



Cite this: *Green Chem.*, 2024, **26**, 5239

Interactions of multiple metrics and environmental indicators to assess processes, detect environmental hotspots, and guide future development†

Michael U. Luescher * and Fabrice Gallou 

The sustainable development in pharmaceutical industries relies on the selection and integration of detailed, unified metrics and indicators. This is particularly important when addressing environmental hotspots, with assessments ideally conducted early in process development. Facing the challenge of data availability, data acquisition, or data accuracy, we propose a simple and standardized procedure to assess and report the environmental footprints of linear and convergent chemical processes. The output focuses on data representation and decision taking making it easier to communicate in cross-functional environments.

Received 18th January 2024,
Accepted 20th March 2024

DOI: 10.1039/d4gc00302k

rsc.li/greenchem

Introduction

Sustainable production of medicines is a fundamental component of a sustainable future and all of us can play vital roles in reducing harmful emissions, stopping the depletion of non-renewable materials, by integrating anthropogenic production processes into natural cycles of materials.¹ To efficiently do so, an understanding of the environmental impacts on a multi-factorial level (e.g., use of scarce resources, emissions of greenhouse gases (GHGs), the use and containment of substances of very high concern (SVHCs),² or the production and treatment of waste streams) of chemicals and pharmaceuticals in particular is critical for to develop low-environmental-impact processes.³

Steps into this direction were made with the introduction of the environmental factor (*E*-Factor) in 1992, bringing attention to the problem of waste generation.⁴ Linking waste to the amount of material produced gave rise to a paradigm shift in the concept of efficient chemical processes. Yields as the sole parameter made room for an additional indicator, one that assigns value to eliminating waste. Recognizing this, several companies came together in 2005 to collaborate on promotion and adoption of green practices leading to the formation of the American Chemical Society Green Chemistry Institute

Pharmaceutical Round Table (ACS GCIPR), from which, the concept of process mass intensity (PMI), originated.⁵ The PMI is a mass-based metric looking at material efficiency in manufacturing defined as all input's material (incl. H₂O) over the desired output.

Environmental assessments of manufacturing processes often make use of such simplified, non-data-rich and simple to use metrics that can enable comparisons of different routes.⁶ However, such comparisons often fail to shed light on whether these routes are sustainable in absolute terms falling short in differentiating environmental hazards, footprints, or the depletion of resources for in- and output materials.

The integration of more detailed, unified metrics, and indicators into process development is key to a sustainable chemical industry and to best and sustainably address environmental hotspots, assessments should be possible at earlier stages during process development. However, the development and manufacture of a new medicine is in itself a complex endeavor and sophisticated multistep manufacturing processes consume sources of materials across the globe. This consumption leads to emissions into the environment that have consequences in the different environmental compartments that are exposed to those emissions. The questions then become how a quantification of environmental impacts can be obtained and how to best detect and display environmental hotspots.

Standardized holistic methods like life cycle assessment (LCA)⁷ require a significant amount of data, which are practically difficult to collect (e.g., manufacturing protocol of start-

Chemical & Analytical Development, Novartis Pharma AG, Basel, Switzerland.

E-mail: michael-1.luescher@novartis.com

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4gc00302k>

ing materials) and require long processing for their completion.⁸ Furthermore, the interpretation of multi-factor LCA results is often challenging making the obtained predictions less meaningful as non-experts might find it difficult to draw conclusions. All the more so as such analyses are meant to guide the research and should not be mere reporting tools, which satisfy one or the other stakeholders. Nevertheless, the past decade brought strong methodological improvements to LCA methods providing multi-factor metrics and data that quantify the damage to human health, the ecosystem, and resources. Databases like ecoinvent⁹ provide simple access to such data and we believe that useful assessment should incorporate state-of-the-art LCA data in simple manner to be useful and to be followed-up on.

For linear syntheses a material's PMI, as a share of the overall PMI, can be linked to its environmental footprint. However, it gets already more complex for convergent syntheses. At the convergent step, there will be a reaction between an intermediate product from the main branch and the terminal product of the convergent branch. Hence, the concept of the cumulative PMI is used, that accounts for the contribution arising from the convergent branch.¹⁰ Several contributions in this direction, linking mass-based green chemistry metrics with LCA data, are published in the literature, as for example the FLASCTM (Fast Life Cycle Assessment of Synthetic Chemistry) tool dealing with eight impact categories, using a material's LCA data in combination with its used mass.¹¹ Other studies with contribution from industry include the Eco-footprint,¹² linking mass-based metrics to transportation footprints, to water consumption, or to energy consumption of production plants, Eco-Scale,¹³ the GREEN MOTIONTM tool,¹⁴ linking the *E*-factor to selected environmental indicators, and more recently, DOZNTM,¹⁵ a tool aligned with the 12 principles of green chemistry. Indicating the footprint of full-scale manufacturing, comparing different routes and raw materials, each tool has its strengths. However, a broad application from a single gram-scale reaction to multi-step manufacturing in combination with easy-to-understand data representation at the laboratory and pilot plant level is not always obvious. While indicating the hotspots for development, the output of such assessments should be accepted by key stakeholders.¹⁶

To achieve this, an approach consistent of a simple-to-use LCA based metrics toolkit in combination with metrics such as PMI or Environment Health & Safety (EHS) attributes should allow us, in the industry in particular, to guide our research towards ever more environmentally sustainable practices. The discussed metrics need to be evaluated over time to ensure that their goal of driving towards more sustainable pharmaceutical process developments are fulfilled. The next few sections highlight the journey we undertook in this direction. Highlighting the challenge of a simple to use method, recent publications compiled some of the most common environmental indicators, efficiency, or mass-based indicators, economic, and energy indicators for sustainability assessments of chemical processes and their data needs.¹⁷

Objectives

Based on extensive analysis and collective thinking, we, at Novartis, concluded a few years ago that a LCA-like assessment framework in combination with selected other metrics like convergence could be applied as early as during the research phase to gain first insights into the environmental footprint of our processes.¹⁸ Having more qualitative read-outs should allow us to map critical hotspots across a product's manufacturing process and predict the incorporation of changes with acceptable accuracy thereby helping in the route selection while more quantitative ones will guide our efforts at later stages. This in turn should enable us to prioritize resource allocation to maximize the potential for environmental improvements.

For such an assessment method to be successful, it is an absolute must to be simple, consistent, and standardized, at times probably losing slightly in accuracy but the urgency of the situation convinced us that further delaying the process was by far a worse option. Furthermore, it should offer scientists with clear guidance and relevant information to act upon.

To do so, we defined a framework consisting of these steps:

(1) Data collection, *i.e.*, the collection of PMI data across all stages of the manufacturing process and the calculation of each step's and material's contribution to the cPMI next to the collection of process specific metrics like convergence, the number of individual solvents used, *etc.*

(2) Combine each material's cPMI with selected environmental indicators from databases and LCA prepared in accordance with ISO 14040 and ISO 14044.⁷ For materials that do not have their environmental indicators in selected LCA databases, the indicators of similar materials or the indicators of materials for their preparation are added. This allows for detection of individual environmental hotspots and to differentiate the impact of different components used in the process. However, it must be stated that hotspots mainly or solely consisting of materials with proxy data require special attention and sometimes further investigation.

(3) The output is then condensed, normalized, and weighted to allow for comparison in a broader portfolio. Furthermore, a simple but clear representation can guide process' development to allocate limited resources where they have the biggest impact.

(4) The structured data and knowledge gained is then collected in databases and re-introduced into future projects, route selection and planning, adding process' sustainable development.

