



# Environmentally benign and catalytic processes Solvents

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# Scope of presentation

- Solvents in medicinal products, active substances and excipients
- Solvents in food regulations
- Case studies

# What is a solvent?

- A solvent is a substance (or mixture) used to dilute or dissolve another substance to create a solution.
- Water is the most common solvent.
- Most solvents used in industry are organic, petroleum-based chemicals.
- There are hundreds of industrial solvents, and they are used in many industries (e.g. pharmaceutical, food, chemical manufacturing, plastics, cleaning, painting, printing etc.)



# Solvents are used in a variety of applications

- Liquid medium for reactions to take place,
- Formation of second phase by separation processes (absorption, adsorption, extraction, crystallization)
- Analytical methodologies
- Favourable physico-chemical properties in transfer and mixing
- Favourable heat transfer properties

# Solvents in medicinal products

- Food and Drug Administration - FDA (USA)
- European Medicines Agency – EMEA (EU)

# Classification of residual solvents by risk assessment

- Title: ICH Topic Q 3 C (R4)  
Impurities: Residual solvents
- Reference: CPMP/ICH/283/95
- Abbreviations :

ICH: International Conference on Harmonization

CPMP: Committee for Proprietary Medicinal Products



# Class 1. : solvents that should be avoided

Solvent r	Concentration limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

## Class 2. : solvents to be limited

Solvent	Exposure limit (PDE*) (mg/day)	Concentration limit (ppm)
*PDE=permitted daily exposure		
Acetonitrile	4,1	410
Chlorobenzene I	3,6	360
Chloroform	0,6	60
Cyclohexane	38,8	3880
1,2-Dichloroethene	18,7	1870
Dichloromethane	6	600
1,2-Dimethoxyethane	1	100
N,N-Dimethylacetamide	10,9	1090
N,N-Dimethylformamide	8,8	880
1,4-Dioxane	3,8	380
2-Ethoxyethanol	1,6	160
Ethylene glycol	6,2	620
Formamide	2,2	220
Hexane	2,9	290



# Class 2.: continue

Solvent	Exposure limit (PDE) (mg/day)	Concentration limit (ppm)
Methanol	30	3000
2-Metoxyethanol	0,5	50
Methylbutylketone	0,5	50
Methylcyclohexane	11,8	1180
N-Methylpyrrolidone	48,4	4840
Nitromethane	0,5	50
Pyridine	2	200
Sulfolane	1,6	160
Tetralin	1	100
Toluene	8,9	890
1,1,2-Trichloroethene	0,8	80
* usually 60% styrene, 14% p-xylene, 9% o-xylene with 17% ethyl benene,	21,7	2170

## Class 3.: solvents with low toxic potential, which should be limited by GMP or other qualitybased requirements

Acetic acid	Isopropyl benzene	Heptane	2-Methyl-1-propanol
Acetone	Dimethylsulfoxide	Isobutyl acetate	Pentane
Anisole	Ethanol	Isopropyl acetate	1-Pentanol
1-Butanol	Ethyl acetate	Methyl acetate	1-Propanol
2-Butanol	Ethyl ether	3-Methyl-1-butanol	2-Propanol
Buthyl acetate	Ethyl formate	Methylethyl ketone	Propyl acetate
Tert-buthylmethyl ether	Formic acid	Methylisobutyl ketone	Tetrahydrofurane

# Class 4.: solvents for which no adequate toxicological data was found

1,1-Diethoxypropane	Methylisopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Petroleum ether
Isooktane	Trichloroacetic acid
Izopropyl ether	Trifluoroacetic acid

# Solvents for extraction of foodstuffs and flavourings

- European Commission directive 88/344/EEC
- (Magyar Élelmiszerkönyv 1-2-88/344)

# Extraction solvents which are acceptable for all uses when used in compliance with GMP

<b><i>Gases</i></b>	<b><i>Liqids</i></b>
Propane	Ethanol <sup>2</sup>
Butane	Ethyl acetate t
Carbon dioxide	acetone <sup>1</sup>
Nitrous oxide	water <sup>2</sup>

<sup>1</sup> Acetone cannot be used for refining of olive oil.

