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PAPER

Expanding GSK's solvent selection guide – embedding sustainability into solvent selection starting at medicinal chemistry†

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Solvents make a large contribution to the environmental impact of manufacturing processes of active pharmaceutical ingredients (API), as well as playing an important role in other chemical industries, with millions of tons used and disposed of each year. GlaxoSmithKline (GSK) has previously reported on the both the development of a GSK solvent selection guide and the incorporation of solvent life cycle inventory and assessment information. The GSK solvent selection guide has been further enhanced by:

• Revising the assessments of factors that impact process safety, separating reactivity from fire and explosion rankings.
• More than doubling the number of solvents in the guide, to a total of 110 from the initial 47.
• Adding a customised solvent selection guide appropriate for medicinal chemistry and analytical laboratories.

The new GSK solvent selection guide enables GSK scientists to objectively assess solvents and determine whether existing or new solvents brought to market as 'greener' alternatives truly represent a more sustainable choice or whether they are just addressing a single issue associated with sustainability.

1. Introduction

GSK's solvent selection guide is one part of GSK's award winning[1] Eco-Design Toolkit, a suite of web based tools that provide clear practical information and guidance to scientists and engineers to enable them to move towards a more sustainable design, and development of the chemical processes used in the manufacture of active pharmaceutical ingredients (API).[2] The first edition of the solvent guide was issued in 1998[3] and this established the GSK approach to improved solvent selection for chemical synthesis. The approach was to rank the most commonly used solvents relative to each other based on their inherent environmental, health and safety issues. The ranking was augmented with guidance on separability (*e.g.*, azeotropes and boiling point ranges) and ICH classifications. Initially the guide was piloted as an Excel spreadsheet and three wallcharts: the solvent guide, solvent separability and solvent guidance for ICH regulations. The implementation of robust corporate intranets and the arrival of web-based environments facilitated the delivery of detailed information and guidance in a structured and layered environment. Such an environment affords users the opportunity of seeing as much or as little information about solvents as required to make the best decisions about which solvent to use. The general philosophy of the original GSK solvent selection guide was to highlight potential adverse issues that needed to be managed if a particular solvent was used and to then provide information about possible alternatives that could be used rather than being proscriptive in the guidance given. The initial intent was to focus on identification and replacement of the worst solvents that could be taken into consideration during the design of synthetic processes.

In 2003, life cycle assessment information was added to each solvent in the guide[4] in response to studies highlighting the strong contribution that solvents have to the life cycle impacts of API manufacturing.[5,6] Constable *et al.*[7] reported on the state of solvent use in a pharmaceutical company in 2005 and reported that solvents constituted 80–90% of the non-aqueous mass of materials used to make an API. This also represents about

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75–80% of the environmental life cycle impacts for an API.[5] More recently in 2007, and again in 2008, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCIPR) published an industry-wide mass efficiency benchmarking study to understand the typical composition of the materials used to manufacture an API.[8,9] These studies corroborated internal GSK studies that highlighted the impacts solvents have on the environmental footprint of a process (Fig. 1). Sheldon[10] reported that the typical production volume of an API is in the range 10 to 1000 metric tonnes per annum. For a commercial process, the ACS GCIPR 2007 benchmarking study showed that the median amount of materials used to make 1 kg of API was 46 kg. Fig. 1 shows that 56% of the mass used is solvent, *i.e.* 22 kg of solvent are needed to make 1 kg of API. So for a 1000 tonne per annum process, this means that 22,000 kg of solvent will be needed.

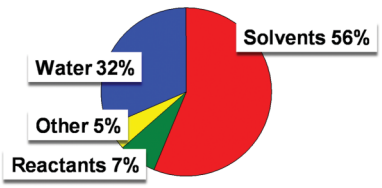

Fig. 1 Composition by mass of the types of material used to manufacture an API.[7]

Constable's review[7] shows how solvent use is evolving towards the use of greener solvents, but also commented that there were still challenges ahead, in particular a need to engage both the academic community and drug discovery scientists. The opportunity to significantly change behaviours in pharmaceutical companies is exemplified by Alfonsi *et al.*[11] where the reported impact of introducing a solvent selection guide was to reduce the routine use of chlorinated solvents by 50%.

2. Developing solvent selection guidance for medicinal chemists in GSK

The first version of GSK's solvent selection guide[3] was focused on providing guidance for chemists and engineers during chemical process development. While this philosophy is still valid, the approach does not suit all users. For example, scientists performing early route development work in medicinal chemistry or those working in analytical laboratories desired a simpler guide to highlight problematic solvents with a smaller list of suitable alternatives to test experimentally. If medicinal chemistry teams choose not to use solvents with significant issues (shown in the red column of Fig. 2), this can result in potential savings of time, effort and money when chemical development teams are scaling up routes for commercial production. To meet this need for simplified guidance, GSK have developed a quick reference solvent guide which contains information and guidance for a smaller number of solvents while remaining consistent with the larger and more comprehensive solvent guide (Fig. 2 and 3).

It is not an easy exercise to replace a complex set of assessments of 110 solvents with a simplified guide containing fewer solvents that states whether a solvent has significant issues or can be considered 'greener'. While the solvents included in the reduced set were chosen because they are commonly used solvents in medicinal chemistry laboratories in GSK, several solvents were added that have been demonstrated to work within GSK as greener alternatives to solvents having significant environmental, health or safety issues.

