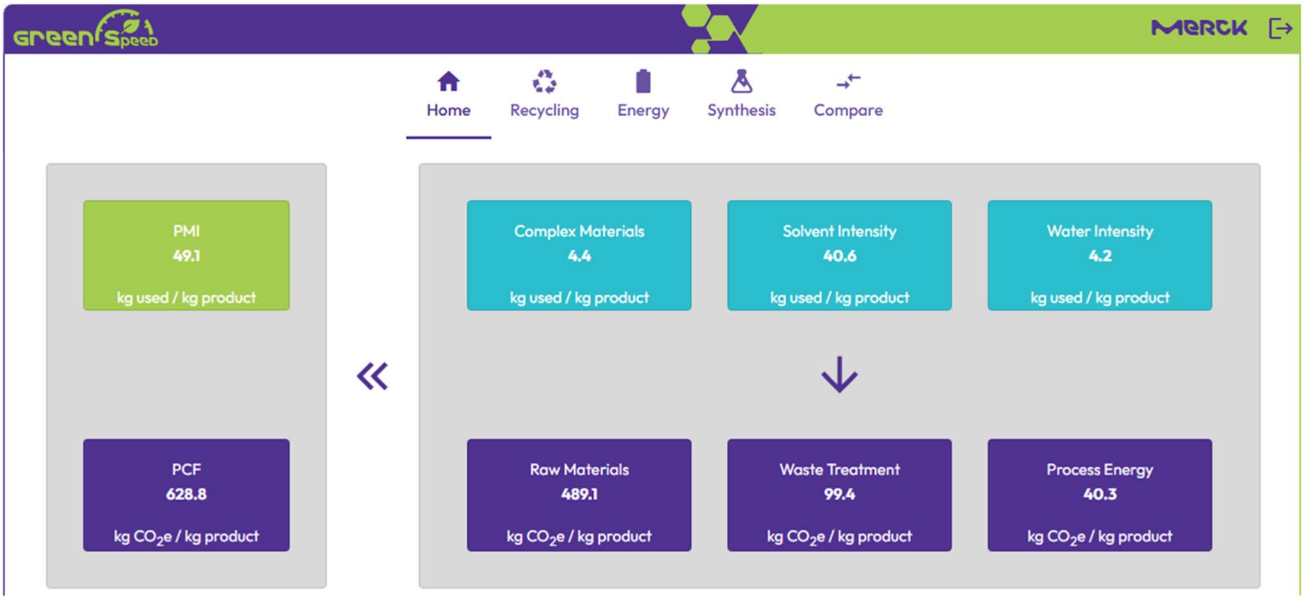


Fig. 1 Interconnectivity between GreenSpeed and ELNs, automated life cycle inventory creation and overview on the main three contributors used for calculating the PCF: purchased goods, energy, and waste treatment.

The tool computes several key metrics essential for evaluating the environmental impact of chemical processes. These metrics include Process Mass Intensity (PMI), Product Carbon Footprint (PCF), Solvent Intensity (SI), Water Intensity (WI), energy consumption, and recycling potentials. Additional environmental footprint categories can easily be added as well, datasets are available, but not yet shown because the focus in chemical R&D in most cases is on improving resource efficiency and lowering GHG emissions. The cumulated PMI is directly calculated using the masses of starting materials and products and is color-coded to give an immediate semi-quantitative evaluation (Fig. 2). The contributions to the PMI from solvents (SI) and water (WI) are shown for the entire synthesis and for each individual step. Fig. 3 displays how the chemical synthesis route is presented. In this case, a linear three-step process to produce an API precursor from a published route[42] is shown as an example. Sankey Diagrams display individual mass contributions of each chemical used in the process and allow quick identification of the largest contributors (Fig. 4).

PCF calculations are based on three primary contributors (Fig. 2) which describe the system boundaries:



PMI
49.1
kg used / kg product

Complex Materials
4.4
kg used / kg product

Solvent Intensity
40.6
kg used / kg product

Water Intensity
4.2
kg used / kg product

PCF
628.8
kg CO_2e / kg product

Raw Materials
489.1
kg CO_2e / kg product

Waste Treatment
99.4
kg CO_2e / kg product

Process Energy
40.3
kg CO_2e / kg product

Fig. 2 PMI and PCF evaluation overview screen in GreenSpeed.

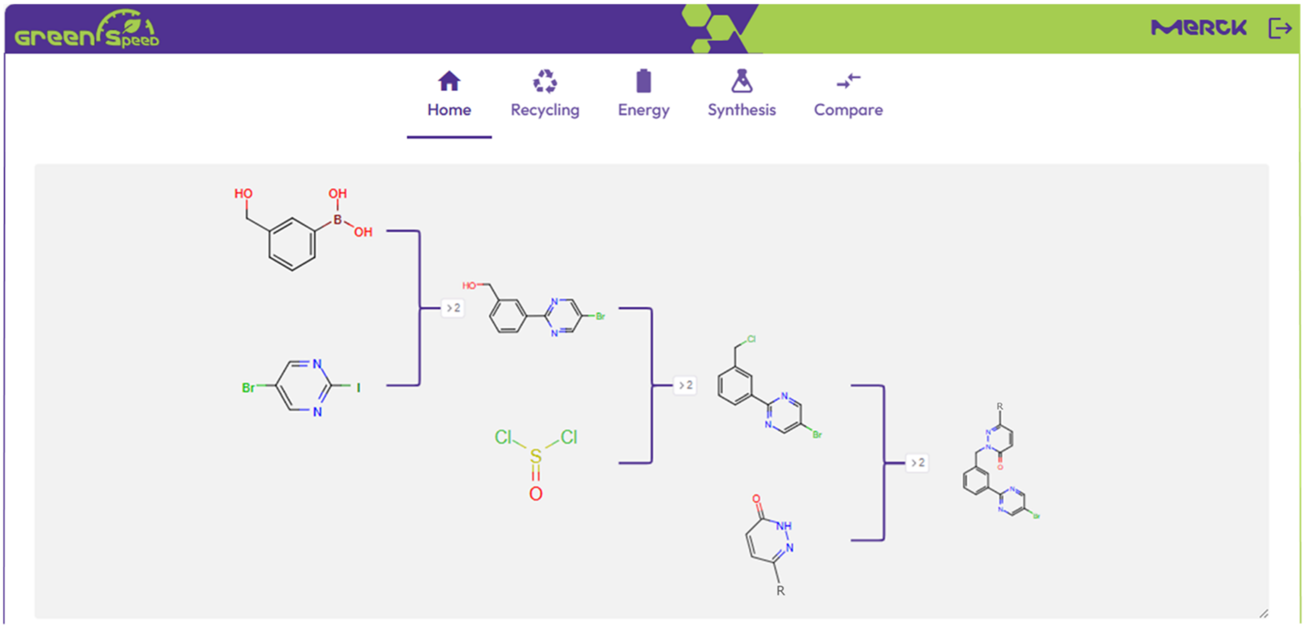


Fig. 3 Chemical synthesis route overview screen in GreenSpeed.

