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A SURVEY OF SOLVENT SELECTION GUIDES

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.

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D. Prat*, J. Hayler[a] and A. Wells[b]

ABSTRACT: Several solvent selection guides have been published, in different formats, reflecting the culture of their institutions. The data given in these guides have been compiled, and where possible combined, in order to allow a ranking comparison. Of the 51 solvents considered, an acceptable alignment of the classifications could be met, permitting a ranking into four categories: recommended, problematic, hazardous and highly hazardous. 17 solvents (33%) could not be unequivocally ranked by this simplified analysis, thus reflecting differences in the weighing of criteria between the institutions.

Introduction

Sustainable Chemistry is a concept of increasing interest in the scientific and business community. Most pharmaceutical companies are making increasing efforts to limit their environmental impact and protect people in the workplace.[1] In order to share the same vision of more sustainable syntheses of pharmaceutical ingredients, companies join working groups, such as the ACS Green Chemistry Institute Pharmaceutical Roundtable (GCI-PR), created in 2005. The Roundtable's mission is to catalyze the implementation of green chemistry and green engineering in the global pharmaceutical industry with strategic priorities to inform and influence the research agenda, develop tools for innovation, and provide an education resource through global collaboration.[2] This has been achieved in part through the production of guides, literature surveys, distribution of grants to universities, and open access to greener technologies through publications.
In 2012, the Innovative Medicines Initiative (IMI)-CHEM21 public-private partnership was created in Europe with similar purposes.[3] It groups six pharmaceutical companies from the European Foundation of Pharmaceutical Industries and Associations (EFPIA),[4] ten universities and five small to medium enterprises. The aim is to develop sustainable biological and chemical methodologies, including identification of more sustainable options for reactions using rare elements. CHEM21 financially supports research projects[5] and will provide training packages to ensure that the principles of sustainable manufacturing are embedded in the education of future scientists. CHEM21 is organized in six work-packages (WP):

- WP1: Identification of the sustainable manufacturing challenges of 2020 and beyond.
- WP2: Development of new greener catalytic methods and assessment of the potential of flow chemistry processes.
- WP3: Development of new enzymatic toolboxes.
- WP4: Investigation of the roadblocks and solutions for synthetic biology implementation.
- WP5: To influence the next generation of medicinal and process chemists by exemplifying cutting edge low environmental impact chemistry, through the preparation and delivery of high quality training and educational materials.
- WP6: Project coordination.

WP1 was the starting point of the project, identifying and validating the targets of the other scientific work packages. One of the tasks was to analyze and understand the differences between the data-rich solvent selection guides available in the public domain. This analysis is reported herein.

Typically, solvents represent at least half of the material used in a chemical process to produce a drug substance.[6] As a result, limiting their amount and selecting the "greenest" ones permits a significant reduction of the environmental impact of a pharmaceutical product.
The selection of the "greenest" solvent for a process is a compromise between constraints which are sometimes contradictory.[7] The criteria to be considered are safety (S), occupational health (H), environment (E), quality (risk of impurities in the drug substance), industrial constraints (e.g. boiling point, freezing temperature, density, recyclability) and cost. Regulations such as REACh are also driving chemical

companies away from the use of some hazardous solvents, such as traditional aprotic solvents like DMF.[8]

In order to help chemists with the selection of more sustainable solvents, several pharmaceutical companies and institutions have elaborated broad, data-rich solvent selection guides.

Pfizer published a simple two-page document targeted towards medicinal chemists.[9] The most classical solvents are classified into three categories: preferred, usable and undesirable. For the undesirable solvents, substitution advice is given.

