Solvent selection guides

A number of solvent selection guides have been published with the purpose of promoting the uptake of more sustainable solvents. These guides give the user a quick method of identifying problematic solvents and subsequently recommending preferred alternatives. Whilst it is important to have a sound understanding of issues and the wider implications surrounding the solvents you use in your research, it is not necessarily practical to spend significant amounts of time analysing each individual substance. One of the advantages of using selection guides is that the data collection and analysis has already been performed. The individual ranking or grouping within the guides allows you to make an informed decision as to the most appropriate choice for your needs. Efforts have been made recently to consolidate and combine solvent guidance. A list of guides and other recommended reading can be found here.

Learning Objectives

By the end of this module you should:

- Understand why solvent selection guides have been developed within the pharmaceutical industry;
- Be aware of available solvent selection guides, and the discrepancies between them;
- Describe the criteria used in devising such guides, and the resulting benefits and limitations;
- Be able to use them in specific case studies;
- Be aware of specific guidance available for special classes of reaction.

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The need for solvent selection guides

In this video Helen Sneddon explains why guidance on solvent selection is needed.

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Transcript

Overwhelmingly, chemists look for precedent either in the literature, via search tools, or precedent on closely related molecules from in own projects, or precedent from their own experience.

When no precedent is available chemists commonly revert to a relatively narrow palette of common solvents.

This simple point is worth emphasizing, because just because a precedent exists in a given solvent, it is by no means a given that that solvent is the optimum choice for that process.

Given a reaction or purification unprecedented solvent, how then, might a chemist be encouraged to find a greener alternative?.

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Criteria for solvent selection

In this video Helen Sneddon describes the criteria used when selecting solvents.

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Transcript

The criterion to generally consider when assessing the environmental credentials of the solvent include: the carbon footprint of the solvent, biodegradability of that solvent, its solubility in water; as solvents that are immiscible with water are less likely to contaminate aqueous waste streams, whether a solvent gives rise to Volatile Organic Compounds, or VOCs.

Solvents with higher boiling points are less like to have this issue.

Whether the solvent is easy to recycle and whether the solvent is produced from renewable feedstock.

Additionally, safety criteria can be incorporated including a solvent's stability, flammability (or flashpoint) and toxicity.

It is also useful to consider legislative issues, such as whether a solvent is a category 1A or 1B carcinogen, mutagen or reprotoxic solvent, or whether it is a solvent known to deplete the ozone layer.

There is no universal approach to solvent selection.

The solvent which has the best sustainability credentials for one application, where recyclability, or avoiding contamination of an aqueous waste stream is paramount may not be appropriate choice for another use; where avoiding VOCs, or a requirement for a compatibility with aqueous media may be a priority.

Accordingly, in addition to providing at-a-glance guidance, solvent guides should seek to explain the rationale behind the ranking of different solvents.

Providing chemists with the information they need to make the right choice for a given task..

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Multiple choice question

1. Which of the following criteria would generally not be considered when assessing a solvent's green credentials?
    1. Reactivity / stability
    2. Flammability / flashpoint
    3. Boiling point
    4. pH
    5. Whether it could give rise to VOCs
    6. Whether the solvent is a 1a/1b carcinogen
    7. Biodegradability
    8. Produced from renewable feedstocks
    9. Molecular weight
    10. Carbon footprint

Answers on last page

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In-house solvent selection guides

A large number of solvent selection guides are available in the literature and have been developed in-house by a number of pharmaceutical companies including GlaxoSmithKline, Pfizer (who have also produced a freely-available printable poster), Sanofi and Astra Zeneca. [1] [2] [3] [4]. The ACS GCI PR has also produced an industry-wide solvent selection guide, which is also available as a free application for mobile phones.

Although there are a number of solvents where strong correlations in classification exist between the different guides, there are a number of discrepancies. The varying needs and priorities of individual businesses will have direct influence over the exact rankings of solvents. The CHEM21 project has undertaken a survey of these guides to compile the data, analyse and understand the differences therein and have subsequently published a combined guide. [5]

[6]

1. C. M. Alder, J. D. Hayler, R. K. Henderson, A. M. Redman, L. Shukla, L. E. Shuster and H. F. Sneddon, Updating and further expanding GSK's solvent sustainability guide, *Green Chem.*, 2016.
2. K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, P. H. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation, *Green Chem.*, 2008, **10**, 31-36.
3. D. Prat, O. Pardigon, H. - W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani and P. Hosek, Sanofi's Solvent Selection Guide: A Step Toward More Sustainable Processes, *Org. Process Res. Dev.*, 2013, **17**, 1517-1525.
4. L. J. Diorazio, D. R. J. Hose and N. K. Adlington, Toward a More Holistic Framework for Solvent Selection, *Org. Process Res. Dev.*, 2016, **20**, 760-773.
5. D. Prat, J. Hayler and A. Wells, A survey of solvent selection guides, *Green Chem.*, 2014, **16**, 4546-4551.
6. Unknown reference.