<sup>2</sup> Ethanol and water



## Extraction solvents for which conditions of use are specified

<b>Solvent</b>	<b>Conditions of use</b>	<b>Maximum residue limits in the extracted foodstuff or food ingredient</b>
Hexane	Production or fractionation of fats and oils and production of cocoa butter	1 mg/kg in final fat,oil or cocoa butter; 10 mg/kg in the food containing the extracted material; 30 mg/kg in the soya product as sold to the final consumer; 5 mg/kg in the defatted germ
Methyl acetate	Decaffeination of or removal of irritants and bitterings from caffee and tea; Production of sugar from molasses	20 mg/kg in the coffee or tea; 1 mg/kg in the sugar
Ethylmethyl ketone	Fractionation of fats and oils; Decaffeination of or removal of irritants and bitterings from caffee and tea	5 mg/kg in the fat or oil; 20 mg/kg in the coffee or tea
Dichloromethane	Decaffeination of or removal of irritants and bitterings from coffee	2 mg/kg in the roasted caffee;

# Extraction solvents used in the preparation flavourings

<b>Solvent</b>	<b>Maximum residue limits in the foodstuff due to the use of extraction solvents in the preparation of flavourings</b>
Diethyl ether	2 mg/kg
Hexane	1 mg/kg
Cyclohexane	1 mg/kg
Methyl acetate	1 mg/kg
butan-1-ol	1 mg/kg
butan-2-ol	1 mg/kg
Ethylmethyl ketone	1 mg/kg
Dichloromethane	0,02 mg/kg
propan-1-ol	1 mg/kg
1,1,1,2-tetrafluoroethane	0,02 mg/kg

# Physico-chemical properties of solvents

<b>Solvent</b>	<b>hexane</b>	<b>isohexane</b>	<b>Ethyl alcohol</b>	<b>Isopropyl alcohol</b>	<b>Ethyl acetate</b>	<b>acetone</b>
CAS-number	110543	107835	64176	67630	141786	67641
Formula	$C_6H_{14}$	$C_6H_{14}$	$C_2H_6O$	$C_3H_8O$	$C_4H_8O_2$	$C_3H_6O$
Molecular weight	86,18	86,18	46,07	60,11	88,11	58,08
Density, kg/m <sup>3</sup>	671	653	785	818	902	791
Melting point, °C	-95	-154	-130	-89	-84	-94
Boiling point, °C	68,7	62	78,4	82,4	77	56
Flashpoint, °C	-23	-7	12	12	-3 - 0	-17 – (-16)
Autoignation, °C	260	264	425	400	460	538
Explosive limits, (V/V)%	1,2 – 7,7	1,2 - 7	3,3 – 19,0	2,5 – 12,0	2,3 – 11,4	2,2 - 13
Heat of vaporization, kJ/kg	334,5	324,1	854,1	667,0	430,8	512,3
Specific heat, kJ/kgK	2,23	2,23	2,55	2,50	2,13	2,14
Solubility in water	no	no	Sol.	Sol.	Partly sol	Sol.





