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Solvent selection guide: a guide to the integration of environmental, health and safety criteria into the selection of solvents

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Abstract A practical, easy to use Solvent Selection Guide has been developed to provide a concise source of selected information and guidance to chemists and engineers to assist with their selection of solvents. It provides a relative ranking, and is limited by design to the inherent environmental, health and safety issues, in combination with general and specific process and facility issues associated with each solvent. These represent areas that are not always considered by R&D chemists and engineers during normal product or process development. The guide is intended to augment existing processes that mostly consider only technical, cost and regulatory aspects so that chemists and engineers may make more broadly considered solvent selections early in the chemical development process. The Guide currently includes a total of 35 solvents which were most commonly used in SmithKline Beecham (SB) Research and Development and manufacturing activities over the past three years, although the methodology used to develop the guide is readily applicable to other solvents. Detailed guidance is provided in a manual, and is summarized within charts which relatively rank and identify solvents and key issue areas, provide information on the new International Conference on Harmonization (ICH) guidelines for residual solvents in final pharmaceutical products, and supply data for co-solvent selection. The latter chart enables a chemist or engineer to choose solvents based on the ease of separation, which maximizes solvent utilization, recovery, and re-use. There is also a summary sheet for each solvent which reviews the scores and major issues for all the key categories used to develop the Environment & Safety Guide and provides essential solvent property data.

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1
Introduction

Solvents play an extremely important role in the chemical and allied industries, and millions of tons are used and disposed of each year. Over the past decade, there have been a variety of government and industry efforts to eliminate, replace, recycle or minimize the use of solvents. This effort has been driven out of a desire to reduce human health impacts, process safety risks, and multiple impacts to the environment. Industry has been forced through an ever-increasing array of regulations and voluntary efforts to judiciously consider solvent use and devise strategies to minimize their use or mitigate their impact. Over time, it has become increasingly evident that further progress in reducing solvent use can only come through pollution prevention efforts that begin in the earliest phases of product development.

Given the need for early consideration of solvent impacts during product development, it is imperative to place tools into the hands of R&D scientists and engineers that allow them to make informed decisions during solvent selection. There have been several noteworthy examples of expert systems such as EPA's SAGE (http://clean.rti.org), the Hazardous Solvent Substitution Data System (http://wannabe.inel.gov/hssds/), the Integrated Solvent Substitution Data System (http://earth2.epa.gov/issds/index.html), and the evolving PARIS II system (Cabezas). These systems have attempted to provide guidance on choosing solvent alternatives and have been largely directed towards cleaning solvent replacements.

While these systems are useful for their intended audiences, we desired to provide a solvent selection guide that would reflect not only solvent property and major "hot-button" global environmental issues, but also specific SmithKline Beecham issues encountered during synthetic chemical processes. We also wanted to integrate process safety considerations into the evaluation process; an aspect usually excluded from most solvent evaluation systems. From a sustainable development perspective, we desired a guide that would allow us to "act locally but think globally." We hope to describe the details of our methodology, assumptions, and models in future publications.

2
Overview

The SmithKline Beecham Solvent Selection Guidelines are based on an assessment of *key categories* which are considered to be most significant in determining the potential environmental, health, and safety impacts associated with each solvent. These categories were chosen from a larger list of possible categories because of their potential for having a significant environmental, health, or safety impact during implementation of a new chemical process. The categories included in the guide are:

1. Incineration (i.e., the relative ease of incineration, the complexity of the incineration process and the by-products of incineration)
2. Recycle (i.e., solvent separability and ease of re-use)
3. Biotreatment (i.e., is the solvent easily mineralized in a wastewater treatment facility?)
4. Volatile Organic Carbon (VOC) (i.e., is there a significant emission potential?)
5. Environmental impact in water
6. Environmental impact in air
7. Health hazard (i.e., what are the acute or chronic toxic effects to humans?)
8. Exposure potential (i.e., is there a potential for workplace exposure?)
9. Safety hazard (i.e., is there a process or inherent safety hazard?)