Example: GSK solvent selection guide

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In this video, Helen Sneddon talks us through the general GSK solvent selection guide.[1]

1. C. M. Alder, J. D. Hayler, R. K. Henderson, A. M. Redman, L. Shukla, L. E. Shuster and H. F. Sneddon, Updating and further expanding GSK's solvent sustainability guide, *Green Chem.*, 2016.

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Example: Sanofi solvent selection guide

In this video, Denis Prat talks us through the Sanofi solvent selection guide.[1].

1. D. Prat, O. Pardigon, H. - W. Flemming, S. Letestu, V. Ducandas, P. Isnard, E. Guntrum, T. Senac, S. Ruisseau, P. Cruciani and P. Hosek, Sanofi's Solvent Selection Guide: A Step Toward More Sustainable Processes, *Org. Process Res. Dev.*, 2013, **17**, 1517-1525.

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Multiple choice question

1. Which of the following statements are not true?
    1. Solvent guides are designed to provide a 'one size fits all' solution to solvent selection
    2. Stability of solvents is a factor when designing solvent guides because less stable solvents tend to produce lower yields: they are more likely to create byproducts
    3. Health and safety factors are important when designing solvent guides

Answers on last page

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Survey of solvent selection guides

In the previous lesson differences in structure and weighting of HSE criteria in published solvent selection guides were discussed. Initial work carried out by the CHEM21 project included building a methodology to compare the 5 guides available (AZ, GCI-PR, GSK, Pfizer, Sanofi). This methodology, explained in the video, consists of a comparison of the rankings (colour codes) of the 51 more represented solvents in these guides. For guides which did not offer a clear ranking (AZ, GSK, GCI-PR), the number of criteria was reduced to three: one for Safety, one for Health, one for Environment. For each guide, three solvent groups of similar size were built around the arithmetical mean, with a classical colour code (green, yellow, red). It was thus easy to compare the colour code of each solvent in the different guides (Table 1).

Table 1 is extracted from D. Prat, J. Hayler and A. Wells, A survey of solvent selection guides, *Green Chem.*, 2014, **16**, 4546-4551..

Table 1: Ranking comparison (extract)

Family	Solvent	AZ	GCI-PR	GSK	Pfizer	Sanofi	Overall*
Alcohols	MeOH	19	14	14	Preferred	Recommended	TBC
	EtOH	16	13	17	Preferred	Recommended	Recommended
	i -PrOH	16	16	17	Preferred	Recommended	Recommended
	n -BuOH	17	13	18	Preferred	Recommended	Recommended
	t -BuOH	20	15	15	Preferred	Subst. advisable	TBC

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Family	Solvent	AZ	GCI-PR	GSK	Pfizer	Sanofi	Overall*
	Benzyl alcohol	-	11	20	-	Subst. advisable	TBC
	Ethylene glycol	-	13	21	Usable	Subst. advisable	TBC
Ketones	Acetone	21	15	15	Preferred	Recommended	TBC
	MEK	21	16	15	Preferred	Recommended	TBC
	MIBK	22	17	15	-	Recommended	TBC
	Cyclohexanone	-	14	20	-	Subst. advisable	TBC
Ethers	Diethyl ether	27	21	3	Undesirable	Banned	Highly Hazardous
	Diisopropyl ether	-	-	4	Undesirable	Subst. advisable	Hazardous
	MTBE	24	21	4	Usable	Subst. advisable	TBC
	THF	23	16	4	Usable	Subst. advisable	TBC
	Me-THF	24	15	11	Usable	Recommended	Problematic
	1,4-dioxane	28	21	11	Undesirable	Subst. requested	Hazardous
	Anisole	18	13	18	-	Recommended	Recommended
	DME	21	23	2	Undesirable	Subst. requested	Hazardous

This colour code comparison gave a clear agreement (large majority) for 34 of the 51 solvents (two thirds of solvents overall). Further discussion permitted the identification of

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the most hazardous solvents. One third of solvents could not be ranked (named “to be confirmed” in Table 1), thus reflecting the different weighting of criteria in the solvent guides [1] . The overall list is given in Table 2.

Table 2 is reproduced from D. Prat, J. Hayler and A. Wells, A survey of solvent selection guides, *Green Chem.*, 2014, **16**, 4546-4551..

Table 2: Overall ranking of solvents

Combined ranking	Solvent
Recommended	Water, EtOH, *i* -PrOH, *n* -BuOH, EtOAc, *i* -PrOAc, *n* -BuOAc, anisole, sulfolane.
Recommended or problematic?	MeOH, *t* -BuOH, benzyl alcohol, ethylene glycol, acetone, MEK, MIBK, cyclohexanone, MeOAc, AcOH, Ac_2O.
Problematic	Me-THF, heptane, Me-cyclohexane, toluene, xylenes, chlorobenzene, acetonitrile, DMPU, DMSO.
Problematic or hazardous?	MTBE, THF, cyclohexane, DCM, formic acid, pyridine.
Hazardous	Diisopropyl ether, 1,4-dioxane, DME, pentane, hexane, DMF, DMAc, NMP, methoxy-ethanol, TEA.
Highly hazardous	Diethyl ether, benzene, chloroform, CCl_4, DCE, nitromethane.

