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Digital Micro-Certification
"**The Challenges of Sustainable Chemistry**"

January – February 2024

Project Managers

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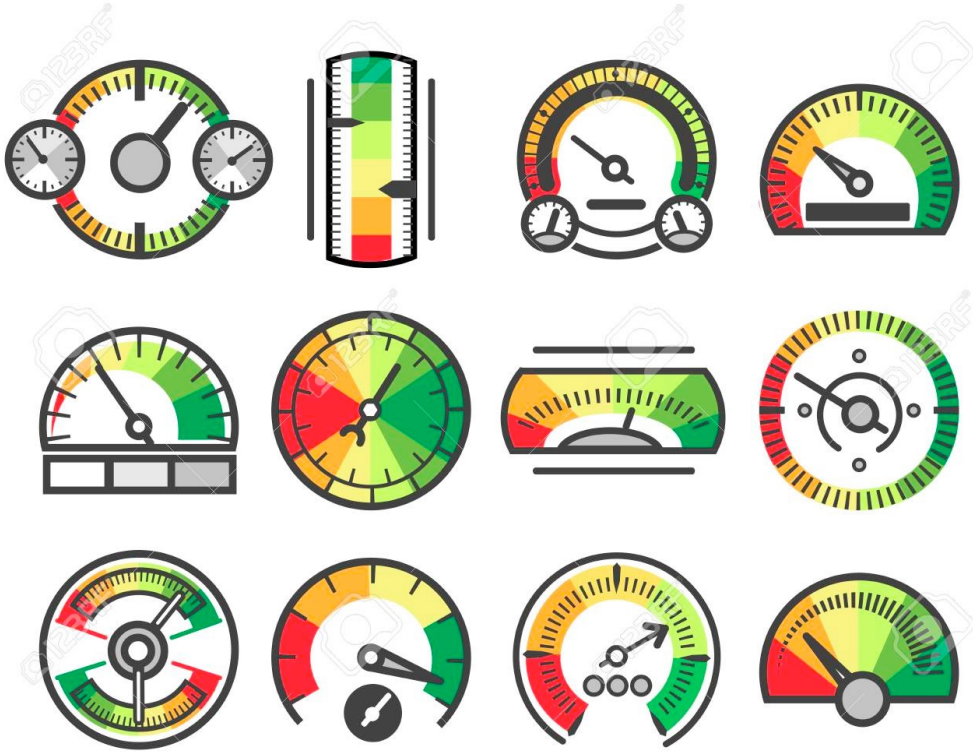
Environmental performance assessment in chemistry

Marie-Christine SCHERRMANN
ICMMO – Université Paris-Saclay

Mass-Based Metrics for Measuring Greenness



Atom economy

12 principles of green chemistry

1. Prevent waste
2. Maximize atom economy
3. Design less hazardous chemical syntheses
4. Design safer chemicals and products
5. Use safer solvents and reaction conditions
6. Increase energy efficiency
7. Use renewable feedstocks
8. Avoid chemical derivatives
9. Use catalysts, not stoichiometric reagents
10. Design chemicals and products to degrade after use
11. Analyze in real time to prevent pollution
12. Minimize the potential for accidents

Anastas and Warner

Atom economy

$$\nu_A\,A \;+\; \nu_B\,B \longrightarrow \nu_P\,P \;+\; \nu_Q\,Q$$

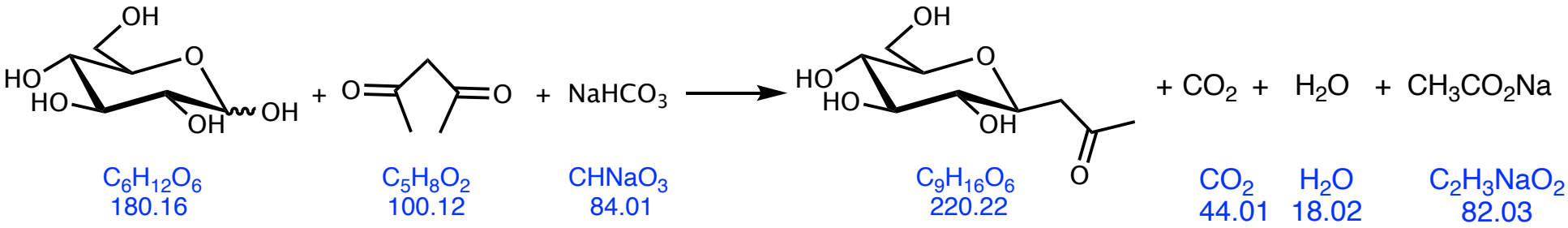
reagents — product — by-products

$$AE = \frac{\nu_p M_P}{\nu_p M_P + \nu_Q M_Q} = \frac{\nu_p M_P}{\nu_A M_A + \nu_B M_B}$$

AE % of the mass of the reactants **could be** incorporated into the product

B. M. Trost, *Science*, **1991**, *254*, 1471–1477.

Atom economy



$C_6H_{12}O_6$ 180.16 | $C_5H_8O_2$ 100.12 | $CHNaO_3$ 84.01 | $C_9H_{16}O_6$ 220.22 | CO_2 44.01 | H_2O 18.02 | $C_2H_3NaO_2$ 82.03

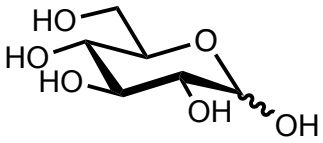
$$AE = \frac{\nu_p M_P}{\nu_a M_A + \nu_b M_B}$$

$$AE = \frac{220.22}{180.16 + 100.12 + 84.01} = 0.60$$

60 % of the mass of the reactants **could be** incorporated into the product

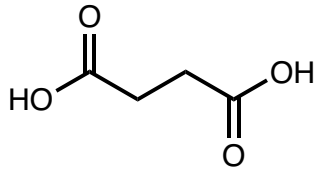
F. Rodrigues, Y. Canac and A. Lubineau, *Chem. Commun.*, **2000**, *20*, 2049.

Atom economy

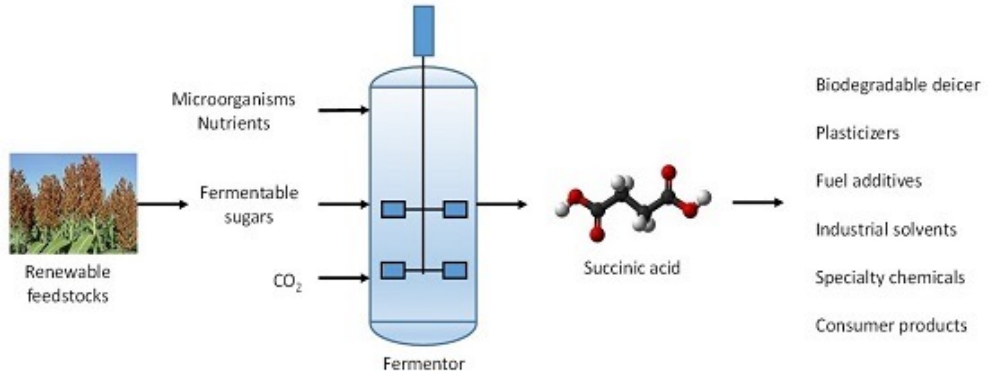


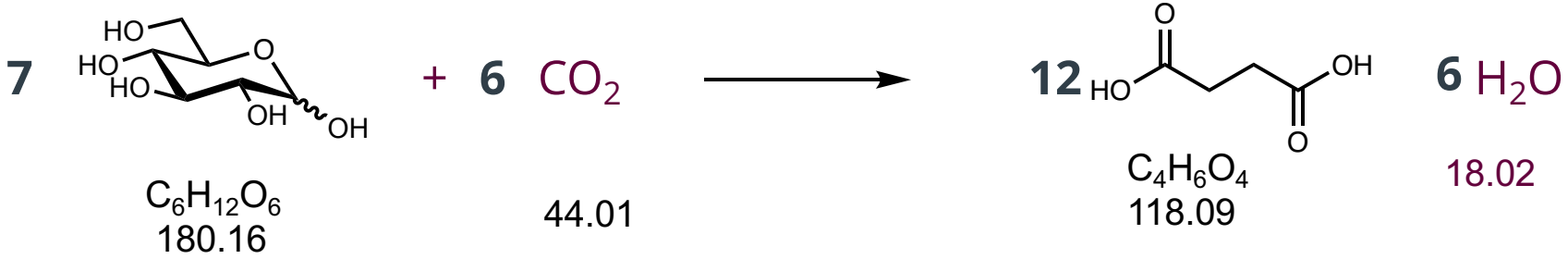
D-glucose

fermentation



Acide succinique





$$AE = \frac{\nu_p M_P}{\nu_p M_P + \nu_Q M_Q} = \frac{\nu_p M_P}{\nu_A M_A + \nu_B M_B}$$

$$AE = \frac{12 * 118.09}{7 * 180.16 + 6 * 44.01} = 0.93$$

93 % of the mass of the reactants **could be** incorporated into the product

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Global atom economy (synthesis sequences)

$\nu_a\mathbf{A} + \nu_b\mathbf{B} \xrightarrow{\text{auxiliaries}} \nu_1\mathbf{P_1}$

$\nu_1\mathbf{P_1} + \nu_c\mathbf{C} \xrightarrow{\text{auxiliaries}} \nu_2\mathbf{P_2}$

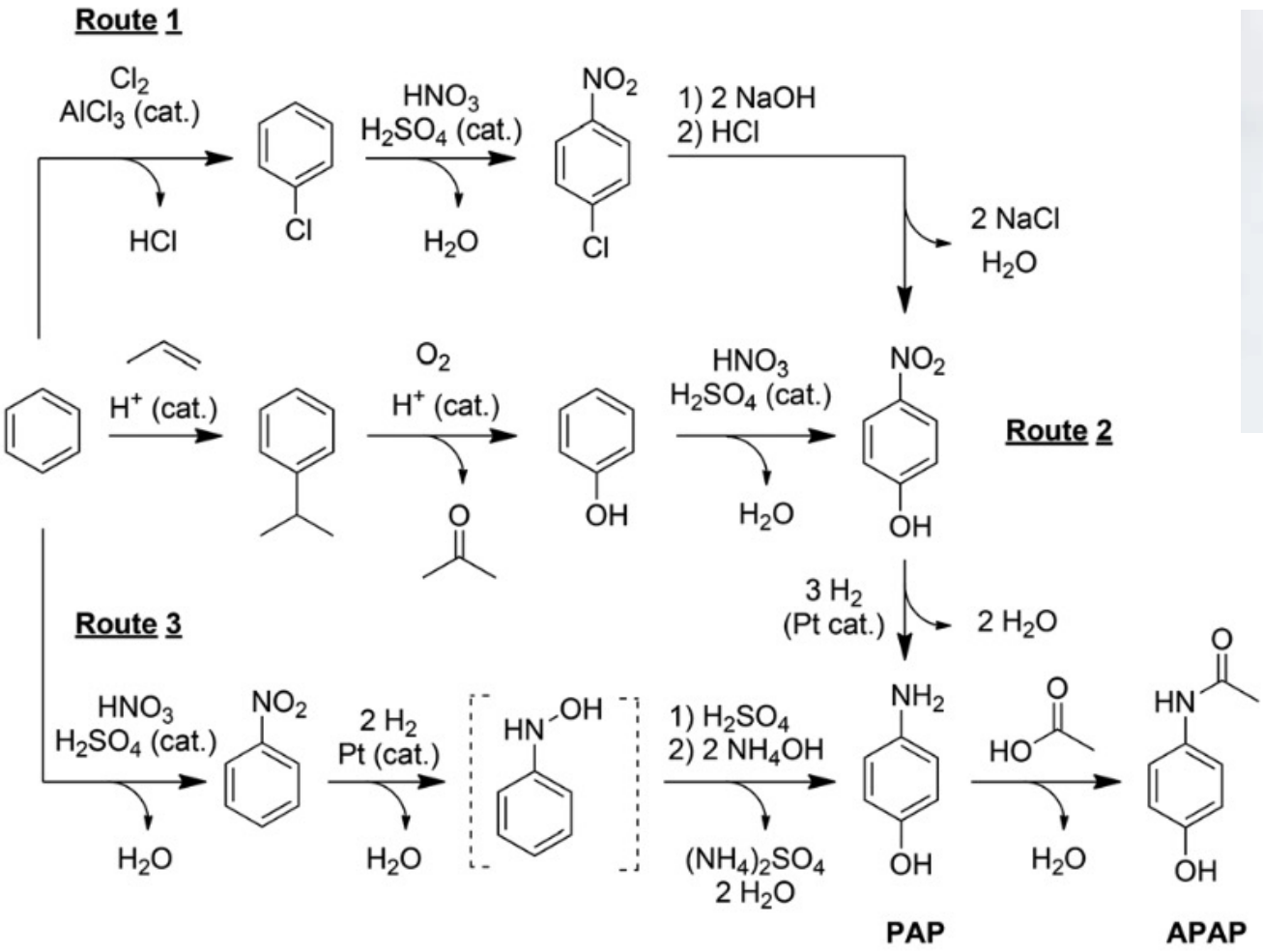
....

$\nu_a\mathbf{A} + \nu_b\mathbf{B} + \ldots + \nu_i\mathbf{I} \xrightarrow{\text{auxiliaries}} \nu_p\mathbf{P}$ overall equation

$$GAE = \frac{\nu_P M_P}{\sum \nu_i M_i}$$

B. M. Trost, *Science*, **1991**, *254*, 1471-1477.

Global atom economy



Scheme 2 Commercial routes for paracetamol production.

R. Joncour, N. Duguet, E. Métay, A. Ferreira and M. Lemaire. *Green Chem.*, **2014**, *16*, 2997

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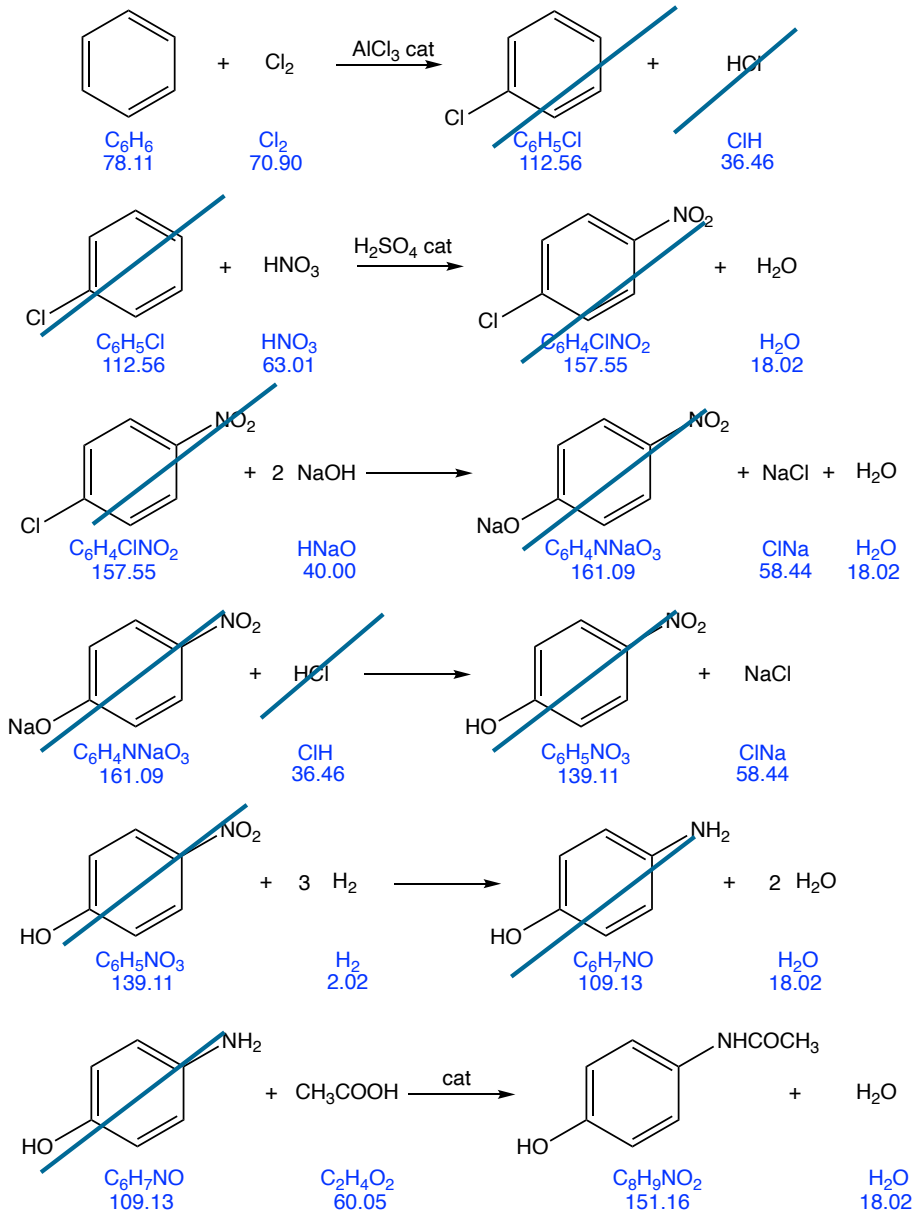
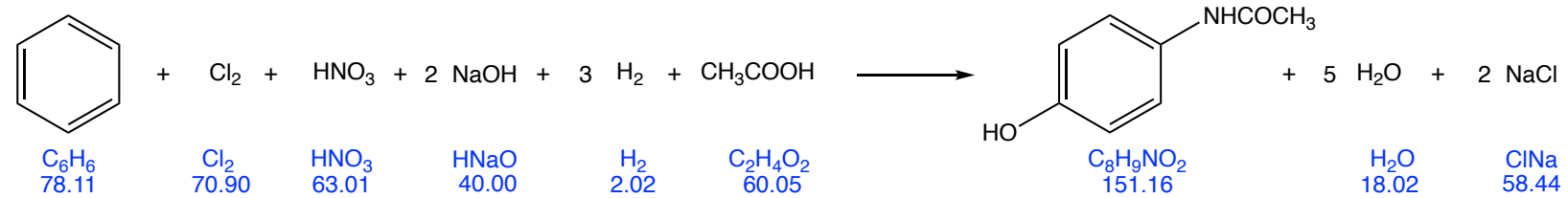