(5) And finally, a culture to support our efforts is built transferring people.

Step-1, data collection

The first step to introduce a reliable, robust, and consistent assessment was the definition of rules for the application across the portfolio. Aspects like the scope, lack of information on upstream manufacturing routes or the inclusion of materials for equipment cleaning¹⁹ or pre-treatment are

covered. The aimed consistency intends to provide confidence in the assessment and help its adaptation. Based on the above, we started with the collection of PMI metrics. PMI is defined as the mass of materials (kg) used to produce 1 kg of product.⁵ For active pharmaceutical ingredients (API), this includes the mass of water, raw materials, solvents, reagents, and other materials used in a reaction to produce 1 kg of the desired step product. The focus is put onto step product, as step PMI's are not additive to afford a process' cumulative PMI (cPMI) to produce 1 kg of final API. Once all step PMI's are collected, the cPMI for the entire process can be generated in adjusting each steps needed to produce 1 kg of the final product of a synthesis.¹⁰ This also generates each step's fractional cPMI (fractional cPMI – step), meaning, each step's contribution to the cumulative PMI of the process (Fig. 1), which are a much better reflection of a step's resource consumption, and therefore footprint, compared to a step's PMI.

While the PMI and for that matter the cPMI are telling of a process' footprint, we found that this mass-based metric is not that meaningful in predicting a process' future development and its potential. To do so, metrics like **convergence** can be used at early stages of process development to help predicting a process' potential development (Fig. 2, Table 1; see Table 3 for the Convergence Formula used).²⁰ Looking at the data, more convergent processes are allowed to have considerably higher step PMI's while showcasing similar cPMIs compared to more linear processes. Higher step PMI's often present more room for development (*e.g.*, solvent reduction or recycling), often giving a more convergent process, starting from a higher cPMI, an edge. While not significant if looked through mass-based metrics, more convergent processes often use less starting building blocks, which come with their individual environmental footprints, not considered in the discussed metrics up to this point.

This, in combination with the **nature** and **number of individual solvents** used, can guide decisions on process development.²¹ More benign solvents are of course preferable while a reduced number of solvents and solvent alignment opportunities over several steps can aid waste treatment efforts, like recycling, thereby lowering a process' footprint.²²

Step-2, calculation of environmental footprint

Analogous to the calculation of the fractional cPMI – step, each individual components fractional cPMI is calculated affording the fractional cPMI – step (material), each step's contribution to the overall cPMI distributed onto the materials used within a step, or the fractional cPMI – process (material), the sum of the fractional cPMI – step (material) for each material. Looking at an example sequence for the preparation of an iron-supported, palladium-nanoparticle catalyst described in Table 2,^{23,24} each material's cPMI contribution, normalized to the preparation of 1 kg of the nano catalyst, is shown. Each material's fractional cPMI – process (material) is then multiplied with its environmental indicators (Table 3) according to Fig. 3.

An essential aspect of such assessment is the standardization of used environmental impact indicators and the method used for their calculation (such as the greenhouse effect or eutrophication according to a specific LCA model). For this matter, we use the European environmental footprint method (2018).²⁵ This method is widely available for a large variety of materials in numerous databases and furthermore contains normalization²⁶ and weighting²⁷ factors used to generate a single numerical environmental score making it easier to compare footprints of different processes or materials.

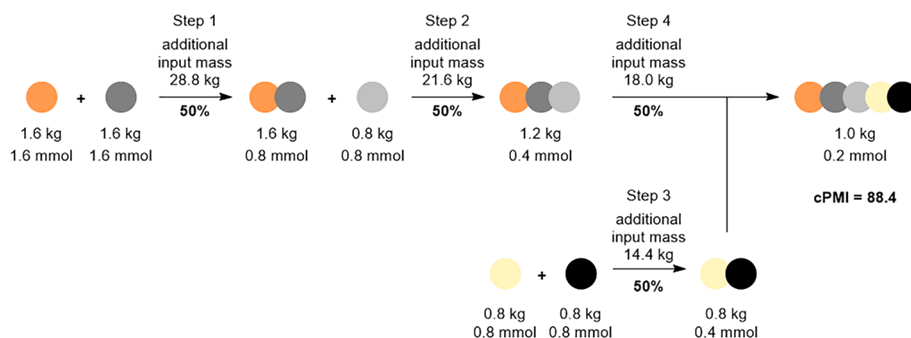
Databases as ecoinvent⁹ contain numerous materials and their environmental indicators. Multiplying these indicators with the calculated cPMI data of materials (Fig. 3a, scenario 1), like the ones in Table 3, provide a more holistic and precise picture of a process' environmental impact.

If the desired material cannot be found in the database, indicators of a substitute material (proxy material) can be used (Fig. 3, scenario 2) or the sum of indicators of the material for its synthesis (Fig. 3, scenario 3). If a material's preparation is unknown but it can be considered as commodity material (≤ 100 USD per mol, found in a reputable online catalogue, non-bulk),²⁰ scenario 4 applies and indicators of a standard organic solvent are used. If this rule is not fulfilled, as it is often the case for more complex materials, and no information on its actual preparation are known, the

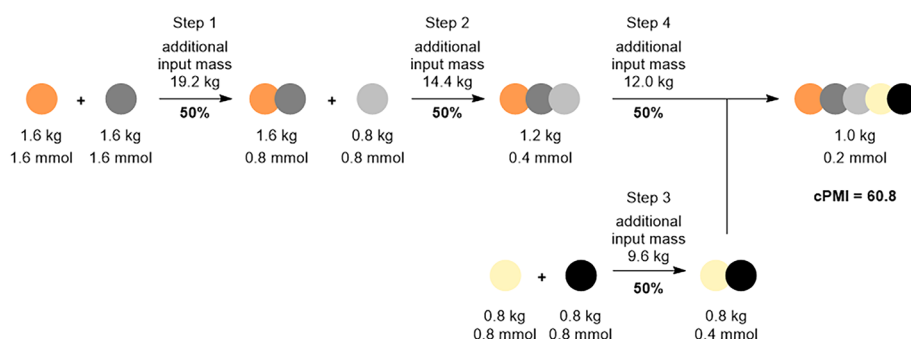


Fig. 1 Example (step) PMI, fractional cPMI – step, and cPMI.

a-1) Conv. = 0.42, step PMI's = 20



a-2) Conv. = 0.42, step PMI's = 14, 30% reduction



b-1) Conv. = 0.36, step PMI's = 10



b-2) Conv. = 0.36, step PMI's = 9, 10% reduction



Fig. 2 Examples of synthesis schemes and their cPMI having different convergence.

material's cPMI contribution is multiplied with the estimated number of steps back to commodity materials, multiplied with 37 for the average amount of waste generated in one synthetic step,²⁸ and finally multiplied with the indicators of a standard organic solvent as proxy material (Fig. 3, scenario 5).

