Updating and Further Expanding GSK's Solvent Sustainability Guide†

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GlaxoSmithKline (GSK) has previously reported on the development of a GSK solvent guide, the incorporation of lifecycle impact and the expansion of the guide including a customisable version intended for posting in different business areas. This guide has recently been enhanced by:

- Adding 44 additional solvents, many of which have literature claims to be "green";
- Adjusting the way in which multiple health, environment, safety, and waste categories are combined to reach a single composite score and colour assignment;
- Updating the data behind all scores, especially toxicology and health hazard assessment, and revising the methodology to reflect current guidelines and data.

The full methodology behind this work is hereby shared. The new GSK Solvent Sustainability Guide enables GSK scientists to objectively assess solvents. It facilitates both comparison of individual sustainability criteria, and a composite score and colour for rank ordering, incorporating multiple facets of sustainability.

1. Introduction

A report on the state of solvent use at GSK in 2007 states that solvents constitute 80-90% of the non-aqueous mass of materials used to make an active pharmaceutical ingredient (API).[1] Given this high impact, solvent guides remain key tools to influence the overall nature of materials used (and waste generated) in the discovery, development and ultimately manufacture of APIs.

The first edition of the GSK solvent guide was published in 1999,[2] with a further version incorporating life cycle analysis (LCA)[3,4] assessments in 2004.[5] A subsequent 2011 expansion revised the assessments of factors impacting process safety, more than doubled the number of solvents considered from 47 to 110, and added a customised version designed with medicinal chemistry and analytical laboratories in mind.[6] Several other pharmaceutical companies (including Pfizer,[7] Sanofi Aventis,[8] and AstraZeneca[9]) also have their own solvent guides. Collaborative groups such as the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCI PR)[10] and IMI: CHEM21[11] are producing guides representing the input of multiple stakeholders. While these efforts tend to agree on the majority of solvent assessments, varied business priorities and factors such as geography and regulatory environments do lead to some differences in final conclusions.[12]

Following this historical model, the GSK solvent guide has again been adapted and updated, taking into account both new data and methods of assessment. This new version facilitates the inclusion of additional solvents and ensures that the data and methods underlying the guide are in line with the most recent available guidance. The overall approach remains the same as with earlier versions of the GSK solvent guide, namely to rank solvents relative to each other based on their inherent waste disposal, environmental, health and safety issues. As before, a score (referred to as a summary score) is assigned for each of the major areas of assessment, with each of these composed from multiple categories. The current guide includes summary scores for waste, environment, health, and safety. The summary scores are further combined to give a single overall score for each solvent, referred to henceforth as the composite score.

This guide now contains an additional 44 solvents beyond those included in the previous version,[6] while still maintaining the original focus of assessing only small molecule, organic solvents.[13] Many of these new solvents have been listed in the literature as potentially green choices. Others were selected primarily to allow full sustainability assessments of a wider range of solvents in certain chemical classes (specifically alcohols and esters). The rationale for the choices of the solvents added is described in further detail in the ESI. As different sources vary in their criteria for assessing green credentials of solvents, we wished to assess all the solvents consistently against our methodology. In addition, the data feeding into previous versions of the guide were comprehensively cross-checked and updated, especially in cases where additional data have been reported over the intervening years.

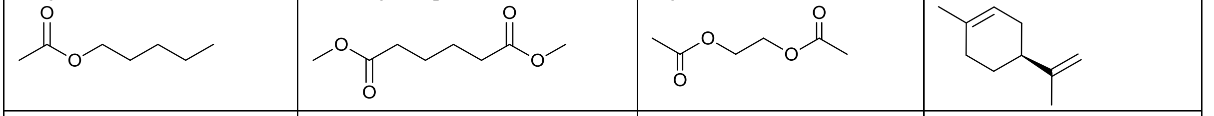
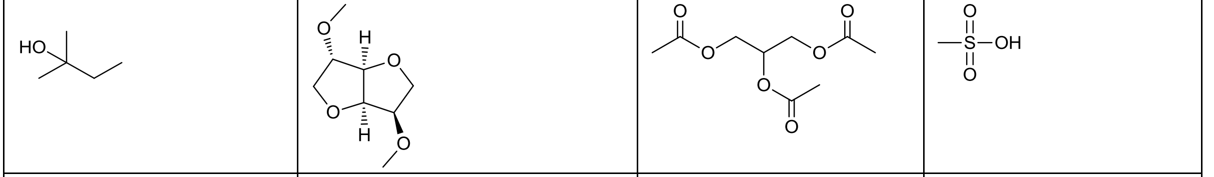
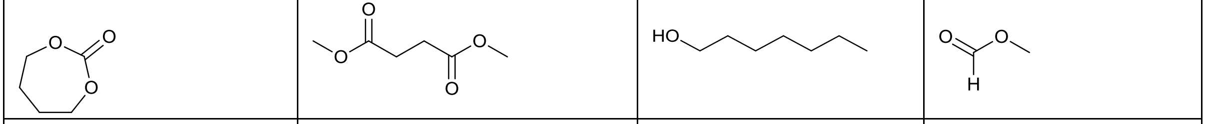
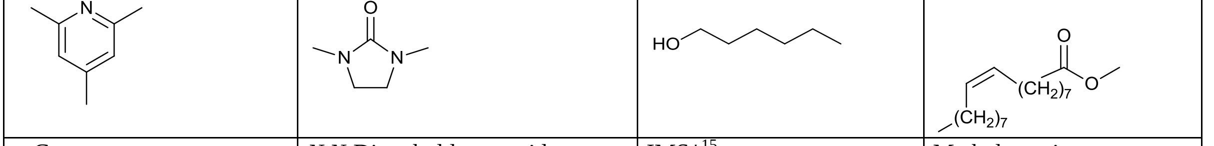
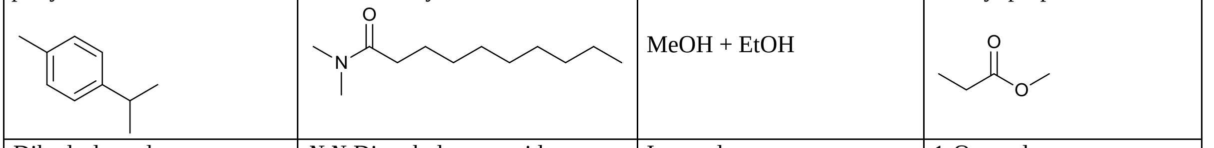
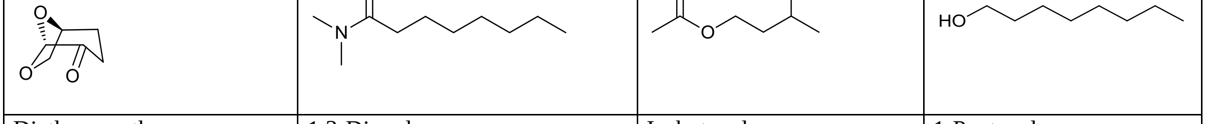
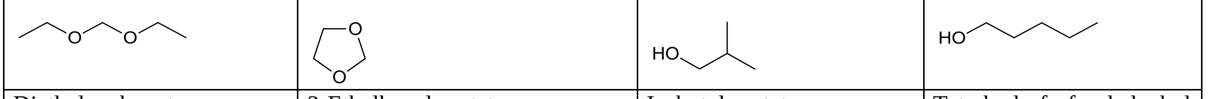
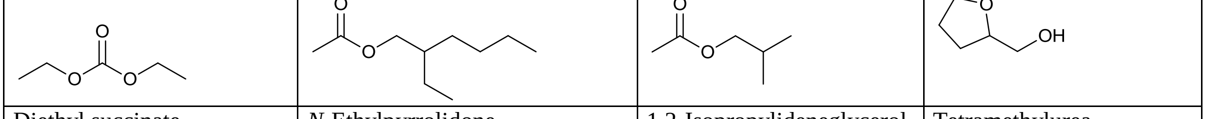
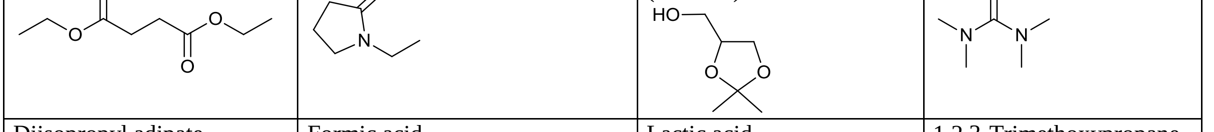
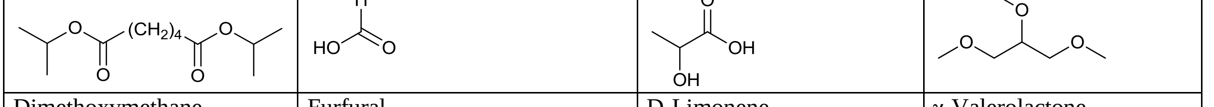
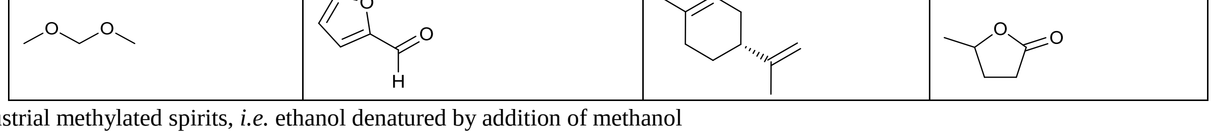
For a number of the newly added solvents, some of the data utilised in the GSK methodology could not be sourced. Such instances necessitated the use of assumptions based on calculation models, chemical class trends, or nearest neighbour solvents, with nearest neighbour defined as the solvent deemed to be closest in chemical structure and size to the solvent in question.[14] Scores for solvents which depend on approximated data must inherently be treated with a lower level of confidence than in cases where extensive data is available.