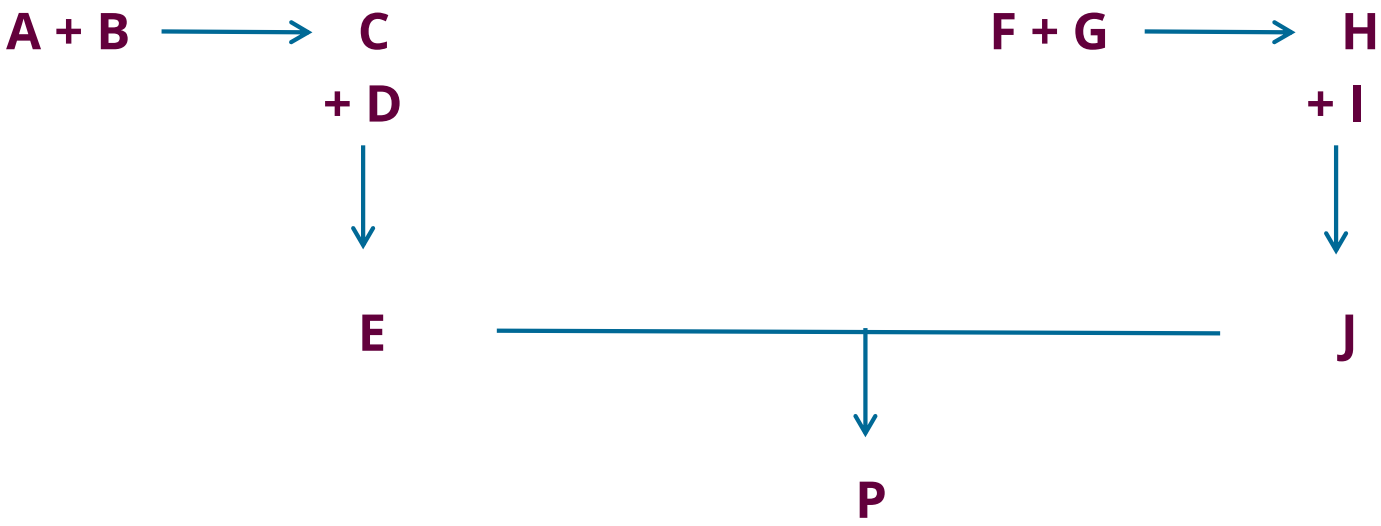


78.11	
+70.90	
+63.01	
+2*40.00	151.16
+3*2.02	+5*18.02
+60.05	+2*58.44
358.13	358.14

$$GAE = \frac{151.16}{358.13} = 0.42$$

42 % of the mass of the reactants **could be** incorporated into the product

Global atom economy (synthesis sequences)



$$GAE = \frac{\nu_P M_P}{\sum \nu_i M_i}$$

$(M_A+M_B+M_D+M_F+M_G+M_D+M_I)$

GAE % of the mass of the reactants **could be** incorporated into the product

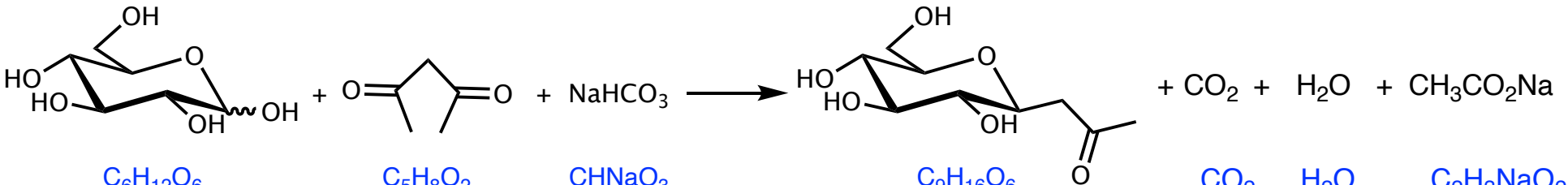
Reaction mass efficiency

Reaction mass efficiency (RME) : the percentage of the mass of the reactants that **is incorporated** in the product

$$RME = \frac{mass\ of\ the\ product}{mass\ of\ the\ reactants}$$

A. D. Curzons, D. J. C. Constable, D. N. Mortimer, V. L. Cunningham, *Green Chem.* **2001**, *3*, 1–6.

Reaction mass efficiency

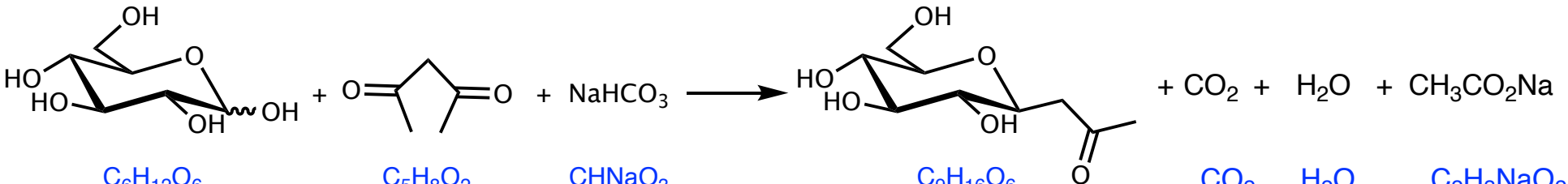


$C_6H_{12}O_6$	$C_5H_8O_2$	$CHNaO_3$	$C_9H_{16}O_6$	CO_2	H_2O	$C_2H_3NaO_2$
180.16	100.12	84.01	220.22	44.01	18.02	82.03

A solution of D-glucose (2.50 g, 13.87 mmol), 2,4-pentanedione (1.75 g, 17.52 mmol), $NaHCO_3$ (1.75 g, 20.83 mmol) in water (10 mL) was refluxed overnight then cooled to r.t. and treated with Dowex 50 X-8 200 H^+ to reach pH 5 (15.30 g). The resin was filtered, rinsed with H_2O (25 mL) and the aqueous solution was washed with AcOEt (20 mL) and concentrated to afford the product (3.05 g, 100%).

$$\boldsymbol{RME = \frac{mass\ of\ the\ product}{mass\ of\ the\ reactants}}$$

Reaction mass efficiency



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$$\textbf{RME} = \frac{\textit{mass of the product}}{\textit{mass of the reactants}}$$

50% of the mass of the reactants **are incorporated** in the product

$$RME = \frac{3.05}{2.5+1.75+1.75} = 0.50$$

$$AE = \frac{220.22}{180.16 + 100.12 + 84.01} = 0.60$$

60 % of the mass of the reactants **could be** incorporated into the product

RME ≤ AE

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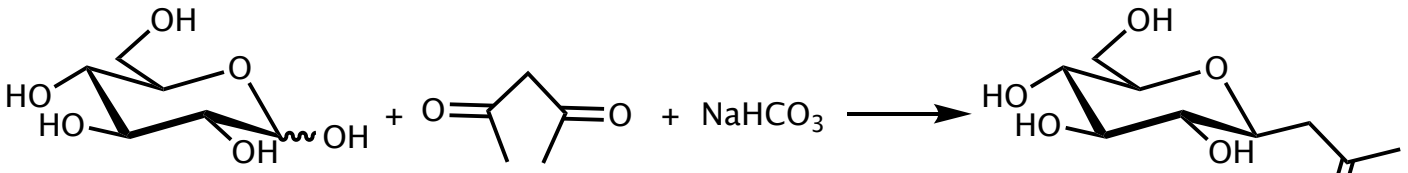
Optimum efficiency (OE) - Greener atomic level

$$OE = 100\frac{RME}{AE}$$

McElroy, C.R.; Constantinou, A.; Jones, L.C.; Summerton, L.; Clark, J.H. Green Chem. 2015, 17, 3111–3121

Also named Greener atomic level

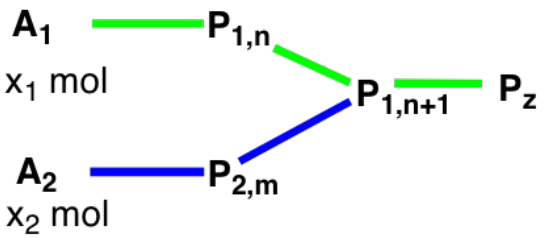
Machado, A.A.S.C. Quim. Nova 2014, 37, 1094–1109

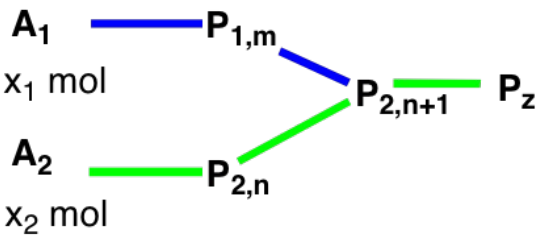


$C_6H_{12}O_6$ 180.16 + $C_5H_8O_2$ 100.12 + $CHNaO_3$ 84.01 → $C_9H_{16}O_6$ 220.22

OE = 100*(0.5/0.6) = 83%

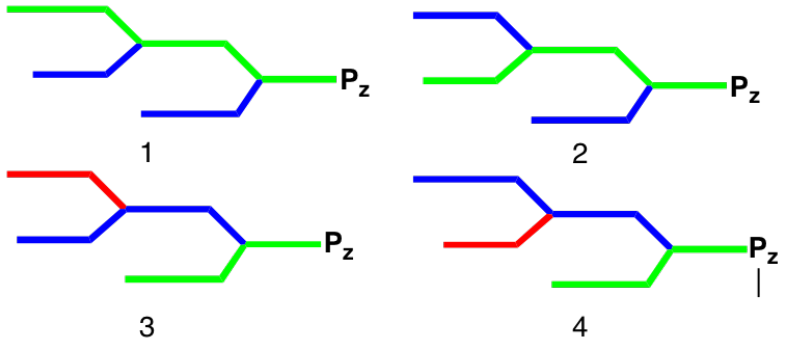
Global material economy (GME) of synthesis sequences





A_1 reference molecule
$B_{1,i}$: reactants of the green sequence
$B_{2,j}$: reactants of the blue sequence

A_2 reference molecule
$B_{1,i}$: reactants of the blue sequence
$B_{2,j}$: reactants of the green sequence



J. Augé, M. -C. Scherrmann, *New J. Chem.* **2012**, *36*, 1091–1098

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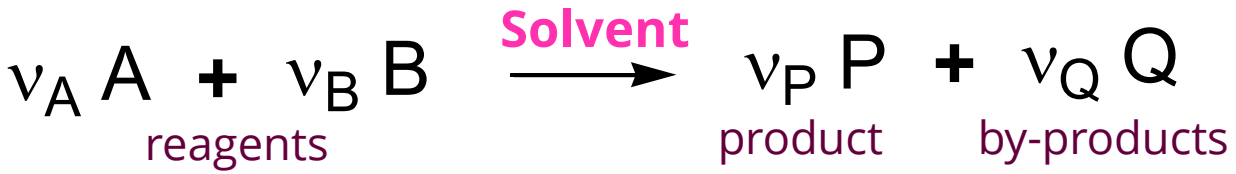
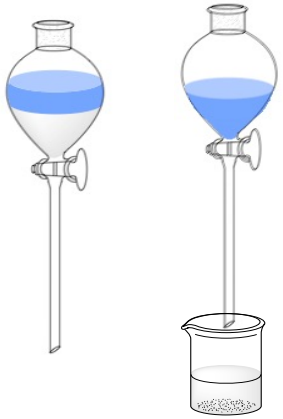
Complete environmental factor- environmental factor



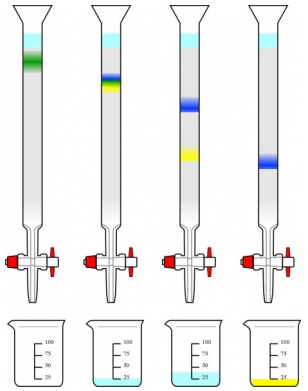
Workup

Neutralization, extraction…



Purification

Distillation, crystallization, chromatography…

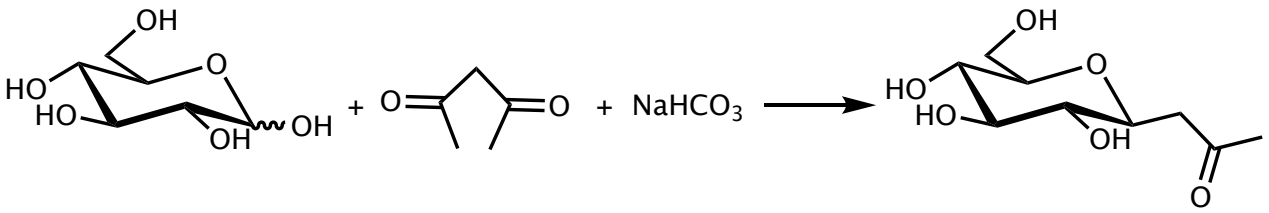


$$E = \frac{mass\ of\ waste\ (except\ water)}{m_{product}}$$

$$cE = \frac{mass\ of\ waste}{m_{product}}$$

R. A. Sheldon *Chemtech* **1994** *March* 38.
F. Roschangar, R. A. Sheldon, C. H. Senanayake, *Green Chem.* **2015**, *17*, 752–768.

Complete environmental factor- environmental factor



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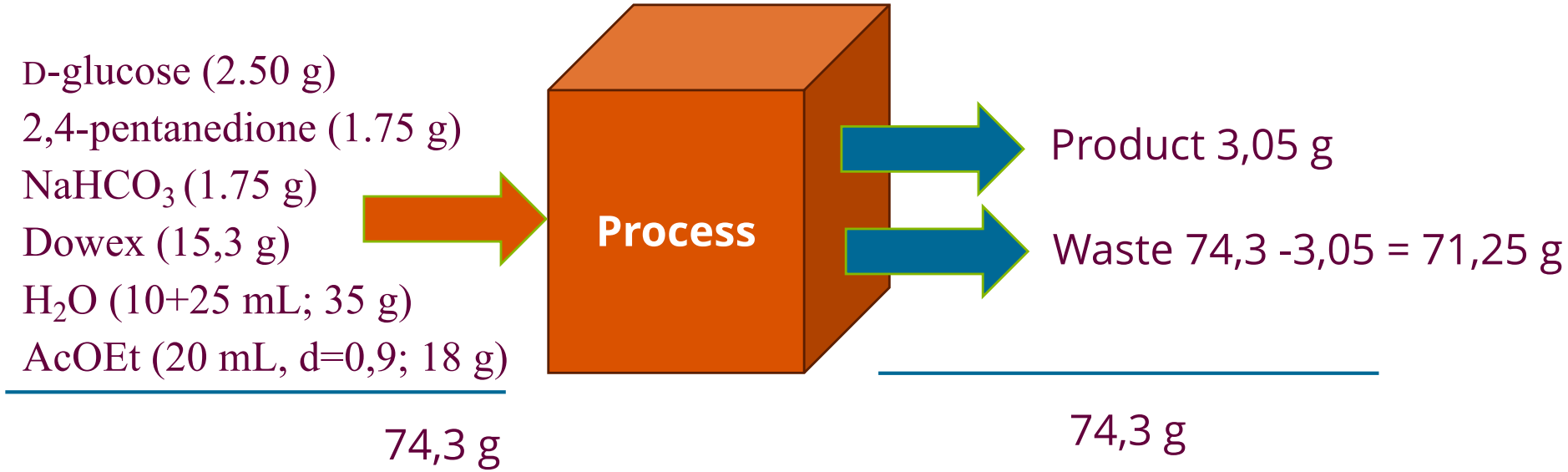
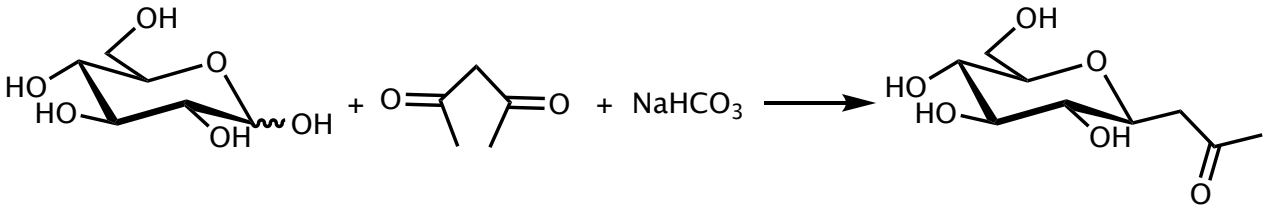


$$cE = \frac{mass\ of\ waste}{m_{product}} = \frac{71{,}25}{3{,}05} = \mathbf{23{,}35}$$