1. D. Prat, J. Hayler and A. Wells, A survey of solvent selection guides, *Green Chem.*, 2014, **16**, 4546–4551.

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Transcript

Survey of solvent selection guides.

As explained in the previous sections, there is no clear definition of solvent greenness.

This is why solvent selection guides have been elaborated by pharma companies or institutions, in order to help their chemists in their choice.

The assessments are based on occupational health, safety and environment criteria but also on other constraints: industrial issues, ICH levels, cost, regulations and so on.

A solvent guide reflects the policy of its company or institution, hence there are different structures, wording and weighing of criteria.

In order to compare the different guides we have built a methodology and established a level of convergence for the ranking of classical solvents.

The comparison of the public solvent guides is not easy at all.

Pfizer and Sanofi guides give clear rankings of solvents, but the wording and number of levels is not the same.

Astra Zeneca and the (ACS GCI) Pharma Roundtable guides are similar.

They do not give a clear ranking and they score the criteria from 1 to 10; but the numbers of criteria are different.

GSK guide is also similar, but more complex with legislation and EHS flags; moreover the scoring order is opposite to this of the former guides.

The survey of solvent guides was made on the 51 more represented solvents.

In order to facilitate a comparison the number of criteria in each guide was reduced to 3: one for safety, one for environment and one for health.

Let's take the Pharma Roundtable guide as an example.

It has one health, one safety and three environment criteria, each scored from one to ten.

The health and safety scores are unchanged but one needs to combine the three environment criteria.

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For this global criterion, the score will be the highest, that is to say, the worst of the three original environment scores.

For ethanol, 6; for [?? methanol ??] 7; and for hexane, 8.

Each guide has now only three global criteria.

Let's continue with the Pharma Roundtable guide.

On the whole, scoring can be given from the HSE scores, based on their sum.

For ethanol: three plus 4 plus 6 gives 13.

For the ranking one calculates the arithmetical mean; here 16.

3 solvent groups of similar size are built around this mean with a classical 3 colour code: green, yellow and red.

The scoring comparison is now very easy.

The figures do not matter; now the ranking wording on these colours matters.

If there is a large majority, the overall ranking is clear.

Recommended, problematic, hazardous.

If not the ranking is to be confirmed.

Either between recommended and problematic, or between problematic and hazardous.

The least desirable solvents are ranked as highly hazardous.

In order to align with regulations we have integrated additional criteria based on CLP hazard statements.

If a solvent is hazardous for the ozone layer, statement 420, the solvent is ranked as highly hazardous.

If the solvent is carcinogenic of category 1 it is also ranked as highly hazardous.

If the solvent is reprotoxic of category 1 it is at least ranked as hazardous.

One ends up with this table in which two-thirds of solvents have a clear ranking: recommended problematic, hazardous or highly hazardous.

The other solvents are in between.

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This work has been published in Green Chemistry in 2014.

In conclusion a large majority of solvents are unambiguously ranked by most solvent guides.

Regulation constraints help flagging the hazardous solvents.

One-third of the solvents could not be ranked by this methodology.

This reflects a different perception and weighing of criteria in the guides.

Debate between experts are needed to establish some rankings; in particular for the borderline solvents, or to flag a solvent as highly hazardous.

In the next section, we will present the CHEM21 solvent selection guide, which was elaborated to rank these borderline solvents..

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The CHEM21 solvent selection guide

In this video Denis Prat explains the work of the CHEM21 consortium in developing its own solvent selection guide of classical and less-classical (including bio-derived) solvents, including its formulation and scope.

This work is also published as an open access article[1] alongside an associated Excel spreadsheet (in the supplementary data) that will enable the user to rank a solvent not included in the list according to the guidelines outlined in the publication.

Furthermore, the spreadsheet has now been adapted into an interactive tool for the platform.

1. D. Prat, A. Wells, J. Hayler, Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, CHEM21 selection guide of classical- and less classical-solvents, *Green Chem.*, 2016, **18**, 288–296.

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Transcript

Many solvents have been presented as 'green' but none of them is really, fully green.

The solvent desirability is influenced by many criteria which, sometimes, are contradictory.

Occupational health, safety environment; which concerns air, water and carbon footprint; industrial issues linked with boiling point, cost, procurement and other constraints.

Besides, greenness depends on the application.

Criteria for a solvent for paint stripping are not the same as for chemical synthesis.

This is why some pharma companies have elaborate solvent guides in order to help chemists in the selection of the most desirable solvents.

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These guides reflect the policy of the company or institution, based on the local constraints, the accidents and their culture.

Not surprisingly they differ by their structure and relative way of criteria.

As part of the Work Package 1 of Chem21 project, we made a survey of solvent selection guides and propose a methodology to establish and compare the ranking of solvents and presented it in the module entitled 'Survey of Solvent Selection Guides.' A combination of HRC criteria for each guide gives a figure and a colour code for the three guides which did not give a clear overall ranking.

And a comparison of the colors for each solvent shows the degree of convergence between these guides.

According to the survey, 67% of the 51 solvents considered are scored with low level of ambiguity as Recommended, Problematic, Hazardous or Highly Hazardous.