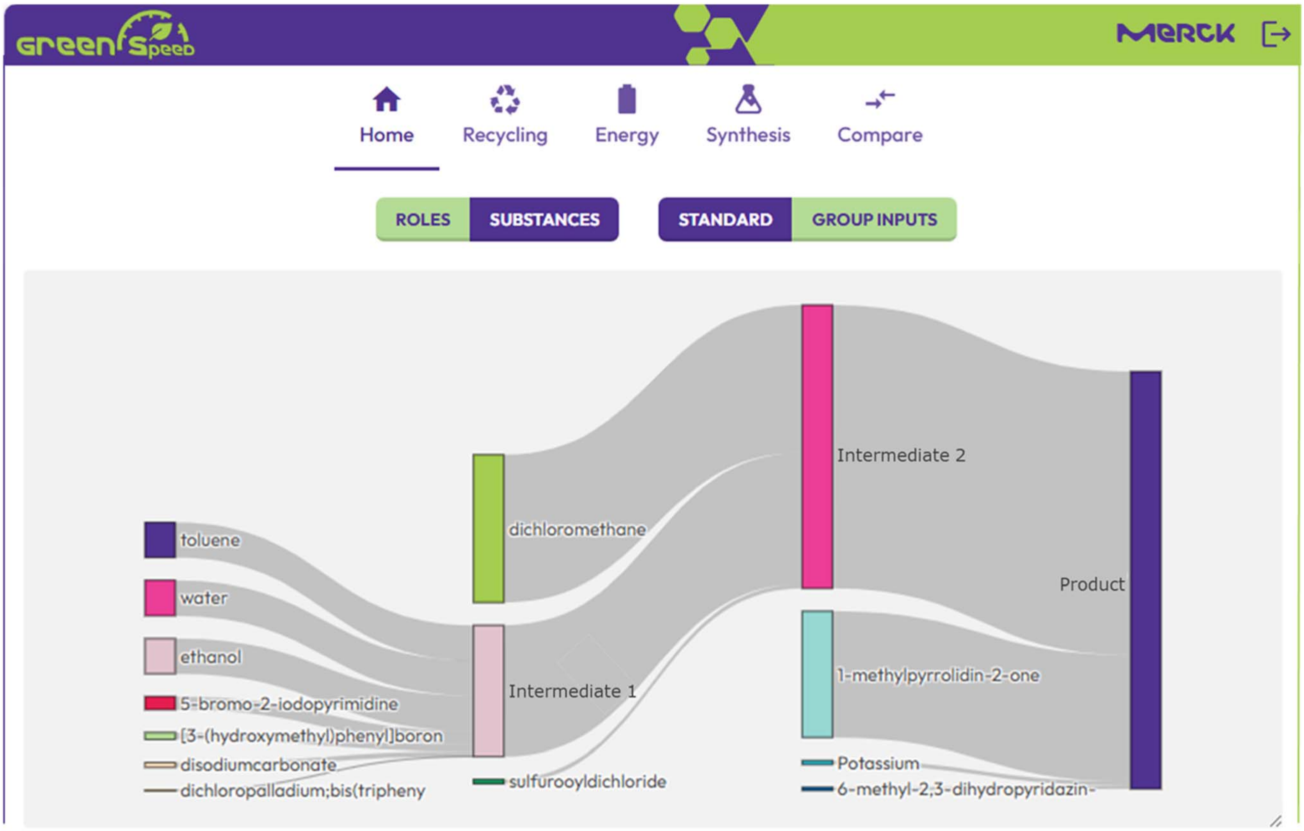


Fig. 4 Sankey diagram to show mass flows for each chemical in the life cycle inventory in GreenSpeed.

- Emissions from purchased raw materials (reactants/building blocks, reagents, solvents, and catalysts), Scope 3.1.
- Waste-related emissions from incineration, Scope 3.5.
- Emissions from energy consumption, Scope 1 and 2.

Emissions from transportation (Scope 3.4 and 3.9) are deemed negligible and outside the R&D scientists' area of influence and are therefore not included. Likewise, the location of the (future commercial) chemical production plant or contract manufacturing organization (CMO) partner is usually still unknown during R&D stages. Thus, emissions from energy consumption are not calculated with production site-specific data and are estimated based on existing average data, complemented with calorimetric and thermodynamic calculations for individual chemical process steps.

The raw material emissions are calculated by matching each chemical from the life cycle inventory (pulled from the ELNs) to EF databases. Other EF impact categories such as water scarcity, eutrophication or acidification could be integrated as well but for now the focus of GreenSpeed and this study is on GHG emissions. The selection hierarchy for raw material carbon footprints in the tool is structured to ensure a comprehensive and systematic approach.

The hierarchy consists of three levels with decreasing data quality:

(1) Expert list: this data source includes a curated selection of carbon footprint data derived from supplier information and secondary databases combined with expert assessments. The entries in this list are limited, focusing on the most relevant and reliable data sources to ensure a high accuracy in the PCF calculations. Most common solvents and frequently used raw materials are covered here.

(2) Proxy list: the proxy list was developed using a combination of carbon footprint mapping methodologies that consider both spend-based and weight-based approaches. It has a wider coverage, but lower data quality compared to the expert list.