The original GSK solvent selection guide was developed to accommodate the fact that different solvents have different associated issues that have to be managed, such as inherent health or environmental hazards. At the time the original guide was developed, no single solvent selection guide was available

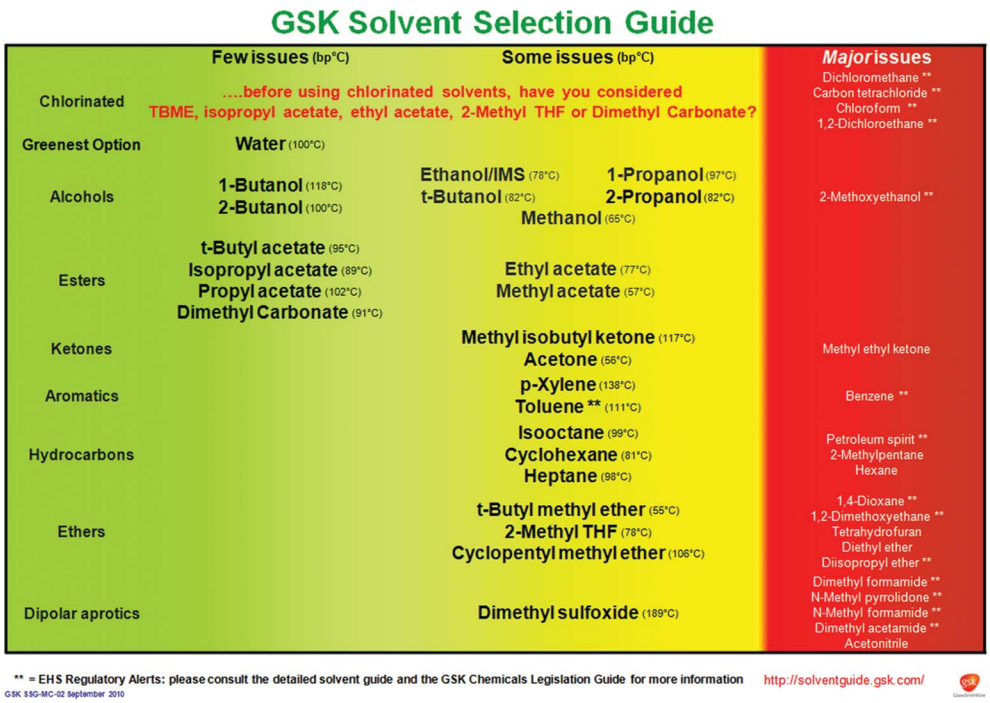

Fig. 2 A quick reference solvent guide for medicinal chemists, analytical scientists *etc.*

Classification	Solvent	CAS number	Melting point °C	Boiling point °C	Waste recycling, incineration, VOC, and biotreatment issues	Environmental Impact fate and effects on the environment	Health acute and chronic effects on human health and exposure potential	Flammability & Explosion storage and handling	Reactivity/ Stability factors affecting the stability of the solvent	Life Cycle Score Environmental impacts to produce the solvent	Legislation Flag alerts regulatory restrictions
Greenest	Water	7732-18-5	0	100	4	10	10	10	10	10	
Alcohols	1-Butanol	71-36-3	-89	118	5	7	5	8	9	5	
	2-Butanol	78-92-2	-115	100	4	6	8	7	9	6	
	Ethanol/IMS	64-17-5	-114	78	3	8	8	6	9	9	
	t-Butanol	75-65-0	25	82	3	9	6	6	10	8	
	Methanol	67-56-1	-98	65	4	9	5	5	10	9	
	2-Propanol	67-63-0	-88	82	3	9	8	6	8	4	
	1-Propanol	71-23-8	-127	97	4	7	5	7	10	7	
	2-Methoxyethanol	109-86-4	-85	124	3	8	2	7	6	7	
Ester	t-Butyl acetate	540-88-5	-78	95	6	9	8	6	10	8	
	Isopropyl acetate	108-21-4	-73	89	5	7	7	6	9	7	
	Propyl acetate	109-60-4	-92	102	5	7	8	6	10	4	
	Dimethyl carbonate	616-38-6	-1	91	4	8	7	6	10	8	
	Ethyl acetate	141-78-6	-84	77	4	8	8	4	8	6	
	Methyl acetate	79-20-9	-98	57	3	9	7	4	9	7	
Ketone	Methylisobutyl ketone	108-10-1	-84	117	6	6	6	7	8	2	
	Acetone	67-64-1	-95	56	3	9	8	4	9	7	
	Methylethyl ketone	78-93-3	-87	80	3	7	8	4	8	3	
Organic Acids	Propionic acid	79-09-4	-21	141	4	8	6	8	8	7	
	Acetic acid (glacial)	64-19-7	17	118	4	8	6	8	7	8	
Aromatics	p-Xylene	106-42-3	-13	138	7	2	6	5	10	7	
	Toluene	108-88-3	-95	111	6	3	4	4	10	7	
	Benzene	71-43-2	6	80	5	6	1	3	10	7	
Hydrocarbons	Isooctane	540-84-1	-107	99	6	4	8	3	10	7	
	Cyclohexane	110-82-7	7	81	5	5	7	2	10	7	
	Heptane	142-82-5	-91	98	6	3	8	3	10	7	
	2-Methylpentane	107-83-5	-153	60	5	4	7	2	10	7	
	Hexane	110-54-3	-95	69	5	3	4	2	10	7	
	Petroleum spirit	8032-32-4	-73	55	6	2	2	3	10	7	
Ethers	t-Butyl methyl ether	1634-04-4	-109	55	4	5	5	3	9	8	
	Cyclopentyl methyl ether	5614-37-9	-140	106	6	4	4	5	8	4	
	2-Methyl THF	96-47-9	-137	78	4	5	4	3	6	4	
	Diethyl ether	60-29-7	-116	35	4	4	5	2	4	6	
	Bis(2-methoxyethyl) ether	111-96-6	-68	162	4	5	2	8	4	6	
	1,4-Dioxane	123-91-1	12	102	3	4	4	4	5	6	
	Tetrahydrofuran	109-99-9	-108	65	3	5	6	3	4	4	
	1,2-Dimethoxyethane	110-71-4	-58	85	4	5	2	4	4	7	
	Diisopropyl ether	108-20-3	-86	68	4	3	8	1	1	9	
Dipolar aprotics	Dimethyl sulfoxide	67-68-5	19	189	5	5	7	9	2	6	
	Dimethyl formamide	68-12-2	-61	153	4	6	2	9	9	7	
	N-Methylformamide	123-39-7	-4	200	4	6	2	10	10	7	
	N-Methyl pyrrolidone	872-50-4	-24	202	5	6	3	9	8	4	
	Dimethyl acetamide	127-19-5	-20	165	5	6	2	10	8	2	
	Acetonitrile	75-05-8	-45	82	2	6	6	6	10	3	
Chlorinated	Carbon tetrachloride	56-23-5	-23	77	4	5	3	4	10	7	
	Dichloromethane	75-09-2	-95	40	3	6	4	6	9	7	
	Chloroform	67-66-3	-64	61	3	6	3	6	9	6	
	1,2-Dichloroethane	107-06-2	-36	84	4	4	2	6	10	7	