Astra Zeneca's guide consists of a table of 46 solvents with ten different criteria: two for safety, one for health and seven for environment, including life cycle analysis.[10] Each criterion is scored between 1 and 10, with a 3-color code (green, yellow and red) to facilitate analysis. GlaxoSmithKline has a similar guide, with two safety criteria, one health criterion, three environmental criteria including life cycle scoring, as well as additional red flags, *e.g.* for solvents governed by regulations.[11]

The GCI-PR solvent guide has the same structure as the AZ and GSK guides: a table with one safety criterion, one health criterion and three environmental criteria, with scores between 1 and 10 for each, and the same three-color code.[12]

Sanofi's solvent guide has recently been published. Solvents are ranked in four classes: "recommended", "substitution advisable", "substitution requested" and "banned". This ranking derives from Safety, Health and Environmental hazards, and industrial issues.[13]

As well as these solvent selection guides, other resources are available in the public domain to aid solvent comparison and selection.[14] Rowan University has published an Excel based tool to compare the solvent impacts on a process.[15] Apart from a comparison tool, this guide is a comprehensive collection of data on the 62 solvents listed. The tool gives a score based on health and environmental parameters including threshold limit value, acute and long-term toxicity, biodegradation, aquatic toxicity, ozone depletion, global warming potential, water solubility *etc*. However, safety issues are not taken into account in the score. ETH Zürich has developed an Excel tool permitting an overall HSE assessment of more than 100 substances, mainly solvents, based on nine effect categories.[16] The overall HSE scores of 26 solvents were compared.[7a] However the output raises some issues as, for example, the irritation effect has the same weight in the overall score as the chronic toxicity effect, and the fire/ explosion effect is almost the same for diethyl ether (Flash Point: -45 °C) and xylene (Flash Point: 27 °C).

Solvent guides comparison

The aim of this work was to compare all of these guides, analyze the level of convergence and the reasons for any differences. All companies have the same vision of safety, health and environmental hazards, and of industrial constraints, so one may suspect that the overall rankings will be similar. However the cultures and in particular, approaches to the construction of guides are different. For instance, in Astra Zeneca's guide the environmental issues are represented by 7 factors. The task is also complicated by the fact that only Pfizer and Sanofi guides give a clear preference ranking.[17] Besides, Pfizer has three categories (preferred, usable, undesirable), whereas Sanofi has four, with a list of "banned" solvents. GSK also has a list of solvents not to be used on their solvent selection intranet site, and these were excluded from the early versions of the solvent selection guide.[11b,c] They were included in the 2011 revision of the guide to ensure informed use of these solvents in screening experiments.

Table 1. Transformation of Astra Zeneca's guide

Solvent	Health	Safety	Envir.	Sum*
MeOH	5	7	7	19
EtOH	2	7	7	16
i-PrOH	3	7	6	16
n-BuOH	4	7	6	17
t-BuOH	6	7	7	20
Acetone	6	7	8	21
MEK	7	7	7	21
MIBK	6	7	9	22
Ethyl acetate	5	7	6	18
i-PrOAc	4	7	7	18
n-BuOAc	2	7	4	13
Diethyl ether	7	10	10	27
MTBE	9	7	8	24
THF	8	7	8	23
Me-THF	8	7	9	24
1,4-dioxane	9	10	9	28
Anisole	2	10	6	18
DME	10	3	8	21
Hexane	6	10	10	26
Heptane	3	10	8	21
Cyclohexane	6	10	9	25
Toluene	5	10	7	22
Xylenes	2	10	7	19
DCM	9	1	10	20
Chlorobenzene	9	7	9	25
Acetonitrile	8	7	9	24
DMF	9	3	8	20
DMAc	9	3	8	20
NMP	9	1	8	18
DMSO	1	1	6	8
Sulfolane	1	1	7	9
Methoxy-ethanol	10	3	8	21
Formic acid	10	3	7	20
Acetic acid	8	3	6	17
Pyridine	9	7	10	26
TEA	10	7	3	23

* Arithmetical mean: 20.3

The philosophy of solvent guides based on different criteria (GSK, AZ, GCI-PR) and not giving an overall ranking is to offer a rich collection of data, from which chemists and engineers can make a choice depending on process considerations. Again, the weighting and scoring of criteria selected in each guide complicates making a direct comparison:

- GSK guide has one health, two safety (flammability/ explosion and reactivity/ stability), and three environment criteria (waste, environmental impact, life cycle), and additional flags for physical constraints (melting point and freezing point), legislation restrictions and highest hazards.
- AZ guide has one health, two safety (flammability and resistivity), and seven environment criteria (impact on air, VOC, impact on water, potential bio-treatment plant load, recycling, incineration and life cycle).
- GCI-PR guide has one health, one safety and three environment criteria (air, water, waste).

Each criterion is scored between 1 and 9 or 10, but in the GSK guide, the highest figure represents the lowest hazard, contrary to the AZ and GCI-PR guides, so caution needs to be exercised in directly scoring for individual categories between the guides.

For comparison purposes, we used the figures given for each criterion and tried to manipulate them in order to obtain a classical 3-color code, with similar numbers of solvents in each category. The simplest way would have been to calculate the arithmetical mean of all criteria, but as their number depends on the guide, this would not have given any satisfactory comparison. Besides, a ranking based on such a calculation tends to homogenize the results, and sometimes gives unacceptable results: for example, the arithmetical mean-based score of DMF in the GCI-PR guide (4.4) is close to that of *n*-butanol (4.2) and *t*-butanol (4.6).

This survey was comprised of 51 solvents, including water. A decision was made to limit the number of criteria to three (heath, safety, environment) and to assign the most stringent figure to each of them (tables 1-2). For example, the environment scores for methyl t-butyl ether (MTBE) in the GCI-PR guide for air, water and waste are 5, 8 and 2 respectively, thus the overall environment figure in our analysis is 8. This permits a comparison with Sanofi's guide, in which each health, safety & environmental ranking band is based on the most stringent factor.

For each solvent, the Heath, Safety and Environment scores were added, and to this overall figure was associated a three-color code, based on the comparison with the arithmetical mean, in such a way that the three colors are relatively equitably represented.

For the GSK guide, we neglected the physical and legislation flags, but applied a value of -8 for solvents with an EHS flag. This gave a more realistic ranking, particularly for the reprotoxic aprotic polar solvents (table 3).

Table 2. Transformation of GCI-PR's guide

Solvent	Health	Safety	Envir.	Sum*
MeOH	5	3	6	14
EtOH	3	4	6	13
i-PrOH	5	5	6	16
n-BuOH	5	3	5	13
t-BuOH	5	3	7	15
Benzyl alcohol	3	4	4	11
Ethylene glycol	3	3	7	13
Acetone	4	4	7	15
MEK	4	5	7	16
MIBK	6	5	6	17
Cyclohexanone	4	4	6	14
Methyl acetate	5	3	6	14
Ethyl acetate	4	5	6	15
i-PrOAc	4	3	6	13
n-BuOAc	4	4	6	14
Diethyl ether	5	9	7	21
MTBE	5	8	8	21
THF	6	5	5	16
Me-THF	6	5	4	15
1,4-dioxane	7	8	6	21
Anisole	4	5	4	13
DME	9	(8)[+]	6	23
Hexane	7	6	8	21
Heptane	4	6	7	17
Cyclohexane	5	6	7	18
Me-Cyclohexane	4	6	(7)[x]	17
Benzene	10	5	6	21
Toluene	7	5	6	18
Xylenes	4	4	7	15
DCM	7	2	9	18
Chloroform	9	2	7	18
CCl_4	8	3	8	19
DCE	9	4	6	19
Chlorobenzene	5	3	8	16
Acetonitrile	5	3	6	14
DMF	7	3	7	17
DMAc	7	2	7	16
NMP	6	3	7	16
DMSO	4	3	8	15
Sulfolane	3	2	8	13
Methoxy-ethanol	9	4	7	20
Formic acid	6	2	7	15
Acetic acid	6	3	6	15
Ac_2O	6	3	7	16
Pyridine	6	3	7	16
TEA	7	4	7	18