(3) Role-based classification: this classification organizes raw materials based on their roles in the synthesis process. It includes the following categories: reactant/chemical building block (100 kg CO_2e per kg), reagent (5 kg CO_2e per kg), catalyst (1000 kg CO_2e per kg), solvent (4.9 kg CO_2e per kg), and water (0.001 kg CO_2e per kg). This is the fall-back option if no data is found for chemicals *via* the other sources and defaults to pre-set values for the applied roles. The values chosen for the various roles were based on rounded averages for the different categories. The catalyst footprints relate to precious metals and include recycling rates (often >90%).

Waste-related emissions assume a worst-case scenario of full waste incineration with the option to evaluate recycling potentials and its immediate impact on reducing GHG emissions. Therefore, specific factors for incinerating solvents, wastewater, and mixed waste also containing inorganics are applied to SI, WI and used raw materials (*e.g.* acids, bases, buffers, by-products) that end up as waste. This modeling of waste incineration procedures is based on existing literature data[32] and internal studies. Scientists can mark individual waste-streams for recycling which will then be considered in the calculations (see below under recycling potential). This contribution to climate change impacts is often neglected due to cut-offs in the system boundaries of cradle-to-gate assessments.[39]

From experience, the contribution of energy-related process emissions in complex small-molecule syntheses to the total GHG emissions footprint is less significant.[43] Therefore, it is sufficient for GreenSpeed to estimate energy-related emissions based on evaluations of approximately 40 different internal syntheses conducted at Merck's production plants on commercial scale. If higher accuracy is needed, researchers can enter the relevant unit operations involved in the synthesis and perform more detailed calculations by employing thermodynamic equations.[44] In the current version, this still requires manual selection of the unit operations as the underlying data in the ELNs lacks consistent structure.

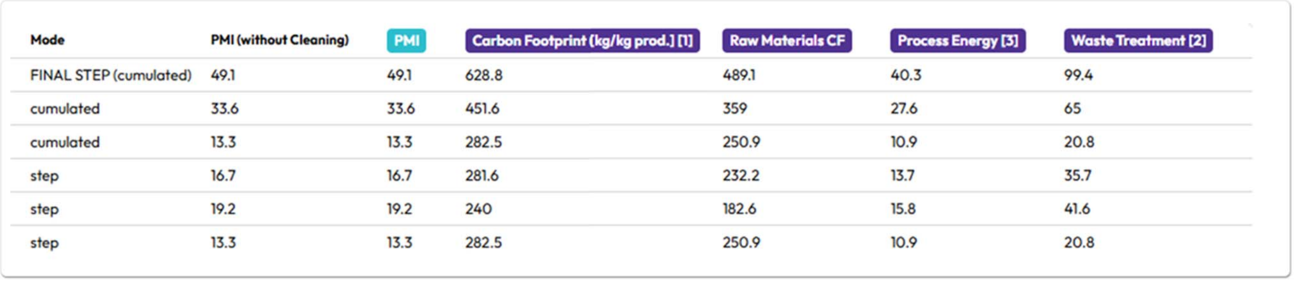
All the above metrics can be displayed for individual steps, as well as cumulated and displayed in tabular form and downloaded as csv files for further analysis (Fig. 5).

By utilizing existing data from ELNs, GreenSpeed minimizes manual data entry errors and allows for rapid calculations, thereby enabling researchers to make informed decisions regarding their synthesis routes and material choices as soon as a chemical reaction is documented.

Current limitations and future development areas include the addition of further environmental footprint categories, a qualitative evaluation of the solvents used *e.g.* based on solvent selection guides like the Chem21 framework[45] and further automatization for entering unit operations to benefit a more detailed analysis of the energy footprint.

Features for the design of greener processes

The data provided from the initial assessment can inform the researchers how synthesis routes perform with regards to emissions and resource efficiency. In addition, GreenSpeed incorporates functionalities that assist researchers in



Mode	PMI (without Cleaning)	PMI	Carbon Footprint (kg/kg prod.] [1]	Raw Materials CF	Process Energy [3]	Waste Treatment [2]
FINAL STEP (cumulated)	49.1	49.1	628.8	489.1	40.3	99.4
cumulated	33.6	33.6	451.6	359	27.6	65
cumulated	13.3	13.3	282.5	250.9	10.9	20.8
step	16.7	16.7	281.6	232.2	13.7	35.7
step	19.2	19.2	240	182.6	15.8	41.6
step	13.3	13.3	282.5	250.9	10.9	20.8

Fig. 5 PMI and PCF evaluation table overview in GreenSpeed.

identifying reduction potentials in environmental impacts for the synthesis under investigation and intentionally design greener processes:

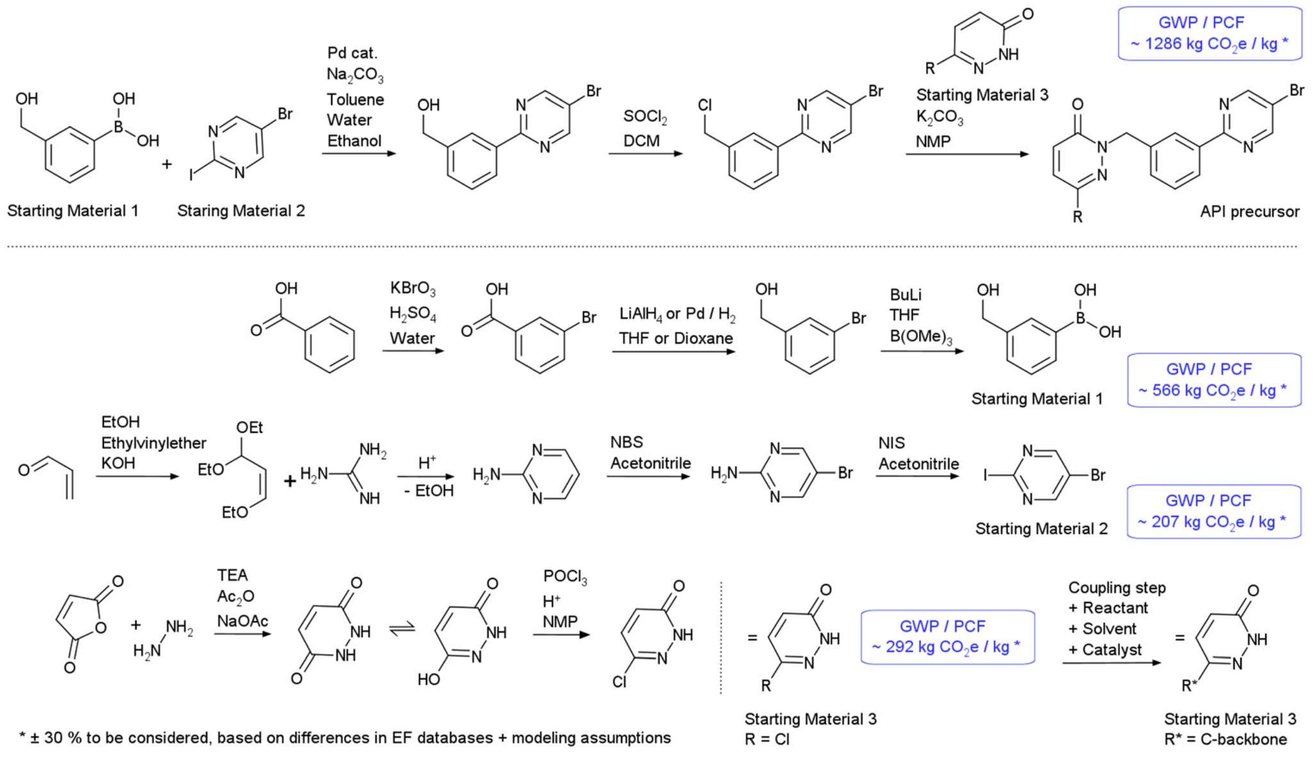
- Direct comparison: two or more synthesis routes can be directly compared and the difference in PMI, PCF and other metrics can be displayed graphically and in table-form. This facilitates identification and quantification of the route with the lowest environmental impact among several candidates. Often, this feature is also used to show the improvement of the same synthesis during process development and optimization.
- What-if scenarios: users can modify material quantities and raw material footprints or adjust energy inputs to evaluate the implications of different choices on sustainability metrics, *e.g.* the effect of omitting a work-up step or substituting a raw material with a low PCF alternative.
- Similarity search: this enables researchers to identify similar transformations among all of Merck's ELN entries, providing yield *vs.* PMI plots that visualize potential improvements for any synthesis step that has been documented in the ELN. Through this, expected targets can be set for new reactions and previous work can inform new approaches.
- Recycling assessment: the application evaluates the recycling potential of materials used in synthesis, promoting practices aligned with the principles of circular economy. Individual material streams can be marked for recycling and the positive effect on the waste treatment footprint is displayed. This enables scientists to not only develop processes but also consider by-products and devise recycling routines.

More details of these extended features in GreenSpeed can be found in the SI. By embedding the use of such features into the routine practice of researchers, GreenSpeed enables chemists to make proactive decisions in the design of greener chemical processes.

Challenges for accurate PCF calculations – API precursor study

The previously published synthesis of a c-Met kinase inhibitor precursor[42] is used in the following as an illustrative use-case to highlight the challenges for accurate climate change impact assessments in small molecule synthesis chemistry. It is a linear three-step synthesis, shown in Scheme 1, with available information on specific catalysts, reagents, and solvents that were used in each step.

In order to create an example for publication, the chemical proxy modeling principles from the above-mentioned PAS2090 standard[23] were applied to create a life cycle inventory for evaluation of environmental footprints of this API precursor. These modeling principles offer industry average assumptions and estimates, provided by the pharmaceutical companies of the Pharma LCA Consortium that developed the standard. Mass- and energy flows can be generated with this approach when no information on weight inputs or energy consumption are known. Such information is extremely helpful when *e.g.* no supplier data and no match in an EF database is available for a specific molecule or a chemical process. This is often the case



Scheme 1 Linear three-step synthesis of an API precursor (upper pathway) based on a published synthesis from Merck and synthesis routes for the starting materials based on retro-synthesis using Merck's Synthia® software.

for fine chemicals and their precursors in contrast to bulk chemicals. For the latter, many datasets exist, often including differences in footprints due to geographical or technological differences in manufacturing. For bulk chemicals (commodities, produced in large volumes and comparatively low priced) one of the most often used set of assumptions follows the so-called "Gendorf approach" to calculate footprints based on mass- and energy flow averages for chemical products at the German chemical industry park in Gendorf.[46,47] Products coming from more complex synthesis processes in organic solvents have thus far not been addressed. This is now delivered with the modeling principles in the PAS2090 standard and enables turning a chemical equation into a more realistic life cycle inventory for assessments. Integrating this information into calculation tools like GreenSpeed and combining this methodology with retro-synthesis tools like Synthia®[48–50] allows to close data-gaps and improve calculation accuracy, which will be shown in this section.

Specific estimates that relate to the manufacturing of small molecule APIs and similar complex organic reactions include, according to the PAS2090 standard:

- 80 mol% yield in synthesis steps.
- 1 mol% catalyst used (homogeneous catalysts).
- 1 mol equivalent of reagents used (acids, bases, buffers).
- 15 kg solvent (or solvent mix) per kg of reactant that undergoes reaction.

In addition to the PAS2090 modeling principles, we recommend in the case of synthesis steps including homogeneous catalysis to consider the complexity of ligands as well as recycling of the metal (we propose 90% recycling in average).

It must be noted that some organic reactions have much lower chemical yield than 80 mol%, and extensive purification or cleaning are not considered in the assumption of 15 kg solvents being consumed per kg of reactant. Resource consumption and related environmental burdens could be higher in such cases, especially when accounting for further purification and cleaning steps.[9] However, the proposed estimates for complex organic reactions allow to create reasonable life cycle inventory data based on the chemical equation in Scheme 1. Energy flow assumptions are not shown in this study because GreenSpeed is using internal datasets, but they are available in the PAS2090 document.[23] In our experience, a crucial step for more accurate evaluations of climate change impacts is to model the actual value chain for a pharmaceutical or fine chemicals product. Since there are often many different pathways that can lead to the same material, they each exert different footprints. Thus, identifying the correct synthesis route combined with good industry average data on yield and resources consumed in complex organic syntheses is key to generate useful life cycle inventory datasets.