No methodology for assessing greenness can ever properly address the challenges of quantitatively scoring qualitative attributes, and individual solvent selection challenges can also have different priorities. To aid chemists to use the guide to best suit their needs, we hereby share the full methodology behind each individual category score, in the awareness that there are some purposes for which one or more specific categories may be of increased significance. Such cases may justify different methods for combining category and summary scores to give a composite score, or obviate the need for composite scores altogether.

The benefits of including a composite score include the ability to determine a rank ordering, which enables the generation of easily understood colour codes. Such codes enable derivatization of metrics on solvent use within different parts of the business, and hence can help to drive behaviour changes. This must however be balanced against a risk of colour codes masking the detail behind each individual solvent's ranking and the complexity that may drive any individual solvent selection decision.

2. New Solvents Evaluated

Forty additional solvents have been assessed since the last GSK solvent guidance publication, as shown in Table 1.

Amyl acetate 	Dimethyl adipate	Glycerol diacetate	L-Limonene
t-Amyl alcohol 	Dimethyl isosorbide	Glycerol triacetate	Methanesulfonic acid
Butylene carbonate 	Dimethyl succinate	1-Heptanol	Methyl formate
2,4,6-Collidine 	1,3-Dimethyl-2-imidazolidinone	1-Hexanol	Methyl oleate
p-Cymene 	*N*,*N*-Dimethyldecanamide	IMS*[15] MeOH + EtOH	Methyl propionate
Dihydrolevoglucosenone (Cyrene™) 	*N*,*N*-Dimethyloctanamide	Isoamyl acetate	1-Octanol
Diethoxymethane 	1,3-Dioxolane	Isobutanol	1-Pentanol
Diethyl carbonate 	2-Ethylhexyl acetate	Isobutyl acetate	Tetrahydrofurfuryl alcohol
Diethyl succinate 	*N*-Ethylpyrrolidone	1,2-Isopropylideneglycerol (Solketal)	Tetramethylurea
Diisopropyl adipate 	Formic acid	Lactic acid	1,2,3-Trimethoxypropane
Dimethoxymethane 	Furfural	D-Limonene	γ-Valerolactone

*Industrial methylated spirits, *i.e.* ethanol denatured by addition of methanol

Table 1: Names and structures of latest solvents added to GSK Solvent Sustainability Guide.

3. Methodology

3.1 General Methods for Score Calculation

Calculation of Individual Data Scores

Each of the summary areas has multiple categories which are individually assessed and combined to give a summary score. Each category in turn is dependent on multiple attributes. These data are assessed to provide individual scores which range from 1 (less green) to 4 (more green); the scores are then expanded to a 1 – 10 scale to provide the category score. Unless specifically described otherwise, cut off values are assigned for each data point to correspond to scores of 1 and 4. These assignments are made either by following specific guidelines that correlate a property to known risks or by examining the range of data points, sorted numerically, and observing where the ends of the data range show significant inflection from the bulk of the data.[16]

With data limits thus assigned, a plot is constructed of data value vs. score and the equation is determined for the corresponding line. This equation is then used to calculate individual data scores for the full set of solvents, which are further combined to give scores for each category.[17]

3.2 Assessment of Waste score (comprising Incineration, Recycling, Biotreatment, and Volatile Organic Compound (VOC) emissions scores)

Assessment of Incineration Score

The incineration score results from a combination of scores determined for water solubility, emissions, and enthalpy of combustion. Highly water miscible solvents score lower than those which are less soluble. The higher the water content, the greater the energy required for incineration which may include dissolved aqueous materials. Solvents which give rise to problematic emissions are penalised, and those which have a high enthalpy of combustion are ranked more favourably than those with a low enthalpy of combustion since the significant release of heat energy upon incineration of these solvents can potentially be harnessed for energy recovery. Such concerns are evaluated to derive scores for solubility, emissions to air, and enthalpy of combustion, which are then combined to reach a category score for incineration.

