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MATHARU, AVTAR and SHERWOOD, JAMES (2026) An interactive solvent selection guide inspired by the Safe and Sustainable by Design framework. RSC Green Chemistry. ISSN: 1463-9270

<https://doi.org/10.1039/d6gc03389j>

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Cite this: DOI: 10.1039/d6gc03389j

Received 9th June 2026,
Accepted 20th August 2026

DOI: 10.1039/d6gc03389j

rsc.li/greenchem

An interactive solvent selection guide inspired by the safe and sustainable by design framework

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Solvent selection is an important aspect of Green Chemistry. A variety of solvent selection guides are available that rank solvents according to environmental impact, hazard, and compatibility with waste treatments. The ubiquitous tabular presentation of solvent selection guides provides a helpful introduction to green solvents but cannot be adapted to reflect the risk arising from each user's circumstances. Safe and Sustainable by Design (SSbD) is a framework for successful chemical substitution that encourages process redesign on a case-by-case basis. Here, we develop a template for a user-defined solvent selection guide based on SSbD principles. The user defines the reaction, acceptable ranges of solvent properties, and calculates the health risk from the process design. Solvents are recommended based on health, safety, environmental hazard, climate change and water use impact, and predicted conversion. Customisable solvent selection guides can be produced using a free online html editor.

Green foundation

1. Solvent selection is central to green chemistry, yet existing guides apply inflexible, one-size-fits-all hazard rankings that do not reflect the actual risk in the user's process. This work advances the field by embedding the European Commission's Safe and Sustainable by Design framework into an open-access, interactive solvent selection guide covering 365 solvents.
2. The guide moves beyond hazard to quantify health risk using occupational exposure models and risk characterisation ratios, while also estimating climate change impact, freshwater use, and predicted reaction conversion. Users can simultaneously optimise safety, environmental impact, and efficiency in a single, bespoke tool.
3. Future work could extend the guide by incorporating absolute environmental sustainability and social life-cycle assessment indicators, estimates of environmental exposure and consumer exposure for commercial products. The database of solvent properties and linear solvation energy relationships can be expanded in subsequent versions.

Introduction

Solvents are used in large quantities in many manufacturing processes, which creates waste, pollution, and presents health and safety risks.¹ In an effort to steer solvent use towards safer solvents, the 'solvent selection guide' became an iconic tool for modern organic synthetic chemistry, settling on a multi-criteria red-amber-green system presented in data tables. Examples of typical solvent selection guides from GSK² and the CHEM21 consortium³ were published in 2016. In the following decade, several complementary solvent selection tools also became available, incorporating principal component analysis,^{4,5} artificial intelligence,^{6,7} and infographics.⁸ Some solvent selection guides have been developed for specific sectors by pre-selecting suitable solvents,^{9–12} or based on conversions in specific reactions.^{13–15} These solvent selection

guides mostly rely on an interpretation of hazards that mirrors risk assessment as routinely performed for small scale chemistry. The broad generality and inflexibility of the major solvent selection guides does not reflect specific processes and practices, and by extension, the case-by-case risk from exposure to solvents.

Recent literature has moved away from the general purpose tabular solvent selection guides and towards more sophisticated and specialised tools. Principal component analysis has become a popular way to visualise the similarity between solvents for substitution on the basis of physical properties. Interactive tools have been embedded into electronic laboratory notebooks so that solvent selection becomes a part of reaction planning.¹⁶ Equivalent tools for analytical chemistry,¹⁷ and materials science,¹⁸ are available. Principal component analysis identifies solvents with similar physical properties, and so a measure of greenness must be attributed by other means (usually the results of classical solvent selection guides are used to add a dimension of health and safety decision making). The same principle has been applied to

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process design, whereby the results of the CHEM21 solvent selection guide³ have been used to complement techno-economic assessment.¹⁹ The life cycle impact of solvents has been used to optimise a conceptual process design for Suzuki–Miyaura coupling for substantial reductions in climate change impact and process costs.²⁰ Thus we see solvent selection becoming integrated with other analyses for process optimisation.

Despite these new innovations, solvent selection remains dependant on generalised hazard assessments which cannot account for the risks specific to the application in question. This will not be sufficient to match the ambitions of future sustainable manufacturing. The European Commission has proposed the ‘Safe and Sustainable by Design’ (SSbD) framework as the blueprint for the chemical industry.²¹ The purpose of SSbD is to guide innovation towards a sustainable industrial transition.^{22,23} Summarised in Fig. 1, it is a multi-stage, iterative process for redesigning product value chains. This involves a reduction in risk arising from hazardous substances to workers, consumers, and the environment. The ‘safety and sustainability assessment’ aspect of SSbD elaborates standard health and safety assessments with an emphasis on risk over hazard, environmental sustainability, and socioeconomic indicators. Data availability has been identified as a barrier to implementation.²⁴ Therefore, a risk-based solvent selection guide that incorporates SSbD principles, is compatible with other types of assessment, and can be quickly tailored to reflect the actual risk of any given processes would be an informative tool for modern discovery chemistry and process redesign.