The categories we considered but ultimately excluded from the guide included Cost, Life Cycle Impacts and Regulatory concerns. These categories were excluded for several reasons. Cost was excluded because solvent costs may change frequently, and regional, national and international differences in price would make the guide practically impossible to maintain. Cost is also among the first questions asked during development, and is carefully and continuously evaluated throughout product and process development. Also, from a sustainability perspective, cost may be a misleading indicator of desirability, if full Life Cycle costs are not factored into the calculations.

Life Cycle issues around solvents remain to be calculated and full Life Cycle impacts for each solvent are planned for later editions of the Guide. In addition, accepted methodologies for Total Cost Assessment (TCA), while being developed, are not currently available. Cost considerations must also include disposal, recovery, abatement and liability costs. Regulations were excluded for several reasons. There are numerous local, regional, national and international regulations governing solvents with which companies must comply, and most chemists and engineers have access to lists of solvents and their associated regulations. However, the appearance of these solvents on one or many different lists is not necessarily a good indicator of specific environmental, health or safety impacts of the solvent, nor does it necessarily identify issues of concern. Also the appearance of a solvent on a list is, generally, a reflection of it's persistence, toxicity, or bioaccumulation potential, and may exclude the broader sustainability perspective in which other impacts may be of equal or greater magnitude.

Table 1. Solvent properties

Emissions on incineration	Solubility in water
Heat (enthalpy) of combustion	Boiling point
Boiling point difference	Azeotropes
Relative ease of drying	Process risk
Reactivity/compatibility	Vapor pressure
Theoretical Oxygen Demand (ThOD)	Acute aquatic toxicity
Log K_{ow}	Degradation in water
Photolysis rate	Photochemical Ozone Creation Potential (POCP)
Odor threshold	Exposure limit
Autoignition temperature	Flash point
Conductivity	

For each category, key properties were identified which contribute to the overall environmental, health or safety issue or performance of a given solvent. The solvent properties used in the development of the Guide are shown in Table 1. The solvents evaluated and their chemical type are shown in Table 2.

3
Properties and associated issues for each category

For each category, the key properties were identified along with the key issues. These are summarized below.

3.1
Incineration

Discussion

Mixed solvents and contaminated aqueous solvent waste streams can be difficult to recover efficiently and the only effective disposal option may be incineration. This may have a significant environmental impact.

Key properties impacting incineration:

- heat of combustion (influencing the energy value for incineration)
- emissions on incineration (especially HCl, dioxins and NO_x)
- water solubility

Issues – The ranking is based on incineration of the pure solvent and assumes an efficient incinerator. For mixtures, the miscibility of solvents is important, with possible layering of solvents in the waste solvent storage tank prior to incineration. A high percentage of synthetic chemical processes include an aqueous work-up or stream washing so the ranking *assumes* an aqueous based work up. Incineration of these streams would require more fuel energy to burn the mixed aqueous stream. Use of water miscible solvents gives the potential for carry through of inorganics, e.g., sulfates, nitrates, etc. which may, if not properly controlled through appropriate treatment technology, have different adverse environmental impacts. It should be noted that for a process which uses a water soluble solvent, but no water or aqueous work-up, the potential environmental impact from the water soluble solvent may be significantly less.

Table 2. Solvents evaluated

Solvent	Type
Acetic acid (glacial)	Organic acid
Acetone	Ketone
Acetonitrile	Polar aprotic
1-Butanol	Alcohol
Butyl acetate	Ester
Diethylene glycol monobutyl ether	Alcohol
Cyclohexane	Hydrocarbon
1,2-Dimethoxyethane	Ether
Dimethyl acetamide	Polar aprotic
Dimethyl formamide	Polar aprotic
Dimethylpropylene urea	Polar aprotic
Ethanol/IMS	Alcohol
Ethyl acetate	Ester
Ethylene glycol	Alcohol
Heptane	Hydrocarbon
Hexane	Hydrocarbon
2-Propanol	Alcohol
Isopropyl acetate	Ester
Diisopropyl ether	Ether
Methanol	Alcohol
2-Methoxyethanol	Alcohol
Bis(2-methoxyethyl)ether	Ether
Methyl acetate	Ester
Dichloromethane	Chlorinated
Methylethyl ketone	Ketone
Methylisobutyl ketone	Ketone
N-Methyl pyrrolidone	Polar aprotic
Petroleum ether	Hydrocarbon
Propionic acid	Organic acid
Propyl acetate	Ester
Pyridine	Organic base
Methyl t-butyl ether	Ether
Tetrahydrofuran	Ether
Toluene	Aromatic
p-Xylene	Aromatic

3.2
Recycle

Discussion

Efficient solvent utilisation, recovery and re-use is essential to minimise environmental impacts.