This has been published in Green Chemistry 2014.

The glass can be seen as 2/3 full or 1/3 empty.

1/3 of solvent could not be ranked by this simplified system.

This is not very surprising as these borderline solvents are often green with respect to one criterion and not for the others.

This also reflects the different perceptions and culture of the institutions.

For the elaboration of Chem21 solvent guide, we needed a methodology permitting a ranking as intermediate solvents.

This methodology should work with a 67 percent of solvents having a clear ranking, and should also be able to give a greenness assessment of any solvent, in particular, bio-derived solvents.

The methodology we elaborated is quite simple and based on GHS statements and some physical data which can be collected from any Safety Data Sheet.

Like for the solvent guides survey, we elaborated one safety, one health and one environment score.

Each from one for the best stead to the worse and we associated a colour-code.

1-3, green, 4-6, yellow, 7-10 red.

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The 'Data Incomplete' corresponding score is 5.

The solvent ranking by default is obtained by simply counting the Safety, Health and Environmental score.

One score greater or equal to 8 or two scores greater or equal to 7 flags a solvent as 'Hazardous'.

One score equal to 7 scores the solvent as 'Problematic' as well as as two scores between 4 and 6.

In other cases, the solvent is considered 'Recommended'.

How does it work? The first task is to collect some data.

Boiling point, flash point, auto-ignition temperature and the GHS statements from the Safety Data Sheets.

Note that the GHS statements may vary depending on the supplier.

In these cases, the advice of an occupational hazards list is useful.

The safety score is mainly based on the flash point, with the same limits as GHS statements, but we define a distinction when the flashpoint is lower than 22 degrees C.

Increments are added for each of the following properties: Auto-ignition temperature lower than 200 degrees C, high resistivity, ability to form explosive peroxides.

For example, diethyl ether, with a flashpoint of minus 45 degrees C, has a basic safety score of 7, but as its auto-ignition temperature is 160 degrees, as it is resistive and forms hazardous peroxides, its final safety score is 10.

The health score derives from the most stringent H300 statements according to this table.

This earmarks solvents of category 1A or 1B are scored 9 and this earmark of category 2, such as dichloromethane and THF, are scored 6.

1 is added to this score if the boiling point is lower than 85 degrees C to take into account the highest occupational risk of more volatile solvents.

For benzene or dichloroethane, one ends up with 10.

The environment score is very qualitative.

It is based of on both the GHS H400 statements and the boiling point.

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Boiling point lower than 50 degrees C or higher than 200 degrees C gives a score of 7, as well as H400, H410 or H411 statements.

For example, diethyl ether is ranked seven because of its low boiling point and heptane is ranked seven because of its eco-toxicity.

Let us apply ranking methodology with a safety, health and environmental score in hand, the ranking, by default, is immediately obtained.

Ethyl acetate, with only one score of 5, is Recommended.

Methyl THF, with two scores between 4 and 6, is Problematic.

Pentane, with one score of 8, is Hazardous.

In this system we didn't make this distinction between Hazardous or Highly Hazardous, but solvents with one score of 10 are always Highly Hazardous according to the survey.

The University of York has developed an Excel tool, which is available in the training package, and which helps you to score any solvent.

All you have to do is to enter the solvent name, the physical data, and put a word in each column corresponding to the relevant H-statements.

The tool gives you the HSE scorings as well as your overall ranking by default.

For the solvents which had a clear ranking according to the survey, the ranking obtained by this system is the same for 81% of solvents, which is more than acceptable.

In some cases, such as dioxane, the ranking by default is less severe.

For anisole, it is more severe.

As the ranking within the regime model is varied, it can be used to predict the desirability of any solvent.

We used it first for the solvents which didn't have a clear ranking after the survey, then for bio-derived solvents and newer solvents, like the ethers proposed to substitute methyl tert-butyl ether.

The intermediates solvents were not easy to rank because of their unclear balance between advantages and hazards.

In some cases we did not agree with the rankings given by the simplified system.

For example, methanol is ranked as problematic by default because of its alarming

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health statements and relatively low boiling point.

But as its occupation limit values are relatively high and as it is really biodegradable we decided to rank it as 'Recommended'.

On the other hand, pyridine was ranked by default as Recommended, but as its occupational limit values are very low, we decided to rank it as hazardous.

Thus, the simplified method has its limits and debate associating chemists and occupational hygienists is needed to give definitive rankings.

For bio-derived solvents we accepted the rankings by default.

As shown in this table, many of the solvents appear as problematic as a result of their high boiling point giving an environment score of seven, such as 1,3 propane diol, glycerol or ethylene carbonate.

In the case of p-cymene, the lack of the data also results ranking by default of Problematic.

This illustrates the current difficulty to integrate these solvents in chemical processes.

In conclusion this guide is based on a survey of published solvent guides and comprises a methodology able to rank any solvent.

This system uses easily available physical data and GHS hazard statements given in the rich dossier and is aligned with the European regulations.

This methodology is not perfect.

The health ranking should be better based on the occupation evaluation limits debates, but they are not always available and not unified even in Europe.