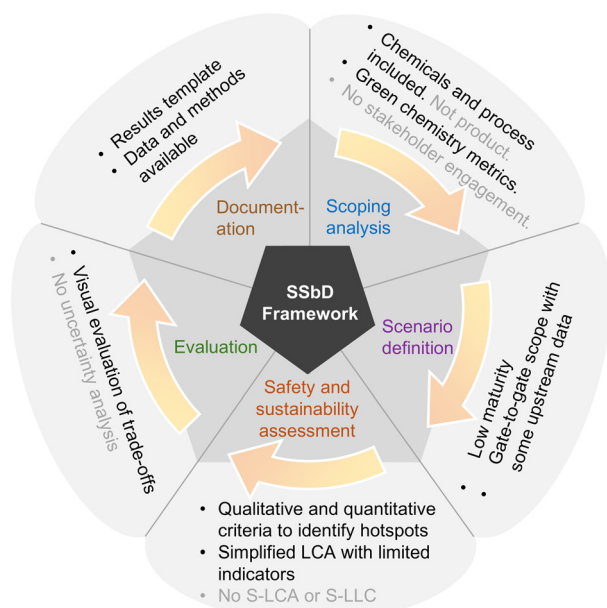


Fig. 1 The five stages of the iterative SSbD concept. Outer annotations refer to the solvent selection guide design choices. Grey text, such as social life cycle assessment (S-LCA) and societal life cycle cost (S-LCC), are not included.

Results and discussion

SSbD for solvent selection in research and development

The SSbD framework was interpreted to create a solvent selection guide using the following principles. 365 solvents were chosen and a database developed to characterise their properties including physical property data, solvent prices, and toxicological data. The solvents are grouped into categories based on popularity, so the more obscure solvents can be removed from the assessment if desired. The scoring system was kept similar to previous solvent selection guides by using three categories for health, safety, and environment. This was accentuated with predicted conversions and environmental impacts (climate change and freshwater use) to help optimise processes. Categories have been ranked A to E, with ‘A’ being ‘high risk’, and ‘E’ representing a negligible risk. The health score is dependent on the type of process, and conversion and impact are dependent on energy use as a result of reaction temperature and duration. Thus the solvent selection guide is dynamic, and changes according to the user. For this reason, an interactive html file was created for users to enter details about their process in order to create a bespoke solvent selection guide. This tool is available online.²⁵ The tool is computationally inexpensive, with calculations taking milliseconds. The code is also available and is free to use and modify.²⁶

The solvent selection guide can be modified to only include relevant solvents. It is possible to add physical property requirements, solubility requirements *via* Hansen Solubility Parameters,²⁷ availability, bio-based content, and exclude certain functional groups and hazards (Table 1). This flexibility permits the user to curate the solvent selection guide to be more relevant to their sector and omit superfluous solvents.

The health score was developed to calculate risk based on exposure compared to regulated occupational exposure limits or derived no-effect levels, a departure from the standard hazard-based health scores in other solvent selection guides. The method is summarised in the SI. This means solvents with relatively minor hazards might be deemed as high risk in some processes (e.g. spraying without good ventilation or res-

Table 1 List of properties for solvent selection

Characteristic	Selection method
Melting point	User defined range
Boiling point	User defined range
Density	User defined range
Viscosity	User defined range
Surface tension	User defined range
Flash point	User defined lower limit
Autoignition temperature	User defined lower limit
Bio-based content	User defined lower limit
Acute toxicity	Select/deselect
Chronic toxicity	Select/deselect
Environmental toxicity	Select/deselect
Functional groups	Select/deselect
Hansen solubility parameters	Target values and radius
State (solid/liquid/gas)	Select/deselect
REACH registration	Select/deselect

piratory protection), and solvents with severe hazards might have a reasonable health rank if used in closed systems with no risk of exposure. The measurement of long term inhalation risk, short term inhalation risk, and dermal risk is calculated with risk characterisation ratios (RCRs).²⁸ The RCR is the actual (calculated) exposure divided by the regulated maximum permissible exposure limit. A RCR above 1 means worker exposure exceeds the regulatory limit, and results in a high risk rank of A. Any RCR below one is acceptable but lower values are preferable and allocated a more favourable ranking.

Safety is based on hazard in line with the GESTIS Column Model.²⁹ Solvents are penalised on the basis of flammability and whether or not they are stored in pressurised cylinders. Solvents with a flash point above 93 °C, and those that inherently do not flash, are ranked E (negligible risk). This methodology is simpler than other solvent selection guides that might also consider auto-ignition point, resistivity, or reactivity. Instead, the SSbD solvent selection guide allows the user to set a minimum acceptable flash point and autoignition point, and remove potentially reactive or resistive functional groups (e.g. aromatic or ether solvents, as stated in Table 1).

The environment score depends on the physical properties of the solvent (see the SI). Each solvent is evaluated based on its environmental fate (air, water, soil or sediment). For example, a non-volatile solvent with an affinity for water is not judged on air quality criteria *i.e.* atmospheric half-life. Biodegradability, bioaccumulation and ecotoxicity are used to rank solvents whose environmental partition favours water. Any substance subject to regulatory intervention within the EU because of its detrimental impact on the environment is ranked as high risk (A) regardless of its environmental fate. Such substances are either ozone depleting, or considered persistent, bioaccumulative and ecotoxic (PBT) or very persistent and very bioaccumulative (vPvB).

Full implementation of a SSbD safety and sustainability assessment includes consumer exposure, environmental sustainability, and socioeconomic impacts.²¹ These aspects are not included in the SSbD solvent selection guide. Consumer exposure depends on the type of product and how much solvent is present (for paints, the solvent content is very high, but the majority of products contain no more than residual solvent). This solvent selection guide is targeted at R&D chemists undertaking organic synthesis, and so there is not usually a final formulated product to base an exposure model on. The preferred interpretation of environmental sustainability is Absolute Environmental Sustainability Assessment (AESA), which uses the context of the product and Planetary Boundaries to calculate sustainable thresholds in different impact categories.³⁰ Without a marketed product, this dimension of SSbD is also impossible to include. Instead, climate change impact and freshwater use were estimated to guide process design. Socioeconomic impact categories have been clarified in the most recent iteration of SSbD,²¹ but a valid assessment of social fairness and competitiveness across stakeholders is a multi-institutional project and beyond the expectations of a solvent selection exercise. Therefore, this

SSbD solvent selection guide should be used as a tool (in cooperation with other tools) to firstly evaluate and optimise chemical processes and build up to more comprehensive sustainability assessments.