F. Pessel, I. Billault, M.-C. Scherrmann, *Green Chem.*, **2016**, *18*, 5558-5568

Complete environmental factor- environmental factor



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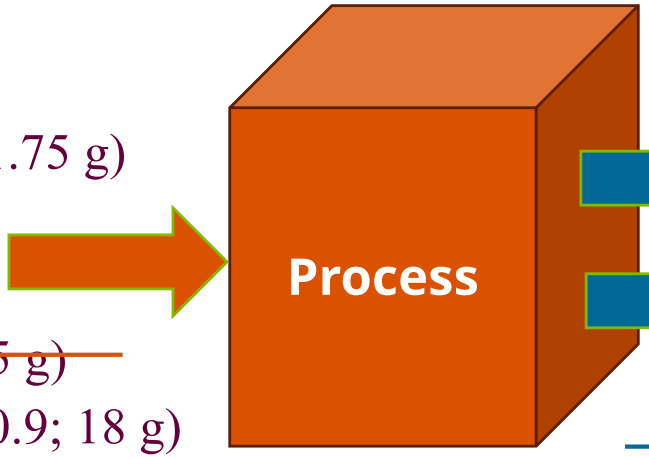
D-glucose (2.50 g)
2,4-pentanedione (1.75 g)
$NaHCO_3$ (1.75 g)
Dowex (15.3 g)
~~H_2O (10+25 mL; 35 g)~~
AcOEt (20 mL, d=0.9; 18 g)

39.3 g



Product 3.05 g

Waste 39.3 -3.05 = 36.25 g

39.3 g

$$E = \frac{mass\ of\ waste\ (except\ water)}{m_{product}} = \frac{36.25}{3.05} = 11.88$$

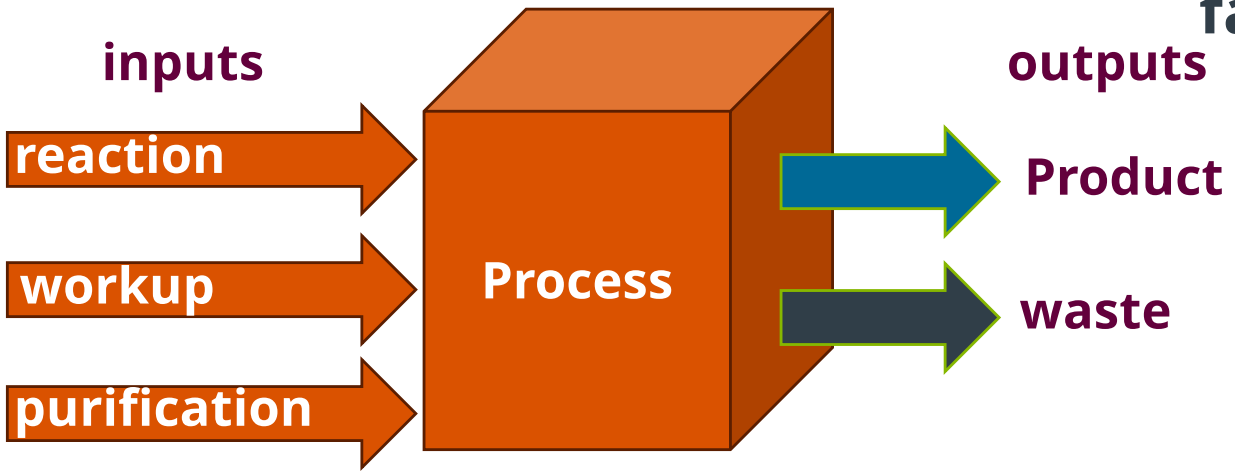
E Factors in the Chemical Industry

R.A. Sheldon, *The E factor at 30: a passion for pollution prevention. Green Chem.*, **2023**, *25*,1704

$$E = \frac{\boldsymbol{mass\ of\ waste\ (except\ water)}}{\boldsymbol{m_{product}}}$$

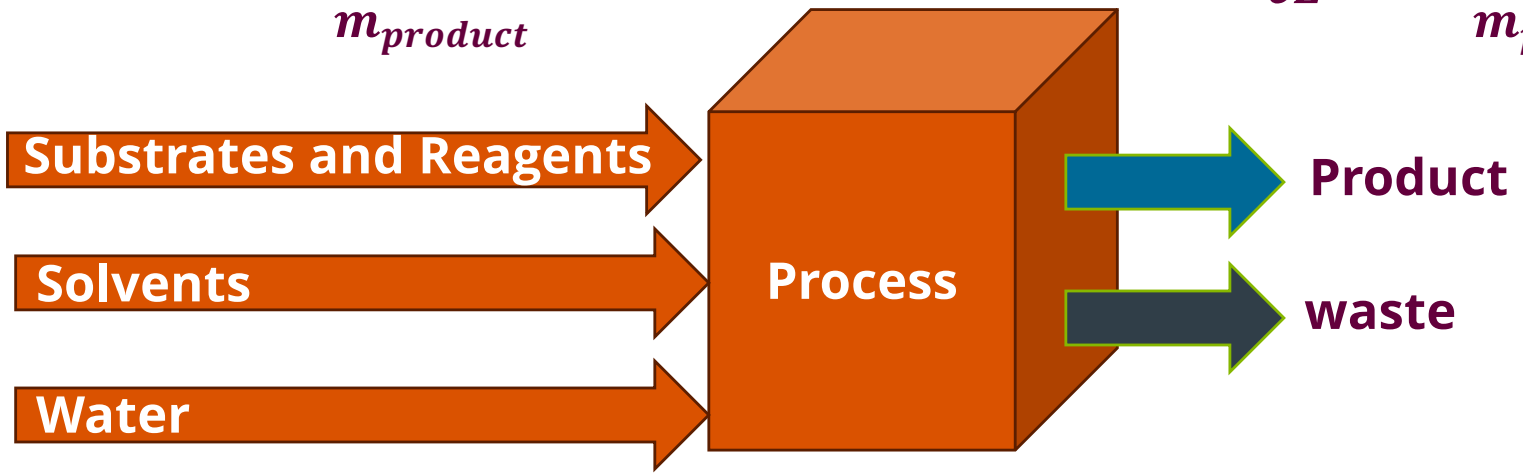
Industry sector	tonnage	E
Oil refinery	10^6-10^8	< 0,1
Bulk chemicals	10^4-10^6	1-5
Fine chemicals	10^2-10^4	5 to >50
Pharmaceuticals	10-10^3	25 to >100

Process Mass Intensity – Complete Environmental factor



$$PMI = \frac{total\ mass\ used\ in\ the\ process}{m_{product}}$$

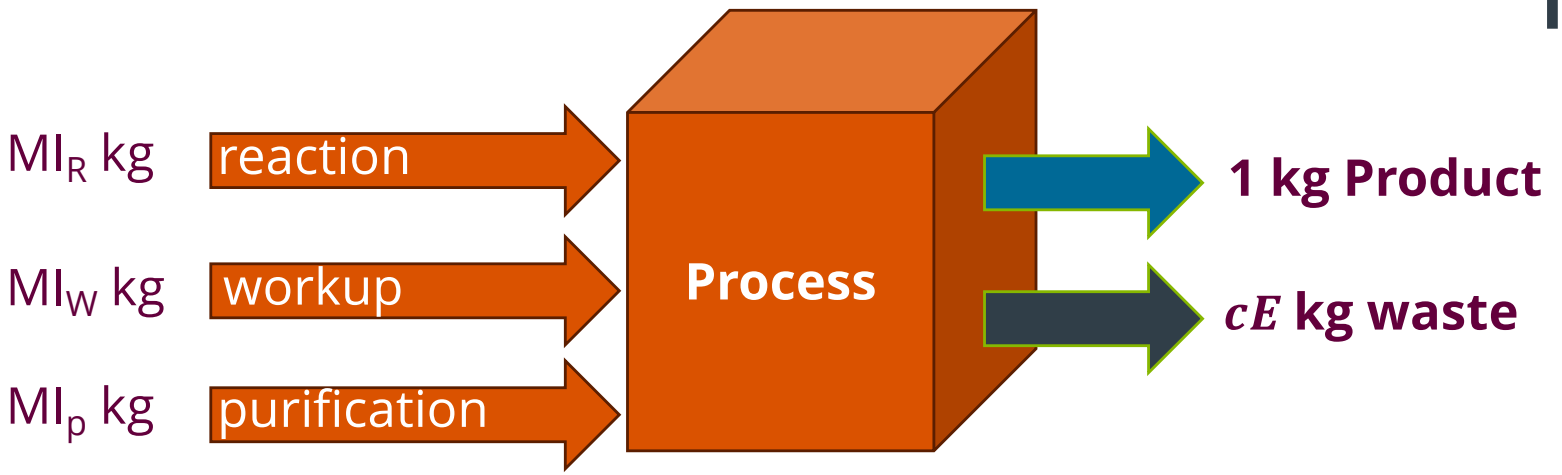
$$cE = \frac{mass\ of\ waste}{m_{product}}$$



$$cE = \frac{mass\ of\ waste}{m_{product}} = PMI - 1$$

D. J. C. Constable, A. D. Curzons, V. L. Cunningham, *Green Chem.*, **2002**, *4*, 521-527.

Process Mass Intensity – Complete Environmental factor



$$MI_R = \frac{total\ mass\ used\ for\ the\ reaction}{m_{product}}$$

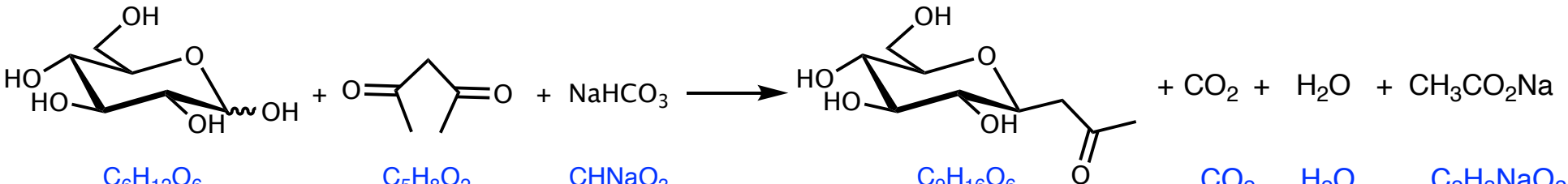
$$MI_w = \frac{total\ mass\ used\ for\ the\ workup}{m_{product}}$$

$$MI_P = \frac{total\ mass\ used\ for\ the\ purification}{m_{product}}$$

$$PMI = \frac{total\ mass\ used\ in\ the\ process}{m_{product}} = MI_R + MI_W + MI_P$$

F. Pessel, I. Billault, M.-C. Scherrmann, *Green Chem.*, **2016**, *18*, 5558-5568

Process Mass Intensity



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$$MI_R = \frac{total\ mass\ used\ for\ the\ reaction}{m_{product}} = 5.24$$

$$MI_w = \frac{total\ mass\ used\ for\ the\ workup}{m_{product}} = 19.11$$

$$MI_P = \frac{total\ mass\ used\ for\ the\ purification}{m_{product}} = 0$$

$$PMI = \frac{total\ mass\ used\ in\ the\ process}{m_{product}} = MI_R + MI_W + MI_P = 24.35$$

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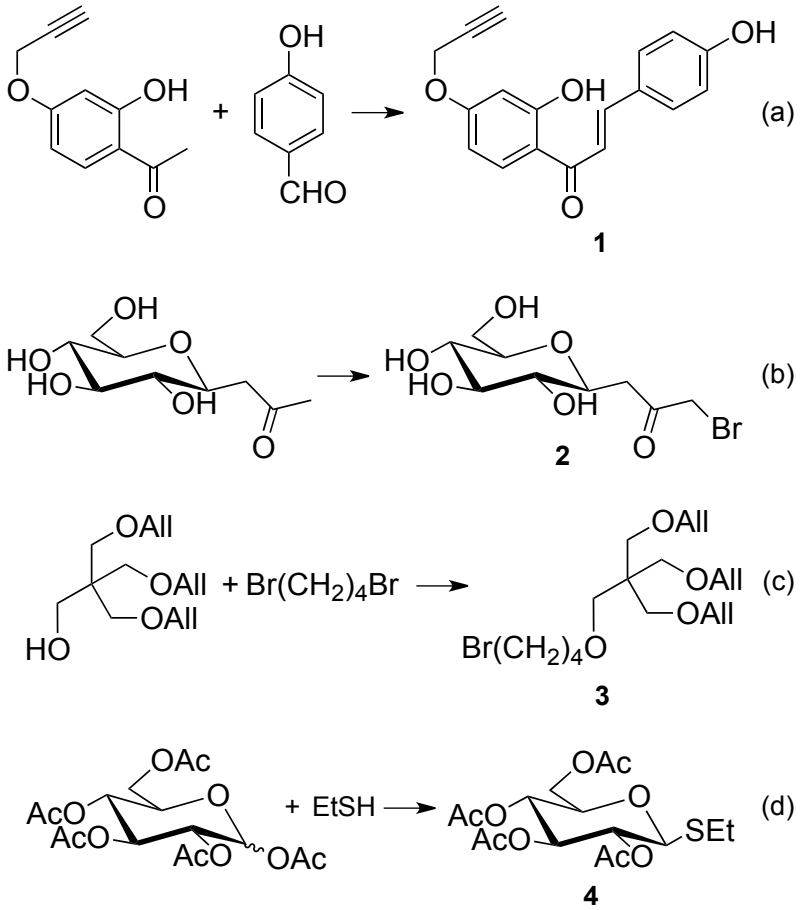
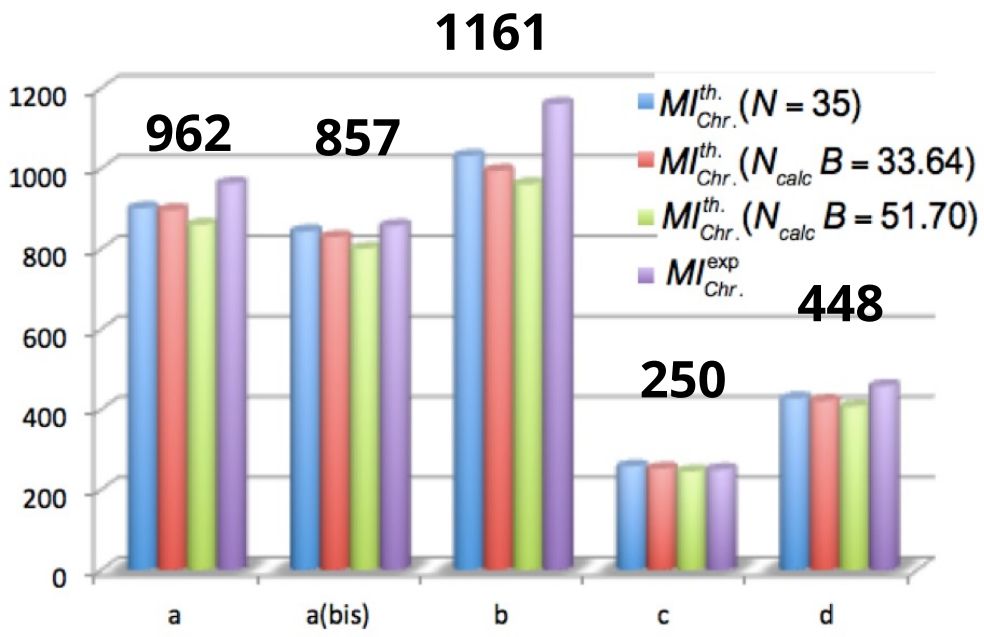
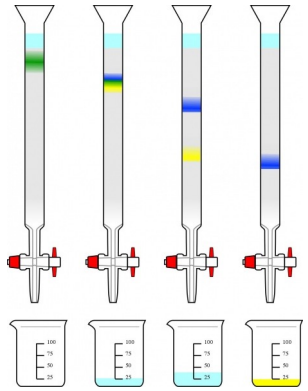
Purification by column chromatography







F. Pessel, J. Augé, I. Billault, M.-C. Scherrmann, *Beilstein J. Org. Chem.*, **2016**, *12*, 2351–2357

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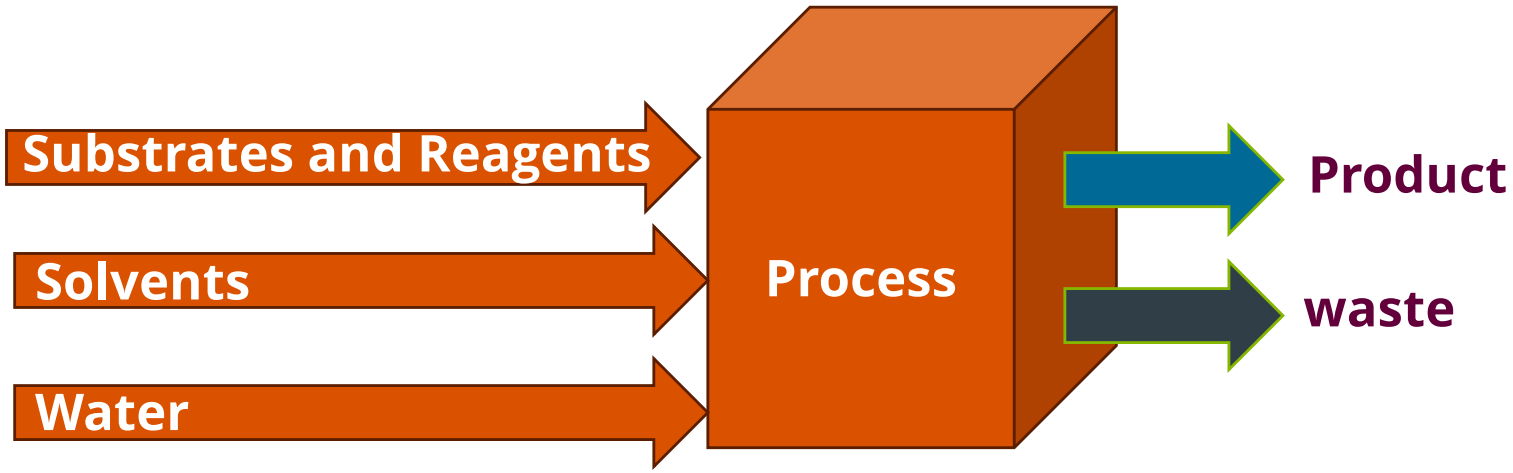
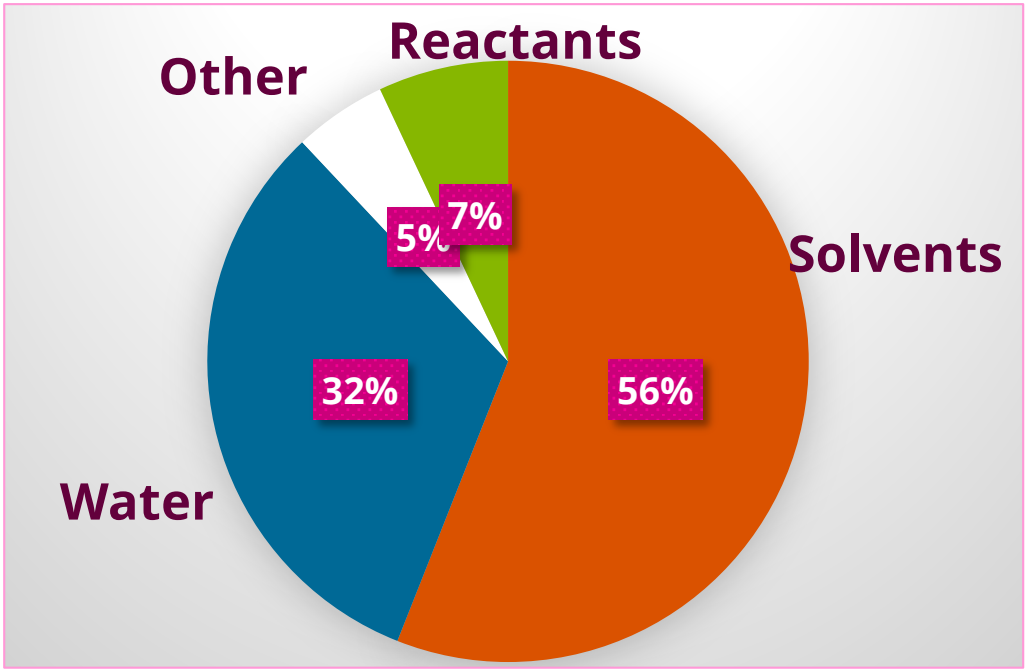
Process Mass Intensity



Composition by mass of the types of material used to manufacture an API.