For the illustrative use-case of the API precursor synthesis shown in Scheme 1, the resulting PMI and PCF with breakdown of the main contributors are shown in Fig. 2.

The total resource consumption (PMI) amounts to 49 kg per kg of API precursor (all chemicals incl. water considered) with organic solvents (SI) as the main driver, contributing about 40 kg per kg API precursor. Water contributes over 4 kg per kg (WI), and the combined amount of all other chemicals is 4.6 kg per kg API precursor. For a three-step synthesis, these numbers seem to be moderate when compared to publicly available data, *e.g.* from ACS GCI PR members,[19,27,29,39,51] with much higher reported PMIs for API synthesis routes. This is probably related to the fact, that solvent intensive purifications and cleaning are not being included in our exemplary use-case as described above. Estimations for such procedures and the related added footprints can be extracted *e.g.* from a study by Gilead and AstraZeneca.[9] The PCF calculated for the synthesis of our illustrative example amounts to 629 kg CO_2e per kg of API precursor (Fig. 2). We propose to evaluate variabilities based on the quality of available datasets and modeling assumptions. PCF calculations often vary (±30% and more) when assessing complex value chains, in some cases the variability is even much higher than that. Such inaccuracies can originate from changes in datasets from EF databases from one version to the next,

Table 1 Comparison of PCF results from GreenSpeed with OpenLCA and the ACS's streamlined PMI-LCA tool for evaluation of the three chemical building blocks used as starting materials. Detailed life cycle inventory data for each evaluation in OpenLCA and the PMI-LCA tool can be found in the SI

Digital tool	PCF (total) in kg CO_2e	kg CO_2e from raw materials	kg CO_2e from waste treatment	kg CO_2e from energy use
Starting material 1				
OpenLCA	684	451	143	89
GreenSpeed	566	353	143	69
ACS PMI-LCA tool	—	320	—	—
Starting material 2				
OpenLCA	237	155	48	34
GreenSpeed	207	143	46	18
ACS PMI-LCA tool	—	115	—	—
Starting material 3				
OpenLCA	309	181	88	40
GreenSpeed	292	178	82	32
ACS PMI-LCA tool	—	141	—	—

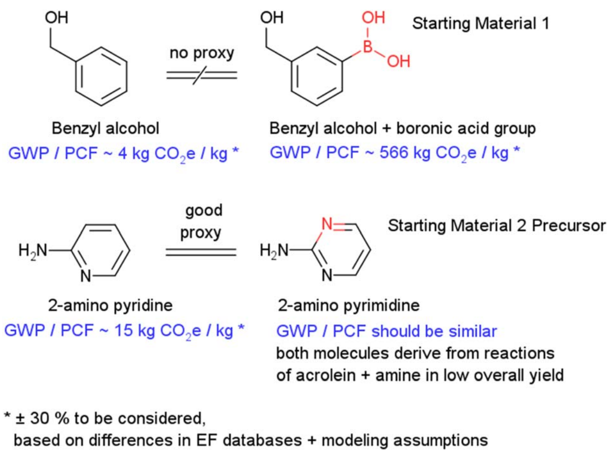
resulting from yearly updates when modeling assumptions in underlying chemical processes change. This is exemplified in more detail below (Table 1 and corresponding discussion). Furthermore, estimations in case of data-gaps also contribute to the variance of the modeled results. Although there is a variability associated with the concrete PCF number, the clear main driver is certainly the footprint coming from the purchased raw materials, including the solvents, with 489 kg CO_2e per kg (Fig. 2, raw materials, → Scope 3.1 emissions), contributions from waste treatment and energy are comparably minor. These results are typical for multi-step organic syntheses with complex starting materials.

Closing data-gaps for raw material PCF calculations

The calculated PCF per kg of API precursor as shown in Fig. 2 is 629 kg CO_2e. It must be noted that for the chemical building blocks (starting materials) that build the API's molecular scaffold only rough carbon footprint estimates were available. While the starting materials are not extensively complex, no reliable carbon footprint data could be found in any of the common available EF databases. This resembles the findings in recent studies,[19,52] in which the large majority of raw materials in an API synthesis could not be found. In such a case, GreenSpeed assigns a role-based carbon footprint of 100 kg CO_2e per kg for organic building blocks, which is close to the estimate provided by the ACS GCI Pharmaceutical Roundtable's streamlined PMI-LCA tool, suggesting a global warming potential (GWP) of 97.3 kg CO_2e per kg of complex starting materials (labeled as Default Non-iGAL Aligned Organic Reagent).[25] This estimate has been used in recent studies for API manufacturing and is a reasonable estimate to differentiate from bulk chemicals footprints if no other data is available.[39] However, due to the obvious limitations we recommend to rather model the chemical value chain of such crucial building blocks using retro-synthesis and derive more accurate data.

When the elaborate synthesis of starting materials 1, 2, and 3 is reflected, much higher footprints need to be considered. We investigated potential synthesis routes using our in-house retrosynthesis software Synthia®.[48–50] Scheme 1 shows the suggested synthesis pathways for the starting materials. The retrosynthesis in all cases was traced back to bulk chemicals for which reliable carbon footprint data was available in EF databases (for this study we used ecoinvent v3.10 datasets).[53] As the exact process conditions were unknown, we resorted to modeling the manufacturing steps for PMI and PCF calculations employing the PAS2090 modeling principles, again. The first building block has the underlying chemical motif of benzyl alcohol but carries a boronic acid functional group which requires a prior bromination and borylation step (Scheme 1): meta-directed bromination of benzoic acid, followed by reduction to the alcohol and subsequent borylation in a third step is a reasonable proposed manufacturing route. This results in a three-step synthesis starting from benzoic acid which appears to be as complex and solvent intensive as the initial API precursor synthesis. The PMI of 84 kg kg^{-1} of building block shows significant resource consumption, the PCF for starting material 1 is calculated to be 566 kg CO_2e per kg (with estimated ±30% variability as described above). Details can be found in the SI. Scheme 2 compares starting material 1 with benzyl alcohol, which could have been mistaken as a suitable proxy dataset based on molecular structure. Since EF datasets for benzyl alcohol do not consider the resource intensive synthesis of the boronic acid functional group, this proxy choice would lead to drastic underestimation of the starting material's footprint. Thus, benzyl alcohol is not a suitable proxy for starting material 1 but rather other building blocks that contain a boronic acid functional group since they underwent analogous reactions. These examples showcase that the choice of proxies needs to be made carefully and requires chemical knowledge. This shows the importance that synthesis know-how needs to be involved in such cases when environmental footprints are assessed.