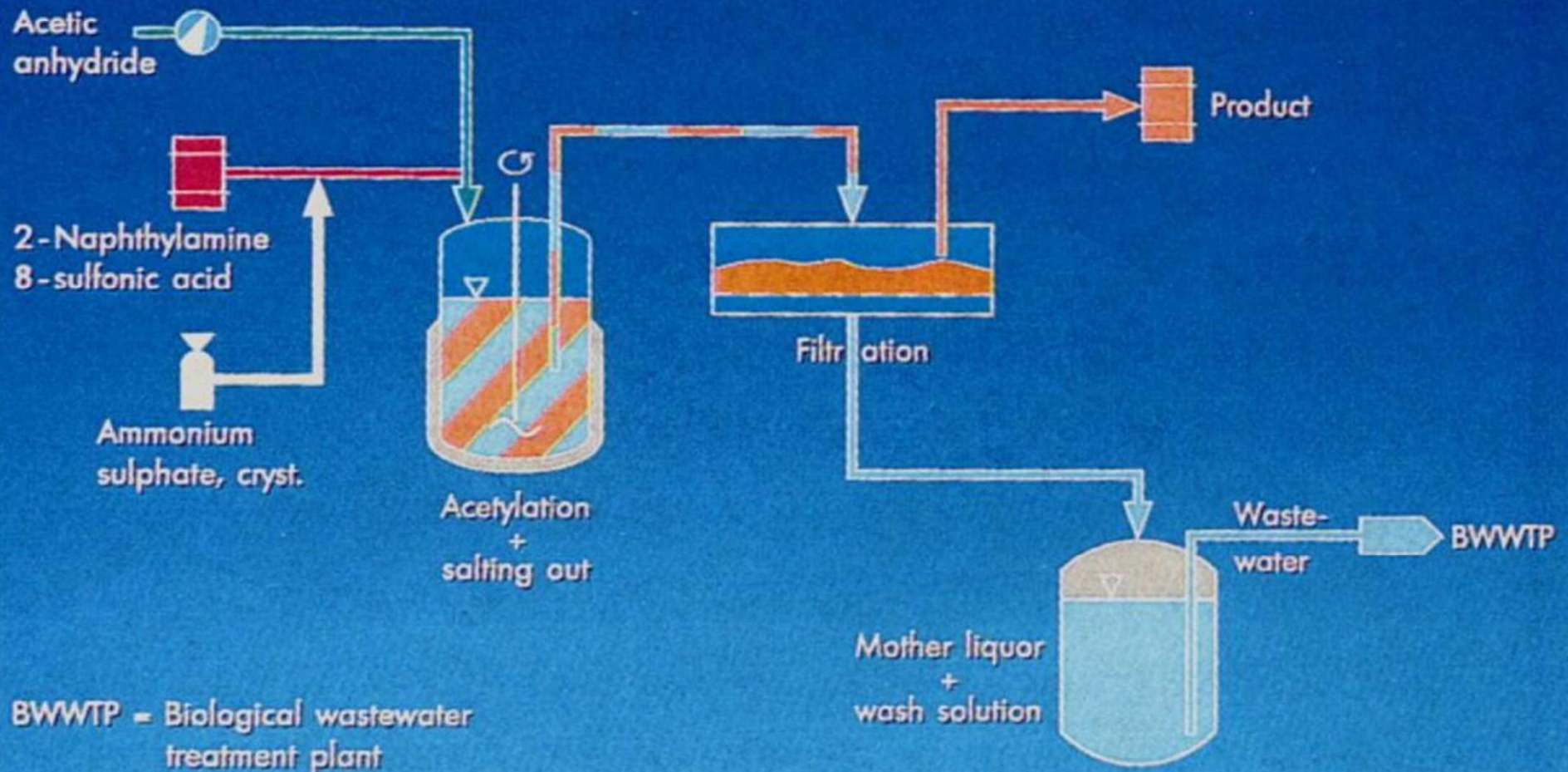
# Problems associated with use of solvents

- Health effects of solvents (cancer, nervous system, liver damage, fertility),
- Environmental problems: pollution of air, water and soil; persistent in nature (are not biodegradable).