The environment criteria should include the impact of the solvent synthesis in terms of carbon footprint, and accumulated energy demand.

Beside which, dossiers are often incomplete.

This is where a discussion with experts is needed to give a definitive ranking.

This work has been published in 2015 in Green Chemistry.

This methodology offer other perspectives.

The Chem21 Solvent Guide has been designed for the pharma chemical industry, but the field of green chemistry is wider and solvent guides are needed for other applications

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with different criteria weight.

Our system can easily be modified to fit with other constraints or requirement.

For example, for coatings or solvents for paint stripping, the flashpoint weighing will be more severe and the environment criteria will favor hi boiling solvents, such as many bio-derived solvents..

Methodology

The tables on this page are reproduced from from D. Prat, A. Wells, J. Hayler, Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, CHEM21 selection guide of classical- and less classical-solvents, *Green Chem.*, 2016, **18**, 288–296..

After the survey of existing solvent guides[1], the CHEM21 solvent team elaborated a methodology, based on easily available physical properties and GHS statements, permitting anyone to establish safety, health and environment criteria of any solvent, even if full data on the solvents are not yet available.[2] A simple way to obtain a preliminary ranking of the solvent (so-called “ranking by default”) was also proposed, based on a combination of these SHE criteria. The methodology was tested on the classical solvents having a clear ranking according to the survey, with a fair predictivity of 81%.

The SHE criteria are scored from 1 to 10, the highest figure representing the highest hazard level. A colour code is associated with these scores: 1 to 3: green, 4 to 6: yellow, 7 to 10: red.

The safety score derives mainly from the flash point, with contributions of the auto-ignition temperature (AIT), the resistivity and the ability to form explosive peroxides (statement EUH019 in GHS/CLP) (Table 1).

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Table 1: Safety score					
Basic Safety score	**1**	**3**	**4**	**5**	**7**
Flash Point (°C)	> 60	23 to 60	22 to 0	-1 to -20	< -20
GHS	-	H226 	H225 or H224 		

1 is added to the safety score for each of the following properties:

- AIT < 200°C
- Resistivity > 10 8 ohm.m
- Ability to form peroxides (EUH019)

Any solvent with a high energy of decomposition (> 500 J/g), like nitromethane, would be scored 10.

As an example, the safety score of diethyl ether, with a FP of – 45°C, an AIT of 160°C, a resistivity of 3.10 11 ohm.m and an EUH019 statement is 7+1+1+1=10.

The health score derives mainly from the most stringent GHS H3xx statements, with a contribution of the boiling point, according to Table 2.

Table 2: Health score					
Health score	**2**	**4**	**6**	**7**	**9**
CMR			H341 H351 H361 (CMR cat. 2) 		H340 H350 H360 (CMR cat. 1) 
STOT	H304 H371 H373 	H334 	H370 H372 		

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Health score	2	4	6	7	9
Acute toxicity	H302 H312 H332 H336 EUH070 		H301 H311 H331 		H300 H310 H330 
Irritation	H315 H317 H319 H335 EUH066 	H318 		H314 	

CMR: carcinogen, mutagen or reprotoxic; STOT: single target organ toxicity

1 is added to this score if the boiling point is <85°C

If, after full REACH registration, there is no H3xx statement, the health score is 1. The score of newer solvents for which the REACH registration is not complete is 5 if the boiling point is 85°C or higher, otherwise, 6, unless a more stringent H3xx is attributed by the supplier.

The environment score takes into account both the volatility of the solvent (ability to form Volatile Organic Compounds) and the energy demand for recycling. Both are linked to the boiling point. The GHS 4xx statements are also important (Table 3). The environment score is based on the most stringent of these factors. For example, the score of 7 for heptane is due to its H410 statement, whereas the score of 7 for dichloromethane is as a result of its low boiling point.

Table 3: Environment score

Environment score	3	5	7	10

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Environment score	3	5	7	10
BP (°C)	70-139	50-69 140-200	<50 >200	
GHS/CLP	No H4xx after full REACh registration	H412, H413 	H400, H410, H411 	EUH420 (ozone layer hazard)
Other		No, or partial REACh registration		
		Water score= 1		

If the REACh registration is not full and no H4xx has been attributed by the supplier, the environment score is 5 by default.

These S, H & E scores are combined according to Table 4 to give an overall scoring of the solvent. The ranking is imposed by the most stringent combination.

Table 4: Ranking by default

Score combination	Ranking by default
One score ≥ 8	Hazardous
Two "red" scores	Hazardous
One score =7	Problematic
Two "yellow" scores	Problematic

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Score combination	Ranking by default
Other	Recommended

The ranking by default does not make the distinction between “hazardous” and “highly hazardous”. The decision to “ban” a solvent necessitates discussion at an organisational level. It is important to remember that the ranking methodology is only a model that gives a ranking by default and this should be critically assessed by occupational hygienists and other experts of any institution using it. For example, the scoring of chloroform as only “problematic” or of pyridine as “recommended” are not acceptable. This illustrates the limits of a health scoring system only based on GHS hazard statements. As the Occupational Threshold Limits of these solvents are available and very low (ppm range), CHEM21 finally ranked them as, respectively, “highly hazardous” and “hazardous”. Other decisions are more the result of the policy of the institution. CHEM21 finally decided to rank methanol and acetone as “recommended”, and on the contrary, cyclohexanone as “problematic”, for reasons which will not be debated here.