Using this approach the consumption of energy is included for a material's production, in accordance with the data found in the ecoinvent database, while the power consumption for the performed reactions themselves are excluded. Metrics related to energy consumption as part of pharmaceutical

Table 1 Scenarios from Fig. 2 to prepare 1 kg of final product using sequences having different convergencies

Scenario	Conv.	Step PMI	Fractional cPMI – step	cPMI	Change	Usage of building blocks	Comments
a-1	0.42	Step 1 – 20 Step 2 – 20 Step 3 – 20 Step 4 – 20	Step 1 – 32.0 Step 2 – 22.4 Step 3 – 16.0 Step 4 – 18.0	88.4	—	5.6 kg	High step PMI's; reduction seems possible! Limited demand in building blocks!
a-2	0.42	Step 1 – 14 Step 2 – 14 Step 3 – 14 Step 4 – 14	Step 1 – 22.4 Step 2 – 15.2 Step 3 – 11.2 Step 4 – 12.0	60.8	–30% step PMI (e.g., solvent reduction)	5.6 kg	—
b-1	0.36	Step 1 – 10 Step 2 – 10 Step 3 – 10 Step 4 – 10	Step 1 – 32.0 Step 2 – 20.8 Step 3 – 13.6 Step 4 – 8.4	74.8	—	9.2 kg	Low step PMI's; reduction could be difficult! High demand in building blocks!
b-2	0.36	Step 1 – 9 Step 2 – 9 Step 3 – 9 Step 4 – 9	Step 1 – 28.8 Step 2 – 18.4 Step 3 – 12.0 Step 4 – 7.4	66.6	–10% step PMI (e.g., solvent reduction)	9.2 kg	—

Table 2 cPMI contributions of all materials used to prepare a literature based nano catalyst

Step PMI = 83.0 Fractional cPMI - Step = 31.4		Step PMI = 17.1 Fractional cPMI - Step = 17.1	Overall cPMI = 48.5
Material	Nature of material	Fractional cPMI – process (material)	Scenario acc. to Fig. 4
2-Bromochlorobenzene	Reagent, substrate	0.298	Scenario 3
1,3-Dimethoxybenzene	Reagent, substrate	0.240	Scenario 3
<i>n</i> -BuLi	Reagent, substrate	0.226	Scenario 3
Chlorodicyclohexyl phosphine	Reagent, substrate	0.363	Scenario 5
Silica gel	Reagent, substrate	0.467	Scenario 2
Cellulose acetate	Reagent, substrate	0.047	Scenario 2
FeCl ₃	Reagent, substrate	0.185	Scenario 1
Pd(OAc) ₂	Reagent, substrate	0.002	Scenario 2
MeMgCl	Reagent, substrate	0.172	Scenario 3
Tetrahydrofuran	Solvent	10.240	Scenario 1
Hexane	Solvent	0.752	Scenario 1
Ethyl acetate	Solvent	20.527	Scenario 1
Acetone	Solvent	4.460	Scenario 1
Methanol	Solvent	0.451	Scenario 1
Pentane	Solvent	10.000	Scenario 1
H ₂ O	H ₂ O	0.037	Scenario 1

process development are often more difficult to grasp and evaluate than mass-based metrics and most of the energy requirements in pharmaceutical settings are related to the energy needs to run the labs or the production plants independently of the process. Today's electricity, however, is still largely obtained from burning fossil fuels, depending on the region, resulting in larger amounts of CO₂ released into the atmosphere. Therefore, more detailed investigations on the power consumption of a reaction, individual unit operations, or process are indicated. However, an accurate measurement

can be challenging, as outlined above. Recent estimations for example suggest that power consumption contribution about 5–20% to each individual environmental indicator.²⁹ Meaning, each calculated environmental indicator in Fig. 4 will likely increase by the mentioned percentage once power consumption is considered. To give an initial indication and to highlight the potential need for further investigations, we propose the usage of a simplified procedure. Reactions performed in the temperature range of 0–60 °C are considered energy efficient, reactions run at –20–0 °C or at 60–100 °C are looked

Table 3 Parameters used for assessments regarding environmental sustainability

Parameter	Description	Stages of project	Unit	Process or single step?	Importance
PMI	Total mass of inputs needed to prepare 1 kg of step product! Each step has its PMI. Step PMIs are not additive to afford a process' cPMI	Early, late	Number	Step	Medium
Cumulative PMI (cPMI)	Total mass of inputs needed to prepare 1 kg of final product! Each step of the entire process is adjusted according to its needs to prepare 1 kg of final product. Once adjusted, the inputs of all steps are cumulated to afford a process' cPMI	Early, late	Number	Process	High
Fractional cPMI – step	Each step's contribution to the overall cPMI	Early, late	Number	Step	High
Fractional cPMI – step (material)	Each step's contribution to the overall cPMI distributed onto the materials used within a step	Early, late	Number	Step	High
Fractional cPMI – process (material)	The cPMI distributed onto all materials used within a process	Early, (late)	Number (0–1)	Process	High
Convergence (CV)	SS₁ = 5 1 → [] → [] → [] SS₂ = 4 2 → [] → [] → [] SS₃ = 2 3 → [] → [] ↓ ↓ ↓ [] → [] → [] → P $SMs = \text{Number of starting materials} = 3$ $SS = \text{Number of subprocess steps}$ $SSS = \sum SS = 5 + 4 + 2 = 11$ $P = \text{Product}$ $CV = \text{Convergence} = \frac{SMs}{SSS} \times 100\% = 27.3\%$ The convergence assesses the number of key construction steps in relation to the number of starting materials. To make product (P), each starting material (1, 2, 3) passes through a number of subprocess steps (SS). The sum of all subprocess steps (SSS) and the number of starting materials is then used to express CV Total number of different solvents used in the manufacturing process Choice of solvents based on environmental, safety, and recyclability	Early, late	Number	Process, step	Low
No. of individual solvents used		Early, late	Number	Process, step	Medium
Solvent selection		Early, late	[%] Preferred, usable, undesirable	Process, step	Medium
Climate change – EF method	The Global Warming Potential (GWP) calculates the radiative forcing over a 100-year time horizon. It assesses the potential impact of different gaseous emissions on climate change	Early, late	kg CO ₂ eq.	Process, step	High
Ozone depletion – EF method	The Ozone Depletion Potential (ODP) calculates the destructive effects on the stratospheric ozone layer over a time horizon of 100 years	(Early), late	kg CFC-11 eq.	Process, step	High
Ionizing radiation – EF method	This category estimates the effect of radioactive emissions on human health	(Early), late	kg U ²³⁵ eq.	Process, step	Medium
Photochemical ozone formation – EF method	This category calculates the effect of summer smog on human health	(Early), late	kg NMVOC eq.	Process, step	Medium
Human toxicity, non-cancer, and cancer effects – EF method	The unit “CTUh” (Comparative Toxic Unit for Humans) expresses the estimated increase in morbidity in the total human population due to different types of emissions entering into the environment	(Early), late	CTUh	Process, step	Low
Acidification – EF method	This impact category describes potential impacts on soil and freshwater that becomes more acid due to the deposition of certain pollutants from air	(Early), late	mole H ⁺ eq	Process, step	Medium
Particulate matter – EF method	This category estimates the potential effect of fine dust emissions on human health	(Early), late	Disease incidence	Process, step	High

Table 3 (Contd.)