D. J. C. Constable, C. Jimenez-Gonzalez and R. K. Henderson, *Org. Process Res. Dev.*, **2007**, *11*, 133–137

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Pharmaceutical Roundtable

PMI calculator

Step 1 Input Table		
	Value	Units
Assay Batch Size (input pure)		kg
Assay Kg product (output pure)		kg
Raw Materials	Physical Charge	Units
Main Substrate (Enter only 1 substrate, prepopulated from assay batch size)		
	0.00	kg
Fragment Substrates (fill top down)		
None		kg
None		kg
None		kg
Reagents		
		kg
Solvents		
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
Aqueous		
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg

https://www.acs.org/greenchemistry/research-innovation/tools-for-green-chemistry.html

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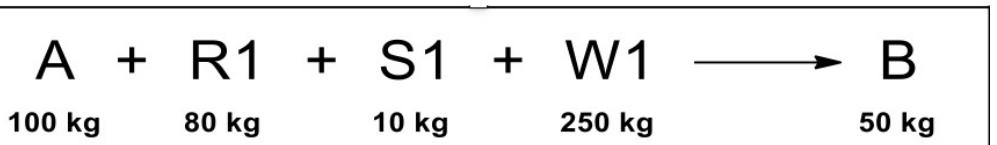
Pharmaceutical Roundtable

PMI calculator

Step 1 Input Table		
	Value	Units
Assay Batch Size (input pure)	100,0	kg
Assay Kg product (output pure)	50,0	kg
Raw Materials	**Physical Charge**	**Units**
Main Substrate (Enter only 1 substrate)		
A	100,00	kg
Fragment Substrates (fill top down)		
None		kg
None		kg
None		kg
Reagents		
R1	80,00	kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
Solvents		
S1	10,0	kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
Aqueous		
W1	250,0	kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg
		kg



Identification of Inputs and Outputs
A = Substrate (assume 100% pure)
R1 = Reagent
S1 = Solvent
W1 = Aqueous Stream
B = Intermediate Product (assume 100% pure)

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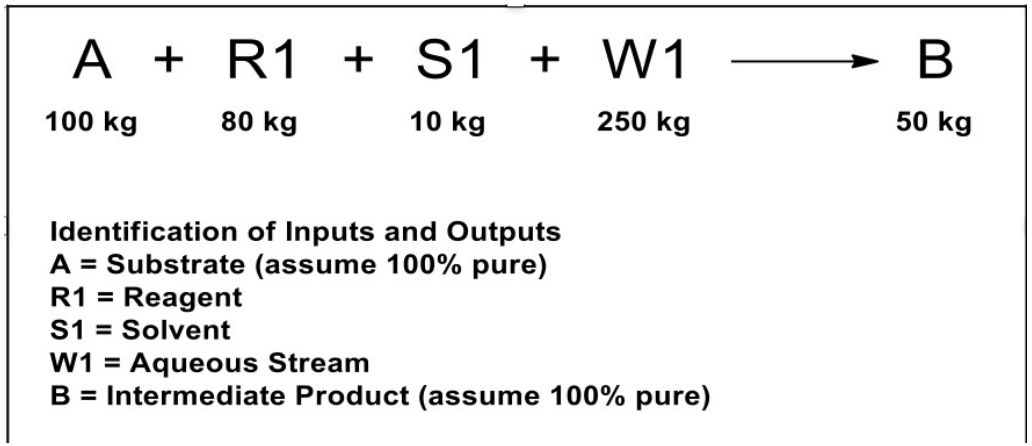
Pharmaceutical Roundtable

PMI calculator



Step 1 Metrics Table	
Mass Substrate (kg)	100
Mass Reagents (kg)	80
Mass Solvents (kg)	10
Mass Aqueous (kg)	250
Step PMI	8,8
Step PMI Substrate, Reagents, Solvents	3,8
Step PMI Substrates and Reagents	3,6
Step PMI Solvents	0,2
Step PMI Water	5,0
Cumulative PMI	8,8
Cumulative PMI Substrate, Reagents, Solvents	3,8
Cumulative PMI Substrates and Reagents	3,6
Cumulative PMI Solvents	0,2
Cumulative PMI Water	5,0

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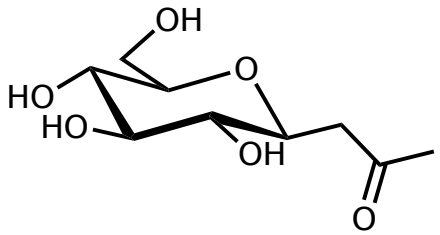
PMI - exemple

Step 1 Input Table		
	Value	Units
Assay Batch Size (input pure)	2,5	g
Assay Kg product (output pure)	3,1	g
Raw Materials	**Physical Charge**	**Units**
Main Substrate (Enter only 1 substrate)		
GLUCOSE	**2,50**	**g**
Fragment Substrates		
None		**g**
Reagents		
2,4 pentanedione	**1,75**	**g**
NaHCO3	**1,75**	**g**
Dowex	**15,30**	**g**
Solvents		
AcOEt	**18,0**	**g**
Aqueous		
H2O	**35,0**	**g**



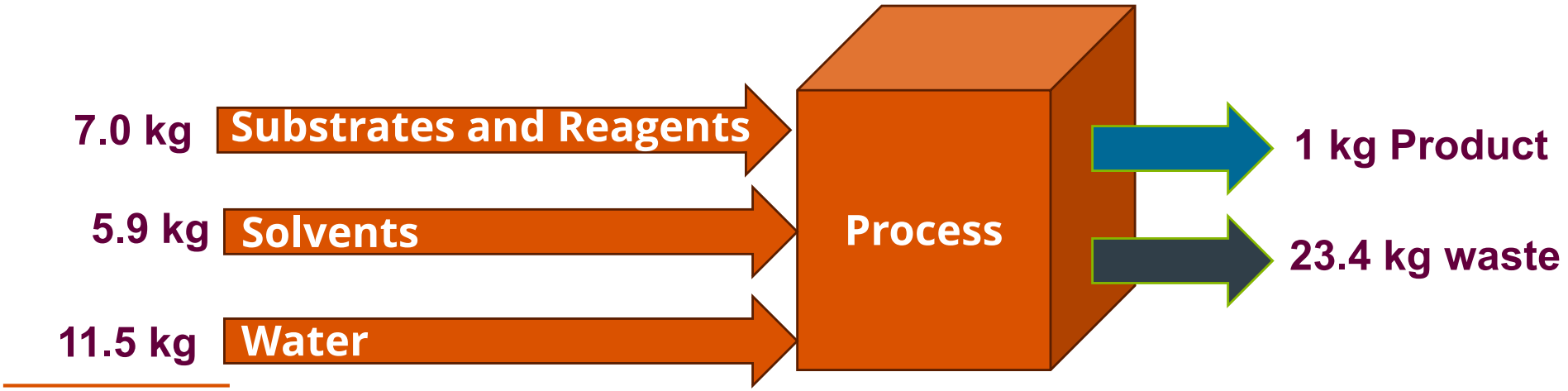
A solution of D-glucose (2.50 g, 13.87 mmol), 2,4-pentanedione (1.75 g, 17.52 mmol), $NaHCO_3$ (1.75 g, 20.83 mmol) in water (10 mL) was refluxed overnight then cooled to r.t. and treated with Dowex 50 X-8 200 H^+ to reach pH 5 (15.30 g). The resin was filtered, rinsed with H_2O (25 mL) and the aqueous solution was washed with AcOEt (20 mL, d=0.9) and concentrated to afford the product (3.05 g, 100%).

PMI - exemple

Step 1 Metrics Table	
Mass Substrate (g)	3
Mass Reagents (g)	19
Mass Solvents (g)	18
Mass Aqueous (g)	35
Step PMI	24,4
Step PMI Substrate, Reagents, Solvents	12,9
Step PMI Substrates and Reagents	7,0
Step PMI Solvents	5,9
Step PMI Water	11,5

cE = 24,4 -1 = 23.4

E = 12.9 -1 = 11.9



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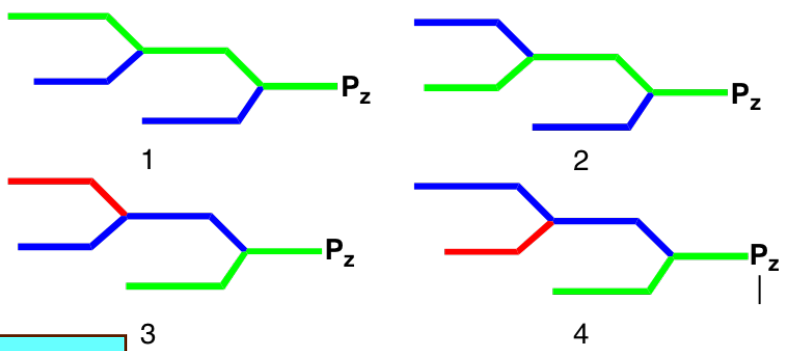
Pharmaceutical Roundtable

Convergent PMI calculator

Step 1 Input Table		
	Value	Units
Assay Batch Size (input pure)		kg
Assay Kg product (output pure)		kg
Raw Materials	**Physical Charge**	**Units**
Main Substrate (Enter only 1 substrate, prepopulated from assay batch size)		
	0.00	kg
Fragment Substrates (fill top down)		
None		kg
None		kg
None		kg
Reagents		
		kg



Step 1 Metrics Table	
Mass Substrate (kg)	100
Mass Reagents (kg)	80
Mass Solvents (kg)	10
Mass Aqueous (kg)	250
Step PMI	8,8
Step PMI Substrate, Reagents, Solvents	3,8
Step PMI Substrates and Reagents	3,6
Step PMI Solvents	0,2
Step PMI Water	5,0
Cumulative PMI	8,8
Cumulative PMI Substrate, Reagents, Solvents	3,8
Cumulative PMI Substrates and Reagents	3,6
Cumulative PMI Solvents	0,2
Cumulative PMI Water	5,0

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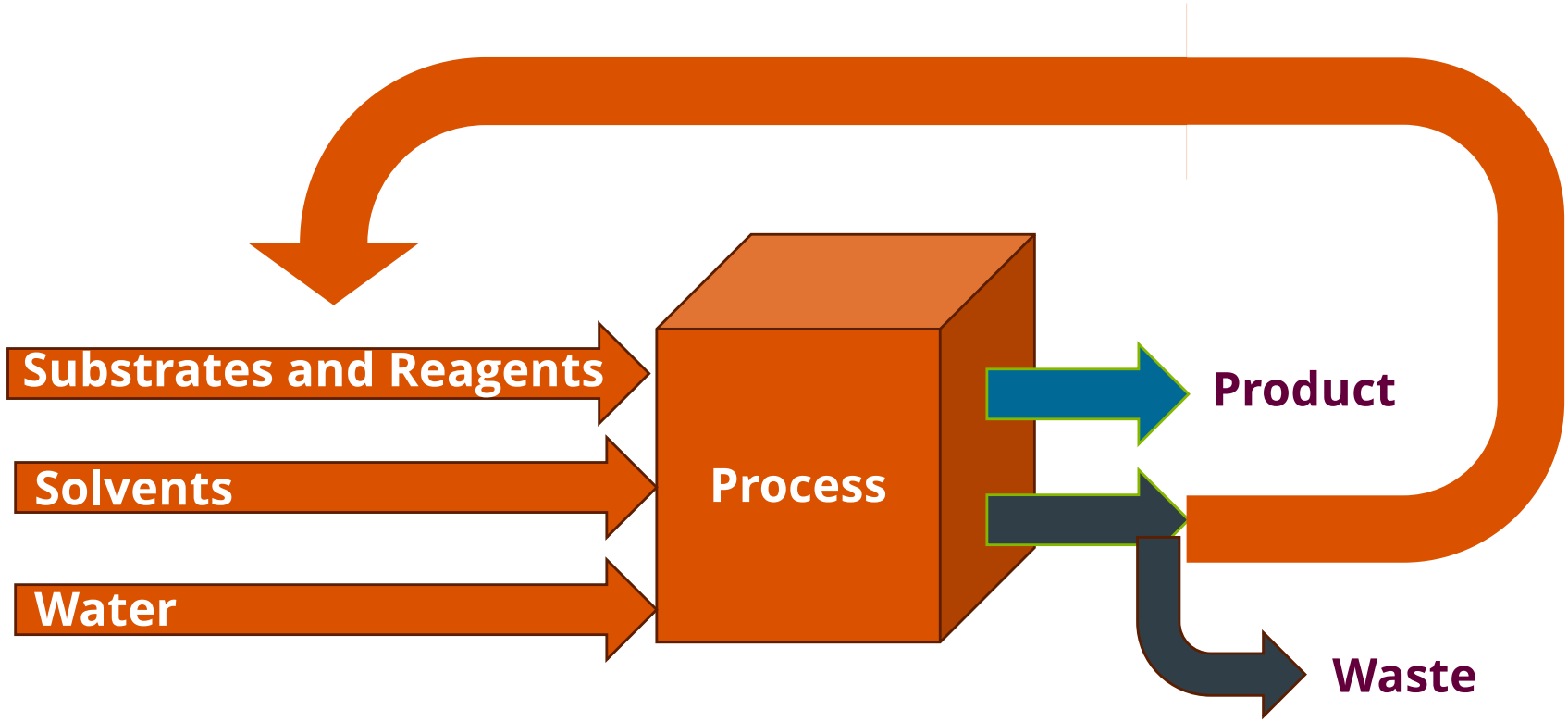
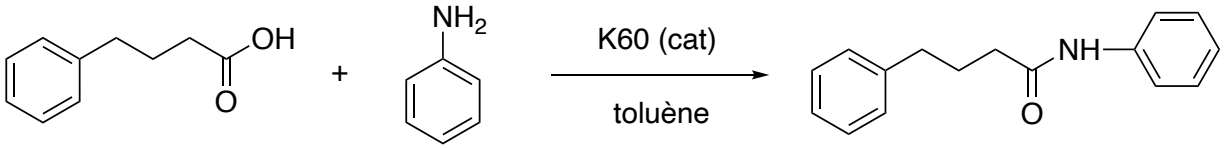
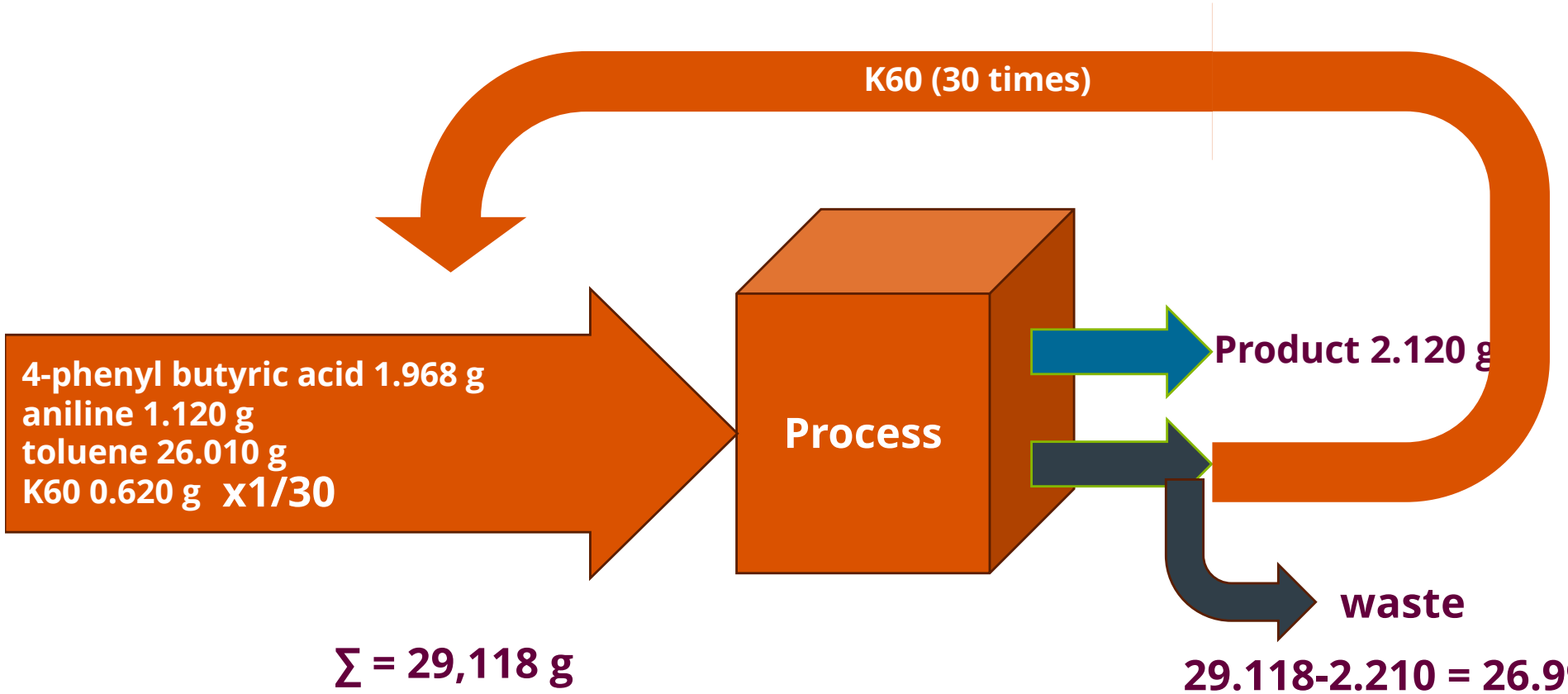
recycling - reuse



