Solvent Substitution (From Chemistry Innovation website – February 2010)

http://www.chemistryinnovation.co.uk/roadmap/sustainable/roadmap.asp?id=84

Many large companies have developed solvent selection and replacement guides. The drivers for this are:

- Training chemists in the use of classical methodologies often involves atom-inefficient reactions, toxic and/or ecotoxic reagents and solvents. Providing a greater appreciation of the principles of environmental and sustainability issues is needed in addition.
- Between 80 and 90% of mass intensity of in a typical fine chemical/pharmaceutical batch chemical operation is due to solvents.
- The implementation of even simple tools (rules of thumb) by companies can lead to widespread reductions in the use of undesirable solvents (and reagents).
- An easy to use and understand tool (backed by a rigorous approach) will be more fully accepted and routinely employed.
- Pollution control has driven process development and manufacturing to adopt lower impact methods but there are numerous advantages to a using a 'greener' approach throughout R&D (safety, speed of development, prevention of impact, lower costs, etc).
- Careful reaction process design that considers how solvents will be (ideally) reused or recovered can have a significant impact on the economics (examples exist where the difference has been sufficient to maintain uncompetitive processes). Solvents are used not only as a reaction medium but for extractions and reactor cleaning and innovations in this area are key research topics.

The solvent guide presented here is taken from:
Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation, K. Alfonsi, J. Colberg, P. J. Dunn, T. Fevig, S. Jennings, T. A. Johnson, H. P. Kleine, C. Knight, M. A. Nagy, D. A. Perry and M. Stefaniak, *Green Chem*., 2008, **10**, 31–36, DOI: 10.1039/b711717e

Solvent Guide

Solvents were assessed in a thorough and systematic way in three general areas:

(i) Worker safety – including carcinogencity, mutagenicity, reprotoxicity, skin absorption / sensitisation, and toxicity
(ii) Process safety – including flammability, potential for high emissions through high vapour pressure, static charge, potential for peroxide formation and odour issues.
(iii) Environmental and regulatory considerations – including ecotoxicity and ground water contamination, potential EHS regulatory restrictions, ozone depletion potential, photoreactive potential.

This detailed assessment was then translated into a simple guidance list and a summary of why each solvent is placed in the red category is provided in (Table 1).

A list of commonly used solvents is reproduced below. For those solvents in the red/undesirable category a suggested replacement (Table 2) is also shown.

Preferred	Usable	Undesirable
water	cyclohexane	pentane
acetone	methylcyclohexane	hexane(s)
ethanol	toluene	di-isopropyl ether
2-propanol	heptane	diethyl ether

1-propanol	methyl t-butyl ether	dichloromethane
ethyl acetate	isooctane	dichloroethane
isopropyl acetate	acetonitrile	chloroform
methanol	2-methyltetrahydrofuran	dimethyl formamide
methyl ethyl ketone	tetrahydrofuran	N-methylpyrrolidinone
1-butanol	xylenes	pyridine
t-butanol	dimethyl sulfoxide	dimethyl acetamide
	acetic acid	dioxane
	ethylene glycol	dimethoxyethane
		benzene
		carbon tetrachloride

Notes: -dichloromethane is the recommended alternative to other chlorinated solvents (i.e. least worst) dipolar aprotic solvents (dimethyl formamide, dimethyl acetamide and N-methylpyrrolidinone) have no satisfactory alternative (acetonitrile is a relatively poor substitute) and replacements are an identified research priority

Table 1 Red category solvents

Red Solvent	Flash Point (˚C)	Reason
pentane	-49	Very low flash point, good alternative available
hexane(s)	-23	More toxic than the alternative heptane, classified as a hazardous airborne pollutant (HAP) in the US
di-isopropyl ether	-12	Very powerful peroxide former, good alternative ethers available
diethyl ether	-40	Very low flash point, good alternative ethers available
dichloromethane	N/A	High volume use, regulated by EU solvent directive, classified as HAP in the US
dichloroethane	15	Carcinogen, classified as a HAP in the US
chloroform	N/A	Carcinogen, classified as a HAP in the US
dimethyl formamide	57	Toxicity, strongly regulated by EU Solvent Directive, classified as a HAP in the US
N-methylpyrrolidinone	86	Toxicity, strongly regulated by EU Solvent Directive
pyridine	20	Carinogenic/mutagenic/reprotoxic (CMR) category 3 carcinogen, toxicity, very low threshold limit value TLV for worker exposures
dimethyl acetamide	70	Toxicity, strongly regulated by EU Solvent Directive
dioxane	12	CMR category 3 carcinogen, classified as HAP in US
dimethoxyethane	0	CMR category 2 carcinogen, toxicity
benzene	-11	**Avoid use**: CMR category 1 carcinogen, toxic to humans and environment, very low TLV (0.5 ppm), strongly regulated in the EU and the US (HAP)
carbon tetrachloride	N/A	**Avoid use**: CMR category 3 carcinogen, toxic, ozone depleter, banned under the Montreal protocol, not available for large-scale use, strongly regulated in the EU and US (HAP)

Table 2 Solvent replacement table

Undesirable solvents	Alternative
pentane	heptane
hexane(s)	heptane
di-isopropyl ether or diethyl ether	2-MeTHF or tert-butyl methyl ether
dioxane or dimethoxyethane	2-MeTHF or tert-butyl methyl ether
chloroform, dichloroethane or carbon tetrachloride	dichloromethane
dimethyl formamide, dimethyl acetamide or N-methylpyrrolidinone	acetonitrile
pyridine	triethylamine (if pyridine used as base)
dichloromethane (extractions)	ethyl acetate, MTBE, toluene, 2-MeTHF
dichloromethane (chromatography)	ethyl acetate/heptane
benzene	toluene

Notes:

Priority in the evaluations was given to health and safety issues and Carcinogenicty, Mutagenicity, Reprotoxicity (CMR) classifications in particular. High skin absorbers and toxic (literature LD_{50} figures) data were also of main concern. EU and US regulatory classifications such as the EU risk phrases and the US hazardous air pollutant and toxic chemical lists were considered for environmental aspects. Ecotoxic solvents (particularly ones affecting wastewater facilities or requiring specialist disposal) were identified. Solvents potentially ozone depleting, photoreactive, biopersistent and/or bioaccumulating are subject to increasingly stringent regulation (US HAPs and EU IPPC - Integrated Pollution Prevention and Control).

Use of guidance like this has been demonstrated to result in a 50% reduction in chlorinated solvent use by organic chemists and widespread adoption of replacement solvents.

Further Reading:

Best Available Techniques for solvent use are also presented in: Organic Fine Chemicals BREF

Expanding GSK's Solvent Selection Guide—application of life cycle assessment to enhance solvent selections, C. Jimenez-Gonzalez, A. D. Curzons, D. J. C. Constable and V. L. Cunningham, *Clean Technol. Environ. Pol.*, 2005, **7**, 42–50. DOI 10.1007/s10098-004-0245-z

Perspective on Solvent Use in the Pharmaceutical Industry, D. J. C. Constable, C. Jimenez-Gonzalez, and R. K. Henderson, *Org. Proc. Res. Dev.*, 2007, **11**, 133-137, DOI 10.1021/op060170h

What is a green solvent? A comprehensive framework for the environmental assessment of solvents, C. Capello, U. Fischer, K. Hungerbühler, Green Chem., 2007, 9, 927–934, DOI: 10.1039/b617536h