Parameter	Description	Stages of project	Unit	Process or single step?	Importance
Eutrophication, freshwater – EF method	Expression of the degree to which the nutrients emitted in Europe reach the freshwater and lead to the problem of eutrophication	(Early), late	kg P eq	Process, step	Medium
Eutrophication, marine – EF method	Expression of the degree to which nutrients emitted in Europe reach the oceans and lead to eutrophication	(Early), late	kg N eq.	Process, step	Medium
Eutrophication, terrestrial – EF method	Eutrophication means that too many nutrients reach ecosystems and harm the plants and animals living in sensitive systems:	(Early), late	mole N eq.	Process, step	Medium
Ecotoxicity, freshwater – EF method	Measurement of environmental toxicity in freshwater due to emissions. The unit “CTUe” (Comparative Toxic Unit for ecosystems) is an expression of an estimate of the potentially affected fraction of species (PAF) integrated over time and volume per unit mass of a chemical emitted (PAF m3 years per kg)	(Early), late	CTUe	Process, step	Low
Land use – EF method	Land use generally refers to the amount and quality deficit of land occupied or transformed	(Early), late	Pt	Process, step	Low
Water use – EF method	Assessment of the water use related to local scarcity of water in different countries	(Early), late	m ³ deprived	Process, step	Low
Resource use, fossils – EF method	Abiotic resource depletion fossil fuels (ADP-fossil); based on lower heating value	(Early), late	MJ eq.	Process, step	Low
Resource use, minerals and metals – EF method	Ultimate reserves model. The model takes both the annual production as well as the availability of the resource into account	(Early), late	kg Sb eq.	Process, step	Low

at as borderline, reactions at 100–140 °C require further investigations, and all reactions outside these boundaries or reactions run at reflux should be avoided whenever possible and require further investigations. While this simple procedure does not represent exact energy needs, it provides the reader with a simple to use system indicating if further actions are advised. And while we do acknowledge the fact that an energy intense step implemented somewhere where the share of renewable energy sources in total production is very high might actually be greener compared to an energy efficient step implemented in a country where the vast majority of energy comes from fossil fuels, the above scheme acts as a good indicator for potential future development of assessed processes.

Step-3, data presentation and analysis

Based on the procedure described on the multiplication of a material's cPMI contribution with its environmental indicator (Fig. 3), each material's contribution to the overall footprint can be calculated and visualized in a heatmap (Fig. 4). Using the described example on the preparation of the nano catalyst, a reduction in use of ethyl acetate or tetrahydrofuran, for example, would have the biggest impact in lowering the carbon footprint, while a reduction in the use of chlorodicyclohexylphosphine might reduce both, ecotoxicity in freshwater and the use of non-renewable energy resources to considerable amounts.

The gathered data furthermore enable us to best position waste treatment efforts. Pentane and THF, for example, are used in almost equal amounts according to the calculated fractional cPMI – process (material) (Table 2). However, THF seems to have by far a larger impact on the environment, therefore, its recycling should be prioritized. It is furthermore worth mentioning, that the indicator for climate change used in Fig. 4 (Climate change (Total)) contains both the generated CO₂-pollution for a material's production back to a material's cradle, including the energy consumption therein according to the cut-off model used in the ecoinvent database, as all other indicators do, and an assumed fixed amount of CO₂-pollution for each material's incineration. As mentioned for the use of proxy data, special attention is required if assumptions based on the data for a material's incineration are made as these are approximations and not compound specific data. If materials are recycled, or otherwise treated instead of being incinerated, adaptations to the data can be made to better reflect their contribution to the process' environmental footprint. In this regard, solvents take a special place as large amounts are used per mass of final product, putting the waste treatment scenarios into the foreground. In general, there are two distinct methodologies most commonly employed when dealing with solvent wastes: thermal treatment in incinerators and solvent recovery. To recover solvents, distillation, or rectification, is most often utilized. From an environmental standpoint, it can however remain unclear whether incineration (with heat regeneration) or recovery is the superior treatment choice as both scenarios facilitate a decrease in the usage of non-renewable resources. Using the energy generated during solvent incinera-

tion, fuel can be replaced for steam and electricity production, for example. On the other hand, the recovery of solvents reduces resource use as the need for the production of petrochemical solvents decreases. For solvents that are associated with an overall lower environmental footprint in their production, for example, the use of incineration often results in a smaller overall environmental impact as the effort needed to recover such solvents can be close to the effort needed to produce them in the first place. If on the other hand solvent production carries a significant environmental burden, environmental benefits “earned” through solvent recovery often surpass those gained through energy production from incineration.³⁰

Embracing transparency in our assessments at the same time fostering trust and acceptance amongst stakeholders, we propose the use of a precision score (Fig. 3–5). Each scenario and for that matter each material's input is linked to a precision score. For example, 95% for exact material matches found in databases or 50% for materials in scenario 5. The highest precision score for materials is set 95% for exact matches due to regional differences and general uncertainties in the calculations of LCA data. Upfront understanding of the reliability of the evaluation *via* the precision score of each material enables stakeholders to best decide in a data-driven process on potential next steps. Besides, it indicates actions to

better understand certain input materials. Linking these scores to a material's fractional cPMI – process (material) then enables us to generate a precision score for the entire process providing the team with data to situate a process' overall impact (Table 4).

Focusing on the carbon footprint as a surrogate for a process' environmental footprint not only allows for simpler presentation and communication to the various stakeholders, it furthermore allows us to split the materials into different steps (e.g. the use of THF in different steps) facilitating the decision on where to focus development efforts (Fig. 5). The latter point is central to our effort, namely, **to be able to prioritize and trigger the most impactful actions from a sustainability standpoint given existing constraints**. Indeed, as much as we would love to tackle more holistically all weaknesses in our syntheses and processes, the reality is that only a handful of opportunities can be grasped. Using this approach, we attempt to more scientifically decide and rationalize the selection of the tasks to the most impactful ones. For example, precious metals as the ones from platinum group (PGMs) often pop-up in discussions as a process most polluting source. Looking for example at the data carbon release data in Fig. 5 from the process described in Table 2, it becomes evident that further reduction in a well developed palladium-catalyzed process will most likely have an impact on palladium's resource depletion,



Fig. 3 Calculation of a process' environmental impact using the material's cPMI contribution times their environmental indicators.

Materials	Acidification EF v3.1 no LT mol H ⁺ eq	Climate change EF v3.1 no LT GWP100 (Production (+ Market)) kg CO ₂ eq	Climate change EF v3.1 no LT GWP100 (Incineration) kg CO ₂ eq	Climate change EF v3.1 no LT GWP100 (Total) kg CO ₂ eq	Ecotoxicity, freshwater EF v3.1 no LT CTUe	Energy resources, non-renewable EF v3.1 no LT MJ eq	Eutrophication, freshwater EF v3.1 no LT kg P eq	Eutrophication, marine EF v3.1 no LT kg N eq
2-Bromochlorobenzene	0.01035450	2.46406895	0.59194730	3.05601625	105.91348811	42.03111044	0.00006079	0.00161635
1,3-Dimethoxybenzene	0.01942815	3.67707236	0.47856189	4.15563425	80.24810825	60.91405049	0.00008505	0.02411897
n-Butyl lithium	0.14256935	19.49315479	0.55959184	20.05274663	361.67137528	232.97795638	0.01345134	0.04742318
Chlorodicyclohexylphosph.	0.22427397	44.98961023	0.72161573	45.71142596	1062.71979747	2193.53632986	0.00070515	0.04518489
Silica gel	0.01099024	0.98596888	0.92872778	1.91471466	13.54821711	11.15479378	0.00003691	0.00094636
Cellulose acetate	0.02953628	4.03842251	0.11593138	4.15435388	74.92793432	48.26634953	0.00278673	0.00982472
Iron(III) chloride	0.00104186	0.15012434	0.36736078	0.51748513	1.22992280	1.83829634	0.00000863	0.00017561
Pd(OAc) ₂	2.10455974	10.43138540	0.00436861	10.43575401	212.49269367	155.57810822	0.00104688	0.05161510
Methylmagnesium chloride	0.02253249	5.32924541	0.42409085	5.75333626	24.37885065	66.92940739	0.00022095	0.00502818
Tetrahydrofuran	0.31616635	63.17235520	25.36667710	88.53903230	183.42930358	1057.44206687	0.00234846	0.05338818
n-Hexane	0.00301502	0.59572956	1.86258125	2.45831081	14.53574513	29.81019326	0.00000927	0.00060602
Ethyl acetate	0.34142729	66.22762224	50.84978101	117.07740325	522.06122251	1484.00720930	0.00604652	0.05966343
Acetone	0.03466154	7.20421301	11.06054699	18.26476000	44.96465529	176.65315803	0.00023564	0.00061389
Methanol	0.00089641	0.34445197	1.11621108	1.46066305	1.07865806	14.60053375	0.00000833	0.00023986
Pentane	0.05229521	11.46541616	24.77166178	36.23707794	6.87779428	796.25235194	0.00002879	0.00979340
Water	0.00000016	0.00001730	0.02323600	0.02325330	0.00192578	0.00020484	0.00000000	0.00000002
SUM	3.31374855	240.56907631	119.24289136	359.81196768	2710.07969230	6371.99212043	0.02707944	0.31503814