1. D. Prat, J. Hayler and A. Wells, A survey of solvent selection guides, *Green Chem.*, 2014, **16**, 4546-4551.
2. D. Prat, A. Wells, J. Hayler, Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, CHEM21 selection guide of classical- and less classical-solvents, *Green Chem.*, 2016, **18**, 288–296.

Solvent tables

The tables on this page are reproduced from from D. Prat, A. Wells, J. Hayler, Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn, CHEM21 selection guide of classical- and less classical-solvents, *Green Chem.*, 2016, **18**, 288–296..

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Table 1: CHEM21 solvent guide: ethers, hydrocarbons, halogenated											
Family	**Solvent**	**CAS**	**BP (°C)**	**FP (°C)**	**Worst H3xx***	**H4xxvel**	**Safety score**	**Health score**	**Env. score**	**Ranking by default**	**Ranking after discussion #**
Water	Water		100	na	none	none	1	1	1	Recommended	Recommended
Alcohols	MeOH	67-56-1	65	11	H301	none	4	7	5	Problematic	Recommended
	EtOH	64-17-5	78	13	H319	none	4	3	3	Recommended	Recommended
	n -PrOH	71-23-8	97	15	H318	none	4	4	3	Problematic	Problematic
	i -PrOH	67-63-0	82	12	H319	none	4	3	3	Recommended	Recommended
	n -BuOH	71-36-3	118	29	H318	none	3	4	3	Recommended	Recommended
	i -Butanol	78-83-1	107	28	H318	none	3	4	3	Recommended	Recommended
	t -BuOH	75-65-0	82	11	H319	none	4	3	3	Recommended	Recommended
	i -Amyl alcohol	123-51-3	131	43	H315	none	3	2	3	Recommended	Recommended
	Benzyl alcohol	100-51-6	206	101	H302	none	1	2	7	Problematic	Problematic

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Family	Solvent	CAS	BP (°C)	FP (°C)	Worst H3xx*	H4xxvel	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion #
	Ethylene glycol	107-21-1	198	116	H302	none	1	2	5	Recommended	Recommended
	1, 3-Propane diol	504-63-2	214	140	none	none	1	1	7	Problematic	Problematic
	Glycerol	56-81-5	290	177	none	none	1	1	7	Problematic	Problematic
Ketones	Acetone	67-64-1	56	-18	H319	none	5	3	5	Problematic	Recommended
	MEK	78-93-3	80	-6	H319	none	5	3	3	Recommended	Recommended
	MIBK	108-10-1	117	13	H319	none	4	2	3	Recommended	Recommended
	Cyclohexanone	108-94-1	156	43	H332	none	3	2	5	Recommended	Problematic
	Methyl acetate	70-20-9	57	-10	H302	none	5	3	5	Problematic	Problematic
	Ethyl acetate	141-78-6	77	-4	H319	none	5	3	3	Recommended	Recommended
	n -PrOAc	109-60-4	102	14	H319	none	4	2	3	Recommended	Recommended

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Family	Solvent	CAS	BP (°C)	FP (°C)	Worst H3xx*	H4xxvel	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion #
Esters	*i* -PrOAc	108-21-4	89	2	H319	none	4	2	3	Recommended	Recommended
	n -BuOAc	123-86-4	126	22	H336	none	4	2	3	Recommended	Recommended
	i -Butyl acetate	110-19-0	115	22	H336	none	4	2	3	Recommended	Recommended
	i -Amyl acetate	123-92-2	142	25	none	none	3	1	5	Recommended	Recommended
	γ-Valerolactone	108-29-2	207	100	n.a.	n.a.	1	5	7	Problematic	Problematic
	Glycol diacetate	111-55-7	186	82	none	none	1	1	5	Recommended	Recommended
	Diethyl succinate	123-25-1	218	91	n.a.	n.a.	1	5	7	Problematic	Problematic
	* Only the highest scoring statements are shown. The lowest figure is given when there are more than one statement in the highest scoring category, for the sake of simplicity;										

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Table 1: CHEM21 solvent guide: ethers, hydrocarbons, halogenated											
Family	**Solvent**	**CAS**	**BP (°C)**	**FP (°C)**	**Worst H3xx***	**H4xx**	**Safety score**	**Health score**	**Env. score**	**Ranking by default**	**Ranking after discussion #**
Ethers	Diethyl ether	60-29-7	34	-45	H302	none	10	3	7	Hazardous	Highly hazardous
	Diisopropyl ether	108-20-3	69	-28	H336	none	9	3	5	Hazardous	Hazardous
	MTBE	1634-04-4	55	-28	H315	none	8	3	5	Hazardous	Hazardous
	ETBE	637-92-3	72	-19	H336	none	7	3	3	Problematic	Problematic
	TAME	994-05-8	86	-7	H302	none	6	2	3	Recommended	Recommended
	CPME	5614-37-9	106	-1	H302	H412	7	2	5	Problematic	Problematic
	THF	109-99-9	66	-14	H351	none	6	7	5	Problematic	Problematic
	Me-THF	96-47-9	80	-11	H318	none	6	5	3	Problematic	Problematic
	1,4-Dioxane	123-91-1	101	12	H351	none	7	6	3	Problematic	Hazardous
	Anisole	100-66-3	154	52	none	none	4	1	5	Problematic	Recommended