The methodology of the solvent selection guide scoring system is illustrated with methyl ethyl ketone (MEK) in Fig. 2. The environmental fate of MEK is calculated as an even split between air and water and so both are evaluated. When there are multiple assessments in a category the worst rank is chosen. In the case of MEK, the air fate presents a greater risk and so the category rank of C is chosen (not the rank D from water fate). Fig. 2b shows a health rank of D in a closed, continuous processing facility which rises to rank A if MEK is used during industrial spraying. Worker exposure is based on established models.²⁸ The exposure to MEK is greatly increased in the spraying process under the conditions specified in Fig. 2a, exceeding occupational exposure limits, so that inhalation RCRs are much greater than 100%.

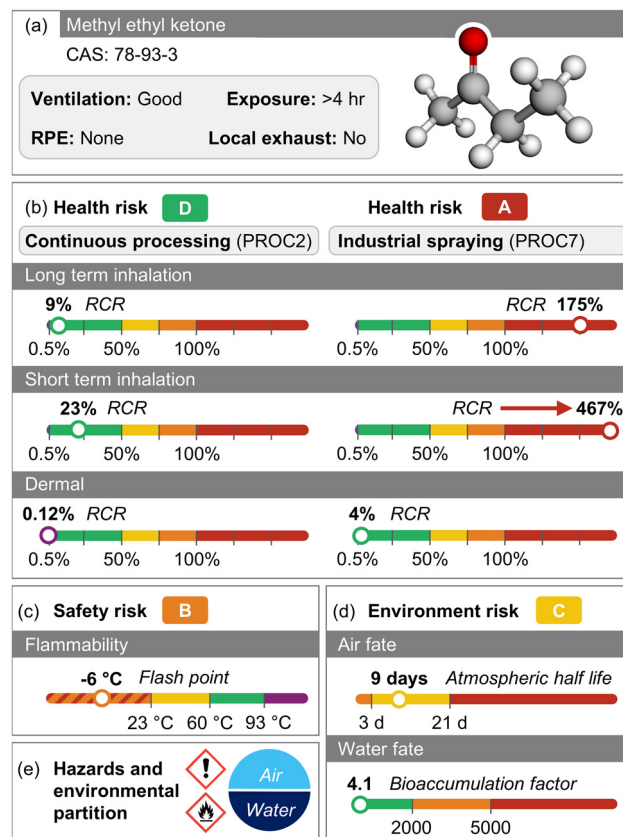


Fig. 2 The evaluation of methyl ethyl ketone (butanone) according to the SSbD solvent selection guide. The scales for each assessment indicate the risk or hazard, and are colour-coded to correspond to the associated rank. (a) Process conditions and solvent structure. (b) Health rank for two scenarios and three routes of exposure. (c) Safety risk based on flash point. (d) Environmental risk based on atmospheric half-life and bioaccumulation (methyl ethyl ketone is not ecotoxic and is biodegradable). (e) Hazard symbols and a calculated 50%–50% environmental partition between air and water.

Changes to the health score are elaborated for dipolar aprotic solvents in Fig. 3. Here, three types of process are compared, in which the worker exposure is varied. Nitromethane and nitrobenzene have been included despite not always being classified with the amide, nitrile, and sulphur-based dipolar aprotic solvents. At the time of writing, nitromethane is not REACH-registered to the highest standard of testing, so cautiously we consider an A rank for health as appropriate. The SSbD solvent selection guide indicates the worse case rank in brackets. Solvents considered Substances of Very High Concern (SVHC) in EU legislation because of their chronic human toxicity or environmental damage are also flagged.³¹ Otherwise, the health rank is based on exposure. Exposure scenarios were taken from the REACH Descriptor System. These are defined in Table S1 of the SI. PROC4 for instance describes a batch synthesis where the opportunity for exposure arises. Industrial spraying is PROC7. PROC7 will result in a greater exposure to workers than PROC, which can be adjusted for exposure time, ventilation and personal protective equipment (e.g. gloves). These variables are inputs in the SSbD solvent selection guide. Most of the dipolar aprotic solvents in Fig. 3 are ranked D in the PROC4 scenario due to low exposure (less than 50% of occupational exposure limits). Industrial spraying (PROC7) results in higher exposure than batch synthesis, even though in this example greater ventilation is operational and the exposure time is less, for example, *N,N*-dimethyl formamide (DMF) increases from rank D to rank A. The transfer of chemicals between vessels (PROC8b) results in the highest exposure of the scenarios presented in Fig. 3 if only basic ventilation is present. Now only dimethyl sulph-

oxide (DMSO) and nitromethane exposure is below the occupational exposure limit (for all exposure routes). DMSO has no inhalation or dermal hazards and so is consistently ranked D for health. Only water is reserved a rank of E.

General purpose SSbD solvent selection guide

Although it is important for users to model a representative scenario and derive their own solvent selection guide, a broadly useful solvent selection guide for R&D chemists is shown in Fig. 4. Fig. 4 contains 80 solvents, but 365 solvents are included in the full guide.²⁵ This iteration is based on process 'PROC4' of the REACH Descriptor System, representing general batch synthesis where exposure occurs, with an exposure time of 1–4 hours at ambient temperature, basic ventilation augmented with local exhaust extraction, no respiratory protection but PPE in the form of gloves. This is an approximation of a research laboratory with fume hoods. Using the exposure model for small scale laboratory work (PROC 15) would also be appropriate and reduce exposure estimates under otherwise identical circumstances, but PROC4 was chosen to increase the variation in the health rank of solvents.