Assessment of Recycling Score

Solvents score highly if they can be readily dried or separated from water, including such considerations as boiling point and whether a given solvent forms an azeotrope with water. Separability of multiple solvents is considered, with those solvents whose boiling points are proximate to those of a list of commonly used solvents, as determined through consultation with the GSK manufacturing organisation, marked down. The flammability and explosivity of solvents is considered such that those likely to cause safety concerns on recycling are penalised. Similarly where the intrinsic reactivity of solvents is likely to cause safety or recovery issues, the scores for those are appropriately adjusted.

Scores covering issues related to boiling point, boiling point range, ease of drying, flammability & explosivity, reactivity & stability, and water solubility are derived and combined to obtain a category score for recycling.

Assessment of Biotreatment Score

The biotreatment score is based on three areas:

- Treatability in aeration tanks, which penalises those solvents which require greater oxidation, as assessed by their theoretical oxygen demand (ThOD), and additionally penalises nitrogen-containing solvents in light of the added demand that oxidation of nitrogenous solvents places on biotreatment and the risks of affecting nitrogen content in the aqueous environment;
- Release to air, which penalises volatile solvents and halogenated solvents likely to give rise to problematic VOCs;
- Potential for a solvent to be present in an aqueous stream (which penalises more miscible solvents).

Scores assessing issues in each of these three areas were combined to obtain a biotreatment category score.

Assessment of VOC Emissions score

VOC emissions may occur as fugitive discharge, through spillages or during the recovery, storage, transport and/or waste management of solvents. This score therefore seeks to address two issues:

- Ease of abatement control within a process;
- Risk of loss during transport, storage, *etc*. or in the instance of spillage.

Vapour pressure is the primary factor which governs both the potential for emission and ease of abatement. In addition, solvents with low boiling points are penalised,[18] as this adds to the likelihood of volatile emissions.

3.3 Assessment of Environmental Impact score (comprising Environmental Impact-Air and Environmental Impact-Aqueous scores)

Assessment of Environmental Impact-Air score

The environmental impact-air score is based on a combination of the photochemical ozone creation potential (POCP) score,[19] where solvents which are more likely to give rise to ozone on exposure to sunlight are penalised, and the odour score, which penalises those solvents with a high ratio of vapour pressure to odour threshold.

Assessment of Environmental Impact-Aqueous score

The environmental impact-aqueous score is based on three areas:

- Acute environmental toxicity, penalising known high toxicity against any aquatic species;
- Chronic environmental toxicity, using partition coefficient as an indicator of chronic hazards as well as relevant Global Harmonised System (GHS)[20] phrase indicators;
- Biodegradation.

3.4 Assessment of Health score (comprising Health Hazard and Exposure Potential scores)

Assessment of Exposure Potential score

The exposure potential score is based on available occupational exposure limits (OELs)[21] and calculation of saturation concentration (SC). These two data points are combined to calculate the vapour hazard ratio (VHR) for each solvent, which then correlates to the exposure potential score.

Assessment of Health Hazard score

Previous versions of this guide relied on European Union risk phrases from the Dangerous Substances Directive (EU R Phrases)[22] to provide essential indicators of risks to human health. From June 1, 2015 onwards, all substances and mixtures are required to comply with the GHS Hazard and Precautionary (H&P) risk phrases,[20] developed to provide a standard framework for international classification and labelling of chemical hazards. The revised GSK Solvent Sustainability Guide utilises GHS hazard phrases as one indicator of human health hazards. The process by which appropriate GHS hazard phrases were sourced for each solvent is described in detail in the ESI.

OEL values, as used in the exposure potential score, are utilised as an initial point of reference to indicate human health hazard. GHS phrases are further categorised and examined to determine if any additional scoring adjustments are warranted, following a decision tree approach (Figure 1).[23] Through this process, those solvents for which GHS phrases suggest high risk of human health issues are given a scoring penalty, with those risks related to carcinogenicity, mutagenicity, or toxicity to reproduction emphasized with a more significant penalty, while those without such risks utilise OEL data to determine the health hazard score, recognising the fact that OELs consider dose as well as intrinsic hazard. Table 2 specifies these high risk GHS phrases, as well as the score assignments for any solvent with one or more of the listed H&P phrases. For a full scoring correlation of GHS phrases, please see the ESI.

GHS Phrases	Health Hazard Score (out of 10)
H340, H341, H350, H360, H362	1
H300, H310, H330, H370	4

Table 2: GHS H&P phrases indicating severe human health risk

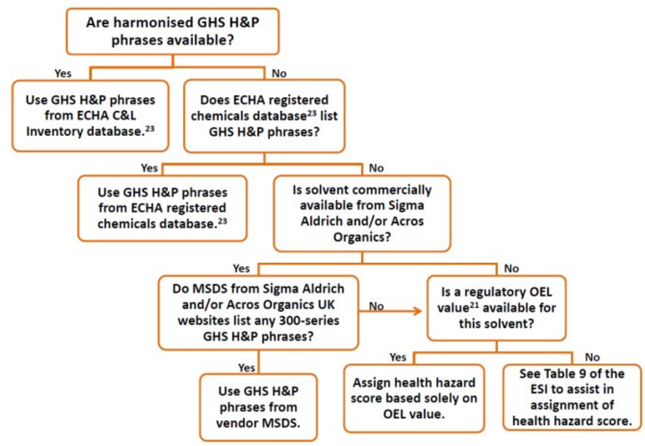


Figure 1: Decision tree for determination of GHS H&P phrases for a given solvent.

3.5 Assessment of Safety score (comprising Flammability & Explosion Potential and Reactivity & Stability scores)

Assessment of Flammability & Explosion Potential score

The flammability and explosion potential score combines assessments for:

- Boiling point;
- Flash point;
- Auto ignition temperature;
- Electrical conductivity, wherein electrically conductive solvents are favoured as they prevent build-up of static charge during solvent pouring or flowing processes;
- Vapour pressure.

Explosion potential is assessed for the solvent molecules themselves, not for potential byproducts such as peroxides, which are later included in the reactivity and stability score.

Assessment of Reactivity & Stability Score

The reactivity & stability score combines assessments for:

- Peroxide formation, to penalise solvents which might form peroxides over time;
- Potential for self-reaction, to penalise special risks such as polymerization or thermal decomposition upon heating;
- National Fire Protection Association (NFPA)[24] Reactivity Rating, to penalise those solvents with intrinsic reactivity which increases the risk of fire;
- Acidity/Basicity, to penalise those solvents with the potential to react with acidic or basic reagents;
- Special hazards, to capture any special or unusual hazards, such as pyrophoric or shock sensitive solvents.

3.6 Assessment of Life Cycle Assessment (LCA) score

In the 2004 update, LCA data was incorporated into the GSK solvent guide.[3] The data utilised in this scoring included the following: net mass of materials consumed, gross energy usage, total water consumption, total organic carbon (TOC),[25] amount of fossil fuels as feedstock, POCP equivalents, greenhouse gas equivalents, and equivalents of acidification and eutrophication. While such data and considerations are extremely useful in considering the overall sustainability impact associated with solvent use, it is an area where significant gaps occur in the current dataset. For many of the newly evaluated solvents, full LCA information is not available. While not strictly incorporated into the scoring for this guide, LCA data for solvents, where available, is still presented in the internal guide, and it is hoped that data on additional solvents will become available over time.