Key properties affecting recyclability:
- boiling point (i.e., ease of distillation)
- number of solvents with a boiling point within 10 °C (influencing ease of solvent separability)
- number of azeotropes with other solvents in the Guide
- relative ease of drying (most solvents are needed dry)
- risk on recovery (e.g., via peroxide formation)
- reactivity (e.g., esters may hydrolyze)
- water solubility (affecting the potential loss in aqueous streams)

Issues – this assessment takes no account of other undesirable contaminants resulting from specific process reactions. Contaminants may have an impact on the potential to recycle or recover solvent and need to be evaluated. Water miscible solvents have a reduced score due to the potential difficulties in recovering solvent from a mixed aqueous system. This may not be a problem, however, if water is not present in the process. This should be taken into account for a non-aqueous route.

3.3
Biotreatment

Discussion

Waste aqueous solvent streams may be biotreatable but the nature and quantity of the solvent present may significantly affect this process.

Key properties affecting biotreatment:
- treatability in aeration basins (considering the carbon load, adverse effects and nitrogen content)
- release to air by solvent stripping (the solvent volatility determines the abatement needed, e.g., carbon adsorption, biofiltration, etc.)
- potential aqueous burden based on water solubility

Issues – Because effluent treatment operations generally use well acclimated activated sludge, biodegradation is not considered to be a major factor. However, introduction of a new solvent would have to be done with care. The assessment only considers impacts at the treatment plant.

3.4
Volatile organic carbon (VOC)

Background

It is important to determine the amount of control technology that will be needed to limit emissions or the potential emission if no control technology is used. For example, a solvent with a low boiling point and a high vapor pressure would tend to require more emission control technology and would be more likely to volatilize in a wastewater treatment plant than another solvent of higher boiling point and vapor pressure.

Key properties affecting VOC:
- vapor pressure
- boiling point

Issues – For this particular category, solvents with low vapor pressures and high boiling points received a higher score than solvents with high vapor pressures and low boiling points. It is based upon use of pure solvents at standard temperature and pressure.

3.5
Environmental impact in water

Key properties affecting environmental impact in water:
- acute toxicity
- log octanol/water partition coefficient (log K_{ow})
- biodegradation

Issues – This category is intended to cover release by either accidental discharge, or continuous release, with the same key factors identified for both scenarios. *Environmental toxicity* is based on the worst case acute LC_{50} data available from fish, daphnia or algae. *Log K_{ow}* is selected as the best guide to environmental fate governing the potential for adsorption or bioconcentration. *Biodegradation* is assumed to be the major depletion mechanism. *Water solubility* – depending on the circumstances of use, high solubility in water may be either good and/or bad. Consequently, the impact of this parameter has been excluded from consideration for these criteria. There is a competing short-term issue. Spillage may cause adverse effects by oxygen removal and starvation. This will be especially serious if the solvent is soluble, rapidly biodegraded, and has high Theoretical Oxygen Demand (ThOD). No attempt has been made to develop an assessment of this issue.

3.6
Environmental impact in air

Key properties affecting environmental impact in air:

- rate of photolysis
- Photochemical Ozone Creation Potential (POCP)
- odor threshold

Issues – The potential to enter (by e.g., evaporation, volatilization, etc.) the air compartment is covered in the VOC category assessment. It is anticipated that there will eventually be other measures, which could be used to assess the air impact, and these will be incorporated in later versions of this Guide. There are little data on ozone depletion, but the available data suggest that all solvents assessed here have similarly very low potential for ozone depletion. The data for photolysis ignore the effect the solvent will have if it remains unphotolysed, and does not take into account the effect of photolytic products. In the case of odor threshold, the potential impact is very dependent on the vapor pressure and the odor threshold, and a ratio of vapor pressure / odor threshold is used as a measure of the potential for odor.