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Family	Solvent	CAS	BP (°C)	FP (°C)	Worst H3xx*	H4xx	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion #
	DME	110-71-4	85	-6	H360	none	7	9	3	Hazardous	Hazardous
Hydrocarbons	Pentane	109-66-0	36	-40	H304	H411	8	3	7	Hazardous	Hazardous
	Hexane	110-54-3	69	-22	H361	H411	8	7	7	Hazardous	Hazardous
	Heptane	142-82-5	98	-4	H304	H410	6	2	7	Problematic	Problematic
	Cyclohexane	110-82-7	81	-17	H304	H410	6	3	7	Problematic	Problematic
	Me-Cyclohexane	108-87-2	101	-4	H304	H411	6	2	7	Problematic	Problematic
	Benzene	71-43-2	80	-11	H350	none	6	10	3	Hazardous	Highly hazardous
	Toluene	108-88-3	111	4	H351	none	5	6	3	Problematic	Problematic
	Xylenes	1330-20-7	140	27	H312	none	4	2	5	Problematic	Problematic
	D-Limonene	5989-27-5	175	49	H304	H400	4	2	7	Problematic	Problematic

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Family	Solvent	CAS	BP (°C)	FP (°C)	Worst H3xx*	H4xx	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion #
	Turpentine	8006-64-2	166	38	H302	H411	4	2	7	Problematic	Problematic
	p-Cymene	99-87-6	177	27	n.a.	n.a.	4	5	5	Problematic	Problematic
Halogenated	DCM	75-09-2	40	na	H351	none	1	7	7	Hazardous	Hazardous
	Chloroform	67-66-3	61	na	H351	none	2	7	5	Problematic	Highly hazardous
	CCl_4	56-23-5	77	na	H351	H420	2	7	10	Hazardous	Highly hazardous
	DCE	107-06-2	84	13	H350	none	4	10	3	Hazardous	Highly hazardous
	Chlorobenzene	108-90-7	132	29	H332	H411	3	2	7	Problematic	Problematic

* Only the highest scoring statements are shown. The lowest figure is given when there are more than one statement in the highest scoring category, for the sake of simplicity;

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Table 2: CHEM21 solvent guide: other solvents.											
Family	**Solvent**	**CAS**	**BP (°C)**	**FP (°C)**	**Worst H3xx***	**H4xx**	**Safety score**	**Health score**	**Env. score**	**Ranking by default**	**Ranking after discussion #**
	Acetonitrile	75-05-8	82	2	H319	none	4	3	3	Recommended	Problematic
	DMF	68-12-2	153	58	H360	none	3	9	5	Hazardous	Hazardous
	DMAc	127-19-5	166	70	H360	none	1	9	5	Hazardous	Hazardous
	NMP	872-50-4	202	96	H360	none	1	9	7	Hazardous	Hazardous
	DMPU	7226-23-5	246	121	H361	none	1	6	7	Problematic	Problematic
	DMSO	67-68-5	189	95	none	none	1	1	5	Recommended	Problematic
	Sulfolane	126-33-0	287	177	H360	none	1	9	7	Hazardous	Hazardous
Aprotic polar	Dimethyl carbonate	616-38-6	90	16	none	none	4	1	3	Recommended	Recommended
	Ethylene carbonate	96-49-1	248	143	H302	none	1	2	7	Problematic	Problematic
	Propylene carbonate	108-32-7	242	132	H319	none	1	2	7	Problematic	Problematic

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Family	Solvent	CAS	BP (°C)	FP (°C)	Worst H3xx*	H4xx	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion #
	Cyrene	53716-82-8	203	61	H319	none	1	2	7	Problematic	Problematic
	HMPA	680-31-9	>200	144	H350	none	1	9	7	Hazardous	Highly hazardous
	Nitromethane	75-52-5	101	35	H302	none	10	2	3	Hazardous	Highly hazardous
Acids	Formic acid	64-18-6	101	49	H314	none	3	7	3	Problematic	Problematic
	Acetic acid	67-19-7	118	39	H314	none	3	7	3	Problematic	Problematic
	Ac_2O	108-24-7	139	49	H314	none	3	7	3	Problematic	Problematic
Amines	Pyridine	110-86-1	115	23	H302	none	3	2	3	Recommended	Hazardous
	TEA	121-44-8	89	-6	H314	none	6	7	3	Problematic	Hazardous

* Only the highest scoring statements are shown. The lowest figure is given when there are more than one statement in the highest scoring category, for the sake of simplicity.