The illustrative solvent selection guide in Fig. 4 is grouped by solvent class, and ordered by severity of risk. The risk changes if the exposure scenario is changed. As expected from other solvent selection guides,^{2,3} alcohols and esters are some of the least concerning solvents, while hydrocarbons, halogenated solvents, ethers and dipolar aprotic solvent categories contain some of the most concerning solvents. Whereas the health rank is dependent on the risk scenario, the safety score is fixed by hazard statement. There are some esters, alcohols and halogenated solvents in particular with an E safety rank due to high flash points or being non-flammable.

The environmental category is established to give the naturally abundant solvents water and carbon dioxide a rank of E to represent negligible risk. The climate change consequence of carbon dioxide emissions is dealt with in the impact category (not shown in the process-agnostic Fig. 4). The remaining organic solvents that tend to enter water in their environmental fate can be ranked D if they are neither persistent, bioaccumulative or ecotoxic. This is most common in alcohol solvents. Conversely, the high risk 'A' rank is achieved by solvents that cause ozone depletion, are long lived in the atmosphere, or are classified as PBT or vPvB. It is the case that dimethyl carbonate, with a half-life of photodegradation by hydroxyl radicals of 35 days *in silico* (calculation using OPERA),³² and 33 days by experiment,³³ exceeds the imposed 21 day threshold and is considered high risk to the environment.

The SSbD framework promotes a flexible, user-determined interpretation of results to suit different sectors and design priorities. The SSbD solvent selection guide methodology has default thresholds that determine the 'A' to 'E' rankings in each category, and an overall risk rating based on the number of 'A' ranked categories, then 'B' ranked categories, and so on. Alternative thresholds and a TOPSIS decision-making analysis

Solvent	Health		
Dipolar aprotic			
Dimethyl sulphoxide	D	D	D
Nitromethane	D (A)	D (A)	C (A)
Acetonitrile	D	C	A
NMP SVHC	D	C	A
DMAc SVHC	D	C	A
DMF SVHC	D	A	A
Sulpholane	A	A	A
Nitrobenzene SVHC	A	A	A
Process:	PROC4	PROC7	PROC8b
Ventilation:	Basic	Enhanced	Basic
Local exhaust:	Yes	Yes	No
RPE:	No	No	No
PPE effectiveness:	90%	90%	90%
Exposure:	1-4 hr	<15 min	<15 min

PROC4 = Batch synthesis
PROC7 = Industrial spraying
PROC8b = Chemical transfer between vessels

Fig. 3 Changes to the SSbD solvent selection guide health score of dipolar aprotic solvents in different processes. NMP, *N*-methyl pyrrolidone; DMAc, *N,N*-dimethyl acetamide; DMF, *N,N*-dimethyl formamide.

Process: Batch synthesis (PROC4)

Ventilation: Basic

Exposure: 1-4 hr

RPE: No

PPE: Yes (90% effective)

Local exhaust: Yes

Solvent	Health	Safety	Environment
Hydrocarbon			
Cyclohexane	D	B	C
<i>p</i> -Xylene	D	C	B
Mesitylene	D (A)	C	B
<i>n</i> -Heptane	D (A)	B	C
<i>d</i> -Limonene	D (A)	C	B
<i>n</i> -Octane	D (A)	B	C
Toluene	D	B	B
Methylcyclohexane	D	B	B
<i>n</i> -Pentane	D (A)	A	B
Benzene	A	B	C
<i>p</i> -Cymene	A	C	B
<i>n</i> -Hexane SVHC	A	B	B
Ether			
Dimethyl isosorbide	E (A)	E	B
Tetrahydrofuran	D	B	D
<i>t</i> -Butyl methyl ether	D	B	C
Anisole	D (A)	C	B
Cyclopentyl methyl ether	D (A)	B	B
Diisopropyl ether	D	B	B
2-Methyltetrahydrofuran	C	B	B
Diethyl ether	D	A	B
1,2-Dimethoxyethane	A	B	C
1,4-Dioxane SVHC	D	B	C
Ester or carbonate			
Glycerol triacetate	E	E	D
γ -Valerolactone	D (A)	E	D (C)
Propylene carbonate	D	E	D
Ethylene carbonate	D (A)	E	C
Butyl acetate	D	C	C
Ethyl acetate	D	B	C
Ethyl formate	D (A)	B	C
Isopropyl acetate	D	B	C
Methyl acetate	D	B	A
Dimethyl carbonate	D	B	A
Dipolar aprotic			
Dimethyl sulphoxide	D	D	C
Acetonitrile	D	B	D
Sulpholane	A	E	C
Nitromethane	D (A)	C	A
NMP SVHC	D	D	C
DMAc SVHC	D	D	C
DMF SVHC	D	C	C
Nitrobenzene SVHC	A	D	C
Halogenated			
Dichloromethane	D	E	A
Tetrachloroethylene	D	E	A
Chlorobenzene	C	C	C
1,2-Dichlorobenzene	D	D	A
Trichloroethylene SVHC	D	E	C
Fluorobenzene	C (A)	B	C
Chloroform	A	E	A
Carbon tetrachloride	A	E	A
1,2-Dichloroethane SVHC	A	B	A
Ketone			
Cyrene	D (A)	E	D
Cyclopentanone	D	C	D
Acetone	D	B	D
Methyl ethyl ketone	D	B	C
Cyclohexanone	D	C	B
2,6-Dimethyl-4-heptanone	D (A)	C	B
4-Methyl-2-pentanone	D (A)	B	B
Alcohols			
1,2-Propanediol	E	E	D
Glycerol	D	E	D
Diethylene glycol	D	E	D
Ethylene glycol	D	E	C
2-Butanol	D	C	D
Solketal	D (A)	D	C
Ethanol	E	B	D
Isobutanol	C	C	D
Isoamyl alcohol	C	C	D
2-Propanol	D	B	D
Methanol	D	B	D
1-Propanol	C	B	D
<i>t</i> -Butanol	D	B	C
Ethyl lactate	A	C	D (C)
1-Butanol	A	C	D
2,2,2-Trifluoroethanol	A	C	C
Hexafluoroisopropanol	A	E	A
2-Methoxyethanol SVHC	A	C	C
Miscellaneous			
Water	E	E	E
Carbon dioxide	E	C	E
Acetic acid	B	C	D
Pyridine	B	B	D
Carbon disulphide	A	B	C
Triethylamine	A	B	B