3.7 Solvent Colour Coding and Assessment of Composite Score

Whilst a major benefit of the solvent sustainability guide lies in highlighting individual issues associated with certain solvents, and in making detailed data available for chemists to make informed choices about solvent selection, there are also benefits to an at-a-glance classification. A method therefore has been defined to categorise solvents on a green, amber, red traffic light inspired scale.

For each general area of assessment (waste, environment, health, and safety), an overall summary score is defined as the geometric mean of each of the relevant category scores. These calculations are represented by the equations:

$$Waste = \sqrt[4]{I \times R \times BT \times VOC}$$

$$Environment = \sqrt{Air \times Aqueous}$$

$$Health = \sqrt{Health\ hazard \times Exposure\ potential}$$

$$Safety = \sqrt{F\&E \times R\&S}$$

where I = incineration score, R = recycle score, BT = biotreatment score, VOC = VOC emissions score, F&E = flammability and explosion potential score, and R&S = reactivity and stability score.

For each of these summary scores, as well as all of the individual category scores that are utilised in the summary score equations, we consider the colour designations of Green, Amber, and Red to follow the value ranges defined in Table 3.

Green	$7.5 \leq$ Score
Amber	$3.5 \leq$ Score < 7.5
Red	Score < 3.5

Table 3: Colour assignments for summary & category scores

Furthermore, a composite score is defined as the geometric mean of the waste, environmental impact, health and safety scores, represented by the equation:

$$Composite = \sqrt[4]{Waste \times Environment \times Health \times Safety}$$

This is then used to rank order the solvents and assist in colour assignment, as described in more detail below.

In examining the range of assessment categories, it was determined that 4 out of the 10 are priority areas (See Table 4) within GSK's general business operations. VOC emissions was chosen as an indicator of volatility. Health hazard is the most robust assessment of human health concerns in the dataset, given than many of these solvents have not been assigned regulatory OEL values. The two safety categories for flammability and reactivity inherently represent serious risk within multiple areas of GSK's day–to-day business operations.

Priority Categories
VOC Emissions
Health Hazard
Flammability & Explosion Potential
Reactivity & Stability

Table 4: List of Priority categories

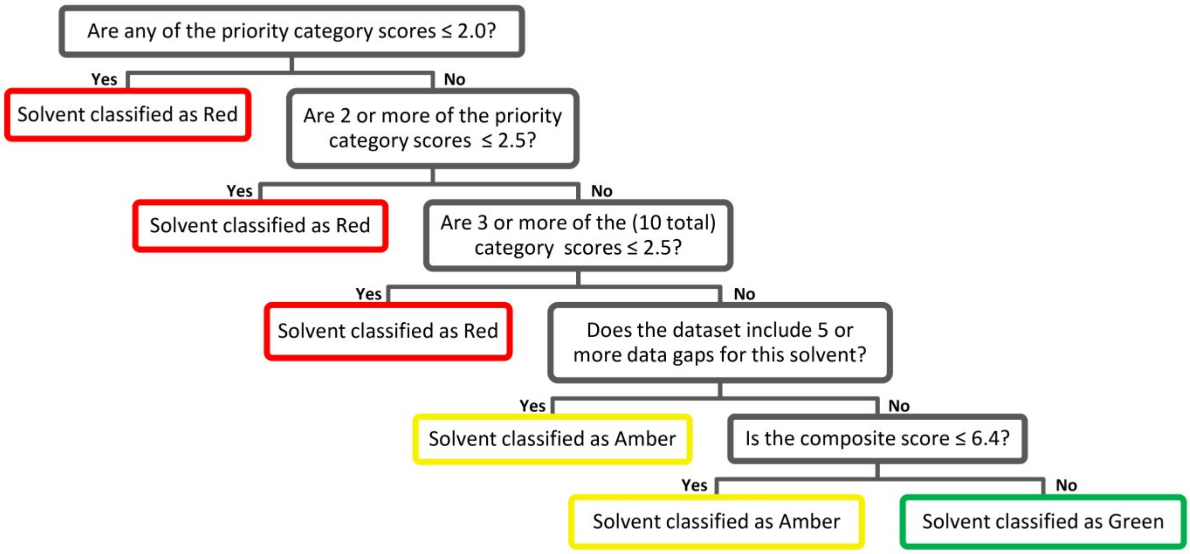


Figure 2: Decision tree for assignment of composite colours.

The final colour assignments were then made via the decision tree illustrated in Figure 2. Once red solvents were defined, those solvents whose assessments include 5 or more data gaps were automatically classified as amber, acknowledging that assessments based on approximations and assumptions are inherently less accurate. This lack of confidence in the end assessment suggests that a precautionary viewpoint should be employed. Where a given solvent does not have significant gaps in data, the composite score was examined to differentiate between amber and green.

These rules were used to rank order all 154 classified solvents, data for which is available in charts by chemical class in the ESI. One advantage of these charts is the ability to rapidly highlight suggestions for more sustainable solvent alternatives. For common solvents, we have also created a single page view (Figure 3).

3.8 Significant Changes from 2011 Guide Classifications

A number of common solvents are classified differently in the 2015 version of the GSK Solvent Sustainability Guide from the version published in 2011, either as a result of updated data or changes in methodology. Acetonitrile was classified as red in the 2011 version of the guide. In resetting of the colour boundaries in 2015, it now falls in the amber, which appropriately recognises its status as one of the less problematic dipolar aprotic solvents. Whilst we have not considered scoring approaches from other companies in the process of this update, it is interesting to note that this is aligned with Pfizer's assessment.[7] This has previously been highlighted as a solvent on which multiple published guides did not agree.[12]

The previous guide combined ethanol and IMS (industrial methylated spirits) into a single entry, the score for which was lowered due to inclusion of the health risks associated with methanol. These have been separated, resulting in a green assessment for pure ethanol, with IMS remaining as amber.

Sulfolane has been highlighted as a potentially favourable solvent from a green chemistry perspective, and had a high composite score in the 2011 GSK guide. However, subsequent data[26] generated in response to concern of potential environmental contamination[27] indicate that sulfolane poses a significant reprotoxicity hazard, which was reflected in assignment of a GHS H360 risk phrase during the course of this revision. Incorporation of this data into the guide methodology leads to an overall red assessment.

3.9 Factors Beyond the Scope of this Guide

We are mindful that there are a multitude of factors which different organisations or individuals may consider as important when choosing solvents appropriate for a given process. Predictive methods to characterize the solubilising characteristics of a potential solvent are often considered,[28] but are beyond the scope of this guide. While issues such as cost and availability can also have significant impact in such decisions, they are variable with respect to time and geography; therefore they are not included in the considerations for this work. Similarly, legislative restrictions are of compelling importance in the pharmaceutical industry, but are also subject to change over time, and are therefore excluded from this static, published view of our solvent guidance. Internally, GSK monitors and reacts to such changes and can update this "living" document. All solvents in our dataset which are of high concern under the REACH[29] legislation do fall into the red colour classification of the GSK Solvent Sustainability Guide.