Materials	Eutrophication, terrestrial EF v3.1 no LT molc N eq	Human toxicity EF v3.1 no LT Carcinogenic CTUh	Human toxicity EF v3.1 no LT Non-Carcinogenic CTUh	Ionizing radiation EF v3.1 no LT kg U235 eq	Land use EF v3.1 no LT Pt	Material resources EF v3.1 no LT Minerals, metals kg Sb eq	Ozone depletion EF v3.1 no LT ODP100 Years kg CFC-11 eq	Particulate matter EF v3.1 no LT Disease incidence
2-Bromochlorobenzene	0.01784169	0.00000001	0.00000003	0.03176807	4.00632996	0.00001495	0.00000028	0.00000011
1,3-Dimethoxybenzene	0.02486935	0.00000000	0.00000004	0.04620371	5.57469535	0.00003007	0.00000019	0.00000017
n-Butyl lithium	0.27319081	0.00000001	0.00000040	0.54033283	73.50484157	0.00033385	0.00000101	0.00000125
Chlorodicyclohexylphosph.	0.44339803	0.00000002	0.00000055	0.46937790	201.55719536	0.00034103	0.00000979	0.00000192
Silica gel	0.01312969	0.00000000	0.00000004	0.01489236	5.38017582	0.00004300	0.00000001	0.00000009
Cellulose acetate	0.05659730	0.00000000	0.00000008	0.11194146	15.22809467	0.00006916	0.00000021	0.00000026
Iron(III) chloride	0.00199502	0.00000000	0.00000000	0.00569752	0.87091239	0.00000588	0.00000006	0.00000001
Pd(OAc) ₂	0.76903396	0.00000001	0.00000030	0.22056791	83.72165178	0.00070005	0.00000010	0.00000274
Methylmagnesium chloride	0.05610293	0.00000003	0.00000004	0.05372214	11.01634059	0.00001130	0.00000163	0.00000366
Tetrahydrofuran	0.59776359	0.00000005	0.00000067	1.98160708	214.06959248	0.00037177	0.00000136	0.00000345
n-Hexane	0.00591724	0.00000000	0.00000001	0.00628679	2.67195620	0.00000460	0.00000004	0.00000002
Ethyl acetate	0.65525283	0.00000003	0.00000085	1.21891829	211.40067227	0.00045631	0.00000114	0.00000334
Acetone	0.06761257	0.00000001	0.00000006	0.06711120	13.70807153	0.00003543	0.00000007	0.00000030
Methanol	0.00264650	0.00000000	0.00000000	0.00245849	0.45459650	0.00000086	0.00000002	0.00000001
Pentane	0.10706393	0.00000000	0.00000002	0.01636056	4.35015874	0.00000954	0.00000008	0.00000066
Water	0.00000018	0.00000000	0.00000000	0.00000053	0.00007529	0.00000000	0.00000000	0.00000000
SUM	3.09241564	0.00000017	0.00000309	4.78724685	847.51536048	0.00242781	0.00001600	0.00001799

Materials	Particulate matter EF v3.1 no LT Disease incidence	Photochem. ozone formation EF v3.1 no LT kg NMVOC eq	Water use EF v3.1 no LT m ³ deprived	Precision Score - Material acc. to Figure 4
2-Bromochlorobenzene	0.00000011	0.01019104	6.44835067	70%
1,3-Dimethoxybenzene	0.00000017	0.01203710	1.64413183	70%
n-Butyl lithium	0.00000125	0.07598894	39.96838526	70%
Chlorodicyclohexylphosph.	0.00000192	0.45346309	20.78250682	50%
Silica gel	0.00000009	0.00379393	0.61007998	80%
Cellulose acetate	0.00000026	0.01574273	8.28030292	80%
Iron(III) chloride	0.00000001	0.00058938	0.12780337	95%
Pd(OAc) ₂	0.00000274	0.28071208	2.79555207	80%
Methylmagnesium chloride	0.00000366	0.02641772	0.56882861	70%
Tetrahydrofuran	0.00000345	0.24060676	142.59338646	95%
n-Hexane	0.00000002	0.00618925	0.27588895	95%
Ethyl acetate	0.00000334	0.32094189	45.48378411	95%
Acetone	0.00000030	0.03427291	3.54771212	95%
Methanol	0.00000001	0.00190840	0.09609906	95%
Pentane	0.00000066	0.06243819	0.81135036	95%
Water	0.00000000	0.00000006	0.00001227	95%
SUM	0.00001799	1.54529349	274.03417489	-

Fig. 4 Environmental footprints of individual materials used. Climate change (total) is compiled of the sum of climate change (Production (+ Market)) as found in ecoinvent and a generic factor for a material's incineration. The incineration factor for liquid waste other than H₂O refers to the treatment of spent solvent mixture, hazardous waste incineration (RoW), that for H₂O refers to 0.628 kg CO₂ per kg H₂O according to ref. 18, and that for solid waste refers to the treatment of hazardous waste, hazardous waste incineration (RoW).

abiotic land use, and toxicity related problems for example, some of the more often mentioned problems associated with PGMs, but it will not lower the process' overall carbon footprint to any meaningful degree. Therefore, it might be more beneficial to look at other input streams, for example solvents as in this specific case. Having said this, we do acknowledge the fact that the carbon footprint contribution of PGMs is often not representative for their actual effect on

a process' pollution. However, we do believe that the carbon footprint of metals can be used to guide further actions, for example, larger carbon footprints of metals indicate additional investigations into other factors, as mentioned before. However, when used in small amounts, their use can enable us to use less solvent or less substrates, for example, thereby lowering the environmental footprint of a process indirectly.

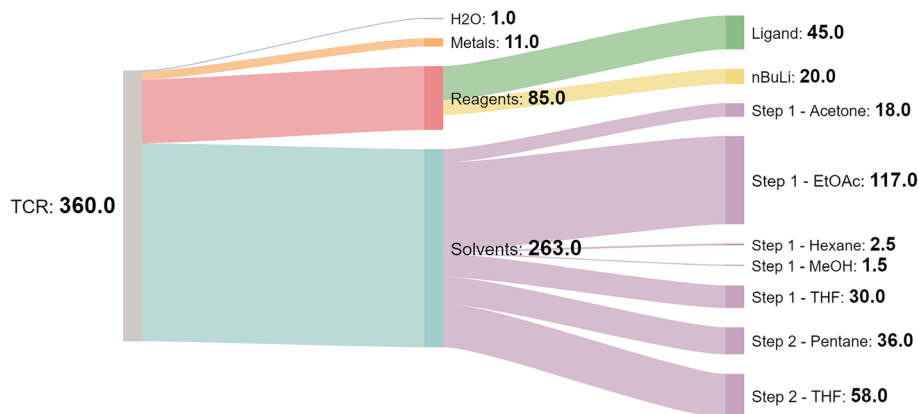


Fig. 5 Sankey diagram on the total carbon release (TCR) and of selected materials used in the process for the preparation of the nano catalyst.