Legislation Flag	
	Substitution recommended - There are no current restrictions but future regulatory restrictions may apply
	Substitution recommended - existing regulatory restrictions apply
	Must be substituted - A regulatory ban applies

Fig. 3 Supporting table (printed on the back) to highlight where issues with these solvents actually lie.

that recognized the inherent complexity of solvent selection nor attempted to reconcile the competing environmental, safety and health issues into a single methodology for selection. There is a danger in calculating an overall average score or oversimplifying the guidance, as this can easily mask the one serious issue for a particular solvent that should prevent its selection. The intent of the simplified guidance presented here is to systematically guide the early route development scientists away from using the most problematic solvents and towards using solvents with fewer issues, without negating the fact that there will still be some issues to be managed as the chemical route is developed. In addition, the boundaries between the red, yellow and green zones in the guide shown in Fig. 2 were carefully set to ensure consistency with the more detailed solvent selection guide.

In contrast to route development teams in medicinal chemistry, teams of chemists and engineers in chemical development (or scale up laboratories) not only require a larger solvent set from which to choose the best solvent for any given process, they also require a greater level of detail to assist in their decision making. This greater level of detail enables these engineers and scientists to compare the pros and cons of choosing solvent A over solvent B, as they need to consider such factors as the ease of solvent recovery and the potential environmental impacts caused by a solvent.

The revised GSK solvent selection guide now includes 110 solvents and as with previous versions, the guidance is provided at different levels of detail depending on specific user requirements.

Level 1: a quick reference guide for medicinal chemists, analytical scientists *etc*. (Fig. 2 and 3), a new feature of the guide as described above.

Level 2: a table of summary rankings for 110 solvents within the areas detailed below (Fig. 4 and 5). Each solvent is scored from 1 (red) to 10 (green) to give a relative ranking for every solvent in the guide in each category, where the score is based on data or a physical observable property:

- Waste: covering recycling, incineration, VOC, and biotreatment issues
- Environmental impacts: covering the fate and effects of solvents on the environment
- Health: covering acute and chronic effects on human health and the potential for exposure