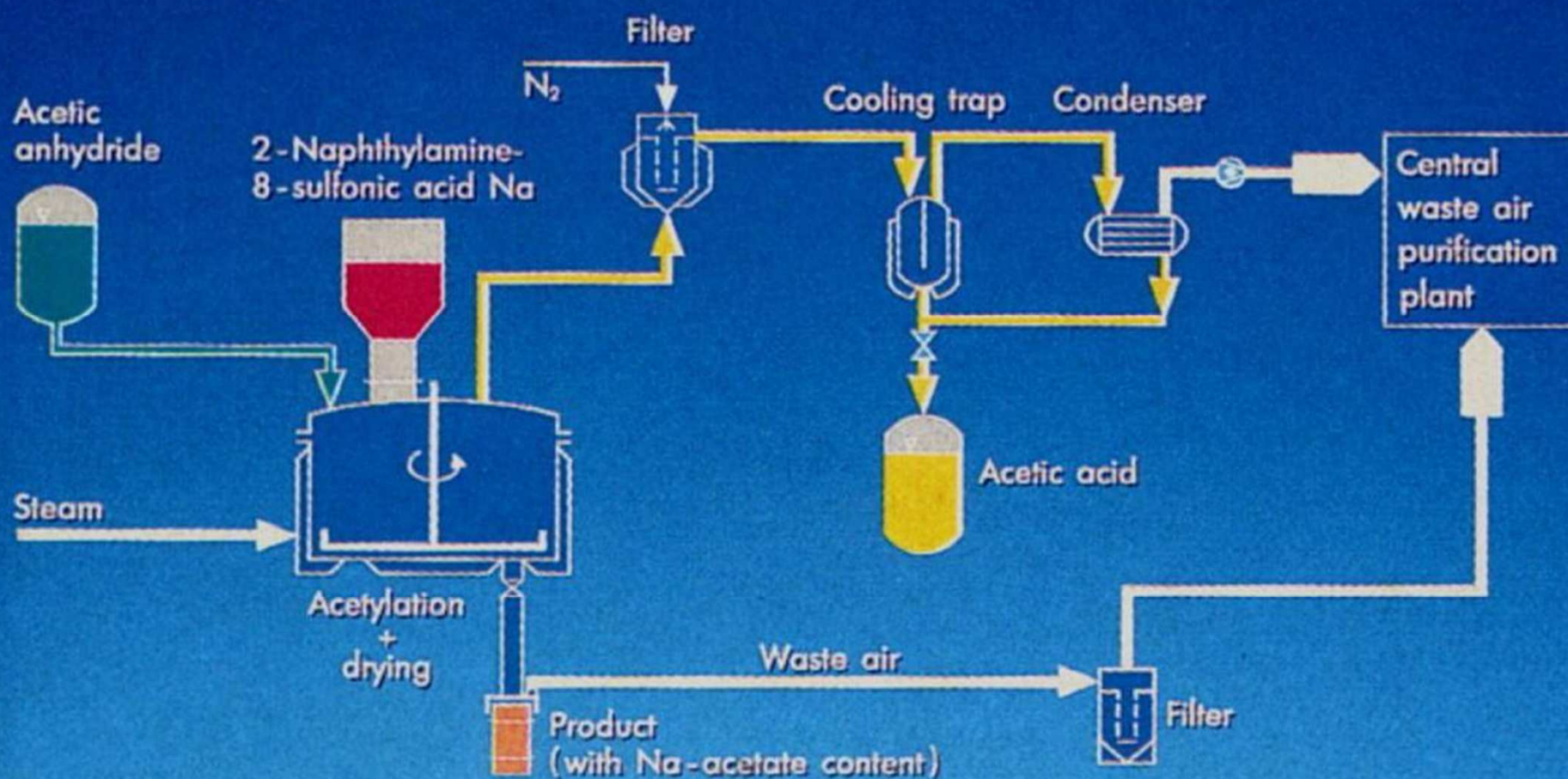
# Case studies

- Christ C. (Hoechst AG): Chem. Tech. Europe, 19-25 (1996)