* Arithmetical mean: 16.3

[+] By analogy with the safety score of 1,4-dioxane

[x] By analogy with the "env.-water" score of cyclohexane

Table 3. Transformation of GSK's guide

Solvent	Health	Safety	Env.	EHS flag	Sum*
Water	10	10	4	0	24
MeOH	5	5	4	0	14
EtOH	8	6	3	0	17
i-PrOH	8	6	3	0	17
n-BuOH	5	8	5	0	18
t-BuOH	6	6	3	0	15
Benzyl alcohol	7	7	6	0	20
Ethylene glycol	7	9	5	0	21
Acetone	8	4	3	0	15
MEK	8	4	3	0	15
MIBK	6	7	2	0	15
Cyclohexanone	6	8	6	0	20
Methyl acetate	7	4	3	0	14
Ethyl acetate	8	4	4	0	16
i-PrOAc	7	6	5	0	18
n-BuOAc	8	8	5	0	21
Diethyl ether	5	2	4	-8	3
DIPE	8	1	3	-8	4
MTBE	5	3	4	-8	4
THF	6	3	3	-8	4
Me-THF	4	3	4	0	11
1,4-dioxane	4	4	3	0	11
Anisole	7	6	5	0	18
DME	2	4	4	-8	2
Pentane	8	2	5	-8	7
Hexane	4	2	3	-8	1
Heptane	8	3	3	0	14
Cyclohexane	7	2	5	0	14
Me-Cyclohexane	8	3	5	0	16
Benzene	1	3	5	-8	1
Toluene	4	4	3	0	11
Xylenes	6	5	2	0	13
DCM	4	6	3	-8	5
Chloroform	3	6	3	-8	4
CCl_4	3	4	4	-8	3
DCE	2	6	4	-8	4
Chlorobenzene	4	8	6	0	18
Acetonitrile	6	6	2	0	14
DMF	2	9	4	-8	7
DMAc	2	8	2	-8	4
NMP	3	8	4	-8	7
DMPU	4	7	3	0	14
DMSO	7	2	5	0	14
Sulfolane	6	10	5	0	21
Nitromethane	4	2	3	-8	1
Methoxy-ethanol	2	6	3	-8	3
Acetic acid	6	7	4	0	17
Ac_2O	4	6	5	0	15
Pyridine	4	7	2	-8	5
TEA	3	4	4	-8	3

* Arithmetical mean: 11.5

The scores and rankings of the 51 solvents were compared (table 4). For 20 of them (39%), the color codes were identical between the guides, or there was a large majority in close agreement (4 out of 5 or 3 out of 4). In this case, the overall ranking was easy (right column). For the name of these categories we tried to be as neutral as possible: “recommended” (green), “problematic” (yellow), “hazardous” (red) and “highly hazardous” (brown).

In four cases (8%) (2-methyl tetrahydrofuran (Me-THF), chlorobenzene, acetonitrile and N-methyl pyrolidone (NMP)), there was a significant divergence, depending on the guide. The first three solvents were ranked as “problematic”, as this reflects the overall trend.

In some cases, including NMP, the regulatory constraints helped to establish an overall ranking, linked with the hazard statements of the Global Harmonized System (GHS):[18]

- Carbon tetrachloride, dangerous for the ozone layer (H420)[19] was ranked as highly hazardous.
- The regulation on carcinogenic, mutagenic or reprotoxic agents (CMR regulation) imposes the substitution of solvents labelled as H340, H350 or H360, or their justification.[20] Solvents which may cause cancer (H350) were classified as highly hazardous, whereas those which may damage fertility or the unborn child (H360) were ranked as hazardous. This distinction is aligned with Sanofi’s guide, and takes into account the fact that carcinogenic solvents of category 1a or 1b (benzene and 1, 2-dichloroethane (DCE)) are more volatile than reprotoxic solvents such as *N,N’*-dimethyl formamide (DMF), *N,N’*-dimethyl acetamide (DMAc) and NMP. As a result, the occupational risk is higher for these carcinogenic solvents.[21]