Starting material 2 can be prepared from 2-amino pyrimidine *via* bromination and subsequent iodination using *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS), respectively (Scheme 1). The preparation of 2-amino pyrimidine is achieved by converting acrolein into the β-ethoxy acrolein diethyl acetal which reacts in the presence of strong acids with guanidine hydrochloride in comparatively low yield of 53%.[54,55] This chemistry resembles the Chichibabin process to produce pyridine, which also starts from acrolein (*via* Knoevenagel condensation from acetaldehyde and formaldehyde) and reacts with acetaldehyde and ammonia to give dihydropyridine, which is then oxidized to pyridine.[56] Interestingly, EF datasets for 2-amino pyridine, which can be prepared from pyridine, are available in the ecoinvent database. This is unusual, as many similarly complex chemicals cannot be found. Since 2-amino pyridine and 2-amino pyrimidine both derive from synthesis routes that involve the reaction of acrolein with ammonia or guanidine in low yields, respectively, the dataset of 2-amino pyridine can be used as a proxy for 2-amino pyrimidine (Scheme 2). Using the GWP of this dataset allows to reduce the synthesis



* ± 30 % to be considered,
based on differences in EF databases + modeling assumptions

Scheme 2 Evaluating chemical proxies for environmental footprinting based on structural similarity.

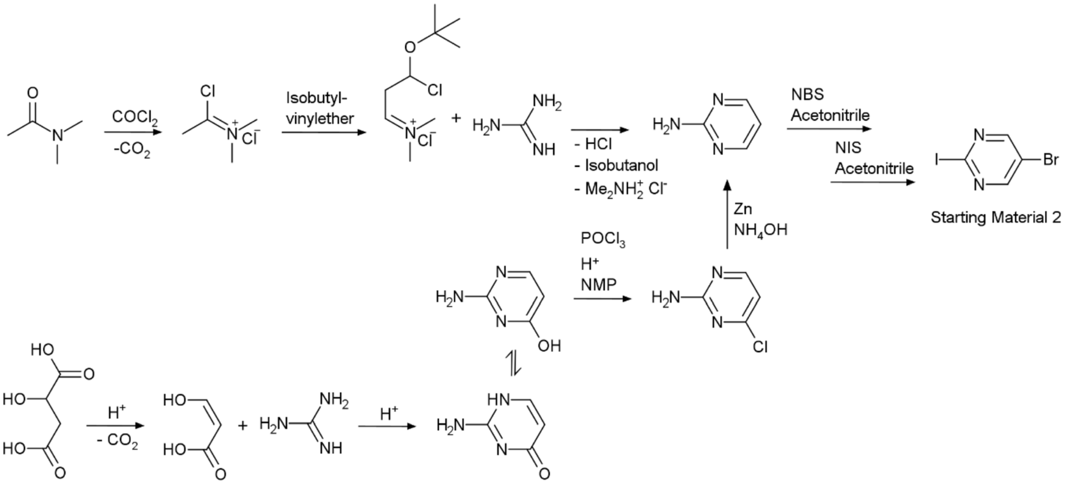
modeling for starting material 2 to the bromination and iodination step. The PMI for this two-step process is just under 22 kg per kg, solvents accounting for almost 20 kg per kg (SI). GHG emissions of purchased raw materials, waste treatment, and energy consumption add up to 207 kg CO_2e per kg in total (±30%).

Starting material 3 can be obtained from maleic anhydride in a two-step process. The first step involves the reaction with hydrazine to produce maleic hydrazide, which undergoes tautomerization and is modeled to further react from the enol form (Scheme 1). In this case-study it was modeled that the functional group labeled with "R" in starting material 3 is chlorine (R = Cl). This substituent is obtained by chlorination of the enol intermediate. The PMI in this case is 39 kg per kg and the PCF adds up to 292 kg CO_2e per kg (±30%). Similar reactions would be possible for other halide-substituents with R = Br, F, and I, respectively. If the substituent was not a halide but rather an aliphatic or aromatic substituent (R = C-backbone), then an additional coupling step (*e.g.* Suzuki) with precious metal catalyst, solvents, and the C-backbone precursor would have to be modeled accordingly. The added footprint for having an aliphatic or aromatic backbone at commonly available building blocks (in this case maleic hydrazide) is often underestimated due to omission of modeling of the solvent-intensive coupling step and the required functionalization of its precursors. Starting materials with such molecular structures must be evaluated carefully. More details on PMI and PCF contributions of the building block syntheses can be found in the SI.

Comparison of footprinting tools, databases, and synthesis modeling

To benchmark these numbers, the PCF results for the chemical building blocks were compared to evaluations performed with OpenLCA (V. 2.4.1)[57] and the ACS's Streamlined PMI-LCA tool.[25] Table 1 shows that the calculated total amount of CO_2e for the synthesis of starting material 1 is 684 kg CO_2e per kg using OpenLCA. This constitutes a 21% higher PCF compared to the 566 kg CO_2e per kg calculated by GreenSpeed and fits well within the described variability of ±30% mentioned earlier. The slight variance is easily explained when comparing the contributions from raw materials, waste treatment, and energy-related CO_2e emissions. OpenLCA and GreenSpeed calculated identical contributions for waste-related emissions, whereas the impacts from raw materials and energy consumption are about 30% and 25% higher, respectively, when using OpenLCA. Such deviations are reasonable when considering that GreenSpeed has access to Merck internal datasets, *e.g.* supplier PCF information and internal energy footprint data. Supplier PCFs were also used in OpenLCA calculations where available but GreenSpeed has access to additional internal data sources that explain the variability within the expected range. In comparison to OpenLCA and GreenSpeed, the Streamlined PMI-LCA tool made available from the ACS Green Chemistry Institute solely focuses on raw material footprints. The results for starting material 1 show about 10% lower footprints for the raw materials when compared to GreenSpeed and 29% lower footprints when compared to OpenLCA. The reason here is the comparatively old ecoinvent version v2.2 which has in many cases much lower footprints than the v3.10 ecoinvent version used in the other tools. One significant update happened from version v3.9 to v3.10 with the so-called sectorial update on steam cracker products and thus, increasing most of the fossil-derived base chemicals, including solvents. This detail highlights again that significant changes of available environmental footprint data can occur on a yearly basis when updates in the underlying databases take place. When comparing the PCF results for the other starting materials between the tools, the same trends are found as for starting material 1: the streamlined PMI-LCA tool shows the lowest footprints for raw material, whereas results from OpenLCA indicate slightly higher footprints when compared to GreenSpeed and all results are in the range of ±30% (Table 1).