	Methoxy-ethanol	109-86-4	125	42	H360	none	3	9	3	Hazardous	Hazardous

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Family	Solvent	CAS	BP (°C)	FP (°C)	Worst H3xx*	H4xx	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion #
Miscellaneous	Ethyl L-lactate	687-47-8	155	47	H318	none	3	4	5	Problematic	Problematic
	Lactic acid	50-21-5	230	113	H318	none	1	4	7	Problematic	Problematic
	TH-furfuryl alcohol	97-99-4	178	75	H360	none	1	9	5	Hazardous	Hazardous
	Carbon disulfide	75-15-0	46	-30	H361	H412	9	7	7	Hazardous	Highly hazardous

Interactive tool: solvent ranking

For the solvent you are assessing, complete the information one question at a time below. When you get to the end, the tool will calculate the scores and overall ranking by default for the solvent.

As a reminder, to rank the solvent you will need access to the following information:

- Boiling point, flash point, auto-ignition temperature, resistivity;
- Whether or not it is an ether that forms explosive peroxides;
- GHS statements and symbols;
- Whether or not it is hazardous to the ozone layer; and
- Whether or not it is fully registered for REACH.

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Solvent guides for specific applications

In this video Helen Sneddon describes guidance available for work-ups, chromatography and some specific types of reaction (amide formation and reductive amination).

» View on YouTube
» Download

Transcript

For purification, eluotropic series can be particularly useful.

The example shown towards the top-right of the screen here is based on eluotropic series published in 1964 and it shows which solvent combinations are equivalent in polarity to which other combinations.

It can therefore be used in combination with a guide to the sustainability of different solvents to choose better chromatography eluent mixtures.

A more focused extension is this shown towards the bottom of the slide where an eluotropic series published by Amgen 2012 shows alternatives to the ones on the present on the dichloromethane/methanol gradient, with different options provided for acidic, basic or neutral molecules.

Sometimes, for a simple process, such as separation of aqueous and organic phases, other tools, such as use of hydrophobic threads can be recommended.

In this case, separations of arrays of compounds, with solvent such as ethyl acetate or 2-methyl THF, can be encouraged rather than separations of those same arrays with dichloromethane in the aqueous phase.

Sometimes, data can be provided as to which solvents work well with which substrate types and even which reagents for certain common transformations.

These grids show that amide formation, for all common substrate types, and a wide range of reagents work well in dimethyl carbonate and ethyl acetate.

And most common reductive aminations work well in ethyl acetate and 2-methy THF..

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Chromatography guides

Amgen have created a chromatography guide for selecting a solvent/eluent mix to replace DCM/MeOH mixtures [1].

Derived from a screened set of drug-like molecules with a range of differing functionalities and physicochemical parameters, the charts allow solvents mixtures with similar eluting strengths to be identified.

For further reading, the ACS GCI PR have published a highly recommended review article on sustainable chromatography [2]

1. J. P. Taygerly, L. M. Miller, A. Yee and E. A. Peterson, A convenient guide to help select replacement solvents for dichloromethane in chromatography, *Green Chem.*, 2012, **14**, 3020-3025.
2. E. A. Peterson, B. Dillon, I. Raheem, P. Richardson, D. Richter, R. Schmidt and H. F. Sneddon, Sustainable chromatography (an oxymoron?), *Green Chem.*, 2014, **16**, 4060-4075.

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Summary and further reading

Solvent selection guides are widely available and can be readily integrated into everyday practice to improve the environmental acceptability of, for example, our reactions, work-ups and purifications.

It is however worth bearing in mind the limitations of such guides and a more in depth look at solvents, including factors to be taken into consideration when selecting a solvent, issues surrounding the use of solvents and solvent replacement strategies are covered in Solvents.

Links to Guides and Recommended reading:

D. Prat, A. Wells, J. Hayler, Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunn , CHEM21 selection guide of classical- and less classical-solvents, *Green Chem.*, 2016, **18**, 288–296.

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L. J. Diorazio, D. R. J. Hose and N. K. Adlington, Toward a More Holistic Framework for Solvent Selection, *Org. Process Res. Dev.*, 2016, **20**, 760-773.

J. P. Taygerly, L. M. Miller, A. Yee and E. A. Peterson, A convenient guide to help select replacement solvents for dichloromethane in chromatography, *Green Chem.*, 2012, **14**,

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3020-3025.

D. S. MacMillan, J. Murray, H. F. Sneddon, C. Jamieson and A. J. B. Watson, Replacement of dichloromethane within chromatographic purification: a guide to alternative solvents, *Green Chem.*, 2012, **14**, 3016-3019.

J. H. Clark, A. J. Hunt, L. Moity and J. Sherwood, Renewable Solvent Selection in Medicinal Chemistry, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, The Royal Society of Chemistry, 2016, ch. 3, pp. 28-40.

H. F. Sneddon, Tools for Facilitating More Sustainable Medicinal Chemistry, in *Green and Sustainable Medicinal Chemistry : Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, L. Summerton, H. F. Sneddon, L. C. Jones and J. H. Clark, Royal Society of Chemistry, Cambridge, UK, 2016, ch. 2, pp. 12-27.

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