3.7
Health hazard

The hazard score was based upon the following classification hierachy:

- minimal concern
- an effect that may be seen at reasonably high exposures
- effects seen in animals at doses that might be a cause for concern, e.g., corrosiveness or severe irritancy
- effects reported under occupational conditions or animal studies at low doses; effects likely to be serious and irreversible

3.8
Exposure potential

Background

The VHR is a combined measure of the hazard and the potential for exposure, as governed by the volatility of the solvent

Key properties – **Vapor Hazard Rating**

Issues – The vapor Hazard Rating is based on Occupational Exposure Limit (OEL) and vapor pressure.

Vapor Hazard Rating (VHR): $\mathrm{VHR} = \dfrac{\mathrm{SC}}{\mathrm{OEL}}$

Where the **saturation concentration** (SC) of vapor in ppm is defined as:

$$\mathrm{SC} = \frac{\mathrm{VP}*10^6}{760\ \mathrm{mmHg@STP}}$$

OEL = Occupational Exposure Limit

The impact of exposure via skin adsorption is not taken directly into account since the operational risk is considered lower. However, some of the OEL data are based on skin data. These data are based on room temperature operations and will not take into account process operations at elevated temperatures.

3.9
Safety hazard

Background

It is important to consider occupational safety, process safety, and fire and explosion potential.

Key parameters:

- flash point (risk of ignition)
- conductivity (a measure of electrical conductance)
- Temperature, ('T′), rating (this is a classification based on the autoignition temperature)
- process/chemistry risk (e.g., peroxide formation)

Issues – where the conductivity and flash point are both low there is a much higher potential risk of ignition by a spark; e.g., alkanes. Process /chemistry risk also includes an assessment of compatability of the solvent with a range of chemicals.

4
Scoring and assessment process

Scores were developed for each property that composed a given category. The scores were designed to highlight specific issues or areas of concern, and where possible, ordinal or graphical relationships were developed to derive individual property scores. This approach was adopted to minimize subjectivity and to provide the most objective ranking mechanism possible for a judgment-based scoring system. The scoring process was first carried out based on a range of 1 to 4 and then transposed to a range of 1 to 10. This was done for at least two reasons. First, when using expert judgment or opinion to rank any particular attribute, it is generally easier to score and achieve consensus opinion over a narrower scoring range. However, the use of a narrow range gives the appearance of small difference between solvents. This perception of such little difference between solvents lead to our decision to transpose the scores to a wider range to help accentuate the differences between solvents. Scores for each of the key solvent properties were geometrically averaged to obtain an overall geometric mean score for the category. Geometric averaging was chosen over other forms of averaging to highlight properties that were viewed as particularly adverse. For the purposes of these guidelines, *the higher the score the better the solvent*.

All scores, together with the assumpions made and graphical or ordinal relationships developed, are included in a database within the Guide to ensure total transparency and provide a platform for discussion or future revision.

Category scores were then derived from multiple property scores comprising a given category. All property and category scores were repeatedly reviewed by internal teams of environment and safety experts to ensure that they were consistent, reflected site concerns, and were as accurate as possible.

To reduce the overall complexity of the guide, ease the interpretation of property and category data in terms of their environmental and safety implications, and enhance the usefulness of the guide by individuals who are not environmental or safety professionals, the nine categories were collapsed into four areas, and composite scores were derived for these areas. These four areas are *Waste*, *Impact*, *Health* and *Safety*. The *Waste* area includes the categories incineration, biodegradation, recyclability and volatile organic carbon. We regard these as measures of the potential multimedia waste load, the degree of control technology required, and the potential for solvent recovery and reuse. The *Impact* area includes potential acute environmental impacts on air and water, and includes the categories environmental impact on air and water. The *Health* area includes the categories Health Hazard and Exposure Potential and is primarily a measure of the potential for human exposure and the resulting acutely toxic, or in some instances, chronic human health effect. Finally, the *Safety* area, which is comprised solely of the Safety Hazard category, includes general occupational safety, process safety, and fire and explosion potential.