Table 4 Precision score of materials and the entire process

Materials	Fractional cPMI – process (material)	Scenario acc. to Fig. 4	Precision score – material	Precision score – overall
2-Bromochlorobenzene	0.298	3	70%	94%
1,3-Dimethoxybenzene	0.241	3	70%	
<i>n</i> -Butyl lithium	0.226	3	70%	
Chlorodicyclohexylphosphine	0.363	5	50%	
Silica gel	0.468	2	80%	
Cellulose acetate	0.047	2	80%	
Iron(III) chloride	0.185	1	95%	
Pd(OAc) ₂	0.002	2	80%	
Methylmagnesium chloride	0.171	3	70%	
Tetrahydrofuran	10.240	1	95%	
<i>n</i> -Hexane	0.752	1	95%	
Ethyl acetate	20.527	1	95%	
Acetone	4.465	1	95%	
Methanol	0.451	1	95%	
Pentane	10.000	1	95%	
Water	0.037	1	95%	

$$\text{Precision score} = \frac{\sum \text{Fractional cPMI (each material)} \times \text{Precision score (each material)} \times 100\%}{\text{cPMI}} \\ = \frac{(0.298 \times 0.7 + 0.241 \times 0.7 + \dots) \times 100\%}{48.473} = 94\%$$

The environmental impact scores presented up to this point, climate change or acidification for example, are linked to physical units often difficult to grasp, such as kg CO₂- or mol H⁺-equivalents. The results of these different impact categories can therefore not be compared or combined as such and personal perception about the relative importance of different impact categories might lead to different interpretations of the presented data. Depending on individual background and expertise, there might be an unconscious bias to optimize a process in the direction of one's own expertise and interest, which is likely to result into unequal outcomes for nature using the same amount of development resources. Whether deliberate or not, personal judgments on decision making are unavoidable and a given cultural aspect to consider. For this reason, we tried to explore a more data-driven process based on clear and empirical guidelines. One way to

make interpretation of scores easier is to normalize and weight them. Normalization embeds the division of each score by a reference score or reference situation. *Via* this process, normalization converts complicated units into fractions for all impact categories.²⁶ Weighing is the final step. It entails the multiplication of the normalized results of the impact categories with a weighing factor that expresses the relative importance of the impact categories to ensure the focus is put on those aspects that matter the most.²⁷ Weighting schemes inherently involve value choices that will depend on policy, cultural and other preferences and value systems. Reaching “consensus” on weighting seems to be rather difficult, a situation that does not only apply to weighting in the context of this manuscript but seems inevitable for many multicriteria approaches. However, we see weighting as essential to further aggregate information with the objective to improve the practi-

cal utility of footprint assessments in complex decision situations. The weighting factors used in the Environmental Footprint (EF) method to prioritize and aggregate the results for the ~15 environmental impact categories – covering *e.g.* climate change, acid rain, human and eco-toxicity, particulate matter but also impacts due to the use of water, land and resources – were chosen according to each categories relevance deduced from a combination of different models or interests.²⁷ Models to determine the categories importance include the distance-to-target model (DtT), in which an indicators distance from a current environmental situation to a defined standard target is considered, panel weighting, in which impacts are weighted on the opinions of a group, or for example monetary weighting, in which impacts are weighted according to their estimated economic values.

The weighted results all have the same unit and can therefore be added up to create one single numerical score representing the environmental impact of a process (Table 5). Reducing the analysis to a single score removes an important level of detail of the assessment as the relative importance of each indicator can be seen as a function of the priorities of a person assessing the process. Showcasing the individual indicators allow for geographic or even personal priorities to be considered, however, a single score enables us to easily compare the environmental impact of different processes or different scenarios, facilitating decision-making. Finding outliers in a large and diverse corporate portfolio consisting of different modalities, creating a simplified overview for communication purposes, and presenting this to key stakeholders, all of this is facilitated using a single environmental impact score. However, one must use caution that important decisions made include the full picture as a single numerical score does not easily allow one to identify areas of concern, or indeed, aspects where improvements are needed and are being made.

Looking at the specific composition of the normalization and weighting factors as described in the EF method,^{25–27} it can be seen that the carbon footprint (climate change) seems to have the biggest impact followed by particulate matter generation in the given example described in Table 2.

Based on the procedure described in the previous steps, development scenarios can be simulated and their impact on the whole process, using the normalization and weighting approach, or on the level of individual indicators, can be expressed. To do so, a simplified output, analogue to the “Green Star” approach, was selected (Fig. 6).³¹ As an example, it can be observed, that an overall reduction of pentane or THF by 50% would lead to similar outcomes in terms of cPMI but to drastically different outcomes in terms of climate change or ionizing radiation, also reflected in the normalized and weighted scores. Visualization *via* a simple spiderweb graph can help to easily grasp our impact in development but also to communicate our work.

The approach is also helping us when time comes to assess the potential impact of certain key technologies. Quite often, or at least within the first few experiments, traditional chemistry in organic solvents and first hits of water-mediated chemistry, which has been of strategic interest for more than a decade,³² or bio-catalysis for example,³³ showcase comparable values assessing them using mass-based metrics. This can be in stark contrast assessing them using the described indicators, such as climate change. This approach helps us to evaluate technologies and key platforms and deploy them where these approaches create the biggest impacts.

To get the full picture of a process in development and to enable decision making on the basis of all data available, it is of course important to complete the described environmental sustainability assessment using additional indicators like costs,³⁴ criticality and scarcity of elements,³⁵ energy consumption,³⁶ the sustainable development goals (SDGs),³⁷ or health

Table 5 Normalization and weighting of environmental indicators from Table 2 according to the EF-method to get a unitless single numerical score; specific impact categories × specific normalization factors × specific weighting factors

Impact categories	Exp. data	Normalization factor	Weighting factor	Transformed exp. data
Climate change	359.8120 kg CO ₂ eq.	0.0001235	21.06	1.0032795
Ozone depletion	0.00001600 kg CFC-11 eq.	18.64	6.31	0.0019287
Ionising radiation	4.7872 kg U ²³⁵ eq.	0.000237	5.01	0.0056842
Photochemical ozone formation	1.5453 kg NMVOC eq.	0.02463	4.78	0.1807477
Particulate matter	0.00001799 disease incidence	1680	8.96	0.2707867
Human toxicity, non-cancer	0.00000309 CTUh	4354	1.84	0.0441492
Human toxicity, cancer	0.00000017 CTUh	59173	2.13	0.0213432
Acidification	3.3137 mol H ⁺ eq.	0.018	6.20	0.3698143
Eutrophication, freshwater	0.02708 kg P eq.	0.6223	2.80	0.0471843
Eutrophication, marine	0.31504 kg N eq.	0.05116	2.96	0.0477074
Eutrophication, terrestrial	3.09242 mole N eq.	0.005658	3.71	0.0649135
Ecotoxicity, freshwater	2710.0797 CTUe	0.00002343	1.92	0.0917351
Land use	847.5154 Pt	0.00000122	7.94	0.0082097
Water use	274.0342m3 deprived	0.00008719	8.51	0.2033298
Resource use, fossils	6371.9921MJ eq.	0.00001538	8.32	0.8153703
Resource use, minerals and metals	0.00242781 kg Sb eq.	15.71	7.55	0.2881466
Sum				3.4643302



Fig. 6 Relative spider diagram of development scenarios and their normalized and weighted score.