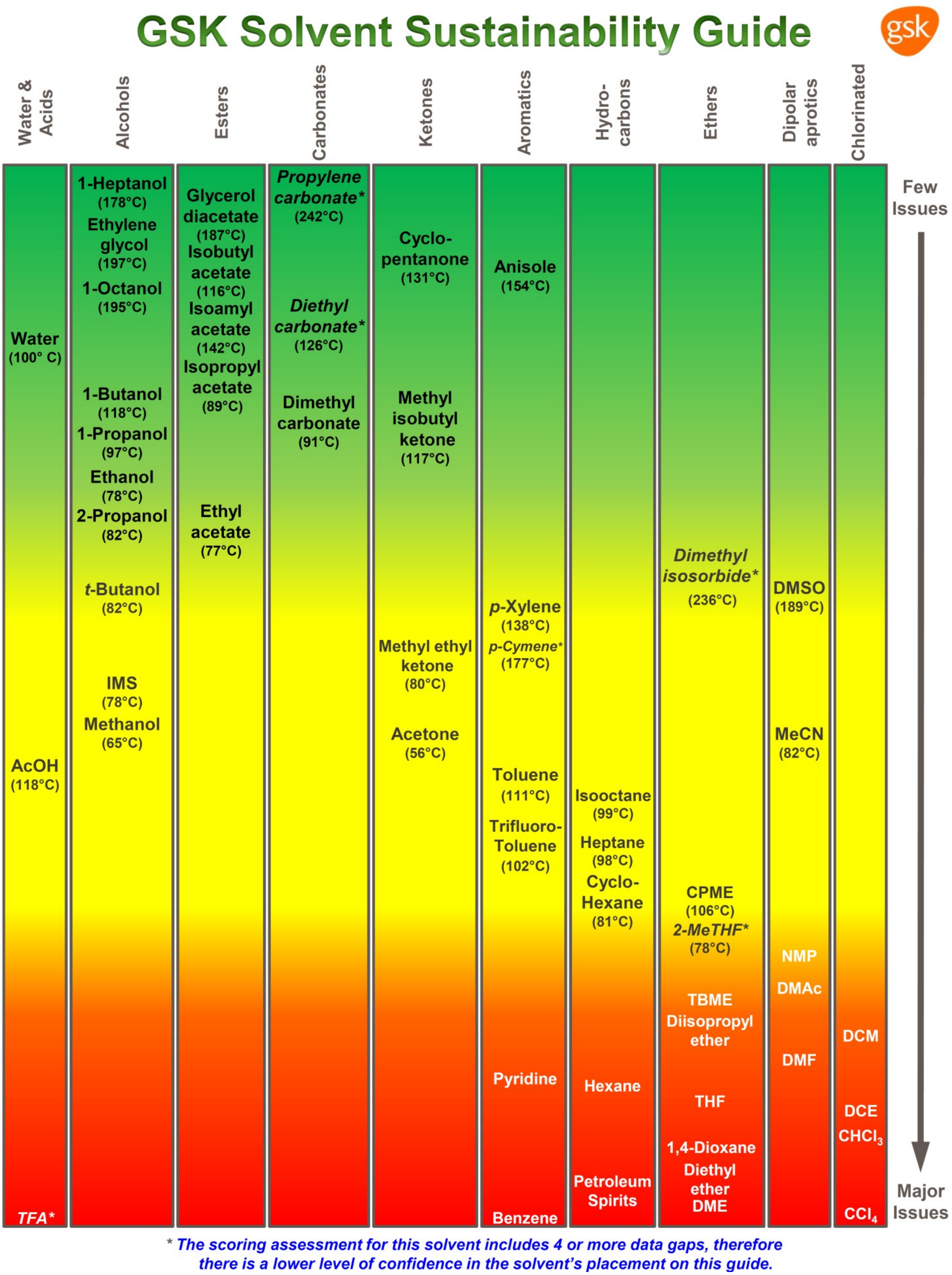


Figure 3: Single page view of GSK Solvent Sustainability Guide, including commonly used solvents and recommended alternatives, sorted by chemical class.