The evaluation process was designed to be as objective and scientifically accurate as possible while reflecting the particular needs of SmithKline Beecham. The Guide is

Table 3

Acetic acid

Incineration	🟥	Water miscible and low heat of combustion.
Recycle	🟥	Water miscible, many azeotropes.
Biotreatability	🟨	
VOC emission	🟨	
Environmental impact to water	🟩	
Environmental impact to air	🟨	
Health hazard	🟨	
Exposure potential	🟨	
Safety hazard	🟩	

🟥 *major issues have been identified; appropriate control procedures need to be in place.*

🟨 *issues have been identified; the need for control procedures should be considered.*

🟩 *no major issues have been identified in this area.*

ICH category	3	Permitted daily exposure limit (mg/day)	> 50

Molecular wt	60.05
Melting point (°C)	17
Boiling point (°C)	118
Vapor pressure (mm)	15.5
Solubility in water (gm/L)	Miscible.
Odor threshold (ppm)	0.1 - 0.2
Density	1.05
Vapor density (air = 1)	2.07
Log K_{ow}	-0.17
Worst case ecotoxicity EC_{50} (mg/L) [species]	47 [daphnia]
Degradation in water	Biodegradable.
Ozone creation potential POCP	16
Half life for evaporation from a river (days)	Very slow
Exposure limit [ACGIH 8hr TWA] (ppm)	10
Flash point (°C)	39
Conductivity (Ps/M)	1120000
Risk phrase(s)	Flammable. Causes severe burns.
Heat of combustion (Btu/lb)	5645
Dielectric constant	6.2
Autoignition temperature (°C)	426

AZEOTROPE DATA

The following azeotropes (excluding zeotropes) with other solvents have been reported:

Solvent	**% acetic acid**	**bp (°C)**
Cyclohexane	9.6	78.8
Dioxane	77	119.5
Ethyl benzene	66	114.6
Heptane	33	91.7
Hexane	6	68.5
Nitroethane	30	112.4
Pyridine	51	138.1
Toluene	28	100.6
Triethylamine	67	163
Xylene	72	115.3

Table 4

Cyclohexane

Incineration	🟩	
Recycle	🟨	
Biotreatability	🟨	
VOC emission	🟥	High vapor pressure.
Environmental impact to water	🟨	
Environmental impact to air	🟨	
Health hazard	🟨	
Exposure potential	🟨	
Safety hazard	🟥	Low flash point and conductivity.

🟥 *major issues have been identified; appropriate control procedures need to be in place.*
🟨 *issues have been identified; the need for control procedures should be considered.*
🟩 *no major issues have been identified in this area.*

ICH category	2
Permitted daily exposure limit (mg/day)	38.8
Molecular wt	84.2
Melting point (°C)	7
Boiling point (°C)	81
Vapor pressure (mm)	98
Solubility in water (gm/L)	0.06
Odor threshold (ppm)	300
Density	0.78
Vapor density (air= 1)	2.9
Log K_{ow}	3.44
Worst case ecotoxicity EC_{50} (mg/L) [species]	3.8 [algae]
Degradation in water	Slow biodegradation.
Ozone creation potential POCP	60
Half life for evaporation from a river (days)	0.15
Exposure limit [ACGIH 8hr TWA] (ppm)	300
Flash point (°C)	-20
Conductivity (Ps/M)	2
Risk phrase	Highly flammable.
Heat of combustion (Btu/lb)	18684
Dielectric constant	2.02
Autoignition temperature (°C)	245

AZEOTROPE DATA

The following azeotropes (excluding zeotropes) with other common solvents have been reported:

Solvent	% cyclohexane	bp (°C)
Acetic acid	91.4	78.8
Methyl ethyl ketone	60	71.8
Methyl acetate	22	55.5
Methanol	63.6	53.9
Isopropanol	68	69.4
Ethyl acetate	44	71.6
Acetone	32.5	53
1-Butanol	90 – 95	80 - 82

currently in use throughout SmithKline Beecham in both R&D and manufacturing.