Table 6 Health and safety statements that warrant considerations

GHS statements – special caution	H200, H201, H202, H203, H240, H300, H310, H330, H340, H350, H360, H362, H400, H410, H411, H420
GHS statements – caution	H220, H224, H225, H227, H241, H301, H311, H314, H318, H331, H341, H351, H361, H370, H372, H412, H413
GHS statements – notable	H226, H310, H304, H312, H315, H317, H319, H332, H334, H335, H336, H371, H373, H401

and safety concerns according to GHS labels (Table 6), or REACH legislation (*e.g.* SVHC)² must be taken into account.

Step-4, data and knowledge storage

Data as cPMI, fractional cPMI, climate change, ozone depletion, and more indicators are currently collected from different projects at different development stages. The combined data is contributing to the foundation of benchmarking and future data science efforts.

Step-5, green culture

Data collection, visualization, added value, and lessons learned are one part of the puzzle, but all is lost if the message is not communicated. We have been communicating and sharing extensively throughout the development of the methodology and continue with regular trainings and

various exchange opportunities. We strongly believe and experienced the dissemination of simple tools, helpful in the daily life of process chemists especially, is needed to reinforce the notion of data-driven decision for each of the critical choice's scientists have to make when design a synthesis, a process.¹⁶ We create awareness and to ensure that the use of such assessments is not limited to “clean up” but to design processes in an environmentally safe and just manner.

Conclusion

Phasing out actual emissions is the goal but, in the meantime, targets and metrics to guide, define, and measure progress are needed. Transparent metrics and procedures as described in this manuscript ensure that efforts are based on consensus of

the best available evidence – and that carbon-accounting methodologies and accepted data sources are included to publish, communicate, or present data.

The presented method bears resemblance to LCA-methods reporting environmental hotspots, points of concern, and the overall environmental costs of our processes with good accuracy in a shorter time frame. Calculating each material's fractional cPMI – process (material) furthermore allows us to simply calculate a process' cost. Linking a material's fractional cPMI – process (material) – kg of a specific material used to prepare one kg of final product – to a material's cost, affords the overall material cost for a given process in a rather straightforward manner.

Generated standardized data from reaction classes, usage of platinum group metals and their impact on processes environmental footprints, data on the preparation of compounds having specific descriptors, data from key platforms such as biocatalysis or micellar chemistry, or data on key ingredients, all can help to reveal trends, opportunities, and identify areas that require more focus to strategically drive improvements in environmental sustainability across an entire portfolio.

It should therefore come to no surprise that we noted, amongst other findings, that solvent use and disposal across the portfolio often are major culprits for the largest parts of emissions in pharmaceutical production. Solvents both are, historically and currently, important to facilitate chemical interactions between materials used to manufacture small molecules. However, the reliance on highly purified solvents (usually fossil-derived) and their often-one-time usage in manufacturing processes not only leads to unacceptable emissions of carbon dioxide but also results in other forms of pollution ultimately harmful to human health and the environment at large, pointing the focus on solvent selection and substitution. This is something we recognized and tried to address long ago using more sustainable media, like water.³² And while organic solvents are likely to be around for years to come, the toolbox for chemistry in water is growing at a fast pace. Meticulous metrics will there help better grasp and identify where to use which medium. In conclusion, we report a pragmatic procedure that allows for standardized environmental assessments applicable for single substances such as small molecules prepared in a single reaction or over the course of complex processes comprised of multiple synthetic steps. Combined with other factors such as hazards, SDGs, and the consistent inclusion of quality indicators like the suggested precision score, the outlined framework can be used to analyze existing processes, simulate potential changes, or to evaluate potential processes. We hope that it sets the stage for the next wave of practical and yet more precise decisive and impactful LCA-type of analyses, and we will be striving at supporting the development of such initiatives. We also hope that it will trigger more efforts to gain in practicality and accuracy for superior adoption.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to Dr Lukas Doulakas, Vinzenz Mueller, Dr Andrej Szijarto, Dr Julien Haber, Dr Christoph Krell, Dr Ulrich Onken, and Stefanie Knobloch for their constant support and their efforts in bringing this idea further, to Dr Andreas Knell and Dr Thomas Heinz for their trust and vision.

References

- (a) J. B. Zimmerman, P. T. Anastas, H. C. Erythropel and W. Leitner, *Science*, 2020, **367**, 397–400; (b) T. Schaub, *Chem. – Eur. J.*, 2021, **27**, 1865–1869.
- (a) Candidate list of substances of very high concern (SVHC) at ECHA, <https://echa.europa.eu/candidate-list-table>, accessed: December 8, 2023; (b) Toxic substance control act (TSCA) at EPA, <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca>, accessed: December 8, 2023.
- (a) C. Jiménez-González, D. J. C. Constable and C. S. Ponder, *Chem. Soc. Rev.*, 2012, **41**, 1485–1498; (b) C. R. McElroy, A. Constantinou, L. C. Jones, L. Summerton and J. H. Clark, *Green Chem.*, 2015, **17**, 3111–3121; (c) P. Jessop, *Green Chem.*, 2020, **22**, 13–15; (d) C. Jiménez-González and C. Lund, *Curr. Opin. Green Sustainable Chem.*, 2022, **33**, 100564–100564.
- (a) R. A. Sheldon, *Green Chem.*, 2007, **9**, 1273–1283; (b) R. A. Sheldon, *Green Chem.*, 2017, **19**, 18–43; (c) R. A. Sheldon, *ACS Sustainable Chem. Eng.*, 2018, **6**, 32–48.
- (a) ACS GCIPR, American Chemical Society, Green Chemistry Institute, Pharmaceutical Roundtable, <https://www.acsgcpr.org>, accessed: December 8, 2023; (b) C. Jiménez-González, C. S. Ponder, Q. B. Broxterman and J. B. Manley, *Org. Process Res. Dev.*, 2011, **15**, 912–917.
- (a) K. Van Aken, L. Strekowski and L. Patiny, *Beilstein J. Org. Chem.*, 2006, **2**, 3–3; (b) A. D. Curzons, C. Jiménez-González, A. L. Duncan, D. J. C. Constable and V. L. Cunningham, *Int. J. Life Cycle Assess.*, 2007, **12**, 272–280; (c) G. Wernet, S. Conradt, H. P. Isenring, C. Jiménez-González and K. Hungerbühler, *Int. J. Life Cycle Assess.*, 2010, **15**, 294–303; (d) M. G. T. C. Ribeiro and A. A. S. C. Machado, *Green Chem. Lett. Rev.*, 2013, **6**, 1–18; (e) D. Kaiser, J. Yang and G. Wuitschik, *Org. Process Res. Dev.*, 2018, **22**, 1222–1235; (f) M. J. Eckelman, M. S. Moroney, J. B. Zimmerman, P. T. Anastas, E. Thompson, P. Scott, M. McKeever-Alfieri, P. F. Cavanaugh and G. Daherb, *Green Chem.*, 2022, **24**, 2397–2408.
- (a) International Standard Organisation (ISO) (200(6a) Environmental management—Life cycle assessment: Principles and framework. ISO14040, Geneva; (b) International Standard Organisation (ISO) (200(6b)