Classification	Solvent click on solvent name for hyperlink to more detail	Cas number	Melting point °C	Boiling Point °C	Waste	Environ-mental Impact	Health	Flamm-ability & Explosio	Reactivity/ Stability	Life Cycle Score	Legislation Flag	EHS Red Flag
Water	Water	7732-18-5	0	100	4	10	10	10	10	10		
Alcohol	2-Ethyl hexanol	104-76-7	-76	185	9	5	6	9	10	6		
	Glycerol	56-81-5	18	290	6	7	8	10	9	8		
	Cyclohexanol	108-93-0	25	161	6	6	7	9	9	8		
	Ethylene glycol	107-21-1	-13	197	5	8	7	10	9	9		
	1,4-butanediol	110-63-4	20	235	6	6	8	10	10	4		
	Isoamyl alcohol	123-51-3	-117	131	6	6	7	9	10	6		
	1,2-propanediol	57-55-6	-60	188	6	6	10	10	10	3		
	1,3-propanediol	504-63-2	-27	214	6	6	9	10	10	3		
	Benzyl alcohol	100-51-6	-15	205	6	6	7	10	7	6		
	2-Pentanol	6032-29-7	-50	119	6	6	6	8	8	6		
	1-Butanol	71-36-3	-89	118	5	7	5	8	9	5		
	2-Butanol	78-92-2	-115	100	4	6	8	7	9	6		
	Ethanol IMS	64-17-5	-114	78	3	8	8	6	9	9		
	t-Butanol	75-65-0	25	82	3	9	6	6	10	8		
	Methanol	67-56-1	-98	65	4	9	5	5	10	9		
	2-Propanol	67-63-0	-88	82	3	9	8	6	8	4		
	1-Propanol	71-23-8	-127	97	4	7	5	7	10	7		
	2-Methoxyethanol	109-86-4	-85	124	3	8	2	7	6	7		
Ester	t-Butyl acetate	540-88-5	-78	95	6	9	8	6	10	8		
	n-octyl acetate	112-14-1	-39	210	9	5	5	8	10	6		
	Butyl acetate	123-86-4	-77	126	7	7	8	8	10	5		
	Ethylene carbonate	96-49-1	36	248	6	7	5	10	9			
	Propylene carbonate	108-32-7	-55	242	6	7	5	8	9			
	Isopropyl acetate	108-21-4	-73	89	5	7	7	6	9	7		
	Ethyl lactate	97-64-3	-23	154	7	5	4	8	10			
	Propyl acetate	109-60-4	-92	102	5	7	8	6	10	4		
	Dimethyl carbonate	616-38-6	-1	91	4	8	7	6	10	8		
	methyl lactate	547-64-8	-66	144	5	9	4	8	9	5		
	Ethyl acetate	141-78-6	-84	77	4	8	8	4	8	6		
	Ethyl propionate	105-37-3	-74	99	5	7	4	6	6			
	Methyl acetate	79-20-9	-98	57	3	9	7	4	9	7		
	Ethyl formate	109-94-4	-80	54	4	6	5	4	9			
Ketone	Cyclohexanone	108-94-1	-32	155	6	8	6	8	9	6		
	Cyclopentanone	120-92-3	-51	131	7	6	6	8	10	6		
	2-Pentanone	107-87-9	-78	102	5	6	6	7	10	4		
	3-Pentanone	96-22-0	-42	102	5	6	8	7	6	4		
	Methylisobutyl ketone	108-10-1	-84	117	6	6	6	7	8	2		
	Acetone	67-64-1	-95	56	3	9	8	4	9	7		
	Methylethyl ketone	78-93-3	-87	80	3	7	8	4	8	3		
Acid	Propionic acid	79-09-4	-21	141	4	8	6	8	8	7		
	acetic anhydride	108-24-7	-73	140	5	8	4	8	6	6		
	Acetic acid	64-19-7	17	118	4	8	6	8	7	8		
Aromatic	Mesitylene	108-67-8	-45	165	8	3	7	6	10	7		
	Cumene	98-82-8	-96	152	7	5	6	8	5	7		
	p-Xylene	106-42-3	-13	138	7	2	6	5	10	7		
	Toluene	108-88-3	-95	111	6	3	4	4	10	7		
	Benzene	71-43-2	6	80	5	6	1	3	10	7		

Legislation Flag	
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	Must be substituted - A regulatory ban applies

GlaxoSmithKline

GSK-SSG-2009-01 http://solventguide.gsk.com/

Fig. 4 The extended GSK solvent guide for 110 solvents (part 1).

• Flammability and explosion: issues affecting storage and handling of solvents

• Reactivity and stability: covering factors affecting the stability of the solvent

• Life cycle: covering the environmental life cycle impacts from producing a solvent

• Regulatory flag: alerting users of potential impacts from current or possible future environmental, health and safety related legislation.

• Melting and boiling points: the boiling points of each solvent were added, with red flags attached to high (>120 °C) and low boiling point (<40 °C) solvents. This simple feature guides scientists away from choosing high boiling solvents which have high energy requirements for separation by distillation. Melting points were added to highlight that some solvents may actually be solids at room temperature.

Most of these areas were included in previous versions of the guide, with three notable additions to this revised version:

• the solvent boiling point and melting point

• the regulatory flag

• the substitution of a general safety area with two additional areas: the reactivity area and the stability, flammability and explosion area.

Level 3: Detailed assessments for each solvent, including physical properties, category information, and how environmental life cycle impacts can be reduced through solvent recovery

Level 4: Supplementary separability guidance, including azeotrope information to assist solvent recovery decision making

3. Enhancing the health and process safety analyses

The original GSK solvent Selection Guide[2] was based on an assessment of ***key categories*** which were considered to be the most significant in determining the potential environmental, health, and safety impacts associated with each solvent. In order to enhance the guide, these key categories and the methodology used to determine the assessments were reviewed and a decision to modify the assessments for recycle, health impacts and