5

Sample solvent summary sheets

Representative Sample Solvent Summary Sheets for two of the solvents, acetic acid and cyclohexane, are shown in Tables 3 and 4, respectively. They provide a summary of the critical environmental, health, and safety issues, as well as selected physical, chemical, biological, and toxicological properties, considered to be of greatest use to the bench chemist or process engineer.

6

Solvent selection summary guides

Figures 1 and 2 contain two of the three summary guides that were produced as part of the guide. As can be seen from Fig. 1, "A guide for the integration of environmental, health and safety factors into the selection of solvents," solvents are listed by solvent class in the left-hand column, and the four composite area scores are contained in the adjacent four columns. It may also be seen that each solvent in the guide has a color for a given area and a score. A traditional red, yellow, green approach was used as a visual cue for highlighting issues that should be considered for a given solvent. The combination of the color and the score allows the chemist or engineers to see where the solvent falls within range, and is a quick way of determining the relative number of issues a given solvent might present. For example, a solvent with a red block could have a score from 1 to 3, a yellow block corresponds to a range of 4 to 7, and a green block corresponds to a range of 8 to 10.

It should also be noted that the solvents are listed within each class so that the most desirable solvents are at the top of the class, and the least desirable solvents are

Fig. 1.

SOLVENT		Waste	Impact	Health	Safety
Alcohols	Ethylene glycol	4	9	8	10
	1-Butanol	5	7	8	8
	Diethylene glycol mono butyl ether	5	8	8	10
	Ethanol / IMS	3	7	9	6
	2-Propanol	3	10	7	7
	Methanol	3	8	4	8
	2-Methoxy ethanol	4	9	2	7
Esters	Butyl acetate	7	7	7	6
	Propyl acetate	7	6	7	6
	Isopropyl acetate	5	7	7	6
	Ethyl acetate	4	9	7	4
	Methyl acetate	2	6	5	5
Aromatics	Xylene	8	4	5	5
	Toluene	7	3	5	4
Ketones	Methylisobutyl ketone	7	4	6	7
	Acetone	2	7	6	5
	Methylethyl ketone	3	6	5	5
Polar aprotics	N-Methyl pyrrolidone	4	7	7	10
	Dimethyl acetamide	4	8	5	9
	Dimethylpropylene urea	4	7	5	9
	Dimethyl formamide	4	8	4	7
	Acetonitrile	2	4	2	8
Acids	Propionic acid	5	8	5	9
	Acetic acid (glacial)	3	6	4	8
Alkanes	Cyclohexane	5	5	6	2
	Heptane	6	2	5	1
	Hexane	5	3	3	1
	Petroleum spirit / ether	4	2	5	1
Chlorinated	Dichloromethane	3	3	1	10
Ethers	1,2-Dimethoxyethane	3	5	4	2
	t-Butylmethyl ether	4	4	3	3
	Bis(2-methoxyethyl) ether	6	5	2	3
	Tetrahydrofuran	2	7	4	2
	Diisopropyl ether	5	2	6	1
Basics	Pyridine	2	3	1	6

Footnotes

1. **Waste** addresses: recycling, incineration, VOC and biotreatment issues.
2. **Impact** addresses fate and effect on the environment.
3. **Health** is based on acute and chronic effect on human health and exposure potential.
4. **Safety** considers explosivity, flammability and operational hazards.
5. Composite scores are given for the four key areas (1 - 4 above) and are based on a scoring range of 1 - 10. ***The higher the better***