- Environmental management—Life cycle assessment: Requirements and Guidelines. ISO14044, Geneva.
- 8 M. C. McManus and C. M. Taylor, *Biomass Bioenergy*, 2015, **82**, 13–26.
 - 9 G. Wernet, C. Bauer, B. Steubing, J. Reinhard, E. Moreno-Ruiz and B. Weidema, *Int. J. Life Cycle Assess.*, 2016, **21**, 1218–1230.
 - 10 J. Andraos, *Green Process. Synth.*, 2019, **8**, 324–336.
 - 11 A. D. Curzons, C. Jiménez-González, A. L. Duncan, D. J. C. Constable and V. L. Cunningham, *Int. J. LCA*, 2007, **12**, 272–280.
 - 12 L. Leseurre, C. Merea, S. Duprat de Paule and A. Pinchart, *Green Chem.*, 2014, **16**, 1139–1148.
 - 13 K. Van Aken, L. Strekowski and L. Patiny, *Beilstein J. Org. Chem.*, 2006, **2**, 3.
 - 14 P. Martz, T. V. T. Phan, J. L'Haridon, M.-H. Beausoleil, K. Lafaye, Y. Gérard and C. Gallardo, *Green Chem.*, 2023, **25**, 6365–6382.
 - 15 DOZN™ Quantitative Green Chemistry Evaluator, Merck, DOZN™ Analysetool für “Grüne Chemie” (sigmaaldrich.com) (accessed on March 11th, 2024).
 - 16 L. J. Diorazio and A. Mullen, *Curr. Opin. Green Sustainable Chem.*, 2022, **5**, 100247–100247.
 - 17 (a) R. L. Smith and M. A. Gonzalez, *Ind. Eng. Chem. Res.*, 2012, **51**, 2309–2328; (b) G. J. Ruiz-Mercado, R. L. Smith and M. A. Gonzalez, *Ind. Eng. Chem. Res.*, 2012, **51**, 2329–2353.
 - 18 U. Onken, A. Koettgen, H. Scheidat, P. Schuepp and F. Gallou, *Chimia*, 2019, **73**, 730–736.
 - 19 C. H. Benison and P. R. Payne, *Curr. Opin. Green Sustainable Chem.*, 2022, **5**, 100229–100229.
 - 20 F. Roschangar, J. Li, Y. Zhou, W. Aelterman, A. Borovika, J. Colberg, D. P. Dickson, F. Gallou, J. D. Hayler, S. G. Koenig, M. E. Kopach, B. Kosjek, D. K. Leahy, E. O'Brien, A. G. Smith, M. Henry, J. Cook and R. A. Sheldon, *ACS Sustainable Chem. Eng.*, 2022, **10**, 5148–5162.
 - 21 (a) D. Prat, J. Hayler and A. Wells, *Green Chem.*, 2014, **16**, 4546–4551; (b) C. M. Alder, J. D. Hayler, R. K. Henderson, A. M. Redman, L. Shukla, L. E. Shuster and H. F. Sneddon, *Green Chem.*, 2016, **18**, 3879–3890; (c) D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehadad and P. J. Dunn, *Green Chem.*, 2016, **18**, 288–296.
 - 22 A. Amelio, G. Genduso, S. Vreysen, P. Luis and B. Van der Bruggen, *Green Chem.*, 2014, **16**, 3045–3063.
 - 23 T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4680–4684.
 - 24 S. Handa, Y. Wang, F. Gallou and B. Lipshutz, *Science*, 2015, **349**, 1087–1091.
 - 25 Niels Jungbluth (2022) Description of life cycle impact assessment methods. ESU-services Ltd, Schaffhausen, Switzerland, <https://esu-services.ch/fileadmin/download/tender/ESU-Description-of-LCIAMethods.pdf>, accessed: Janaury 10, 2024.
 - 26 R. Pant, S. Sala and E. Crenna, *et al.*, European Commission, Joint Research Centre, Global normalisation factors for the environmental footprint and Life Cycle Assessment, Publications Office, 2017, <https://data.europa.eu/doi/10.2760/88930>, accessed: Janaury 10, 2024.
 - 27 A. Cerutti, R. Pant and S. Sala, European Commission, Joint Research Centre, Development of a weighting approach for the environmental footprint, Publications Office, 2018, <https://data.europa.eu/doi/10.2760/945290>, accessed: Janaury 10, 2024.
 - 28 F. Roschangar, J. Colberg, P. J. Dunn, F. Gallou, J. D. Hayler, S. G. Koenig, M. E. Kopach, D. K. Leahy, I. Mergelsberg, J. L. Tucker, R. A. Sheldon and C. H. Senanayake, *Green Chem.*, 2017, **19**, 281–285.
 - 29 D. Ott-Reinhardt, D. Kralisch, I. Dencic, V. Hessel, Y. Laribi, P. Perrichon, C. Berguerand, L. Kiwi-Minsker and P. Loeb, *ChemSusChem*, 2014, **7**, 3521–3533.
 - 30 (a) C. Capello, U. Fischer and K. Hungerbühler, *Green Chem.*, 2007, **9**, 927–934; (b) A. Amelio, G. Genduso, S. Vreysen, P. Luis and B. Van der Bruggen, *Green Chem.*, 2014, **16**, 3045–3063.
 - 31 M. G. T. C. Ribeiro, D. A. Costa and A. A. S. C. Machado, *Green Chem. Lett. Rev.*, 2010, **3**, 149–159.
 - 32 (a) F. Gallou, N. A. Isley, A. Ganic, U. Onken and M. Parmentier, *Green Chem.*, 2016, **18**, 14–19; (b) B. H. Lipshutz, F. Gallou and S. Handa, *ACS Sustainable Chem. Eng.*, 2016, **4**, 5838–5849; (c) M. Cortes-Clerget, J. Yu, J. R. A. Kincaid, P. Walde, F. Gallou and B. H. Lipshutz, *Chem. Sci.*, 2021, **12**, 4237–4266.
 - 33 (a) M. Cortes-Clerget, N. Akporji, J. Zhou, F. Gao, P. Guo, M. Parmentier, F. Gallou, J.-Y. Berthon and B. H. Lipshutz, *Nat. Commun.*, 2019, **10**, 2169–2169; (b) H. Gröger, F. Gallou and B. H. Lipshutz, *Chem. Rev.*, 2023, **123**, 5262–5296.
 - 34 J. L. Tucker, *Curr. Opin. Green Sustainable Chem.*, 2022, **35**, 100606–100606.
 - 35 (a) T. E. Graedel, G. Gunn and L. T. Espinoza, *Critical Metals Handbook*, John Wiley & Sons, 1st edn, 2014. DOI: [10.1002/9781118755341.ch1](https://doi.org/10.1002/9781118755341.ch1); (b) M. L. C. M. Henckens, P. P. J. Driessen and E. Worrell, *Resour., Conserv. Recycl.*, 2014, **93**, 1–8; (c) T. E. Graedel, E. M. Harper, N. T. Nassar and B. K. Reck, *Proc. Natl. Acad. Sci. U. S. A.*, 2015, **112**, 6295–6300; (d) T. Henckes, *Resour., Conserv. Recycl.*, 2021, **169**, 105511–105511; (e) Report on critical raw materials for the EU, 2014, https://mima.geus.dk/report-on-critical-raw-materials_en.pdf, accessed: Janaury 9, 2024.
 - 36 (a) C. Jiménez-González and M. R. Overcash, *J. Chem. Technol. Biotechnol.*, 2000, **75**, 983–990; (b) P. S. Bieler, U. Fischer and K. Hungerbühler, *Ind. Eng. Chem. Res.*, 2003, **42**, 6135–6144; (c) F. Tieves, F. Tonin, E. Fernandez-Fueyo, J. M. Robbins, B. Bommarius, A. S. Bommarius, M. Alcalde and F. Hollmann, *Tetrahedron*, 2019, **75**, 1311–1314.
 - 37 Sustainable Development Goals, <https://www.undp.org/sustainable-development-goals>, accessed: Janaury 9, 2024.