Classification	Solvent (click on solvent name for hyperlink to more detail)	Cas number	Melting point °C	Boiling Point °C	Waste	Environmental Impact	Health	Flammability & Explosio	Reactivity/ Stability	Life Cycle Score	Legislation Flag	EHS Red Flag
Hydrocarbon	cis-Decalin	493-01-6	-43	196	7	3	7	6	7	7		
	ISOPAR G	64742-48-9	-60	163	8	2	9	6	10			
	Isooctane	540-84-1	-107	99	6	4	8	3	10	7		
	Methyl cyclohexane	108-87-2	-127	101	6	5	8	3	10	7		
	Cyclohexane	110-82-7	7	81	5	5	7	2	10	7		
	Heptane	142-82-5	-91	98	6	3	8	3	10	7		
	Pentane	109-66-0	-130	36	5	6	8	2	10	7		
	Methylcyclopentane	96-37-7	-142	72	6	4	5	2	9	7		
	2-Methylpentane	107-83-5	-153	60	5	4	7	2	10	7		
	Hexane	110-54-3	-95	69	5	3	4	2	10	7		
	Petroleum spirit	8032-32-4	-73	55	6	2	2	3	10	7		
Ether	Di(ethylene glycol)	111-46-6	-10	246	6	8	7	9	9	8		
	Ethoxybenzene	103-73-1	-29	170	8	4	7	10	10			
	Tri(ethylene glycol)	112-27-6	-7	285	6	8	6	10	9	7		
	Sulfolane	126-33-0	28	282	5	9	6	10	10			
	DEG monobutyl ether	112-34-5	-68	231	6	7	7	9	6	7		
	Anisole	100-66-3	-38	154	6	6	7	7	6	5		
	Diphenyl ether	101-84-8	27	258	8	5	4	8	6			
	Dibutyl ether	142-96-1	-95	140	7	7	4	5	5	4		
	t-Amyl methyl ether	994-05-8	-80	86	5	5	5	5	9	8		
	t-Butylmethyl ether	1634-04-4	-109	55	4	5	5	3	9	8		
	Cyclopentyl methyl ether	5614-37-9	-140	106	6	4	4	5	8	4		
	t-Butyl ethyl ether	637-92-3	-74	70	5	5	4	4	9	8		
	2-Methyltetrahydrofuran	96-47-9	-137	78	4	5	4	3	6	4		
	Diethyl ether	60-29-7	-116	35	4	4	5	2	4	6		
	Bis(2-methoxyethyl) ether	111-96-6	-68	162	4	5	2	8	4	6		
	Dimethyl ether	115-10-6	-141	-25	3	5	7	1	4	7		
	1,4-Dioxane	123-91-1	12	102	3	4	4	4	5	6		
	Tetrahydrofuran	109-99-9	-108	65	3	5	6	3	4	4		
	1,2-Dimethoxyethane	110-71-4	-58	85	4	5	2	4	4	7		
	Diisopropyl ether	108-20-3	-86	68	4	3	8	1	1	9		
Dipolar aprotic	Dimethylpropylene urea	7226-23-5	-23	247	7	7	4	9	7	3		
	Dimethyl sulphoxide	67-68-5	19	189	5	5	7	9	2	6		
	Formamide	75-12-7	3	220	4	7	2	10	8	8		
	Dimethyl formamide	68-12-2	-61	153	4	6	2	9	9	7		
	N-Methylformamide	123-39-7	-4	200	4	6	2	10	10	7		
	N-Methyl pyrrolidone	872-50-4	-24	202	5	6	3	9	8	4		
	Propanenitrile	107-12-0	-93	97	3	6	4	6	9			
	Dimethyl acetamide	127-19-5	-20	165	5	6	2	10	8	2		
	Acetonitrile	75-05-8	-45	82	2	6	6	6	10	3		
Halogenated	1,2-Dichlorobenzene	95-50-1	-17	180	7	4	6	10	9	8		
	1,2,4-Trichlorobenzene	120-82-1	17	214	7	4	4	9	10	8		
	Chlorobenzene	108-90-7	-45	132	6	6	4	8	10	8		
	trichloroacetonitrile	545-06-2	-42	83	5	6	6	7	10			
	Chloroacetic acid	79-11-8	61	189	4	6	6	10	8	7		
	trichloroacetic acid	76-03-9	58	197	3	6	6	10	6	7		
	Perfluorotoluene	434-64-0	-66	104	5	3	4	5	10			
	Perfluorocyclohexane	355-68-0	51	53	5	5	3	5	10			
	Carbon tetrachloride	56-23-5	-23	77	4	5	3	4	10	7		
	Dichloromethane	75-09-2	-95	40	3	6	4	6	9	7		
	Perfluorohexane	355-42-0	-86	57	4	4	3	5	10			
	Fluorobenzene	462-06-6	-42	85	5	3	6	5	9	1		
	Chloroform	67-66-3	-64	61	3	6	3	6	9	6		
	Perfluorocyclic ether	335-36-4	-88	103	5	2	3	7	10			
	Trifluoracetic acid	76-05-1	-15	72	2	5	6	7	8			
	Trifluorotoluene	98-08-8	-29	102	5	4	1	5	9			
	1,2-Dichloroethane	107-06-2	-36	84	4	4	2	6	10	7		
	2,2,2-Trifluoroethanol	75-89-8	-43	74	3	5	2	6	9	7		
Base	N,N-Dimethylaniline	121-69-7	3	194	7	5	4	8	8	3		
	Triethylamine	121-44-8	-115	89	4	5	3	4	8	7		
	Pyridine	110-86-1	-42	115	3	4	4	7	9	2		
Other	Nitromethane	75-52-5	-29	101	3	8	4	7	2			
	carbon disulfide	75-15-0	-111	46	4	6	2	1	6	8		

Legislation Flag	
	Substitution recommended - There are no current restrictions but future regulatory restrictions may apply
	Substitution recommended - existing regulatory restrictions apply
	Must be substituted - A regulatory ban applies

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Fig. 5 The extended GSK solvent guide for 110 solvents (part 2).

process safety impacts was made. The assessments for the other original categories remained unchanged.[1] A general description of the key parameters and rationale of the methodology for the modified assessments is given below.

Recycle

The recycle category was revised to add the two redeveloped process safety categories to the previous key parameters, with the ranking now expanded to an assessment of seven parameters.