Recycling - Reuse





∑ = 29,118 g

29.118-2.210 = 26.998

$$E = \frac{mass\ of\ waste\ (except\ water)}{m_{product}} = \frac{26.998}{2,120} = 12.73$$

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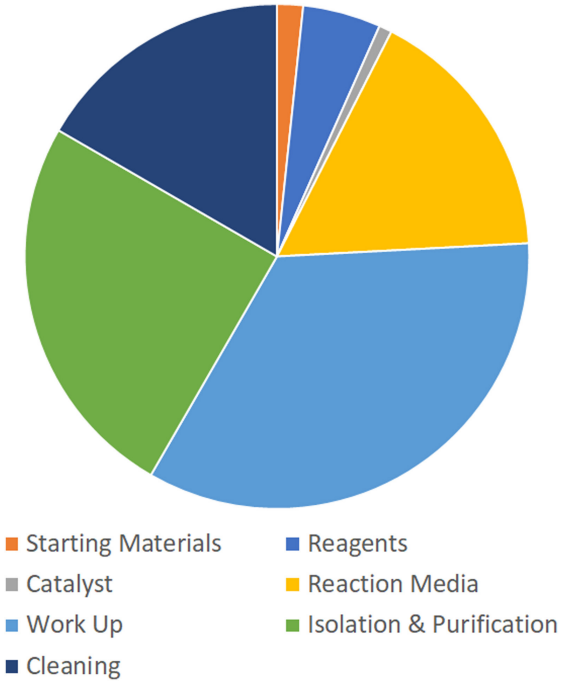
Manufacturing mass intensity



$$\mathbf{MMI = U[PMI] + U_1[MI_1] + U_2[MI_2] + \ldots U_n[MI_n]}$$

PMI = Process Mass Intensity of stages of proccess under consideration;
MI = Mass intensity of component under consideration (cleaning, conditioning, etc);
U = Utilization factor of component.

$$U = \frac{number\ of\ times\ required}{number\ of\ batches}$$

C. H. Benison, P. R. Payne, *Curr. Res. Green Sustain. Chem.* **2022**, *5*, 100229.

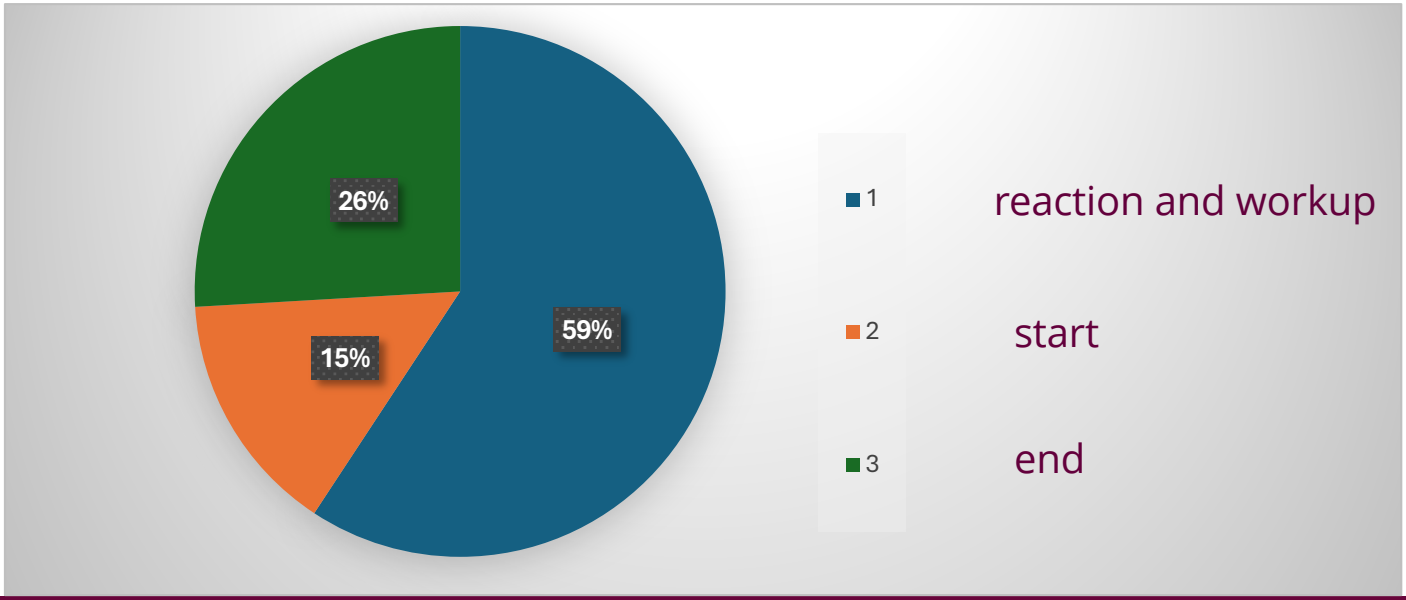
Manufacturing mass intensity

one batch :

Start: Vacant Reactor A (1000 L)		During process: Reactor A		End: Vacant Reactor A (1000 L)	
Equipment preparation	100 kg water rinse 100 kg organic solvent	Reaction and work-up	800 kg material input 40 kg product output	Reactor cleaning	100 kg water rinse, 150 kg organic solvent, 100 kg analysis rinse

$$\boldsymbol{PMI} = \frac{Mass\ of\ process\ material\ input}{Mass\ of\ product} = \frac{800\ kg}{40\ kg} = \mathbf{20}$$

$$\boldsymbol{MMI} = U\,[PMI] + U_1\,[M_1] + U_2\,[M_2] = 20 + \frac{1}{1}\left[\frac{100\ kg + 100\ kg}{40\ kg}\right] + \frac{1}{1}\left[\frac{100\ kg + 150\ kg + 100\ kg}{40\ kg}\right] = \mathbf{34}$$



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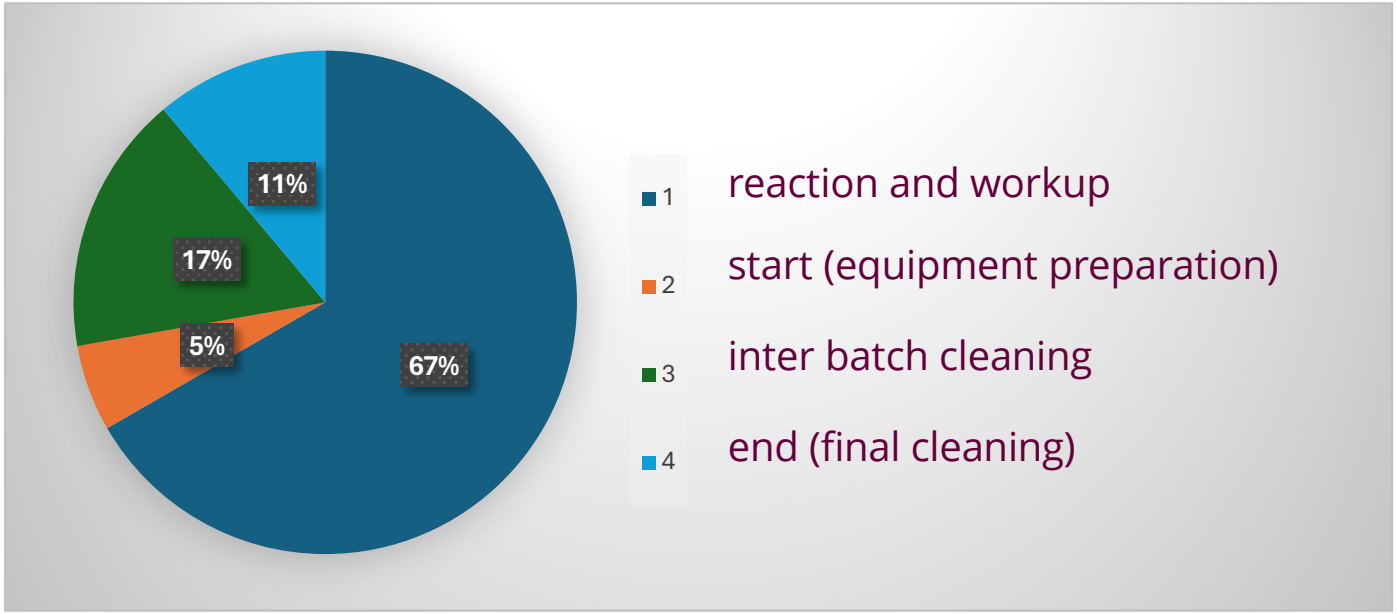
Manufacturing mass intensity

3 batches & inter-batch cleaning

$$MMI = U[PMI] + U_1[MI_{prep}] + U_2[MI_{clean\ inter\text{-}batch}] + U_3[MI_{clean\ final}]$$

$$MMI = \frac{3}{3}\left[\frac{800}{40}\right] + \frac{1}{3}\left[\frac{200}{40}\right] + \frac{2}{3}\left[\frac{300}{40}\right] + \frac{1}{3}\left[\frac{400}{40}\right] = 30$$

$$U = \frac{number\ of\ times\ required}{number\ of\ batches}$$



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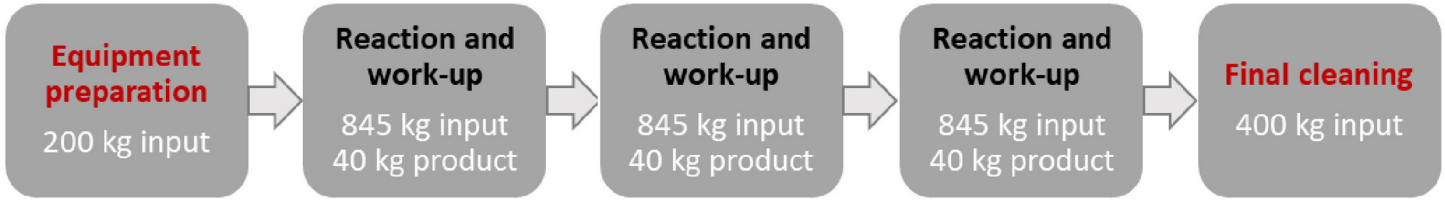
Manufacturing mass intensity

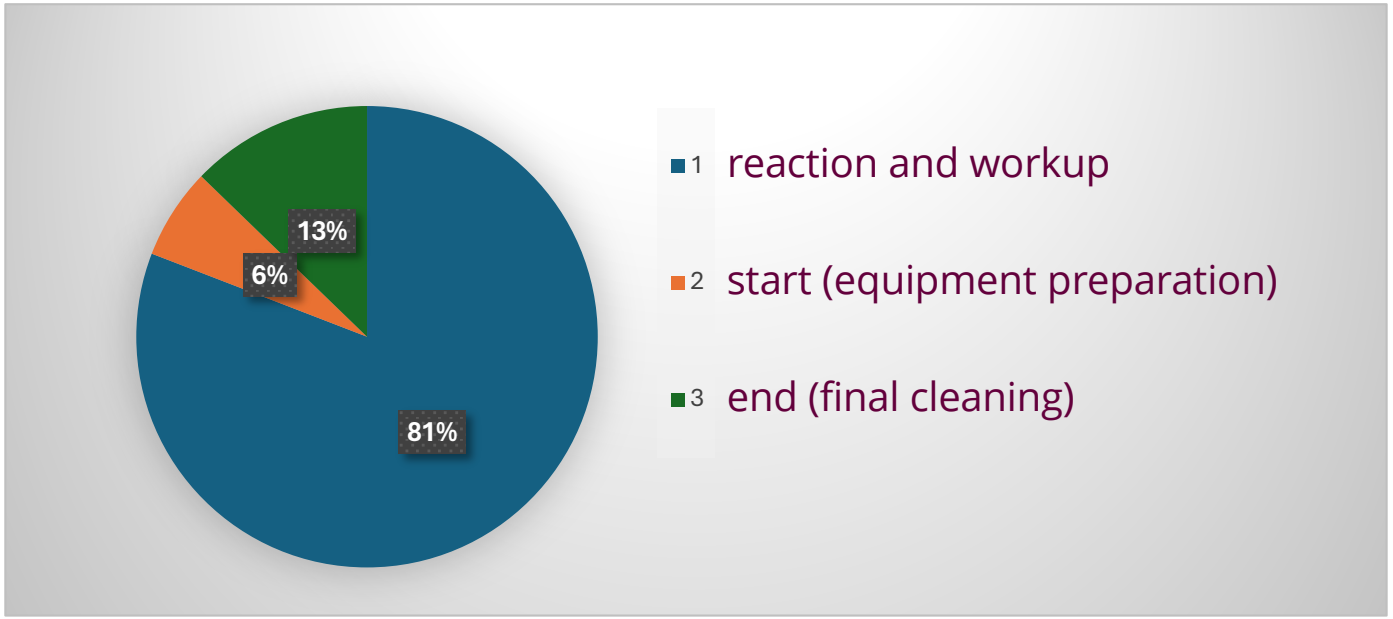
3 batches no inter-batch cleaning



$$MMI = U[PMI] + U_1[MI_{prep}] + 0\,[MI_{clean\ inter\text{-}batch}] + U_3[MI_{clean\ final}]$$

$$MMI = \frac{3}{3}\left[\frac{845}{40}\right] + \frac{1}{3}\left[\frac{200}{40}\right] + \frac{1}{3}\left[\frac{400}{40}\right] = 26$$

$$U = \frac{number\ of\ times\ required}{number\ of\ batches}$$



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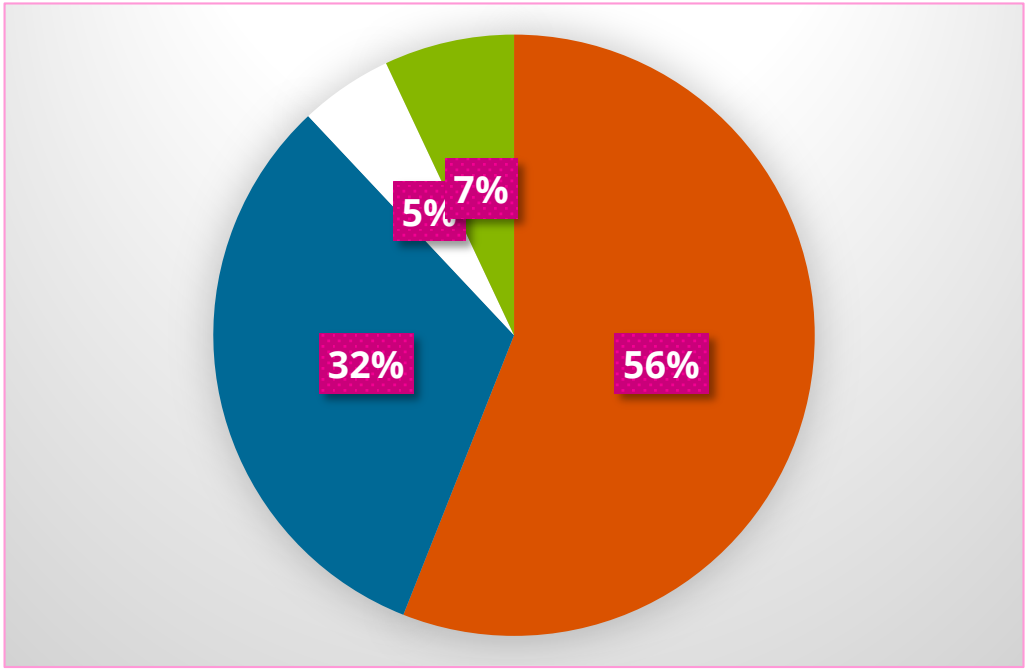
Criteria for green solvents

Composition by mass of the types of material used to manufacture an API.