The distinction between hazardous and highly hazardous is a source of endless discussions, complicated by the fact that only Sanofi published a list of “banned” solvents.[22] Three non-CMR solvents (6%) were also classified as highly hazardous:

- Chloroform, which is toxic, and can easily be substituted by dichloromethane.
- Diethyl ether, as a result of its low flash point and boiling point (H224) but also of its resistivity, ability to form peroxides and its low temperature of auto-ignition (160°C).
- Nitromethane, because of its high energy of decomposition.[23]

Diisopropyl ether, which easily forms peroxides,[24] and pentane, which is very volatile and resistive, are not mentioned in AZ or GCI-PR guides. It may mean that they were banned from these guides, but on the other hand diethyl ether, which cumulates these issues, is present. They have been ranked as “hazardous” by default.

Table 4. Ranking comparison

Family	Solvent	AZ	GCI-PR	GSK	Pfizer	Sanofi*	Issues	Overall**
Water	Water	-	-	24	Preferred	Recom.	-	Recommended
Alcohols	MeOH	19	14	14	Preferred	Recom	-	TBC
	EtOH	16	13	17	Preferred	Recom	-	Recommended
	i-PrOH	16	16	17	Preferred	Recom	-	Recommended
	n-BuOH	17	13	18	Preferred	Recom	-	Recommended
	t-BuOH	20	15	15	Preferred	Subst. adv.	-	TBC
	Benzyl alcohol	-	11	20	-	Subst. adv.	-	TBC
	Ethylene glycol	-	13	21	Usable	Subst. adv.	-	TBC
Ketones	Acetone	21	15	15	Preferred	Recom	-	TBC
	MEK	21	16	15	Preferred	Recom	-	TBC
	MIBK	22	17	15	-	Recom	-	TBC
	Cyclohexanone	-	14	20	-	Subst. adv.	-	TBC
Esters	Methyl acetate	-	14	14	-	Subst. adv.	-	TBC
	Ethyl acetate	18	15	16	Preferred	Recom	-	Recommended
	i-PrOAc	18	13	18	Preferred	Recom	-	Recommended
	n-BuOAc	13	14	21	-	Recom	-	Recommended
Ethers	Diethyl ether	27	21	3	Undesirable	Banned	H224	HH
	Diisopropyl ether	-	-	4	Undesirable	Subst. adv.	Perox.	Hazardous
	MTBE	24	21	4	Usable	Subst. adv.	-	TBC
	THF	23	16	4	Usable	Subst. adv.	H351	TBC
	Me-THF	24	15	11	Usable	Recom	-	Problematic
	1,4-dioxane	28	21	11	Undesirable	Subst. req.	-	Hazardous
	Anisole	18	13	18	-	Recom	-	Recommended
	DME	21	23	2	Undesirable	Subst. req.	H360	Hazardous
Hydrocarbons	Pentane	-	-	7	Undesirable	Banned	H224	Hazardous
	Hexane	26	21	1	Undesirable	Subst. req.	-	Hazardous
	Heptane	21	17	14	Usable	Subst. adv.	-	Problematic
	Cyclohexane	25	18	14	Usable	Subst. adv.	-	TBC
	Me-Cyclohexane	-	17	16	Usable	Subst. adv.	-	Problematic
	Benzene	-	21	1	Undesirable	Banned	H350	HH
	Toluene	22	18	11	Usable	Subst. adv.	H351	Problematic
	Xylenes	19	15	13	Usable	Subst. adv.	-	Problematic
Halogenated	DCM	20	18	5	Undesirable	Subst. adv.	H351	TBC
	Chloroform	-	18	4	Undesirable	Banned	-	HH
	CCl_4	-	19	3	Undesirable	Banned	H420	HH
	DCE	-	19	4	Undesirable	Banned	H350	HH
	Chlorobenzene	25	16	18	-	Subst. adv.	-	Problematic
Aprotic polar	Acetonitrile	24	14	14	Usable	Recom	-	Problematic
	DMF	20	17	7	Undesirable	Subst. req.	H360	Hazardous
	DMAc	20	16	4	Undesirable	Subst. req.	H360	Hazardous
	NMP	18	16	7	Undesirable	Subst. req.	H360	Hazardous
	DMPU	-	-	14	-	Subst. adv.	-	Problematic
	DMSO	8	15	14	Usable	Subst. adv.	-	Problematic
	Sulfolane	9	13	21	-	Subst. adv.	-	Recommended
	Nitromethane	-	-	1	-	Banned	Explo.	HH
Miscellaneous	Methoxy-ethanol	21	20	3	-	Subst. req.	H360	Hazardous
Acids	Formic acid	20	15	-	-	Subst. req.	-	TBC
	Acetic acid	17	15	17	Usable	Subst. adv.	-	TBC
	Ac_2O	-	16	15	-	Subst. adv.	-	TBC
Amines	Pyridine	26	16	5	Undesirable	Subst. adv.	-	TBC
	TEA	23	18	3	-	Subst. req.	-	Hazardous