◦ *Key parameters*:

- Boiling point (for the energy impact and ease of distillation)
- Number of solvents with a boiling point within 10 °C (ease of solvent recovery)
- Number of azeotropes with other solvents in the guide (ease of distillation)
- Relative ease of drying
- Solvent flammability and explosion risk (boiling point, flash point, autoignition temperature, electrical conductivity and vapour pressure)
- Solvent stability and reactivity (peroxide formation, acidity, special hazards)

• Water solubility (affecting the potential loss in aqueous streams)

This assessment only considers single solvents and takes no account of other undesirable contaminants resulting from specific process reactions or complex mixtures of solvents. Solvent recovery from complex mixtures should be done on a case-by-case basis; the aim of this assessment is to indicate the potential issues associated with using a particular solvent as part of the solvent mix. Water miscible solvents have a reduced score due to the potential difficulties in recovering solvent from a mixed aqueous-organic solvent system. This may not be a problem if no water is used in the process and this would be highlighted in a detailed assessment of such a route.

Health hazard

The original health hazard categorisation in the first version of the solvent guide was based on a classification hierarchy that went from solvents with minimal health hazard concerns following occupational exposure to solvents that would result in anticipated serious or irreversible effects following occupational exposure. Health hazard information was derived from human case reports or animal studies.[3] Subsequently, the health score was revised basing it on the key health hazards of a solvent as described by the assigned European Union Risk Phrases. With this version of the solvent selection guide, the health hazard category was revised again to include a consideration of the GSK occupational hazard categories and occupational exposure limits (OEL) assigned by either GSK, a third party supplier or an official regulatory body such as the UK Workplace Exposure Limits defined by the UK Health and Safety Commission or the Threshold Limit Values defined by the American Conference of Governmental Industrial Hygienists. This was done because the OEL assigned to some solvents is more stringent than would be expected by simply classifying them according to their EU Risk Phrases.

◦ *Key parameters*:
- The GSK occupational hazard category
- Occupational exposure limit
- EU Risk Phrases
- Vapour hazard ratio

The approach to developing the health hazard ranking was to first classify each solvent using GSK occupational hazard categories. These initial classifications were then modified if the assigned OEL in ppm was more restrictive than that described by the GSK occupational hazard categories. The OEL used was the lowest found for an 8 h time weighted average after reviewing data from predominantly EU and US sources. This inherent health hazard information is then coupled with the potential for exposure in order to produce a ranking for the health area, as in previous versions of the guide. The potential for exposure is based on the vapour hazard ratio which is calculated from the ratio of the relative rate of evaporation of a solvent to butyl acetate with its OEL.

Flammability and explosion safety hazard

The earlier versions of the guide presented a single process safety score, combining occupational safety (mainly process chemistry risks related to reactivity), and fire and explosion potential. The approach in the new version of the guide was to separate fire and explosion issues from stability and reactivity. The fire and explosion safety hazard area covers issues affecting solvent storage and handling and focuses on the management of volatile solvents in zoned areas to prevent explosions from static discharge or some other unforeseen ignition source.

◦ *Key parameters*:
- Boiling point °C
- Flash point °C
- Autoignition temperature °C
- Electrical conductivity
- Vapour pressure

For example solvents with low boiling points and high vapour pressures can form volatile mixtures in air and solvents with low electrical conductivity and low flash points present a much higher potential risk of ignition by static discharge.

Stability and reactivity safety hazard

This area addresses issues associated with the chemical reactivity of a solvent. It does not provide a detailed process safety risk assessment for a process which will still need to be performed on a case-by-case basis, but offers guidance on whether there are likely to be issues if a particular solvent is used.

◦ *Key parameters*:
- Peroxide formation
- Potential for self-reaction
- NFPA rating
- Acidity/basicity
- Special hazards

Peroxide formation: solvents that form peroxides upon storage present a risk of explosion. The rate of peroxide formation is dependent on the individual solvent, and the risk can be mitigated by the addition of a stabiliser after purification by distillation.

Potential for self-reaction/special hazards: A very small number of solvents have the potential for self-reaction or present some other special hazard, for example nitromethane is highly explosive. This assessment is to highlight these special cases.

NFPA rating: Other organisations such as the US National Fire Protection Association (NFPA) have assessed many chemicals for reactivity. Their assessment is included as a benchmark and to highlight the more hazardous solvents.

Acidity/basicity: The pK_a and pH give an indication of the reactivity of an acidic or basic solvent.

Regulatory Flags

This update of the solvent selection guide connects this guide with a tool also developed in-house which is used to highlight potential and actual environmental, health and safety regulatory concerns: the GSK chemicals legislation guide. This is achieved by providing a colour coded flag where a solvent has a known or potential regulatory issue along with advice and a link to the GSK chemicals legislation guide where more detailed information and guidance about the specific regulation can be found.

The scores of the updated GSK solvent selection guide have also been integrated into an R & D tool known as the PCA viewer. This is a tool that helps engineers and scientists visualise

solvent chemical properties in 3-dimensions and is used to identify solvents with similar properties as part of a desk-based screening approach to selecting solvents.

4. Strategic behavioural change

This revision and expansion of the GSK solvent selection guide was only one part of the strategy to introduce and reinforce behavioural change. The target objective of introducing guidance into medicinal chemistry laboratories is to reduce the use of chlorinated solvents in early routes and so reduce their carry over into scale up laboratories and manufacturing scale processes. To support the introduction of a GSK solvent selection guide for medicinal chemistry, certain barriers to adoption were identified and overcome in a pilot study:

• *The need to provide reference spectra of the greener solvents identified in the guide*. The spectral peaks (NMR and LCMS) of traditional solvents that have been in routine use for decades are embedded in the minds of most synthetic chemists. A library of solvent spectra has been developed to allow swift identification of peaks from greener solvents that are being used possibly for the first time.