D. J. C. Constable, C. Jimenez-Gonzalez and R. K. Henderson, Org. Process Res. Dev., 2007, 11, 133–137



A survey of solvent selection guides

Family	Solvent	AZ	GCI-PR	GSK	Pfizer	Sanofi[a]	Issues	Overall[b]
Water	Water	—	—	24	Preferred	Recommended	—	Recommended
Alcohols	MeOH	19	14		ferred	Recommended	—	TBC
	Et		13		rred	Recommended	—	Recommended
	i-P		16		rred			Recommended
	n-I		13		erred			Recommended
	t-B		15		eferred			TBC
	Be		11		—	Subst. adv.	—	TBC
	Et		13		Usable	Subst. adv.	—	TBC
Ketones	Acetone	21	15		Preferred	Recommended	—	TBC
	MEK	21	16	15	Preferred	Recommended	—	TBC
	MIBK	22	17	15		nended	—	TBC
	Cycloh					dv.	—	TBC
Esters	Methyl					dv.	—	TBC
	Ethyl a					nended	—	Recommended
	i-PrOA					nended	—	Recommended
	n-BuO					nended	—	Recommended
Ethers	Diethyl						H224	HH
	Diisop					dv.	Perox.	Hazardous
	MTBE	24	21	4		dv.	—	TBC
	THF	23	16	4	Usable	Subst. adv.	H351	TBC
	Me-THF	24	15	11	Usable	Recommended	—	Problematic
	1,4-Dioxane	28	21	11	Undesirable	Subst. req.	—	Hazardous
	Anisole	18	13	18	—	Recommended	—	Recommended
	DME	21	23	2	Undesirable	Subst. req.	H360	Hazardous
Hydrocarbons	Pentane	—	—	7	Undesirable	Banned	H224	Hazardous
	Hexane	26	21	1	Undesirable	Subst. req.	—	Hazardous

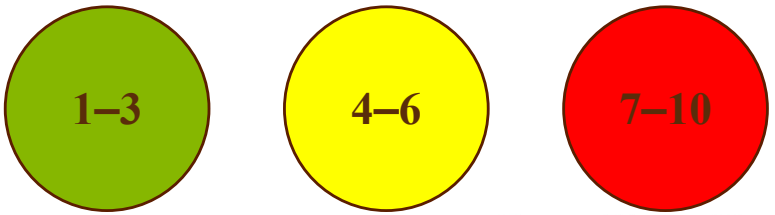
Subst. adv.: substitution advisable; Subst. req.: substitution requested; TBC: to be confirmed; HH: highly hazardous

D. Prat, J. Hayler and A. Wells, *Green Chem.*, **2014**, *16*, 4546
D. Prat et al. *Green Chem.*, **2016**, *18*, 288

Criteria for green solvents

Family	Solvent	BP (°C)	FP (°C)	Worst H3xx[a]	H4xx	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion[b]
Water	Water	100	na	None	None	1	1	1	Recommended	Recommended
Alcohols	MeOH	65	11	H301	None	4	7	5	Problematic	Recommended
	EtOH	78	13	H319	None	4	3	3	Recommended	Recommended
	i-PrOH	82	12	H319	None	4	3	3	Recommended	Recommended
	n-BuOH	118	29	H318	None	3	4	3	Recommended	Recommended
	t-BuOH[c]	82	11	H319	None	4	3	3	Recommended	Recommended
	Benzyl alcohol	206	101	H302	None	1	2	7	Problematic	Problematic
	Ethylene glycol	198	116	H302	None	1	2	5	Recommended	Recommended
Ketones	Acetone	56	−18	H319	None	5	3	5	Problematic	Recommended
	MEK	80	−6	H319	None	5	3	3	Recommended	Recommended
	MIBK	117	13	H319	None	4	2	3	Recommended	Recommended
	Cyclohexanone	156	43	H332	None	3	2	5	Recommended	Problematic
Esters	Methyl acetate	57	−10	H302	None	5	3	5	Problematic	Problematic
	Ethyl acetate	77	−4	H319	None	5	3	3	Recommended	Recommended
	i-PrOAc	89	2	H319	None	4	2	3	Recommended	Recommended
	n-BuOAc	126	22	H336	None	4	2	3	Recommended	Recommended
Ethers	Diethyl ether	34	−45	H302	None	10	3	7	Hazardous	HH
	Diisopropyl ether	69	−28	H336	None	9	3	5	Hazardous	Hazardous
	MTBE	55	−28	H315	None	8	3	5	Hazardous	Hazardous
	THF	66	−14	H351	None	6	7	5	Problematic	Problematic
	Me-THF	80	−11	H318	None	6	5	3	Problematic	Problematic
	1,4-Dioxane	101	12	H351	None	7	6	3	Problematic	Hazardous
	Anisole	154	52	None	None	4	1	5	Problematic	Recommended
	DME	85	−6	H360	None	7	10	3	Hazardous	Hazardous
Hydrocarbons	Pentane	36	−40	H304	H411	8	3	7	Hazardous	Hazardous

Criteria for green solvents



Family	Solvent	BP (°C)	FP (°C)	Worst H3xx[a]	H4xx	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion[b]
Water	Water	100	na	None	None	1	1	1	Recommended	Recommended
Alcohols	MeOH	65	11	H301	None	4	7	5	Problematic	Recommended
	EtOH	78	13	None	None	4	3	3	Recommended	Recommended
	1-Propanol	97	15	H318	None	4	3	3	Recommended	Recommended
	2-Propanol	82	12	H318	None	3	4	3	Recommended	Recommended
	1-Butanol	117	29	H318	None	4	3	3	Recommended	Recommended
	2-Butanol	99	24	H318	None	1	2	7	Problematic	Problematic
	2-Methyl-1-propanol	108	28	H318	None	1	2	5	Recommended	Recommended
	2-Methyl-2-propanol	83	11	H319	None	5	3	5	Problematic	Recommended
Esters	EtOAc	77	−4	H319	None	5	3	3	Recommended	Recommended
	iPrOAc	89	4	None	None	4	2	3	Recommended	Recommended
	MeOAc	57	−10	H319	None	3	2	5	Recommended	Problematic
	nBuOAc	126	22	None	None	5	3	5	Problematic	Problematic
	iBuOAc	118	18	None	None	5	3	3	Recommended	Recommended
	EtOBu	120	25	None	None	4	2	3	Recommended	Recommended
	EtOPr	99	12	None	None	4	2	3	Recommended	Recommended
Ethers	2-MeTHF	80	−11	H319	None	10	3	7	Hazardous	HH
	THF	66	−14	H319	H351	9	3	5	Hazardous	Hazardous
	MTBE	55	−28	H319	None	8	3	5	Hazardous	Hazardous
	CPME	106	−1	H319	None	6	7	5	Problematic	Problematic
	Diethyl ether	35	−40	H319	None	6	5	3	Problematic	Problematic
	Diisopropyl ether	68	−28	H319	None	7	6	3	Problematic	Hazardous
	Anisole	154	52	None	None	4	1	5	Problematic	Recommended
	DME	85	−6	H360	None	7	10	3	Hazardous	Hazardous
Hydrocarbons	Pentane	36	−40	H304	H411	8	3	7	Hazardous	Hazardous

Safety criteria

Basic safety score	1	3	4	5	7
Flash point (°C)	>60	24 to 60	23 to 0	−1 to −20	<−20
GHS	—	H226		H225 or H224	

1 is added to the safety score for each of the following properties:
- AIT < 200 °C
- Resistivity > 10^8 Ω m
- Ability to form peroxides (EUH019)

Any solvent with a high energy of decomposition (>500 J g^{-1}), like nitromethane,[13] would be scored 10.

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Criteria for green solvents

Health criteria

Health score	2	4	6	7	9
CMR			H341 H351 H361		H340 H350 H360
STOT	H304 H371 H373	H334	H370 H372		
Acute toxicity	H302 H312 H332 H336 EUH070		H301 H311 H331		H300 H310 H330
Irritation	H315 H317 H319 H335 EUH066	H318 (eyes)		H314 (skin/ eyes)	

CMR: carcinogen, mutagen or reprotoxic.[22] STOT: single target organ toxicity. 1 is added to the health score if BP < 85 °C.

Health score	Env. score	Ranking by default	Ranking after discussion[b]
1	1	Recommended	Recommended
7	5	Problematic	Recommended
3	3	Recommended	Recommended
3	3	Recommended	Recommended
4	3	Recommended	Recommended
3	3	Recommended	Recommended
2	7	Problematic	Problematic
2	5	Recommended	Recommended
3	5	Problematic	Recommended
3	3	Recommended	Recommended
2	3	Recommended	Recommended
2	5	Recommended	Problematic
3	5	Problematic	Problematic
3	3	Recommended	Recommended
2	3	Recommended	Recommended
2	3	Recommended	Recommended
3	7	Hazardous	HH
3	5	Hazardous	Hazardous
3	5	Hazardous	Hazardous
7	5	Problematic	Problematic
5	3	Problematic	Problematic
6	3	Problematic	Hazardous
1	5	Problematic	Recommended
10	3	Hazardous	Hazardous
3	7	Hazardous	Hazardous

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Criteria for green solvents

Family	Solvent	BP (°C)	FP (°C)	Worst H3xx[a]	H4xx	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion[b]
Water	Water	100	na	None	None	1	1	1	Recommended	Recommended
								5	Problematic	Recommended
								3	Recommended	Recommended
								3	Recommended	Recommended
								3	Recommended	Recommended
								3	Recommended	Recommended
								7	Problematic	Problematic
								5	Recommended	Recommended
								5	Problematic	Recommended
								3	Recommended	Recommended
								3	Recommended	Recommended
								5	Recommended	Problematic
								5	Problematic	Problematic
								3	Recommended	Recommended
								3	Recommended	Recommended
								3	Recommended	Recommended
								7	Hazardous	HH
								5	Hazardous	Hazardous
								5	Hazardous	Hazardous
								5	Problematic	Problematic
								3	Problematic	Problematic
								3	Problematic	Hazardous
								5	Problematic	Recommended
								3	Hazardous	Hazardous
								7	Hazardous	Hazardous

Environment criteria

Environment score	3	5	7
BP (°C)	70–139	50–69 140–200	<50 >200
GHS	No H4xx after full REACh registration	H412 H413 	H400 H410 H411 
Other		No, or partial REACh registration	

Water: score = 1.H420 (ozone layer hazard): score = 10.

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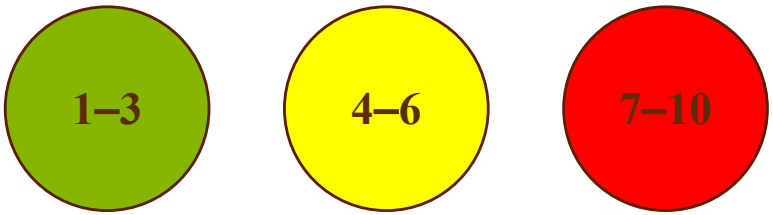
Criteria for green solvents



Family	Solvent	BP (°C)	FP (°C)	Worst H3xx[a]	H4xx	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion[b]
Water	Water	100	na	None	None	1	1	1	Recommended	Recommended
Alcohols	MeOH	65	11	H301	None	4	7	5	Problematic	Recommended
	EtOH	78	13	H319	None	4	3	3	Recommended	Recommended
	i-PrOH	82	12	H319	None	4	3	3	Recommended	Recommended
	n-BuOH	118	29	H318	None	3	4	3	Recommended	Recommended
	t-BuOH[c]	82	11	H319	None	4	3	3	Recommended	Recommended
	Benzyl alcohol	206	101	H302	None	1	2	7	Problematic	Problematic
	Ethylene glycol	198	116	H302	None	1	2	5	Recommended	Recommended

Ranking by default

Score combination	Ranking
One score ≥8	Hazardous
Two “red” scores	Hazardous
One score = 7	Problematic
Two “yellow” scores	Problematic
Other	Recommended

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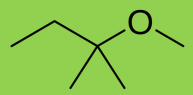
Water	H_20		
Alcohols	MeOH EtOH iPrOH nBuOH iBuOH tBuOH Ethylène glycol	Benzyl alcohol 1,3 propane diol Glycerol	
Ketones	Acetone MEK MIBK	Cyclohexanone	
Esters	Ethyl acetate iPrOAc nBuOAc iBuOAc Glycol diacetate	Methyl acetate γ-Valerolactone	
Ethers	Anisole TAME (tert-amyl ethyl ether) 	THF MeTHF CPME ETBE	**Diethyl ether** Diisopropyl ether MTBE 1,4 dioxane DME
Hydrocarbons		Heptane Cyclohexane Toluene Xylenes D-Limonene p-Cymene	Pentane Hexane **Benzene**

Halogenated		Chlorobenzene	DCM **Chlorforme** **CCl4** **DCE**
Aprotic polar	Dimethyl carbonate	CH_3CN DMPU DMSO Ethylene carbonate Cyrene	DMF DMAc NMP Sulfolane **HMPA** **Nitromethane**
Miscellaneous		Ethyl lactate	Methoxyethanol **CS2**
Acids		Formic acid Acetic acid	
Amines			Pyridine TEA

Efforts to Replace Methylene Chloride in Pharmaceutical Process Chemistry
R. Yogesh, N. Srivastava, and B. M. Mulik. *Macromol. Symp.* **2023**, *407*, 2100502

Designing Safer Solvents to Replace Methylene Chloride for Liquid Chromatography Applications Using Thin-Layer Chromatography as a Screening Tool. A. Sharma et al *Separations* **2021**, *8*, 172.

Replacement of dichloromethane within chromatographic purification:a guide to alternative solvents. D. S. MacMillan et al. *Green Chem.*, **2012**, *14*, 3016.

A convenient guide to help select replacement solvents for dichloromethane in chromatography. J. P. Taygerly et al. *Green Chem.*, **2012**, *14*, 3020.

Global Metrics for Measuring Greenness

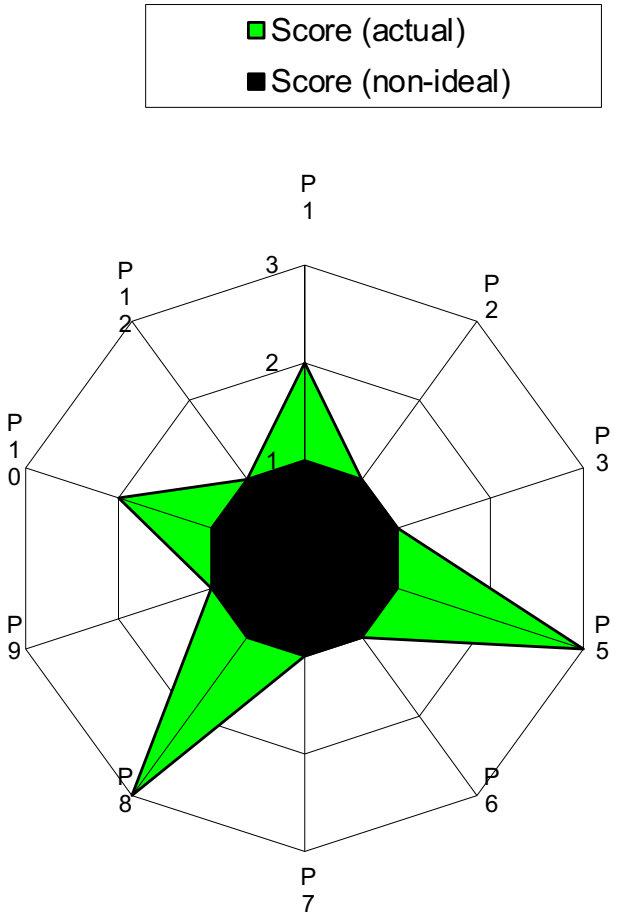
Mass-Based Metrics

12 principles of green chemistry

1. Prevent waste
2. Maximize atom economy
3. Design less hazardous chemical syntheses
4. Design safer chemicals and products
5. Use safer solvents and reaction conditions
6. Increase energy efficiency
7. Use renewable feedstocks
8. Avoid chemical derivatives
9. Use catalysts, not stoichiometric reagents
10. Design chemicals and products to degrade after use
11. Analyze in real time to prevent pollution
12. Minimize the potential for accidents