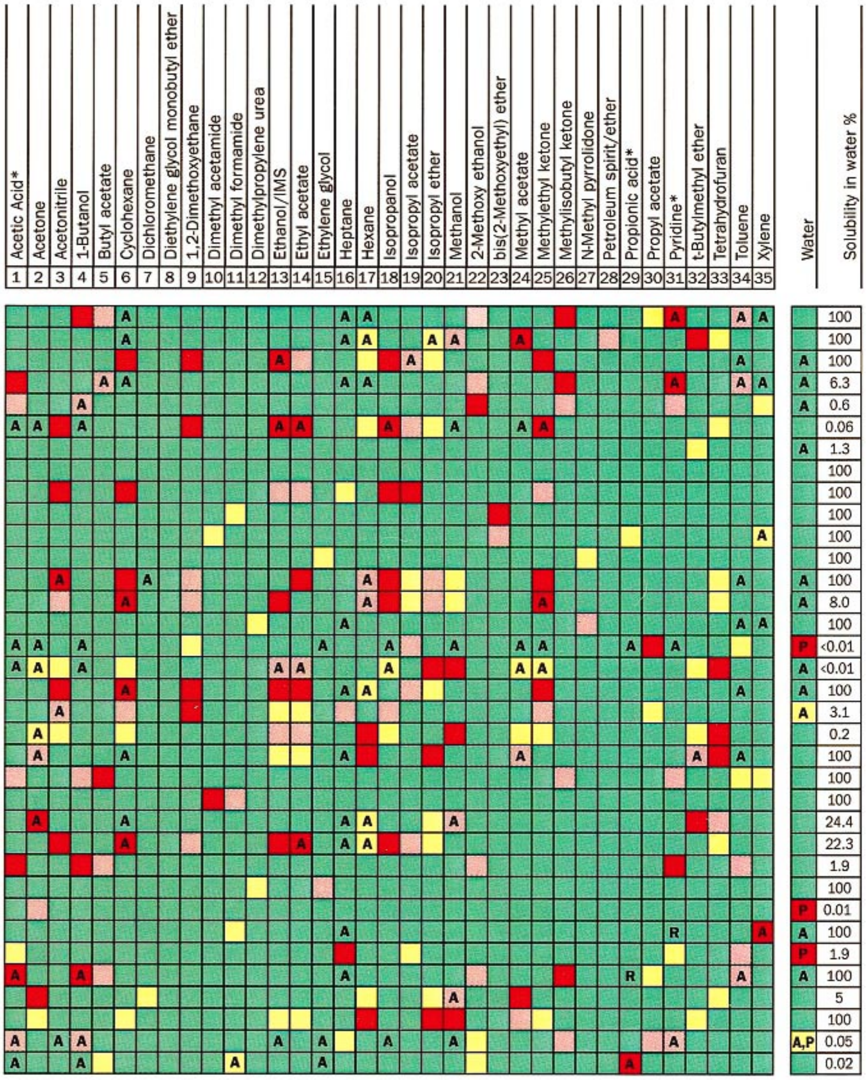
Legend

🟥 Major issues have been identified.
Appropriate control procedures need to be in place.

⬜ Issues have been identified.
The need for control procedures should be considered.

🟩 No major issues identified in this area.

A guide to the selection of co-solvents to enable the easiest separation by distillation



Solvent	Code	Bp°C AP		Water	Solubility in water %
Acetic Acid*	🟨	118	1		100
Acetone		56	2		100
Acetonitrile		82	3	A	100
1-Butanol	🟨	118	4	A	6.3
Butyl acetate	🟨	126	5	A	0.6
Cyclohexane		81	6		0.06
Dichloromethane		40	7	A	1.3
Diethylene glycol monobutyl ether	🟥	231	8		100
1,2-Dimethoxyethane		85	9		100
Dimethyl acetamide	▨	165	10		100
Dimethyl formamide	▨	153	11		100
Dimethylpropylene urea	🟥	146/44mm	12		100
Ethanol/IMS		78	13	A	100
Ethyl acetate		77	14	A	8.0
Ethylene glycol	🟥	197	15		100
Heptane		99	16	P	<0.01
Hexane		69	17	A	<0.01
Isopropanol		82	18	A	100
Isopropyl acetate		89	19	A	3.1
Isopropyl ether		69	20		0.2
Methanol		65	21		100
2-Methoxy ethanol	🟨	124	22		100
bis(2-Methoxyethyl) ether	▨	162	23		100
Methyl acetate		57	24		24.4
Methylethyl ketone		80	25		22.3
Methylisobutyl ketone	🟨	117	26		1.9
N-Methyl pyrrolidone	🟥	202	27		100
Petroleum spirit/ether		varies	28	P	0.01
Propionic acid*	▨	141	29	A	100
Propyl acetate		102	30	P	1.9
Pyridine*	🟨	115	31	A	100
t-Butylmethyl ether		55	32		5
Tetrahydrofuran		66	33		100
Toluene		111	34	A,P	0.05
Xylene	▨	138	35		0.02

KEY

Boiling point **Code**

Very high 🟥

High ▨

Fairly high 🟨

Colour coding reflects the ease of solvent distillation based on its boiling point.