• *Adding greener solvent data to electronic lab books*. Many pharmaceutical (and other) institutions now use electronic lab notebooks to design and record the outputs from experiments. One benefit is the automatic generation of health and safety risk assessments for solvents prior to commencing work. Where the newer solvents were not in the electronic lab notebook database, scientists were faced with manually preparing risk assessments (taking up to 10 min), and this was found to be a significant barrier to their adoption in a busy working environment.

• *Making the greener solvents instantly available*. The creation of a local solvent cabinet containing "free" samples (500 ml bottles) of the new, greener solvents facilitated the immediate investigation of these solvents, in contrast to the delay involved when ordering from either a central store or a commercial manufacturer. Pressure of work means that a less green solvent that is readily available will be usually be used by default if a greener solvent alternative is not immediately to hand.

• *Providing laminated copies of the guide for easy and timely reference at desks and by fume-cupboards*. These also provided highly visible "icons" advertising the approach and the individual chemists' commitment to others.

• *Highlighting practical advantages offered by the greener solvents*. For example, in contrast to tetrahydrofuran, reactions conducted in either 2-methyltetrahydrofuran or cyclopentyl methyl ether can readily form two-phase mixtures during aqueous quench/extraction.

The outcome of the pilot study showed that there were other positive consequences of raising awareness and challenging the use of chlorinated solvents.

• Scientists demonstrated an instinctive willingness to develop more sustainable chemistries. The study suggested that they will choose a greener solvent for their chemistry if they are aware of greener alternatives and these alternatives are readily available.

• A number of simple and effective technologies were found to be already available to assist the adoption of greener solvents. For example, Chromabond PTL phase separation cartridges (Macherey-Nagel) conveniently allow aqueous phases to be run off from less dense organic solvents. We had observed that one driver for chlorinated solvent use in labs was simply the convenience afforded by their greater density over water during separations.

• The challenge to use the identified alternative solvents also provided a watershed experience to the chemistry community involved in the pilot study. A change of mind-set opened up new possibilities for both chemistry and analytical sciences. Teams began to re-evaluate their solvent toolbox which challenged and engaged their passion for chemistry to find optimal solvents for their reactions and analyses. For example introducing *t*-butyl methyl ether into automated normal-phase silica chromatography systems was found to facilitate purification of the increasingly polar and less-UV chromophoric molecules originating from recent fragment-based drug design efforts.

• This is a valid and real business benefit that gives analytical chemists more options.

5. Application examples - evaluating solvent alternatives

One of the main aims of updating the GSK solvent selection guide was to incorporate new solvents that have come to market that are supposed to be "green" or "greener" than existing solvents and to highlight other potential "green" or "greener" solvents that have limited availability and thereby provide incentives to solvent manufacturers to make them more available. Since 2003 GSK's solvent selection guide has included a life cycle score that ranks solvents based on their supply chain environmental impacts.[4] This demonstrates that our guide incorporates issues related to solvent manufacture as well as addressing the traditional environment, health and safety issues associated with solvents. For example, a comparison of ethers shows that *t*-amyl ethyl ether would be a highly desirable solvent for use in extractions, in the place of *t*-butyl methyl ether which has a very low flash point and a low boiling point of 55 °C both of which lead to handling difficulties, especially at commercial scale. Cyclopentyl methyl ether and 2-methyltetrahydrofuran are two other solvents that are fairly new to the market, and whose EHS characteristics are comparatively more favourable to other ethers as shown in Fig. 6. 2-Methyltetrahydrofuran is increasingly being used in route development in GSK. For example it was used on average in 16% of all pilot plant campaigns in GSK 2007-2009 compared an average of 3.5% of all pilot plant campaigns in 2005-6.

GSK's solvent selection guide can also be used to identify and compare alternatives to chlorinated solvents such as dichloromethane (Fig. 7) by showing where the issues in using chlorinated solvents lie.

As with previous versions of the guide,[3–4] the level of detail available in addition to the scores provided in the tables enables teams to develop solvent recovery strategies to mitigate poor environmental life cycle scores. As described in detail by Jimenez-Gonzalez *et al.*[4] the life cycle scores developed in the previous version of the guide are calculated on a scale of 1 to 10 by comparing the life cycle environmental impact data of a solvent relative to the data from the entire dataset of the other solvents in the guide where data is available. Some estimations based on a nearest neighbour approach were made where there

Classification	Solvent	Cas number	Melting point °C	Boiling Point °C	Waste	Environmental Impact	Health	Flammability & Explosio	Reactivity/ Stability	Life Cycle Score
Ether	t-Amyl methyl ether	994-05-8	-80	86	5	5	5	5	9	8
	t-Butylmethyl ether	1634-04-4	-109	55	4	5	5	3	9	8
	Cyclopentyl methyl ether	5614-37-9	-140	106	6	4	4	5	8	4
	t-Butyl ethyl ether	637-92-3	-74	70	5	5	4	4	9	8
	2-Methyltetrahydrofuran	96-47-9	-137	78	4	5	4	3	6	4
	Diethyl ether	60-29-7	-116	35	4	4	5	2	4	6
	Bis(2-methoxyethyl) ether	111-96-6	-68	162	4	5	2	8	4	6
	Dimethyl ether	115-10-6	-141	-25	3	5	7	1	4	7
	1,4-Dioxane	123-91-1	12	102	3	4	4	4	5	6
	Tetrahydrofuran	109-99-9	-108	65	3	5	6	3	4	4
	1,2-Dimethoxyethane	110-71-4	-58	85	4	5	2	4	4	7
	Diisopropyl ether	108-20-3	-86	68	4	3	8	1	1	9

Fig. 6 A comparison of ethers used for extraction as assessed in the GSK solvent selection guide.