Anastas and Warner

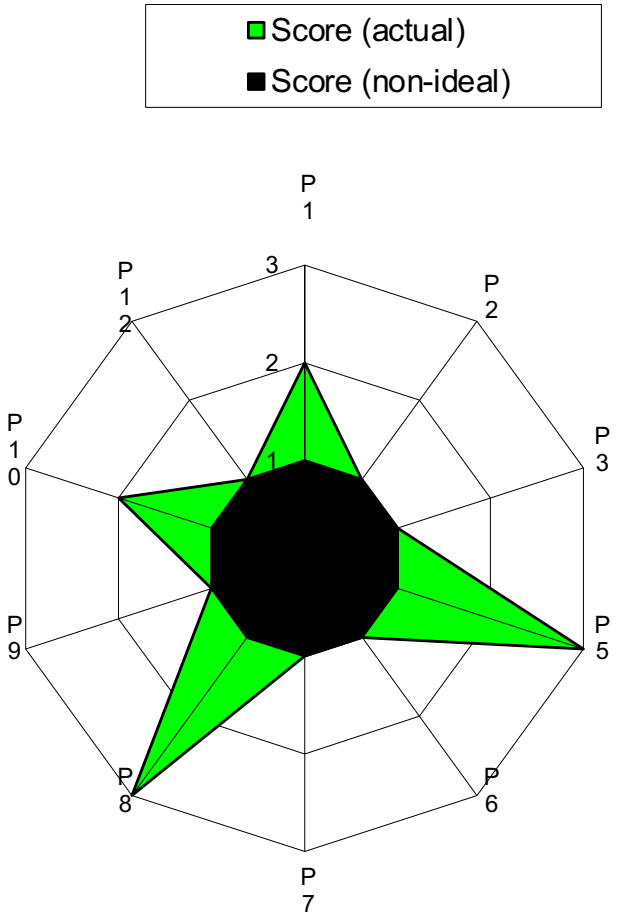
Green star



GC Principle	Criteria	Score
P1 – prevention	Waste is innocuous (S = 3, Table 1)	3
	Waste involves a moderate risk to human health and environment (S = 2, Table 1, for at least one substance)	2
	Waste involves a high risk to human health and environment (S = 1, Table 1, for at least one substance)	1
P2 – atom economy	Reactions without excess of reagents (<10%) and without formation of by-products	3
	Reactions without excess of reagents (<10%) and with formation of by-products	2
	Reactions with excess of reagents (>10%) and without formation of by-products	2
	Reactions with excess of reagents (>10%) and with formation of by-products	1
P3 – less hazardous chemical synthesis	All substances involved are innocuous (S = 3, Table 1)	3
	Substances involved have a moderate risk to human health and environment (S = 2, Table 1, for at least one substance)	2
	At least one substance involved has a high risk to human health and environment (S = 1, Table 1)	1
P4 – designing of safer products	Not applicable	NA
P5 – safer solvents and auxiliary materials	Solvents and auxiliary substances are not used, but if used are innocuous (S = 3, Table 1)	3
	Solvents or/and auxiliary substances are used but have a moderate risk to human health and environment (S = 2, Table 1, for at least one substance)	2
	At least one solvent or auxiliary substance has a high risk to human health and environment (S = 1, Table 1)	1
P6 – increasing energy efficiency	Room temperature and pressure	3
	Room pressure and temperature between 0 and 100 deg C when cooling or heating is needed	2
	Pressure different from room pressure and/or temperature >100 deg C or less than 0 deg C	1
P7 – use renewable feedstocks	All substances involved are renewable (S = 3, Table 3)	3
	At least one substance involved is renewable, water is not considered (S = 3, Table 3)	2
	None of substances involved are renewable, water is not considered S = 1, Table 3)	1
P8 – reduce derivatives	Derivatizations are not used	3
	Only one derivatization or similar operation is used	2
	More than one derivatization or similar operations are used	1
P9 - catalysts	Catalysts are not used and if used are innocuous (S = 3, Table 1)	3
	Catalysts are used but have a moderate risk to human health and environment (S = 2, Table 1)	2
	Catalysts are used and have a high risk to human health and environment (S = 1, Table 1)	1
P10 – design degradation	All substances are degradable and break down to innocuous products (S = 3, Table 3)	3
	All substances not degradable may be treated to render them degradable to innocuous products (S = 2, Table 3)	2
	At least one substance is not degradable nor may be treated to render it degradable to innocuous products (S = 1, Table 3)	1
P11 – real time monitoring for pollution prevention	Not applicable	NA
P12 – safer chemistry for accident prevention	Substances used have a low risk to cause chemical accidents (S = 3, Table 2)	3
	Substances used have a moderate risk to cause chemical accidents (S = 2, Table 2, for at least one substance)	2
	Substances used have a high risk to cause chemical accidents (S = 1,Table 2, for at least one substance	1

M.G.T.C. Ribeiro,;D. A. Costa, A.A.S.C. Machado, *Green Chem. Lett. Rev.* **2010**, *3*, 149-159.

Green star



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	Reactions without excess of reagents (<10%) and with formation of by-products	2
	Reactions with excess of reagents (>10%) and without formation of by-products	2
	Reactions with excess of reagents (>10%) and with formation of by-products	1
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	Substances involved have a moderate risk to human health and environment (S = 2, Table 1, for at least one substance)	2
	At least one substance involved has a high risk to human health and environment (S = 1, Table 1)	1
P4 – designing of safer products	Not applicable	NA
P5 – safer solvents and auxiliary materials	Solvents and auxiliary substances are not used, but if used are innocuous (S = 3, Table 1)	3
	Solvents or/and auxiliary substances are used but have a moderate risk to human health and environment (S = 2, Table 1, for at least one substance)	2
	At least one solvent or auxiliary substance has a high risk to human health and environment (S = 1, Table 1)	1
P6 – increasing energy efficiency	Room temperature and pressure	3
	Room pressure and temperature between 0 and 100 deg C when cooling or heating is needed	2
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	At least one substance involved is renewable, water is not considered (S = 3, Table 3)	2
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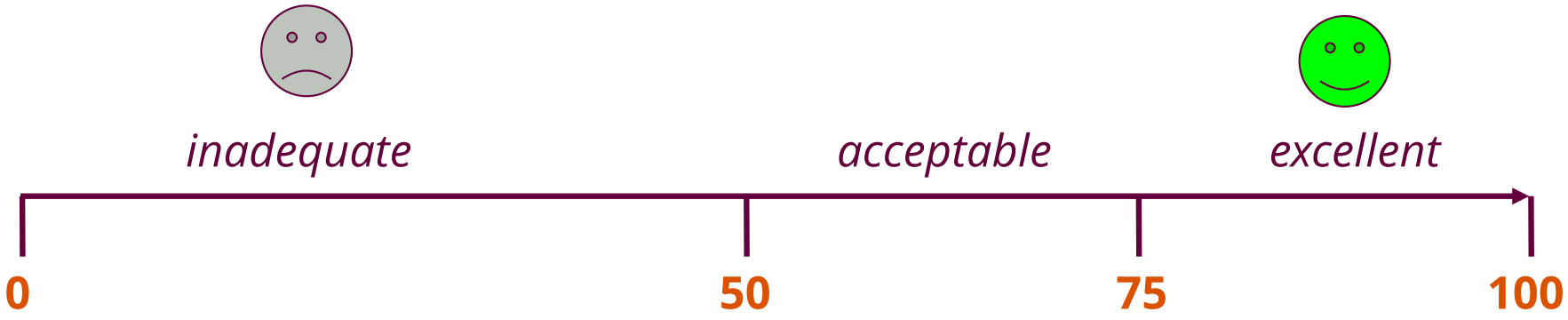
P10 – design degradation	All substances are degradable and break down to innocuous products (S = 3, Table 3)	3
	All substances not degradable may be treated to render them degradable to innocuous products (S = 2, Table 3)	2
	At least one substance is not degradable nor may be treated to render it degradable to innocuous products (S = 1, Table 3)	1
P11 – real time monitoring for pollution prevention	Not applicable	NA
P12 – safer chemistry for accident prevention	Substances used have a low risk to cause chemical accidents (S = 3, Table 2)	3
	Substances used have a moderate risk to cause chemical accidents (S = 2, Table 2, for at least one substance)	2
	Substances used have a high risk to cause chemical accidents (S = 1,Table 2, for at least one substance	1

M.G.T.C. Ribeiro,;D. A. Costa, A.A.S.C. Machado, *Green Chem. Lett. Rev.* **2010**, *3*, 149-159.

Ecoscale



totally failed reaction
(0% yield)

Ideal reaction
Compound A (substrate) undergoes a reaction with (or in the presence of) inexpensive compound(s) B to give the desired compound C in 100% yield at room temperature with a minimal risk for the operator and a minimal impact for the environment.

EcoScale = 100 - sum of individual penalties

(*specifically designed for laboratory scale conditions*)

K. Van Aken, L. Strekowski, L. Patiny, *Beilstein J. Org. Chem.* **2006**, 2, 3.

The penalty points to calculate the EcoScale

1. Yield	(100 – %yield)/2
2. Price of reaction components (to obtain 10 mmol of end product)	
Inexpensive (< $10)	0
Expensive (> $10 and < $50)	3
Very expensive (> $50)	5
3. Safety[a]	
N (dangerous for environment)	5
T (toxic)	5
F (highly flammable)	5
E (explosive)	10
F+ (extremely flammable)	10
T+ (extremely toxic)	10
4. Technical setup	
Common setup	0
Instruments for controlled addition of chemicals[b]	1
Unconventional activation technique[c]	2
Pressure equipment, > 1 atm[d]	3
Any additional special glassware	1
(Inert) gas atmosphere	1
Glove box	3
5. Temperature/time	
Room temperature, < 1 h	0
Room temperature, < 24 h	1
Heating, < 1 h	2
Heating, > 1 h	3
Cooling to 0°C	4
Cooling, < 0°C	5
6. Workup and purification	
None	0
Cooling to room temperature	0
Adding solvent	0
Simple filtration	0
Removal of solvent with bp < 150°C	0
Crystallization and filtration	1
Removal of solvent with bp > 150°C	2
Solid phase extraction	2
Distillation	3
Sublimation	3
Liquid-liquid extraction[e]	3
Classical chromatography	10

[a]Based on the hazard warning symbols. b Dropping funnel, syringe pump, gas pressure regulator, etc. [c] Microwave irradiation, ultrasound or photochemical activation, etc. [d]scCO2, high pressure hydrogenation equipment, etc. [e]If applicable, the process includes drying of solvent with desiccant and filtration of desiccant.

http://ecoscale.cheminfo.org/calculator

Ecoscale calculator | Manual | Paper | Contact

Ecoscale calculator

Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1	+ - Name, MF or RI					100%				

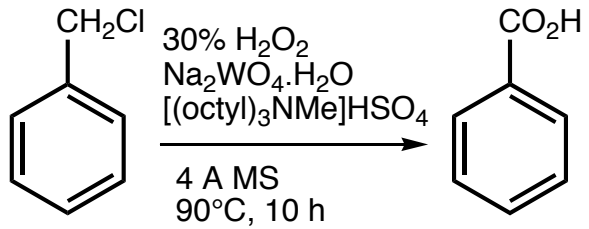
Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:

Conditions

Reagents			
Yield			0
Price / availability			0
Safety			0
Technical setup	Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique	Selected items	0
Temperature / time	Possible items: Room temperature, < 1h; Room temperature, < 24h; Heating, < 1h	Selected items	0
Workup and purification	Possible items: None; Cooling to room temperature; Adding solvent	Selected items	0

EcoScale 0



Reagents

Link

	identifier*	name	MF*	MW	density	purity*	ml	g	mmoles	equiv.
1		Benzyl chloride	C7H7Cl	126.58558	1.1	100%	1.150778	1.265856	10	1
2		Sodium tungstate dihydrate	Na2O4W.2H2O	329.8577	4.18	100%	0.078913	0.329858	1	0.1
3		Hydrogen peroxide	H2O2	34.01468		100%	0	0.340147	10	1
4		Methyltrioctylammonium hydrogen sulfate	C25H55NO4S	465.776		99%	0	5	10.6274260E	1.06274260E

Products

identifier*:	name:	MF*:	MW:	g:	mmoles:	g theor:	yield:
	Benzoic acid	C7H6O2	122.12344	1.06	8.67974239E	1.221234	86.7975

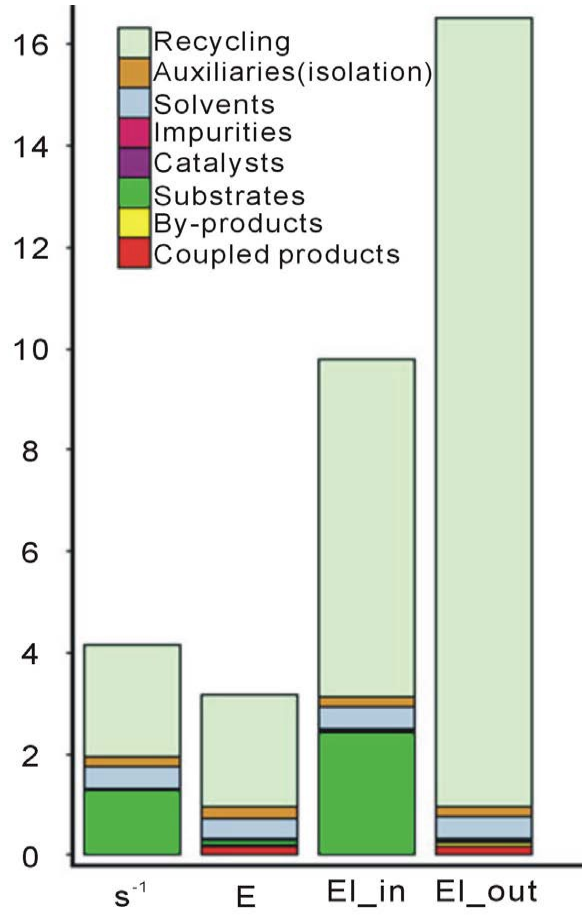
Conditions

Reagents

Name	mmoles	eq.	Bp	Hazard	Price
Benzyl chloride	9.43	1	179		
Sodium tungstate dihydrate	0.94	0.1			
Hydrogen peroxide	9.43	1			
Methyltrioctylammonium hydrogen sulfate	10.02	1.06	249		

Yield	87	-7
Price / availability		-5
Safety		-5
Technical setup	Possible items: Common set-up; Instruments for controlled addition of chemicals; Unconventional activation technique — Selected items: Instruments for controlled addition of chemicals	-1
Temperature / time	Possible items: Heating, < 1h; Heating, > 1h; Cooling to 0°C — Selected items: Heating, > 1h	-3
Workup and purification	Possible items: Removal of solvent with bp < 150°C; Crystallization and filtration; Removal of solvent with bp > 150°C — Selected items: Liquid - liquid extraction or washing; Liquid - liquid extraction or washing; Crystallization and filtration	-7
EcoScale		72

Environmental Assessment Tool for Organic Syntheses: EATOS



S^{-1} = PMI

$$E = \frac{mass\ of\ waste\ (except\ water)}{m_{product}}$$

EI_{in}

EI_{out}

Environmental indices

$$EI_{in} = \frac{\Sigma Q[PEI].m_{input}}{m_{product}}$$

$$EI_{out} = \frac{\Sigma Q[PEI]m_{output}}{m_{product}}$$

PEI = potential environmental impact

M. Eissen and J. O. Metzger *Chem. Eur. J.* **2002**, *8,* 3580–3585

to download software see http://www.metzger.chemie.unioldenburg.de/eatos/english.htm.

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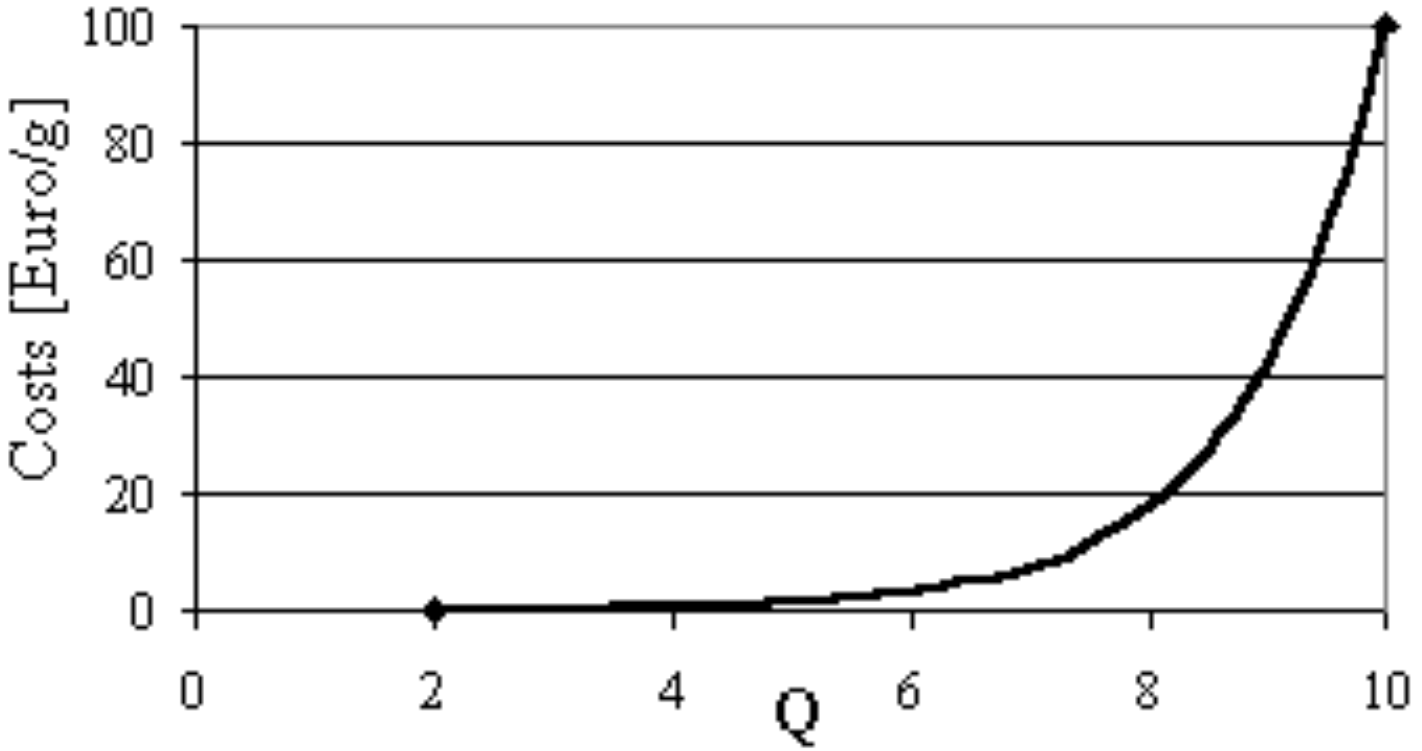
$$EI_{in} = \frac{\Sigma Q[PEI].m_{input}}{m_{product}} \qquad EI_{out} = \frac{\Sigma Q[PEI]m_{output}}{m_{product}}$$