# Manufacture of 2-acetaminonaphthalene-8-sulfonic acid - Wet acetylation -

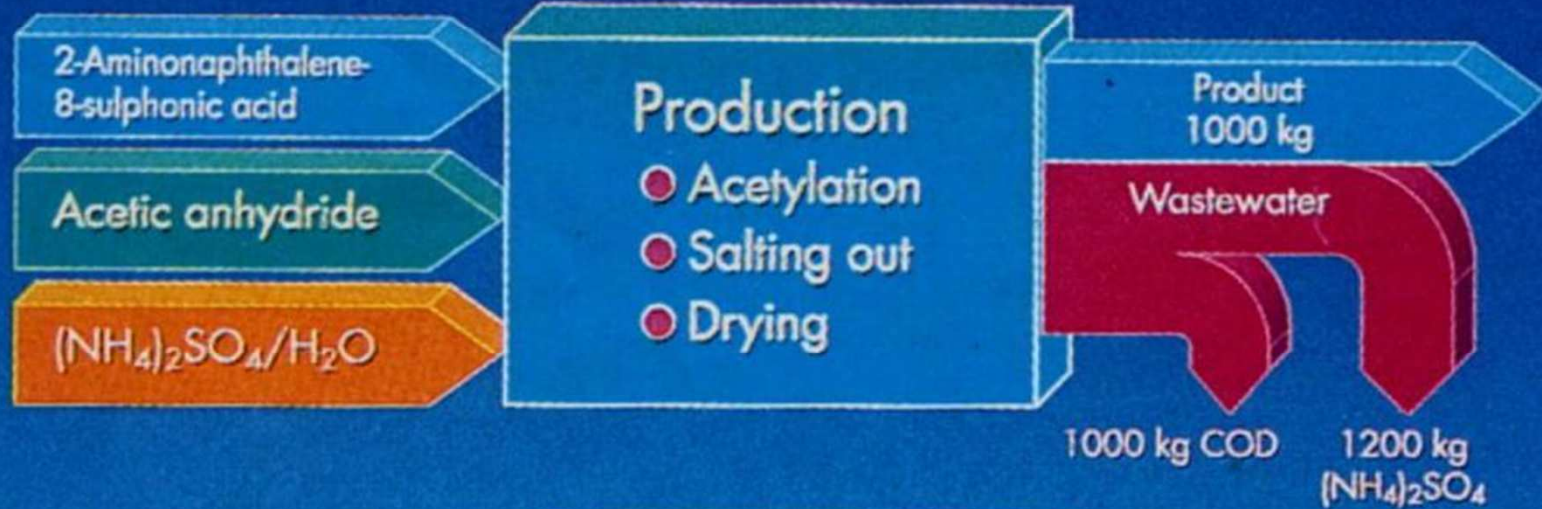


# Manufacture of 2-acetaminonaphthalene-8-sulfonic acid - Dry acetylation -

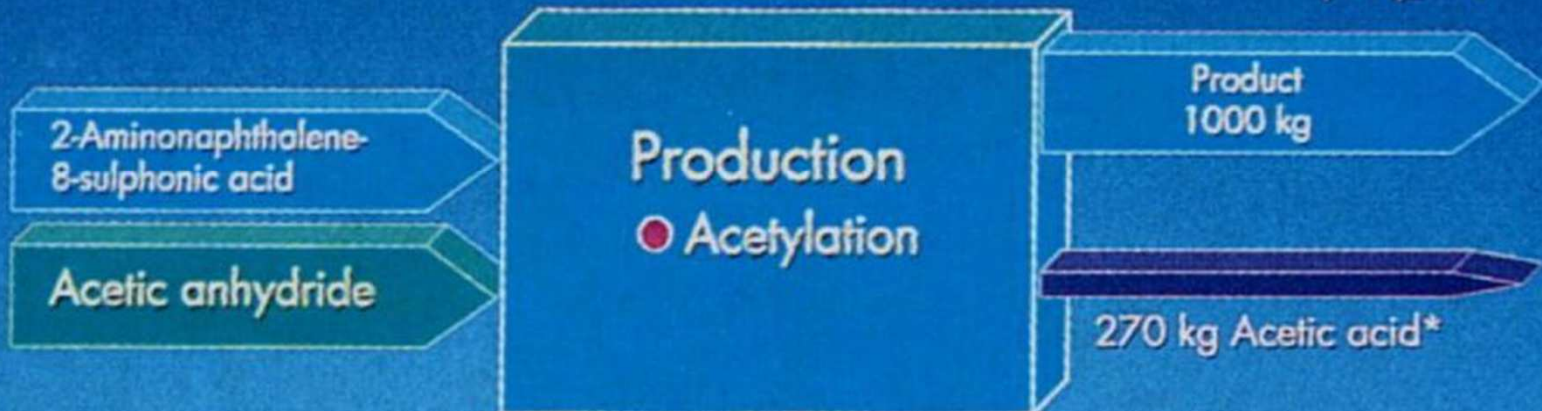


# Manufacture of 2-acetaminonaphthalene-8-sulphonic acid

Previously



Today



\*Utilization

## *Reactor with double helix stirrer*



*Thank you for your kind attention!*