Fig. 4 A generic example of a solvent selection guide for synthesis with moderate protective measures for workers. The colour coded square beside each solvent is an indicative overall rank based on the three category scores and penalising SVHC status. This SSbD solvent selection guide is one iteration and not appropriate for all processes and lab users.

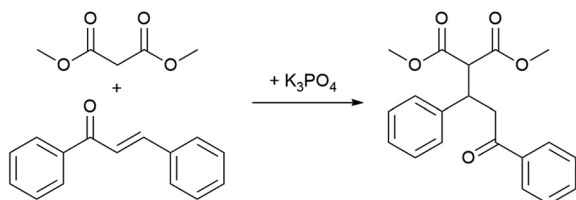
are available in the SSbD solvent selection guide to give the user more flexibility to implement category trade-offs, rather than having to treat each category as equally important.

Ultimately the user must justify and communicate these decision-making choices. The default settings (as explained in the SI) have been used in the following case studies

Case study: Michael addition solvent selection guide

To illustrate the use of this interactive solvent selection guide, a case study based on a Michael addition is now presented (Scheme 1). Previous research by Day *et al.* identified 2-methyl tetrahydrofuran (2-MeTHF) as a greener solvent for the reaction between dimethyl malonate and *trans*-chalcone.³⁴

The reactants are preset in the database of the online solvent selection guide,²⁵ along with the underlying solvent effect that governs this reaction at room temperature (data for 18 reactions are available in total). The mass of base required for the smallest reactor size, and estimates of additional climate change and water use impact from non-solvent substances, were added manually. Potentially reactive solvents were excluded and a restriction on boiling point was placed between 50 °C and 120 °C. Solvents were also subject to fulfilling polarity criteria. All variables including the risk scenario settings are provided in the SI, but essentially they describe a R&D facility with minimal worker exposure (PROC15). Furthermore, solvents with chronic toxicity were excluded. The final solvent selection guide is shown as Fig. 5. Only twelve solvents pass all the property, functional group, polarity, and hazard requirements. In a risk scenario with negligible



Scheme 1 A Michael addition between *trans*-chalcone and dimethyl malonate.

Process: R&D laboratory (PROC15)			Ventilation: Basic		
Exposure: 1 hr to 4 hr			RPE: No		
PPE: Yes (90% effective)			Local exhaust: Yes		
Solvent	Health	Safety	Env.	Conv.	Impact
Acetonitrile	D	B	D	E	B
<i>t</i> -Butyl methyl ether	D	B	C	B	D
Ethyl acetate	D	B	C	C	B
Isopropyl acetate	D	B	C	B	B
Pyridine	D	B	D	E	?
<i>n</i> -Heptane	D (A)	B	C	A	D
Cyclohexane	D	B	C	A	C
Ethyl formate	D (A)	B	C	C	?
2-MeTHF	D	B	B	D	A
CPME	D (A)	B	B	C	?
Diisopropyl ether	D	B	B	A	?
111-Trichloroethane	D (A)	E	A	A	?

Fig. 5 A bespoke solvent selection guide for the Michael addition between *trans*-chalcone and dimethyl malonate performed in a typical research laboratory.

exposure to non-chronically toxic solvents, the health scores are all at rank D. Aside from 1,1,1-trichloroethane (which does not flash), the remaining solvents are flammable and ranked 'B' for safety. There is greater variation with the environment scores in Fig. 5. The long atmospheric half-life of 1,1,1-trichloroethane results in the highest risk rank. Some solvents, cyclopentyl methyl ether (CPME) for example,³⁵ have very short atmospheric half-lives, and their break-down products can lead to air pollution. This is recognised with an environment rank of B. The lack of environmental persistence, bioaccumulation or ecotoxicity of acetonitrile results in an environment rank of D.

The SSbD solvent selection guide provides an estimated conversion for a given reaction based on the reaction duration and solvent choice. This is limited to preset reactions with a known solvent effect correlated to the reaction kinetics. The method is the same as that reported by Day *et al.*,³⁴ using the variable time-normalisation analysis (VTNA) developed by Burés.³⁶ If the order of the reaction is known, then the VTNA method can be reversed to calculate the time for a reaction product to reach any given concentration. From this analysis, the predicted conversion is used as a measure of reaction efficiency, and also impacts waste and therefore Green Chemistry metrics such as Process Mass Intensity (PMI). Atom economy and reaction mass efficiency are included alongside conversion and PMI in the online solvent selection guide database tab where two solvents can be compared side-by-side.²⁵

In the specific example of the reaction depicted in Scheme 1, the reaction in 2-MeTHF is calculated as 92% complete, and in acetonitrile it is 99% complete after 2 hours. The SSbD solvent selection guide ranks conversions over 95% as rank E. The difference in conversion also affects PMI, which is lower for acetonitrile (13.1) compared to 2-MeTHF (15.2) (see the SI).