GSK Solvent Sustainability Guide

Classification	Solvent Name	CAS Number	Composite Colour‡	Boiling Point (°C)	Incineration	Recycling	Biotreatment	VOC Emissions	Aquatic Impact	Air Impact	Health Hazard	Exposure potential	Flammability & Explosion	Reactivity & Stability	Life Cycle Analysis†
Water & Acids	Water	7732-18-5		100	4	2	4	6	10	8	10	9	7	10	10
	Acetic Acid	64-19-7		118	3	5	4	7	8	4	7	5	8	6	8
	*Trifluoroacetic acid**	76-05-1		72	1	5	2	4	4	4	4	3	7	6	
Alcohols	1-Heptanol	111-70-6		178	9	8	10	9	8	4	10	7	9	10	
	Ethylene glycol	107-21-1		197	4	5	5	10	10	8	7	10	10	10	9
	1-Octanol	111-87-5		195	9	7	8	10	5	4	7	10	9	10	
	1-Butanol	71-36-3		118	6	7	5	8	9	3	7	7	8	9	5
	1-Propanol	71-23-8		97	5	3	3	6	10	4	10	7	8	10	7
	Ethanol	64-17-5		78	5	5	3	4	9	5	10	8	6	10	
	2-Propanol	67-63-0		82	5	5	3	5	8	7	10	6	6	8	4
	t-Butanol	75-65-0		82	5	5	3	5	9	7	7	5	6	10	8
	IMS (ethanol, denatured)	64-17-5		78	5	5	3	5	9	5	4	7	6	10	
	Methanol	67-56-1		65	4	7	3	3	10	7	4	6	5	10	9
Esters	Glycerol diacetate	111-55-7		187	5	6	6	10	6	8	10	8	10	10	
	Isobutyl acetate	110-19-0		116	7	9	8	6	9	6	10	6	8	10	
	Isoamyl acetate	123-92-2		142	9	9	8	8	4	6	7	8	8	10	
	Isopropyl acetate	108-21-4		89	6	7	5	5	9	5	10	6	6	10	7
	Ethyl acetate	141-78-6		77	5	6	5	4	9	5	10	7	5	10	6
Carbonates	*Propylene carbonate**	108-32-7		242	4	5	6	10	10	10	10	10	10	10	
	*Diethyl carbonate**	105-58-8		126	7	9	9	7	9	8	4	5	8	10	
	Dimethyl carbonate	616-38-6		91	4	3	5	5	9	7	10	6	6	10	8
Ketones	Cyclopentanone	120-92-3		131	8	9	6	7	10	5	7	6	8	10	6
	Methylisobutyl ketone	108-10-1		117	7	8	5	7	9	3	7	6	7	9	2
	Methylethyl ketone	78-93-3		80	5	5	3	4	8	4	10	6	5	9	3
	Acetone	67-64-1		56	5	6	2	2	10	6	10	6	4	9	7
Aromatics	Anisole	100-66-3		154	8	8	8	8	7	6	7	8	7	9	5
	p-Xylene	106-42-3		138	10	9	6	7	5	2	7	7	5	10	7
	*p-Cymene**	99-87-6		177	10	8	7	9	3	2	10	6	6	9	
	Toluene	108-88-3		111	10	7	6	7	7	2	7	6	5	10	7
	Trifluorotoluene	98-08-8		102	4	4	5	6	3	8	10	4	4	10	
	Pyridine	110-86-1		115	3	6	2	7	7	3	4	4	8	9	2
	Benzene	71-43-2		80	9	6	6	4	7	5	1	1	3	10	7
Hydrocarbons	Isooctane	540-84-1		99	10	4	5	6	2	5	10	7	3	10	7
	Heptane	142-82-5		98	10	4	5	6	3	5	10	6	3	10	7
	Cyclohexane	110-82-7		81	10	6	5	4	3	5	10	6	2	10	7
	Hexane	110-54-3		69	10	8	4	3	3	5	7	4	2	10	7
	Petroleum spirits	8032-32-4		55	8	9	4	2	5	5	1	6	2	10	7
Ethers	*Dimethyl isosorbide**	5306-85-4		236	4	4	5	10	9	6	4	9	9	8	
	Cyclopentyl methyl ether	5614-37-9		106	8	4	5	6	4	3	4	4	6	9	4
	*2-Methyltetrahydrofuran**	96-47-9		78	6	5	3	4	7	4	4	3	4	6	4
	t-Butylmethyl ether	1634-04-4		55	7	8	4	2	7	5	7	4	3	9	8
	Diisopropyl ether	108-20-3		68	9	7	6	3	5	4	10	6	4	3	9
	Tetrahydrofuran	109-99-9		65	5	5	2	3	9	3	7	5	4	6	4
	1,4-Dioxane	123-91-1		102	4	1	3	6	8	4	4	3	4	6	6
	Diethyl ether	60-29-7		35	7	7	3	1	5	3	10	4	2	6	6
	1,2-Dimethoxyethane	110-71-4		85	4	4	3	5	8	7	1	4	4	6	7
Dipolar Aprotics	Dimethyl sulphoxide	67-68-5		189	3	4	4	9	8	6	7	9	9	5	6
	Acetonitrile	75-05-8		82	3	5	1	4	10	8	7	5	6	10	4
	N-Methyl pyrrolidone	872-50-4		202	3	4	3	10	10	6	1	9	9	9	4
	N,N-Dimethyl acetamide	127-19-5		165	3	6	3	9	10	6	1	7	9	9	2
	N,N-Dimethyl formamide	68-12-2		153	3	6	3	8	10	4	1	6	9	9	7
Chlorinated	Dichloromethane	75-09-2		40	2	10	4	1	8	6	7	4	4	10	7
	1,2-Dichloroethane	107-06-2		84	2	7	5	5	9	7	1	2	5	10	7
	Chloroform	67-66-3		61	3	9	5	3	7	5	4	1	5	10	6
	Carbon tetrachloride	56-23-5		77	3	7	5	4	4	1	4	1	4	10	7

Column Headings Colour Key

- Waste
- Environment
- Human Health
- Safety

Composite Colour Key

- Few Known Issues
- Some Known Issues
- Major Known Issues

The scoring assessment for this solvent includes 4 or more data gaps, therefore there is a lower level of confidence in the solvent's placement on this guide.

†A blank value for Life Cycle Analysis (LCA) indicates that this data is currently not available.

‡The composite colour represents an overall categorization of the holistic sustainability of a solvent, taking all category scores into consideration.

Figure 4: Reverse side of updated GSK Solvent Sustainability Guide single page view, providing scoring breakdowns for selected solvents.

Data for Newly Assessed Solvent Options

Few Issues → Major Issues

Solvent Name	CAS Number	Solvent Classification	Composite Colour	Boiling Point (°C)	Incineration	Recycle	Biotreatment	VOC Emissions	Environmental Impact: Aqueous	Environmental Impact: Air	Health Hazard	Exposure potential	Safety: Flammability & Explosion	Safety: Reactivity	Number of Data Gaps*
Glycerol triacetate	102-76-1	Ester		259	5	5	7	10	9	10	10	10	9	10	4
1-Pentanol	71-41-0	Alcohol		137	7	8	8	9	9	4	10	9	9	10	0
1-Heptanol	111-70-6	Alcohol		178	9	8	10	9	8	4	10	7	9	10	3
Glycerol diacetate	111-55-7	Ester		187	5	6	6	10	6	8	10	8	10	10	1
Isobutyl acetate	110-19-0	Ester		116	7	9	8	6	9	6	10	6	8	10	1
Amyl acetate	628-63-7	Ester		146	7	8	8	8	9	5	7	8	8	10	2
2,4,6-Collidine	108-75-8	Aromatic		171	7	9	6	8	10	5	7	8	9	9	4
2-Ethylhexyl acetate	103-09-3	Ester		199	9	7	9	10	4	6	10	7	9	10	2
1-Octanol	111-87-5	Alcohol		195	9	7	8	10	5	4	7	10	9	10	1
Methyl oleate	112-62-9	Ester		218	9	6	8	10	5	8	4	10	7	10	3
Isoamyl acetate	123-92-2	Ester		142	9	9	8	8	4	6	7	8	8	10	1
Diethyl carbonate	105-58-8	Carbonate		126	7	9	9	7	9	8	4	5	8	10	4
Isobutanol	78-83-1	Alcohol		108	6	3	5	7	10	6	7	7	8	9	0
1-Hexanol	111-27-3	Alcohol		157	5	6	3	9	8	5	7	9	9	10	1
Dimethyl succinate	106-65-0	Ester		200	4	5	6	10	9	7	4	7	9	10	4
Lactic acid	50-21-5	Acid		122	3	6	5	10	9	6	4	9	10	8	4
Furfural	98-01-1	Other		162	7	8	8	8	8	4	4	6	9	9	1
t-Amyl alcohol	75-85-4	Alcohol		102	6	3	4	7	9	5	7	6	8	10	2
Diethyl succinate	123-25-1	Ester		218	7	7	9	10	9	8	4	8	9	10	6
N,N-Dimethyldecanamide	14433-76-2	Other		291	6	7	6	10	4	6	10	10	10	10	5
Dimethyl adipate	627-93-0	Ester		110	8	5	10	10	8	8	4	8	9	10	5
Butylene carbonate	4437-85-8	Carbonate		250	5	5	7	10	9	9	4	9	9	10	9
γ-Valerolactone	108-29-2	Ester		207	8	7	10	9	10	6	4	7	9	10	9
Diisopropyl adipate	6938-94-9	Ester		136	5	7	6	10	7	8	4	10	9	10	8
Dihydrolevoglucosenone	1087696-49-8	Other		203	4	4	5	10	9	6	4	8	10	10	9
Dimethyl isosorbide	5306-85-4	Ether		236	4	4	5	10	9	6	4	9	9	8	10
1,2-Isopropylideneglycerol	100-79-8	Alcohol		192	6	5	5	10	4	6	4	8	10	10	5
N,N-Dimethyloctanamide	1118-92-9	Other		261	5	6	5	8	7	5	4	6	9	10	6
1,3-Dimethyl-2-imidazolidinone	80-73-9	Dipolar aprotic		225	3	4	3	10	7	6	4	8	9	9	6
Methanesulfonic acid	75-75-2	Acid		167	2	5	5	10	6	6	4	10	9	6	2
Formic acid	64-18-6	Acid		101	5	4	8	6	8	8	4	4	7	7	0
1,2,3-Trimethoxypropane	20637-49-4	Ether		143	4	5	4	8	7	7	4	5	8	9	10
Methyl propionate	554-12-1	Ester		79	5	5	5	4	10	6	7	3	4	10	4
L-Limonene	5989-54-8	Hydrocarbon		175	10	8	7	9	3	3	4	6	5	10	2
D-Limonene	5989-27-5	Hydrocarbon		175	10	8	7	9	3	3	4	7	5	10	1
p-Cymene	99-87-6	Aromatic		177	10	8	7	9	3	2	4	6	6	9	5
1,3-Dioxolane	646-06-0	Ether		75	4	4	3	4	7	5	7	5	2	9	2
Diethoxymethane	462-95-3	Ether		88	6	5	4	4	5	5	4	3	4	8	5
N-Ethylpyrrolidone	2687-91-4	Dipolar aprotic		212	3	4	3	10	9	6	1	8	9	9	6
Methyl formate	107-31-3	Ester		33	3	7	3	1	9	9	7	4	3	9	0
Dimethoxymethane	109-87-5	Ether		42	5	6	3	1	6	6	10	7	3	5	2
Tetrahydrofurfuryl alcohol	97-99-4	Alcohol		178	4	4	4	8	9	6	1	5	9	6	3