Lastly, two possible synthesis routes are presented for the preparation of the 2-amino pyrimidine intermediate in the



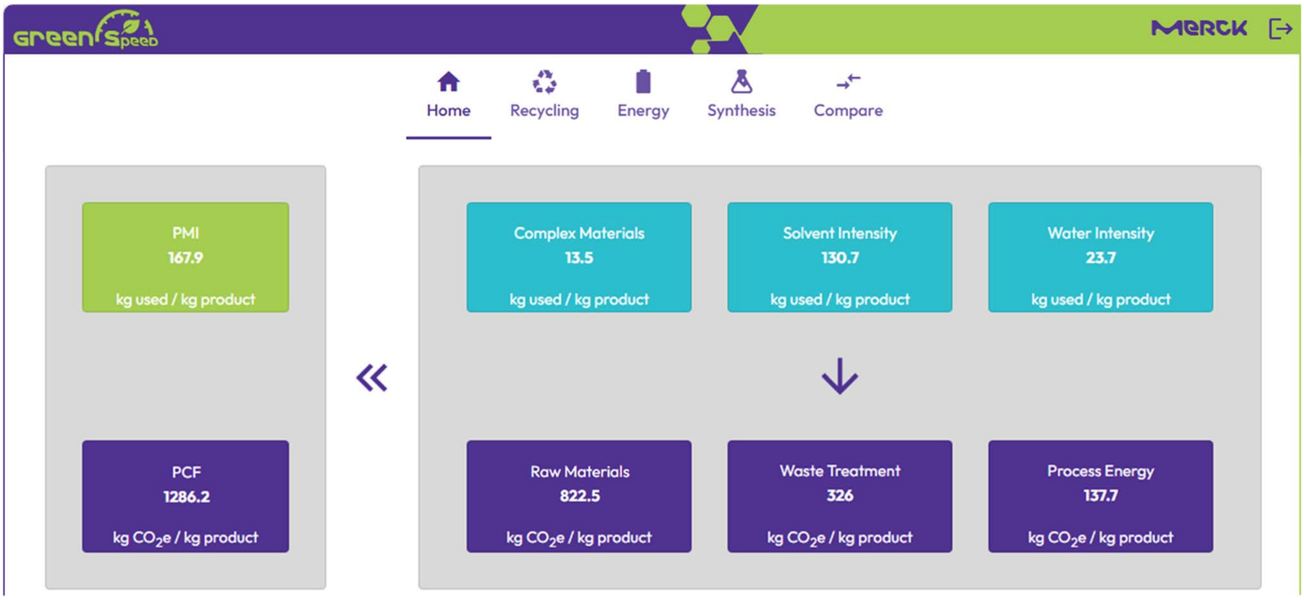
Scheme 3 Alternative synthesis routes that lead to starting material 2 *via* the 2-amino pyrimidine intermediate.

starting material 2 synthesis (Scheme 3). This example was chosen intentionally to show once more that value chains need to be assessed carefully. Presumptions such as "synthesis routes that originate from biogenic feedstocks are always more environmentally friendly than fossil-based routes" need to be checked closely with properly calculated PCFs. A feasible synthesis route to 2-amino pyrimidine can be envisaged starting from bio-based malonic acid, a product from sugar fermentation, which leads to an amino pyrimidine derivative that carries a hydroxyl group as an additional functional group (Scheme 3, lower pathway).[58,59] This substituent needs to be removed *e.g.* by chlorination and subsequent elimination[60,61] which requires a considerable amount of reagents and solvents. In contrast, another route to produce 2-amino pyrimidine was developed by BASF starting from a Vilsmeier salt that leads to an intermediate which reacts with guanidine to form the pyrimidine ring in high 97% yield[62] and without the need of eliminating an additional functional group (Scheme 3, upper pathway). The fossil-based route appears to be "greener" due to much higher reported yields and the avoidance of solvent intensive elimination reactions as in the other route starting from the bio-based raw material. Although accurate PCF calculations for these two synthesis routes have not been performed, it is still evident that chemical processes are not automatically advantageous when they start from biogenic feedstocks. All synthesis steps need to be evaluated on a case-by-case basis instead of focusing only on specific raw materials.

Recalculating the carbon footprint of the target molecule (the API precursor) initially shown in Scheme 1 with the updated starting material footprints (PCFs of 566, 292, and 207 kg CO_2e per kg, respectively) results in more than +100% increase (Fig. 6). The PCF of the API precursor is now calculated to be 1286 kg CO_2e per kg (±30%), the PMI has increased by +240% to 168 kg (materials consumed) per kg. Such numbers for the PMI are realistic for multi-step synthesis routes and compare well to previously presented data for API manufacturing.[27,29] The large increase in resource consumption now reflects how much solvents are consumed (purchased, used, and incinerated) to prepare starting material 1, 2, and 3, as well as the final API precursor. It shows the importance of modeling the whole value chain back to bulk chemicals for which reliable EF datasets are available (in this case: benzoic acid, acrolein, maleic anhydride, and hydrazine based on Scheme 1). Considering that cleaning and purification are not included for any of the reactions shown in Scheme 1, one can assume that actual footprints could be even higher than shown here.[9] It is also evident that very good understanding of the underlying chemical manufacturing processes of purchased materials is mandatory, combined with know-how in environmental footprinting. To make this combination of knowledge available across companies and the broader chemical industry we propose to combine the use of digital tools like Synthia® (automating retro-synthesis) and GreenSpeed (automating PMI and PCF calculations with additional features).