*These may be separable from other solvents by aqueous extraction as a salt.

AP is Atmospheric Pressure.

KEY

Coding based on boiling point proximity

🟥 Very difficult separation by distillation based on bp difference (1-5°C)

▨ Difficult separation by distillation based on bp difference (6-10°C)

🟨 Separation by distillation may be inefficient based on bp difference (11-15°C).

🟩 The bp's are sufficiently different to allow efficient separation by distillation (>15°C).

A – Forms a binary azeotrope with the solvent [tertiary azeotropes are not considered]
R – Reaction or neutralisation
P – Solvent and water are immiscible and simple phase separation is possible.

Alternative methods of separation, e.g., extraction, membranes, should be considered where appropriate.

Fig. 2. A guide to the selection of co-solvents to enable the easiest separation by distillation

at the bottom of the class. There is a further ranking in the order of the classes; i.e., alcohols as a class of solvents are generally more desirable than solvents in the bases or ethers class.

This particular guide might be used as follows: A chemist exploring a reaction from the literature notes that a desired reaction is run in methanol. The chemist repeats the reaction in methanol and obtains the desired yield and purity. At this point, the chemist is faced with a number of possible decisions. First, he/she could proceed with the reaction in methanol, and accept whatever environmental, health and safety issues are associated with using this solvent for this process. Second, the chemist might have a look at the guide, observe the superior environmental, health and safety ranking of 1-butanol, and decide to try the reaction in 1-butanol. The reaction may or may not be successful; but if it is successful, the use of the 1-butanol, while perhaps more costly for the raw material, may prevent considerable regulatory, safety and environmental costs throughout the life of the process or product. If the reaction is not quite as successful, but nearly so, the process development managers, in consultation with site managers, could investigate whether or not the particular environmental, health and safety benefits outweigh the effects of the lower yield and possible solvent cost increase, taking into account all other issues. Third, the chemist might try a different synthetic approach to get around the use of methanol altogether. The purpose of this particular part of the guide is to make significant environmental, health and safety issues transparent to both chemists and managers so that more sustainable decisions are made early in the process.

Figure 2, “A guide to the selection of co-solvents to enable the easiest separation by distillation,” is designed to assist chemists and process engineers with decisions regarding solvent separability. Solvent exchanges through distillation are quite common in pharmaceutical syntheses, and not all solvent mixtures are easily separated. This guide color codes solvents based upon boiling point differences and indicates azeotrope formation-two major issues governing solvent recyclability. How this guide is used should be readily apparent.

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Conclusion

The development and implementation within SB of the SmithKline Beecham Solvent Selection Guidelines has demonstrated that a systematic, semi-quantitative and scientific approach to the environmental, health, and safety evaluation of materials such as solvents can be of great utility in supporting pollution prevention initiatives. Providing chemists and engineers with an easy to use tool to guide solvent selection should, over time, lead to processes with less environmental and safety impact. The philosophy is that where possible, based on the specifics of chemistry and process requirements, the higher scoring solvents should be preferred. In addition, since the Guide highlights environment and safety issues for each solvent, process development chemists and chemical engineers may focus on addressing potential issues before introducing a new process into production. It should be noted that the decision-making process used to derive the scores were based on specific issues related to manufacturing operations within SmithKline Beecham and may not be applicable to other types of operations. However, the general methodology should be readily applicable to other solvents and uses.

References

Cabezas H, Zhao R (1998) US EPA National Risk Management Research Laboratory. 2nd Annual Green Chemistry and Engineering Conference, Washington, DC, June 30-July 2