At least one piece of data is not available as part of this subscore. Values have been estimated where possible via calculation or comparison to structurally similar solvents.

*A red value in the number of data gaps column highlights those solvents with 4 or more data gaps.

Figure 5: Data chart for the 44 newly scored solvents, showing all category scores and the total number of data gaps for each solvent. Solvents are rank ordered by composite score within each colour designation.

4. Discussion

4.1 Determination of Scope of Solvent Guide

The solvents included in the GSK Solvent Sustainability Guide cover a wide range of organic small molecule solvents. Previous versions of the guide contain a number of solvents known to be highly problematic, including ones with severe human health and environmental hazards. We feel that displaying such solvents alongside greener alternatives provides useful data to the researcher and improves the likelihood that the greener options will be further examined. In determining which solvents to add to this updated version, a number of sources were consulted,[14] and it is acknowledged that many of the newly added solvents are ones which as of yet have limited known utility in synthetic organic processes.

4.2 Relative Weight of Boiling Point and Vapour Pressure in Scoring Assessments

Throughout the guide methodology, there are multiple instances in which a single property value feeds into multiple assessment categories. For example, while odour threshold is relevant only to the environmental impact-air score, water solubility impacts both the incineration and biotreatment waste categories. In examining the final solvent rankings, it was noted that many solvents with relatively high boiling points are assessed as green. Both the VOC emissions and flammability & explosion scores favour a high boiling point. However, a low boiling point is preferred from a waste recycling standpoint and boiling point is given extra weight in the recycling score. Therefore, high boiling point on its own does not tend to result in an overall positive assessment. Indeed a solvent's vapour pressure has a greater impact than boiling point on the composite score. As seen in Table 5, a high vapour pressure is disfavoured within 5 discrete assessment categories.

Summary Area	Category	Vapour Pressure (P_{vap}) Scoring Relationship
Waste	Biotreatment	High P_{vap} → Low score
Waste	VOC Emissions	High P_{vap} → Low score
Environment	Air Impact	High ratio of P_{vap}: odour threshold → Low score
Health	Exposure Potential	High ratio of P_{vap}: TLV* →Low score
Safety	Flammability & Explosion	High P_{vap} → Low score

*TLV refers to the minimum threshold limit value as set by key regulatory agencies.

Table 5: Impact of vapour pressure on category scores

This in turn explains the observation regarding the green classification of many high boiling point solvents, given that there is a high correlation within the dataset[30] between high boiling point and low vapour pressure (Figure 6).

While vapour pressure clearly has a greater impact on the composite score than other solvent properties, the authors are confident that such emphasis is not disproportionate, but rather reflective of the fact that high vapour pressure solvents do cause significant concerns across a wide range of waste, health, environment, and safety categories, each of which must be taken into account in this holistic assessment. In fact, there are several relatively high vapour pressure solvents (*e.g.* EtOAc and 2-MeTHF) which are still assessed favourably in the final guide, where data in other categories do not indicate significant hazards.

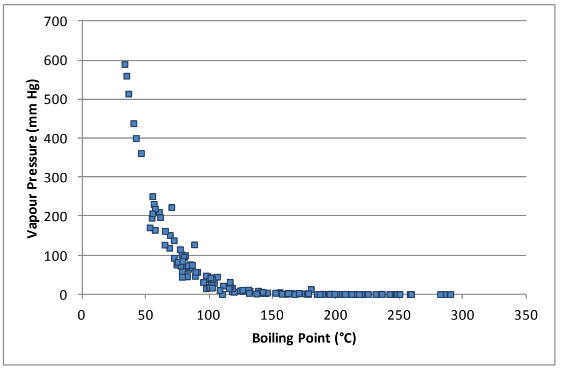


Figure 6: Graph of boiling point vs. vapour pressure across solvent dataset[30]

4.3 Observed Variability in Reported Data

In compiling the data which underlies this guide, it was sometimes found that differing values were reported for the same data point. Even on relatively simple physical properties such as vapour pressure, the value could vary among multiple well known and respected databases or peer-reviewed publications. While such differences tended to be relatively minor, there were still instances in which the choice of values could significantly affect the end scoring. In such cases, as long as all pieces of data were deemed to be reliable, in following with the precautionary principle, whichever value would result in the most conservative assessment was chosen. Such inconsistency in data is inherent with varied experimental techniques and has indeed been well documented in the case of auto-ignition temperature, for which many solvents have an unusually large range of reported experimental values.[31]

4.4 Customisation of the Guide

With this extensive set of data compiled for 154 solvents, there are many potential ways in which final assessments may be displayed. We have prepared a single page view (Figure 3) including those solvents which are most widely used at GSK, as well as several greener alternatives which may at present be less frequently employed. This view provides an at-a-glance comparison both of solvents in a single chemical class and across multiple classes. It also emphasises the fact that members of certain chemical classes (*e.g.* alcohols, esters, and carbonates) tend to be greener than structurally similar solvents from other categories. From top to bottom, the placement of solvents reflects the continuum from green to red, showing that even within a colour classification, there is a range of sustainability assessments. Boiling points are provided for those solvents that fall within the green or amber boundaries. For solvents where 4 or more data gaps occur, the names have been annotated, reminding users that multiple approximations imply a lower level of confidence.