The impact of each reaction is calculated using the energy and water use equations of Piccinno and Ansar.^{37,38} Energy use is converted to climate change impact based on user-defined carbon intensity. In this instance, the SSbD solvent selection guide was modelled to include a distillation to recover the solvent at 90% efficiency. Recovery of the solvent offsets the cradle-to-gate impact of the solvent.³⁹ In the case of 2-MeTHF, the water use used in the production of this bio-based solvent is very high at approximately 40 l per kg,⁴⁰ and even at 90% recovery the freshwater use impact is the highest of the solvents in Fig. 5. Note there are several solvents with insufficient data to rank in the impact category. For solvents with full data, with the specific settings of this solvent selection guide, acetonitrile appears to be the leading candidate and not 2-MeTHF as previously recommended. Further explanation is provided in the SI.

Four additional case studies have been compiled to ascertain the general difference between conventional solvent selection and SSbD decision making (Table 2). Settings and reactants can be found in Fig. S3–S6 of the SI.

As already discussed, MeCN is a better overall solvent choice than 2-MeTHF for Michael addition when viewed through the broad lens of a SSbD assessment. Likewise, the

Table 2 Solvent selection results of five case studies contrasted with the previously recommended solvent option. Citations are provided for previous studies and examples where the SSbD recommended solvent has been used in the named reaction

Reaction	Previous solvent	Justification	SSbD recommendation
Michael addition	2-MeTHF ³⁴	Polar and bio-based	MeCN ^{41,42}
Menschutkin reaction	Nitro-methane ⁴³	Large rate constant provided by dipolar solvents	DMSO ⁴⁴
Hydrogenation	Trifluoro ethanol ⁴⁵	High conversion favours protic solvents	Ethanol ⁴⁶
Ring closing metathesis	DCM ⁴⁷	Catalyst stability	Acetic acid, ethyl acetate, cyclohexane. ^{48,49}
Thermal amidation	D-Limonene ⁵⁰	Non-polar and bio-based	<i>p</i> -Xylene or toluene ³⁴

SSbD solvent selection guide found different optimum solvents for Menschutkin heteroatom alkylation, hydrogenation, ring closing metathesis and amide formation (Table 2). Previous computational modelling suggested nitromethane as the optimum reaction solvent for the Menschutkin reaction.⁴³ This is consistent with Abraham's early work on kinetics and solvent effects,⁵¹ where dipolarity promotes the S_N2 reaction mechanism. Reaction performance is one of five categories in the SSbD solvent selection guide, and several less hazardous solvents become preferred to nitromethane. Dimethyl sulphoxide (DMSO) is the top ranked solvent, followed by the renewable solvents γ -valerolactone and dimethyl isosorbide (Fig. S3). Nitromethane is ranked 18th.

The hydrogenation of nitrobenzene to aniline with a palladium catalyst is a robust model reaction, in which protic solvents enhance the rate of reaction.⁴⁵ 2,2,2-Trifluoroethanol has been suggested as a high-performance solvent before aliphatic alcohols,⁴⁵ but 2,2,2-trifluoroethanol is a PFAS with acute and chronic toxicity, making it a poor solvent from the perspective of human health and the environment. The SSbD solvent selection guide suggests ethanol, methanol, and other short chain aliphatic alcohols are a more balanced solvent option for the hydrogenation of the nitro group (Fig. S4).

Ring closing metathesis with ruthenium catalysts is routinely performed in dichloromethane (DCM) because it inhibits catalyst degradation.^{47–49} However, if the reaction is being performed at small scale and/or the catalyst is not being recovered, a safer solvent may become a higher priority than catalyst preservation. The SSbD solvent selection guide was used with settings that reflected an efficient process (high conversion) conducted with high worker protection standards (PROC15, see Fig. S5 of the SI). With solvent Health ranks of mostly 'D' and Conversion ranks of mostly 'E', the ability of the method to distinguish between solvents was tested. Even though only the Safety, Environment, and Impact categories offered meaningful variation, the results concurred with previous studies that have shown alkanes, acetic acid and ethyl acetate to all have advantages as greener solvents for ring closing metathesis (Fig. S5).^{48,49} *t*-Butyl methyl ether is the top-rated candidate. The properties of these solvents are quite different from DCM and each other. The SSbD solvent selection guide conducts solvent selection on the basis of process requirements rather than trying to find structurally similar solvents to the incumbent (as PCA methods tend to do), thus facilitating the replacement of hazardous classes of solvent with substitutes that are not intuitively obvious in order to reduce risk.

The final case study is a thermally-activated amidation (avoiding the use of a coupling agent). Previous work replace toluene with D-limonene in support of bio-based solvents.⁵⁰ A later study suggested that reaction optimisation in toluene is a superior approach (especially if worker exposure is low).³⁴ The SSbD solvent selection guide concurred with the latter approach and found *p*-xylene and toluene to be the primary candidates (Fig. S6). Terpenes such as D-limonene ranked poorly (28th in the guide), partly due to missing LCA data and its health hazards.