*Recom.: recommended; Subst. adv.: substitution advisable; Subst. req.: substitution requested.
**TBC: to be confirmed; HH: highly hazardous.

At this level of the survey, 34 solvents (67%) have been ranked in the four categories, but for the 17 remaining, no clear ranking could be made, because the majority was too low (≤ 67%) and no obvious justification could be made. Depending on the guide, 11 of them are either "recommended" or considered as "problematic", and 6 are considered as either "problematic" or "hazardous" (table 5).

Table 5. Overall ranking of solvents

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.

Conclusion

The aim of this survey is not to create a universal solvent selection guide. It is quite normal that some differences exist between pharmaceutical companies, or between companies and academic institutions, based on their culture and policy. It is up to each company or group to make its own ranking, and the ranking of GCI-PR guide, inspired by pharmaceutical companies, may differ to that of the future CHEM21 guide, oriented towards academic partners and students.

As this analysis is partly based on an interpretation of three guides which do not give any overall ranking it can be criticized. However, other calculations gave similar results.[25]

There is an overall good agreement between the different guides, and part of the divergence is solved by the regulation constraints (*e.g.* on CMR and ozone depleting agents). Solvents which could not be directly ranked often present balances between advantages and drawbacks which are subject to discussion. So, despite the simplified methodology used, the results are globally consistent.

This work, based on only 51 solvents, is incomplete. Carbon disulfide and HMPA, which are often not even mentioned because they have been banned as solvents in industry, can be added to the list of highly hazardous solvents. Besides, a scoring can change as a result of new toxicity data or classification: for example, NMP has been classified as reprotoxic (H360) since 2009, and THF classified as suspected carcinogenic (H351) since 2012. Nevertheless, our analysis provides a first intention comparison and will help any chemist with the selection of more sustainable solvents. It will also serve as a basis for the CHEM21 solvent guide, currently under elaboration, which will also include newer solvents (such as supercritical carbon dioxide, alkyl carbonates, etc.), and more especially bio-derived solvents.

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[*] To whom correspondence should be addressed. Sanofi-Aventis Research & Development, 13 quai Jules Guesde, BP 14, 94403 Vitry sur Seine, France; e-mail: denis.prat@sanofi.com; tel : (33) 155718014; fax : (33) 155713835

[a] Glaxo-SmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, UK..

[b] Charnwood Technical Consulting, Parklands, Northage Close, Quorn, Leicestershire, LE12 8AT, UK..

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