The challenge to reduce carbon footprints

The central question at this point is, how much of this carbon footprint can be realistically reduced and what efforts would be necessary for such a reduction. First, increasing material and energy efficiency through intentional process development and optimization (*e.g.* by using tools like GreenSpeed) will have to be the starting point of any emission reduction effort. This usually comes with the added benefit of cost reduction for decreased amounts of starting materials, energy consumption and waste treatment requirements and is therefore a double positive.



PMI
167.9
kg used / kg product

Complex Materials
13.5
kg used / kg product

Solvent Intensity
130.7
kg used / kg product

Water Intensity
23.7
kg used / kg product

PCF
1286.2
kg CO_2e / kg product

Raw Materials
822.5
kg CO_2e / kg product

Waste Treatment
326
kg CO_2e / kg product

Process Energy
137.7
kg CO_2e / kg product

Fig. 6 PMI and PCF for the three-step API precursor synthesis with updated starting material footprint data.

Efforts beyond efficiency increase are feasible and must be part of the solution but can incur added costs and/or the need to adapt established procedures. Emissions from waste treatment (Scope 3.5) can be significantly reduced by avoiding waste incineration. As highlighted above, the use of recycling assessments as integrated in GreenSpeed can help in planning. In a report by the European Solvent Recycler Group (ESRG) a potential reduction by 85% *vis-à-vis* virgin solvents was estimated.[63] Barriers for this approach can include the need for logistical adaptations and regulatory hurdles, especially in GMP relevant syntheses.[41] Switching from fossil to renewable (recycled or biobased) solvents further increases the reduction potential of Scope 3.5 as outlined in a TfS Whitepaper for accounting details.[64] However, availability at the right scale and cost is in many cases still uncompetitive when compared to solvents from fossil origins.

By increasing the share of renewable electricity and heat, the corresponding process emissions from energy (Scope 1 and 2) can be reduced to virtually zero, if appropriate allocations are applied. Renewable electricity has become widely available at competitive costs in many regions of the world and many companies are making use of either self-produced renewable electricity or mechanisms like (virtual) power purchase agreements to cover their demand. However, in some regions the expansion of renewable electricity is slower and the steadily increasing demand for green power *e.g.* through increasing electrification and lack of large-scale storage solutions pose a notable challenge. Likewise, the development of green heat and cold is not yet at a level that could sufficiently provide all producing industries with the required energy.[65,66] In all areas, the pharmaceutical and fine chemicals industries have to rely on further work, regulation and policy making outside their direct sphere of influence.

As demonstrated, the biggest contribution to the emissions of pharmaceutical ingredients and complex fine chemicals comes from the raw materials (Scope 3.1). This is at the same time the most difficult abatement area. Consistent closed-loop recycling of solvents and circulating transition metal catalysts in the upstream value-chain will also reduce the impact of Scope 3.1 emissions. We showed that the PMI of an API precursor synthesis can easily exceed 100 kg of consumed chemicals per kg of product with solvents being the main driver.[67] Optimizing resource efficiency upstream (lowering PMI) will reduce the amount of purchased emissions. A stringent supplier engagement is needed to communicate these messages upwards through the supply chain and demand corresponding actions. Supplier engagement can furthermore lead to a decarbonization of the energy-related emissions at the suppliers' sites and a subsequent reduction in the carbon footprint of their products. However, the majority of the embedded carbon of most chemicals is still fossil. Therefore, the only way forward lies in a switch to raw materials that are predominantly produced from renewable or circular feedstocks (biogenic, recycled, and CO_2 captured carbon) using only renewable energy. Using the what-if scenario functionality of GreenSpeed can help model the impact of such choices on the overall footprint. Currently, for most bulk chemicals, the fossil routes are highly optimized and efficient.[18] Circularity approaches exist *e.g.* for bionaphtha & pyrolysis oil but they are usually less mature, seldom at the required scale and cost and in some cases need entirely new value chains.[68]

This somewhat sobering summary is not intended to discourage net-zero efforts. On the contrary, a realistic view of the status quo is necessary to incite the right vision and highlight important research and development areas. It also showcases clearly, how important digitalization and improving data quality is as well as interdisciplinary collaboration across various industry and academic boundaries. Only a concerted effort will make a change, and we should use what is at our disposal – our tools, our expertise, our experience, our connections and networks, our communication and our financial resources to drive towards a net-zero industry.

Conclusion

The need for greener products coming from greener manufacturing processes in the pharmaceutical and fine chemicals industry is undeniable. The decisions necessary for such a shift must be taken early in the design phase, before processes get locked in. To this end, scientists making these decisions need to be enabled by automated and fit-for-purpose information without the need to be sustainability experts themselves and without the burden of additional manual evaluations and data entry. Our illustrative case-study for an API precursor synthesis highlighted that data quality must be improved to properly calculate GHG emissions related to the manufacturing of complex target molecules, especially for raw materials that are more complex than bulk chemicals. Going one step further, digital design tools are quintessential to evaluate reduction potentials by increasing material- and energy efficiency. More so, to really design for sustainability, what-if scenario assessments are key to identify abatement areas and evaluate possible impacts. Due to the highly dynamic nature and development in the field *e.g.* of renewable raw material availability, suitable enabling tools need to be able to accommodate changes and give actionable information about the respective impacts quickly. We have demonstrated that our internally developed GreenSpeed tool unifies many of these requirements through the integration of ELN data and environmental footprint information. In combination with features like direct comparison of synthesis routes, what-if-scenario assessments, similarity search and the evaluation of recycling potentials the tool provides essential features that process development chemists need to innovate greener pharmaceutical products.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: GreenSpeed core and advanced features GreenSpeed PMI and PCF calculation results for starting materials 1, 2, and 3 OpenLCA calculation results ACS Streamlined PMI-LCA tool calculation results. See DOI: https://doi.org/10.1039/d5su00636h.

Acknowledgements

We acknowledge Dr Ewa Gajewska and the Synthia® Team, as well the peers in the ACS GCI Pharmaceutical Roundtable community for fruitful discussions and collaboration.

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