Solvent	Cas number	Melting point °C	Boiling Point °C	Waste	Environmental Impact	Health	Flammability & Explosio	Reactivity/ Stability	Life Cycle Score	Legislation Flag
Isopropyl acetate	108-21-4	-73	89	5	7	7	6	9	7	
Dimethyl carbonate	616-38-6	-1	91	4	8	7	6	10	8	
Ethyl acetate	141-78-6	-84	77	4	8	8	4	8	6	
t-Butylmethyl ether	1634-04-4	-109	55	4	5	5	3	9	8	
2-Methyltetrahydrofuran	96-47-9	-137	78	4	5	4	3	6	4	
Dichloromethane	75-09-2	-95	40	3	6	4	6	9	7	
Chloroform	67-66-3	-64	61	3	6	3	6	9	6	

Fig. 7 A comparison of substitute solvents for dichloromethane and chloroform.

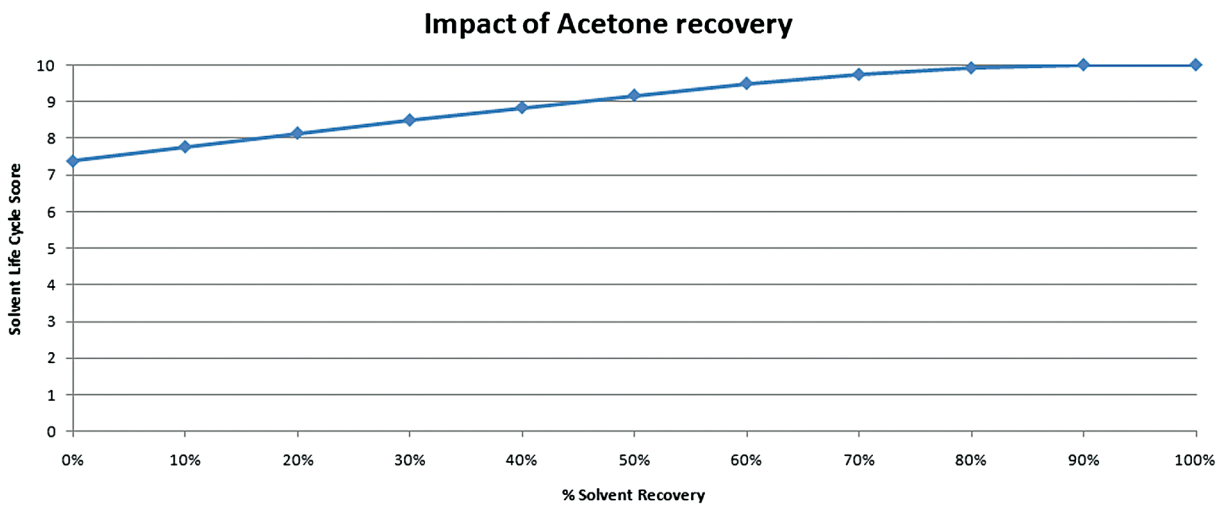

Fig. 8 The impact of acetone recovery on the life cycle score.

were gaps in the data. The life cycle scores in the high-level guide are calculated without taking any solvent recovery into account. However, different recovery cases were also modelled and the impact of solvent recovery on the life cycle score was included for each solvent in the guide. For example the plot in Fig. 8 shows that recovering 50% of acetone brings the life cycle impact score of acetone to > 9 which is equivalent to the life cycle impact of virgin ethanol produced by a fermentation process.

6. Conclusions and future work

The revised GSK solvent selection guide is an example of how GSK continuously strives to make choosing the sustainable option not only the right thing to do but the easy thing to do. The addition of a guide tailored for laboratory based medicinal chemists could and should have a transformational impact in reducing the use of chlorinated solvents in GSK. The GSK approach to solvent selection has and continues to influence other companies and organisations in the pharmaceutical sector, with the most recent development being the proposed launch of a solvent guide assessing around 60 solvents developed by the ACS GCIPR[12] which aims to bring guidance to all its member companies. As well as being a member company of the ACS GCIPR, GSK have been active contributor to this project including donating available data for the solvents to be assessed in the ACS GCIPR guide, as the authors had already collected the data for this piece of work.

The GSK approach to solvent assessment continues to provide a comparative and relative assessment of the solvents in the guide, but it now includes the vast majority of common solvents along with some less common and some solvents that have only recently come to market or wider attention for their green credentials such as cyclopentyl methyl ether and 2-methyltetrahydrofuran. The systematic approach to assessing solvents enables new or extra solvents to be added to the guide so that it can continue to evolve to remain current and up to date. Guidance such as that provided in this tool is of increasing value to companies and other institutions to enable scientists in research and development roles to develop processes that are demonstrably more sustainable based on objective assessments. This is especially important in light of adoption of regulations such as the EU REACH Legislation that aims to restrict the marketing and use of hazardous chemicals.

GSK also seeks to move towards more sustainable business practices in all areas of its business, and this guide is a part of current and future initiatives and strategies to embed sustainability into our operations.

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