Conclusions

An update to the classic solvent selection guide is presented, inspired by the Safe and Sustainable by Design framework. The interactive features allow the user to choose a relevant risk scenario and exclude unsuitable solvents to create a valid, bespoke tool for greener chemistry. Aspects of the standard tabular solvent selection guide and reaction-specific solvent selection guides that report conversions in different solvents have been combined into a unified system. Various guises of the SSbD solvent selection guide have been demonstrated, including the case study of a Michael reaction. The source code and data for 365 solvents are made available so users can make informed solvent selection decisions and create their own solvent selection guides.

For early-stage discovery chemistry, this SSbD solvent selection guide can be used independently, but to fully optimise process safety and sustainability, complementary tools and assessments are required. Guiding reaction design principles²¹ should include reactants and equipment, encouraging renewable materials and non-critical elements, and evaluate the benefits of the product(s) against any negative consequences. Broader impacts, for example social-life cycle assessment, are important for mature processes. Thorough and accountable decision-making systems are also needed to incorporate solvent selection criteria into a full SSbD assessment.

Author contributions

Conceptualisation, supervision, validation, writing – review & editing: ASM; data curation, formal analysis, investigation, methodology, software, visualization, writing – original draft: JS.

Conflicts of interest

There are no conflicts to declare.

Data availability

The code for the solvent selection guide code is publicly and freely available on GitHub.²⁶ The database has citations to source material. Any data the user enters is stored locally on their device and is not visible or accessible to other users. The database shall be updated on an annual basis. Please contact the authors with notification of errors or suggested additions.

Supplementary information (SI): data sources, methods, additional Michael addition case study data. See DOI: <https://doi.org/10.1039/d6gc03389j>.

Acknowledgements

This research received funding from the European Union's Horizon Europe research and innovation programme under grant agreement no. 101057816 (TransPharm).

References

- 1 J. Sherwood, Solvent Impact on Chemical Processes, in *Encyclopedia of Green Chemistry*, ed. L. Vaccaro and B. Török, Elsevier, Amsterdam, 1st edn, 2025, vol. 1, pp. 66–84.
- 2 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.
- 3 D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehadeh and P. J. Dunn, *Green Chem.*, 2016, **18**, 288–296.
- 4 L. J. Diorazio, D. R. J. Hose and N. K. Adlington, *Org. Process Res. Dev.*, 2016, **20**, 760–773.
- 5 P. M. Piccione, J. Baumeister, T. Salvesen, C. Grosjean, Y. Flores, E. Groelly, V. Murudi, A. Shyadligeri, O. Lobanova and C. Lothschütz, *Org. Process Res. Dev.*, 2019, **23**, 998–1016.
- 6 H. Sels, H. D. Smet and J. Geuens, *Molecules*, 2020, **25**, 3037.
- 7 R. Datta, J. Nistane, A. Sose, H. Sahu and R. Ramprasad, *Adv. Sci.*, 2026, e16851, advanced article.
- 8 J. Heeley, S. Boobier and J. D. Hirst, *J. Cheminf.*, 2024, **16**, 60.
- 9 A. J. Doolin, R. G. Charles, C. S. P. D. Castro, R. G. Rodriguez, E. V. Péan, R. Patidar, T. Dunlop, C. Charbonneau, T. Watson and M. L. Davies, *Green Chem.*, 2021, **23**, 2471–2486.
- 10 L. Pilon, D. Day, H. Maslen, O. P. J. Stevens, N. Carslaw, D. R. Shaw and H. F. Sneddon, *Green Chem.*, 2024, **26**, 9697–9711.
- 11 Y. Ma, S. Gao, N. Mehta, Q. Fu, W. Li and B. Benyahia, *Green Chem.*, 2025, **27**, 12621–12641.
- 12 E. Stampolaki, A. Mondello, E. Alladio, P. Oliveri, A. Mazzoleni, F. Pena-Pereira and E. Psillakis, *TrAC, Trends Anal. Chem.*, 2026, **194**, 118531.
- 13 F. I. McGonagle, D. S. MacMillan, J. Murray, H. F. Sneddon, C. Jamieson and A. J. B. Watson, *Green Chem.*, 2013, **15**, 1159–1165.
- 14 K. Skowerski, J. Bialecki, A. Tracz and T. K. Olszewski, *Green Chem.*, 2014, **16**, 1125–1130.
- 15 P. Lei, Y. Mu, Y. Wang, Y. Wang, Z. Ma, J. Feng, X. Liu and M. Szostak, *ACS Sustainable Chem. Eng.*, 2021, **9**, 552–559.
- 16 S. Boobier, J. Heeley, T. Gärtner and J. D. Hirst, *ACS Sustainable Chem. Eng.*, 2025, **13**, 4349–4368.
- 17 E. Stampolaki, A. Mondello, E. Alladio, P. Oliveri, A. Mazzoleni, F. Pena-Pereira and E. Psillakis, *TrAC, Trends Anal. Chem.*, 2026, **194**, 118531.
- 18 F. Wang, M. Parhizkar, A. Harker and M. Edirisinghe, *J. Cleaner Prod.*, 2025, **530**, 146871.
- 19 S. Zapata-Boada, M. Gonzalez-Miquel, M. Jobson and R. M. Cuéllar-Franca, *ACS Sustainable Chem. Eng.*, 2022, **10**, 472–485.
- 20 T. Yamaki, T. T. H. Nguyen, N. Hara, S. Taniguchi and S. Kataoka, *Green Chem.*, 2024, **26**, 3758–3766.
- 21 Commission Recommendation (EU) 2026/510 of 6 March 2026 on revising the European assessment framework for safe and sustainable by design chemicals and materials, 2026, <https://data.europa.eu/eli/reco/2026/510/oj>.
- 22 C. Apel, A. Sudheshwar, K. Kümmerer, B. Nowack, K. Midander, E. Strömberg and L. G. Soeteman-Hernández, *RSC Sustainability*, 2024, **2**, 2833–2838.
- 23 L. G. Soeteman-Hernández, J. A. Tickner, A. Dierckx, K. Kümmerer, C. Apel and E. Strömberg, *RSC Sustainability*, 2025, **3**, 2185–2191.
- 24 C. Apel, K. Kümmerer, A. Sudheshwar, B. Nowack, C. Som, C. Colin, L. Walter, J. Breukelaar, M. Meeus, B. Ildefonso, D. Petrovykh, C. Elyahmadi, E. Huttunen-Saarivirta, A. Dierckx, A. C. Devic, E. Valsami-Jones, M. Brennan, C. Rocca, J. Scheper, E. Strömberg and L. G. Soeteman-Hernández, *Curr. Opin. Green Sustainable Chem.*, 2024, **45**, 100876.
- 25 Safe and Sustainable by Design (SSbD) Solvent Selection Guide (SSG) user interface, 2026, <https://jamesrsherwood.github.io/SSG/>.
- 26 GitHub Safe and Sustainable by Design (SSbD) Solvent Selection Guide (SSG) code and readme files, 2026, <https://github.com/jamesrsherwood/SSG>.
- 27 D. Mathieu, *ACS Omega*, 2018, **3**, 17049–17056.
- 28 N. Savic, J. Urbanus, O. Henschel, Q. Li, D. Marsh, C. Money, D. Noij, P. van de Sandt, J. van Rooij and M. Wormuth, *Ann. Work Exposures Health*, 2023, **67**, 496–507.
- 29 The GESTIS Column Model 2025: an aid to substitute assessment, 2025, <https://publikationen.dguv.de/widgets/pdf/download/article/3737>.
- 30 Z. Hussein, E. Benetto and M. Saidani, *Sustainable Prod. Consum.*, 2025, **60**, 64–77.