This allows the individual chemist to make a more meaningful solvent selection, emphasizing those areas which are of highest relevance for them.

We have also separated out the data on the 44 newly assessed solvents in this latest update of the GSK Solvent Sustainability Guide (Figure 5). This table should allow the user to become more familiar with these solvents. Annotations via underlined italicised text throughout the table highlight those category scores which depend on one or more data gaps, and represent areas in which other researchers may wish to devote resources to generating the data necessary for more accurate assessments.[32] This guide will be a "living" document at GSK, and would greatly benefit from additional experimental data in order to further refine our assessments.

Internally, employees can also access all the data that underlies these guides on the company's intranet. An interactive spreadsheet is available, allowing users to filter by name, solvent class, and/or any scoring category or data point, as well as to access single page data sheets for individual solvents.

Several groups within the GSK organisation have expressed interest in creating unique views of these data, customised for their scientific and business needs. Such tailored views are useful to increase the utility of these guides to the end user. In addition, the process of creating such formats allows scientists to directly engage in deciding which data categories and solvents are most relevant to their work, as well as creating annotations specific to their business area. It has even been noted that these guides may be useful beyond synthetic chemistry departments, as those who work in analytical chemistry, biology, and other scientific disciplines often utilise solvents which may carry significant hazards.

5. Conclusions

The new version of the GSK Solvent Sustainability Guide is a useful update to previous guides.

- It offers confidence that scores are based on data current as of 2016.
- It highlights key instances where assumptions have had to be made.
- It includes an additional 44 solvents. For many of these, detailed evaluations using such a wide range of green chemistry considerations were not previously available.

The process of updating the guide and making decisions on methodology was facilitated by review from a team whose members represent a wide scope of GSK disciplines, including drug discovery, product development, manufacturing, process safety, and occupational toxicology. This group also spans a wide geographical range.

Different disciplines may choose to use different aspects of the guide, and in particular we would highlight that the colour assignment alone may not always be appropriate when comparing solvent options.

We would encourage all chemists to use the data provided by this tool to make their own judgements based on the requirements of their chemistry.

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Notes and References

[a] *Green Chemistry, GSK, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts., UK, SG1 2NY.*
[b] *API Chemistry, GSK, Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts., UK, SG1 2NY.*
[c] *Environmental Sustainability Centre of Excellence, GSK, Park Road, Ware, Herts., UK, SG12 0DP.*
[d] *Green Chemistry, GSK, 5 Moore Drive, Research Triangle Park, NC 27709, USA*
[e] *Green Chemistry, GSK, 1250 South Collegeville Road, Collegeville, PA 19426, USA.*

†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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9 While Astra Zeneca has not publicly published their internal solvent guide, it was presented in 2008 to the GCIPR. Please see document entitled Collaboration to deliver a solvent selection guide for the pharmaceutical industry, by C. R. Hargreaves, and J. B. Manley at http://www.acs.org/content/dam/acsorg/greenchemistry/industriainnovation/roundtable/solvent-selection-guide.pdf, accessed 23 Feb 2016.
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12 D. Prat, J. Hayler, and A. Wells, *Green Chem*., 2014, **16**, 4546-4551.

[13] There are also a range of choices available beyond traditional organic small molecule solvents. Much literature has been devoted to solvents such as ionic liquids, supercritical fluids, and polymeric solvents, among others. While some of these may be considered to be green, they are felt to be beyond the scope of this guide, and are not frequently employed at the current time in pharmaceutical chemistry.

[14] For a list of where nearest neighbour and chemical class estimates were utilised in the dataset, and a rationale behind solvent choice please see the ESI.

[15] Ethanol/IMS (industrial methylated spirits) was previously included in the guide. This has now been split into two separate solvents to reflect the different assessment of pure ethanol as compared to ethanol denatured with methanol, which incorporates methanol's health risk phrases.

[16] See the ESI for a graphical example of how these data limits are assigned.

[17] See the ESI for details of how these equations are determined and the specific data as it relates to the scoring categories

[18] Dihydrolevoglucosenone, which is known to decompose upon heating before reaching the boiling point phase transition, is manually given a boiling point score of 4.

[19] Most POCP data came from or agree with data in M. E. Jenkin and G. D. Hayman, *Atmospheric Environment*, 1999, **33,** 1275-1293.

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[21] Sources used for regulatory data include internal GSK OEL values, threshold limit values (TLVs) from: American Conference of Governmental Industrial Hygienists (ACGIH), National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration (OSHA); time weighted average (TWA) values from: European Agency for Safety and Health at Work (EU-OSHA) Directive 2000/39/EC, EU-OSHA Directive 2006/15/EC, EU-OSHA Directive 2009/161/EU, EU-OSHA Directive 91/322/EEC, American Industrial Hygiene Association (AIHA) Workplace Environmental Exposure Levels (WEELs), ACGIH 8 hour values, United Kingdom - Workplace Exposure Limits (WELs); and German OEL values from the Technische Regel für Gefahrstoffe 900 (TRGS 900).

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[23] Sources utilised include: European Chemicals Agency (ECHA) Classification & Labeling (C&L) Inventory database (http://echa.europa.eu/information-on-chemicals/cl-inventory-database, ECHA Registered Substances Database (http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances), and UK versions of MSDS from both Sigma Aldrich and Acros Organics websites. Websites last accessed 13 Jan 2016.

[24] The National Fire Protection Association was established in 1896 and serves as the world's leading advocate of fire prevention. It is an authoritative source on public safety. The NFPA give scores for flammability, health and reactivity (as well as indicators of any special information) to each chemical and these are embedded into Material Safety Data Sheets.

[25] Total of soluble and insoluble organic matter going into water bodies

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[27] https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2011/december/presentations/5_blystone_sulfolane.pdf, Last Accessed 13 Jan 2016

[28] L. Moity, M. Durand, A. Benazzouz, C. Pierlot, V. Molinier, and J.-M. Aubry, *Green Chem.*, **2012**, *14*, 1132-1145.

[29] http://ec.europa.eu/enterprise/sectors/chemicals/reach/index_en.htm. accessed 30 Jan 2015

[30] The correlation of boiling point to vapour pressure is examined using only solvents for which experimental vapour pressure data is known. In addition, dimethyl ether (bp = -24.8 °C, P_{vap} = 4450 mm Hg) has been omitted for clarity of scale.

[31] C.-C. Chen, H.-J. Liaw, C.-M. Shu, and Y.-C. Hsieh, *J. Chem. Eng. Data*, 2010, **55**, 5059-5064.

[32] In the process of preparing this updated guide, the authors contacted several solvent suppliers, enquiring if these companies would be able to provide data to fill in specifically identified data gaps. Zeon Chemicals (supplier of CPME) and Circa Group (supplier of dihydrolevoglucosenone) both offered to run additional experiments in order to provide data. These experiments supplied flash point and autoignition temperature values for dihydrolevoglucosenone and a POCP value for CPME which were accordingly used in the solvent guide calculations.