- 31 Candidate List of substances of very high concern for Authorisation, 2026, <https://www.echa.europa.eu/candidate-list-table>.
- 32 K. Mansouri, C. M. Grulke, R. S. Judson and A. J. Williams, *J. Cheminf.*, 2018, **10**, 10.
- 33 Y. Katrib, G. Deiber, P. Mirabel, S. L. Calvé, C. George, A. Mellouki and G. L. Bras, *J. Atmos. Chem.*, 2002, **43**, 151–174.
- 34 D. M. Day, T. J. Farmer, J. Granelli, J. H. Lofthouse, J. Lynch, C. R. McElroy, J. Sherwood, S. Shimizu and J. H. Clark, *Molecules*, 2022, **27**, 8427.
- 35 C. Mapelli, *Atmospheric chemistry of new 'green' solvents*, University of York, 2023, <https://etheses.whiterose.ac.uk/id/eprint/33968>.
- 36 J. Burés, *Angew. Chem., Int. Ed.*, 2016, **55**, 16084–16087.
- 37 F. Piccinno, R. Hischier, S. Seeger and C. Som, *J. Cleaner Prod.*, 2016, **135**, 1085–1097.
- 38 M. A. Ansar, R. van Zelm and A. M. J. Ragas, *ACS Sustainable Chem. Eng.*, 2025, **13**, 20363–20376.
- 39 C. Capello, U. Fischer and K. Hungerbühler, *Green Chem.*, 2007, **9**, 927–934.
- 40 N. Leroy-Parmentier, P. Loubet, M. Saint-Jean, N. Patouillard and G. Sonnemann, *ACS Sustainable Resour. Manage.*, 2024, **1**, 1548–1562.
- 41 Kartikey, D. Jaiswal, S. Singh, S. Jaiswal, M. Saquib, S. Singh, S. P. Verma, J. Singh and J. Singh, *J. Heterocycl. Chem.*, 2024, **61**, 1248–1260.
- 42 S. Maiti, P. T. Perumal and J. C. Menéndez, *Tetrahedron*, 2010, **66**, 9512–9518.
- 43 H. Struebing, Z. Ganase, P. G. Karamertzanis, E. Sioumkrou, P. Haycock, P. M. Piccione, A. Armstrong, A. Galindo and C. S. Adjiman, *Nat. Chem.*, 2013, **5**, 952–957.
- 44 J. C. Schleicher and A. M. Scurto, *Green Chem.*, 2009, **11**, 694–703.
- 45 B. Wahyudianto, T. Yamaki, N. Hara, Y. Takebayashi and S. Kataoka, *React. Chem. Eng.*, 2025, **10**, 311–319.
- 46 S. Viggiano, H. Peng, T. Romero, V. Papaefthimiou, M. L. Alfieri, L. Panzella, A. Napolitano and V. Ritleng, *Mol. Catal.*, 2026, **588**, 115540.
- 47 É. de Brito Sá and J. M. E. de Matos, *Inorg. Chim. Acta*, 2015, **426**, 20–28.
- 48 C. S. Adjiman, A. J. Clarke, G. Cooper and P. C. Taylor, *Chem. Commun.*, 2008, 2806–2808.
- 49 K. Skowerski, J. Bialecki, A. Tracz and T. K. Olszewski, *Green Chem.*, 2014, **16**, 1125–1130.
- 50 J. H. Clark, D. J. Macquarrie and J. Sherwood, *Green Chem.*, 2012, **14**, 90–93.
- 51 M. H. Abraham, *J. Chem. Soc. D*, 1969, **5**, 1307–1308.