		Risk		Human toxicity (acute)[d]				Human toxicity (chron.)				Ecotoxi-cology	
Substance		R-phrases	**Q** [PEI/kg]	MAK[b] [mg/m³]	Hazard sym-bol[e]	LD_{50} oral [mg/kg]	**Q** [PEI/kg]	Cance-rogen.	Muta-gen.	Teratogen.	**Q** [PEI/kg]	WGK[c]	**Q** [PEI/kg]
Acetic acid		10-35	**4**	25	unknown	3310	**5**	no	no	no	-	1	**4**
Acetic anhydride		10-20/22-34	**4**	21	unknown	1780	**5**	no	no	no	-	1	**4**
Acetyl chloride		11-14-34	**6**		unknown	910	**2**	no	no	no	-	1	**4**
$AlCl_3$		34	**2**		unknown	3450	**1**	no	no	no	-	1	**4**
$AlCl_3$ (aq)		36/37/38	**1**		unknown	3450	**1**	no	no	no	-	1	**4**
Anisole		10-36/37/38	**2**		unknown	3700	**5**	no	no	no	-	2	**7**
Carbon disulfide		11-36/38-48/23-62-63	**10**	16	T	3188	**5**	no	no	yes	**10**	2	**7**
Dichloroethane; 1,2-		45-11-22-36/37/38	**9**		T	670	**7**	yes	no	no	**10**	3	**10**
Diethyl ether		12-19-22-66-67	**6**	1200	Xn	1250	**2**	no	no	no	-	1	**4**
Ethanol		20/22-36/37/38	**3**	960	unknown		**2**	no	no	no	-	1	**4**
HCl (37%aq)		34-37	**3**	8	unknown	900	**6**	no	no	no	-	1	**4**
HCl		34-37	**3**	8	unknown	900	**6**	no	no	no	-	1	**4**
Iodine		20/21-50	**1**	1.1	Xn	14000	**7**	no	no	no	-	1	**4**
$MgSO_4$		20/21/22	**1**		unknown		**-**	no	no	no	-	1	**4**
Methoxyacetophenone; 4-		36/37/38	**1**		Xn	1720	**4**	no	no	no	-	3	**10**
K_2CO_3		22-36/37/38	**2**		Xn	1870	**4**	no	no	no	-	1	**4**
$Na_2S_2O_5$		22-34	**2**		Xn	1540	**4**	no	no	no	-	-	-
Na_2CO_3 (aq.)		36	**1**		unknown	4090	**1**	no	no	no	-	1	**4**
NaOH (10%aq)		35	**3**		unknown		**-**	no	no	no	-	1	**4**
NaOH (2%aq)		35	**3**		unknown		**-**	no	no	no	-	1	**4**
NaI		61-42/43-36/38	**10**		unknown	4340	**1**	no	no	yes	**10**	1	**4**
Na_2SO_4		36/37/38	**1**		unknown	5989	**1**	no	no	No	-	1	**4**
Water					unknown		**-**	no	no	No	-	-	-
Zeolite H-Beta					unknown		**-**	no	no	No	-	-	-

[a] Most data can be obtained from [4]; [b]MAK = workplace threshold value (Maximale Arbeitsplatzkonzentration) [5, 6]; [c]WGK = water hazard class (Wassergefährdungsklasse) [6]; [d] The categories are considered hierarchically, i.e. if the MAK is indicated, neither the hazard symbol nor the LC_{50} will be used for the determination of the Q-value; [e] Others than Xn, T or T^+ are ignored in this column. When data are not available or a different representative of Human toxicity (acute) is considered as sufficient than 'unknown' is noted.

$$EI_{in} = \frac{\Sigma Q[PEI].m_{input}}{m_{product}} \qquad EI_{out} = \frac{\Sigma Q[PEI]m_{output}}{m_{product}}$$

	Claiming of resources		Risk		Human toxicity (acute)[d]				Human toxicity (chron.)				Ecotoxi-cology	
Substance	[EUR/ kg]	**Q** [PEI/kg]	R-phrases	**Q** [PEI/kg]	MAK[b] [mg/m³]	Hazard sym-bol[e]	LD_{50} oral [mg/kg]	**Q** [PEI/kg]	Cance-rogen.	Muta-gen.	Teratogen.	**Q** [PEI/kg]	WGK[c]	**Q** [PEI/kg]
Acetic acid	5.94	**1**												
Acetic anhydride	16.99	**1**												
Acetyl chloride	12.32	**1**												
$AlCl_3$	16.11	**1**												
$AlCl_3$ (aq)	16.11	**1**												
Anisole	19.88	**1**												
Carbon disulfide	20.18	**1**												
Dichloroethane; 1,2-	7.15	**1**												
Diethyl ether	30.67	**1**												
Ethanol	19.63	**1**												
HCl (37%aq)	9.11	**1**												
HCl		**1**												
Iodine	105.1	**2**												
$MgSO_4$	54.07	**1**												
Methoxyacetophenone; 4-	58.39	**1**												
K_2CO_3	10.58	**1**												
$Na_2S_2O_5$	8.75	**1**												
Na_2CO_3 (aq.)	8.43	**1**												
NaOH (10%aq)	11.58	**1**												
NaOH (2%aq)	12.78	**1**												
NaI	80.89	**1**												
Na_2SO_4	12.52	**1**												
Water	0.001	**1**												
Zeolite H-Beta	25.56	**1**												



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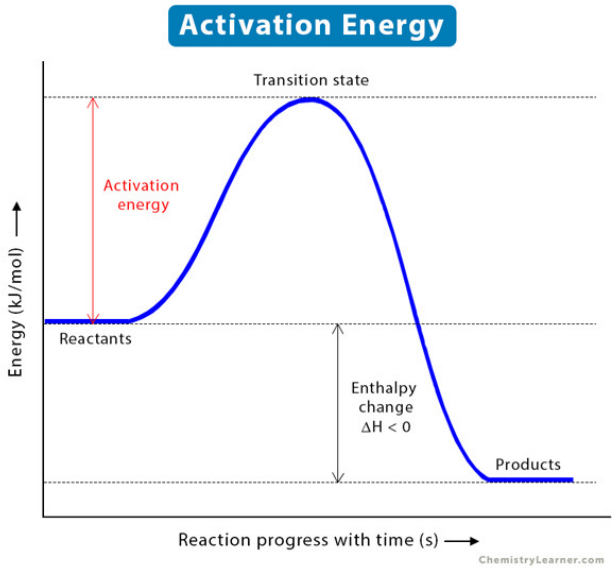
Energy

600 W



850 W

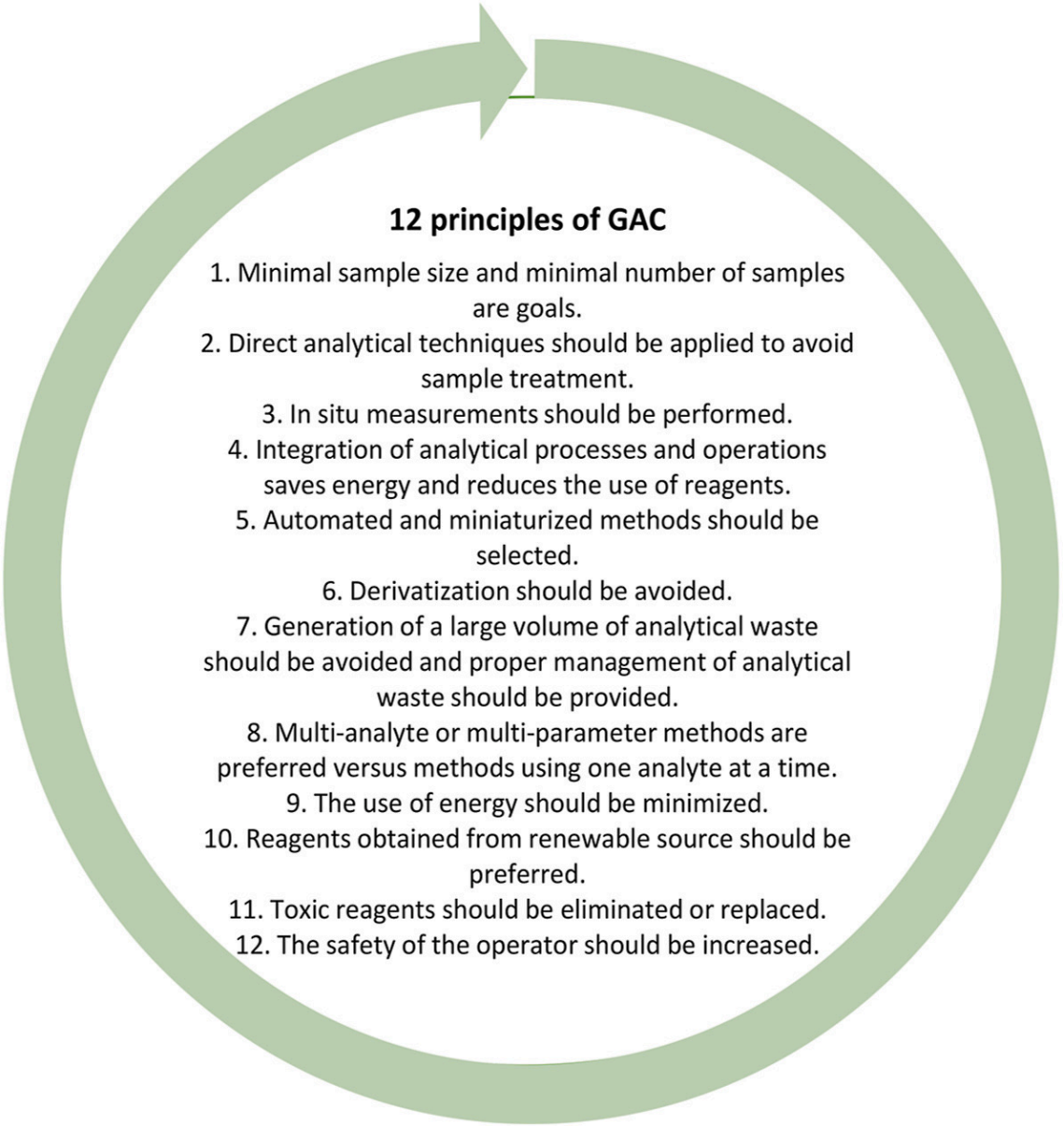
450 W

1400 W

Energy = power * duration

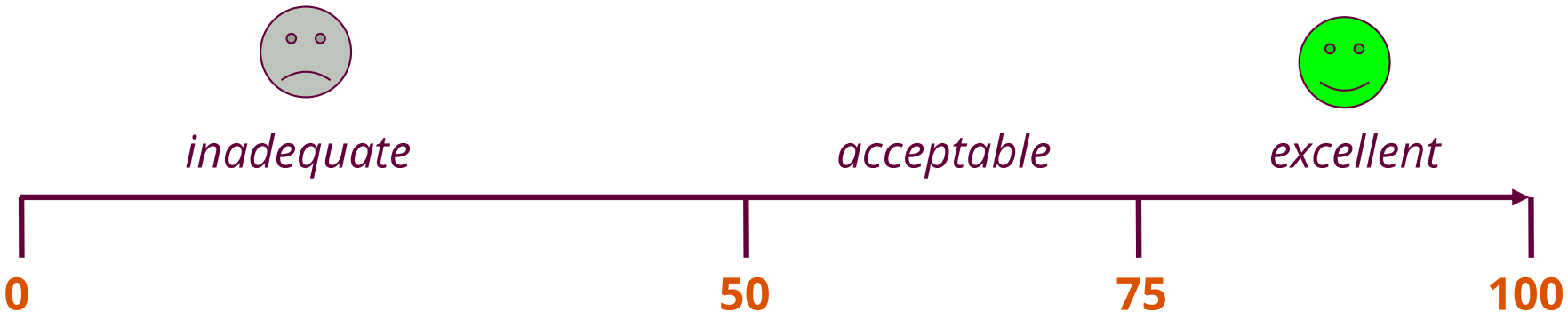
Power (W)	Duration (h)	Energy (kWh)
600	8	4,8
450	8	3,6
850	8	6,8
1400	8	11,2

Green Analytical Chemistry



M. Sajid, J. Plotka-Wasylka *Talanta*, **2022**, *238*, 123046

Analytical Eco-Scale



Application of off-line systems

Time, reagent and energy consuming

Using hazardous, unsafe, persistent reagents

Application of methods producing a large volume of waste

Sample collection

Sample preparation

Analysis

Application of in-line systems

Choosing direct analytical method

Using energy-efficient, direct methods

EcoScale = 100 - sum of individual penalties

A. Gałuszka, P. Konieczka, Z.M. Migaszewski,, J. Namieśnik, *TrAC Trends Anal. Chem.* **2012**, *37* , 61–72,

université PARIS-SACLAY

Penalty points to calculate analytical eco-scale

Reagents and solvents		
Amount		amount PP X hazard PP
<10 mL (g)	1	
10-100 mL (g)	2	
>100 mL (g)	3	
Hazard		
Pictograms	Number of x	
Risk label:		
-	0	
Warning	1	
Danger	2	
	Eg. CH_3CN	

Instruments	
Energy	
≤ 0.1 kWh per sample (FTIR, spectrofluorometry, UPLC, UV-Vis)	0
≤ 1.5 kWh per sample (AAS (Atomic absorption spectroscopy), GC, ICP-MS, LC)	1
> 1.5 kWh per sample (NMR, GC-MS, LC-MS, XRD)	2
Occupationnal hazard	
Analytical process hermetization	0
Emission of vapor and gases to the air	3
Waste	
None	0
< 1 mL	1
1-10 mL	3
>10 mL	5
Recycling	0
Degradation	1
Passivation	2
No treatment	3

1 GHS Classification

1 of 6

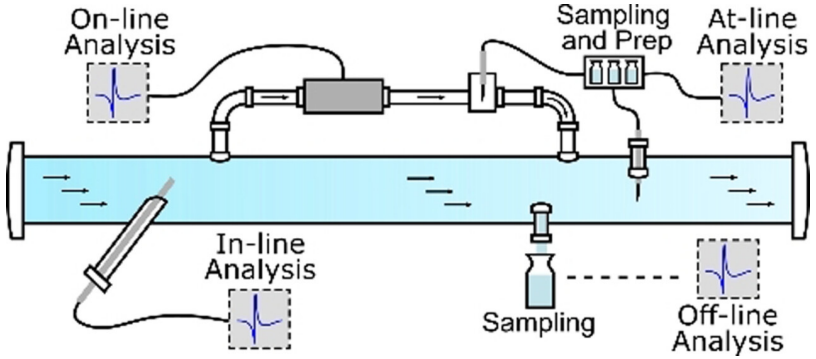
Pictogram(s)

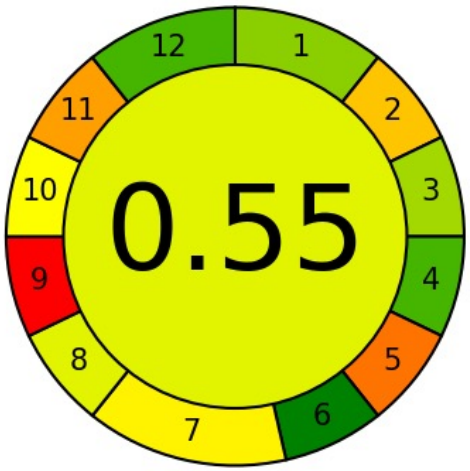
Flammable Irritant

Signal Danger

hazard PP = 2*2 =4

AGREE: Analytical GREEnness Metric Approach



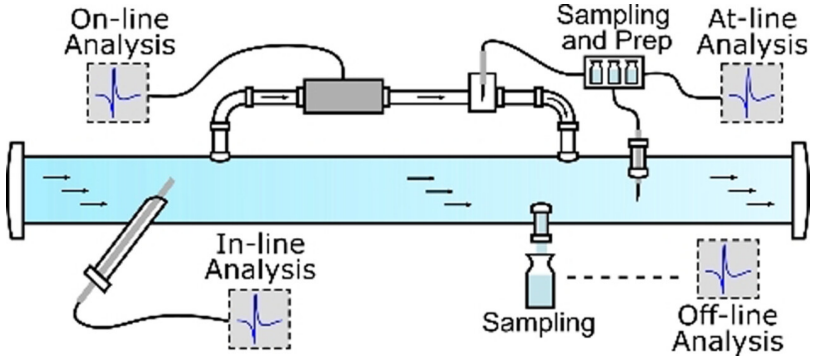


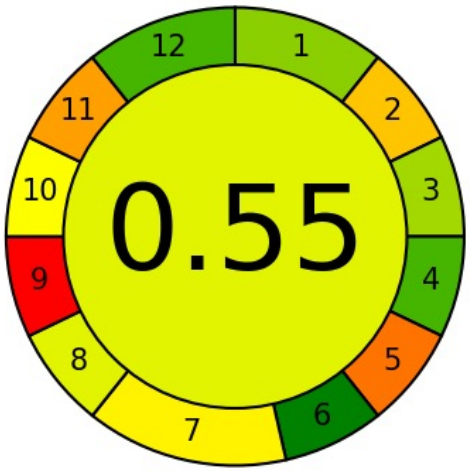
1. Sample treatment
2. Sample amount
3. Device positioning
4. Sample prep. stages
5. Automation, miniaturization
6. Derivatization
7. Waste
8. Analysis throughput
9. Energy consumption
10. Source of reagents
11. Toxicity
12. Operator's safety

In line analysis: The device is integrated directly into the processing line, allowing for real-time monitoring and control of the process.

AGREE: F. Pena-Pereira, W. Wojnowski, M. Tobiszewski, *Anal. Chem*. 2020, *92*, 10076–10082
Sampling and Analysis in Flow: M. A. Morin et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 20606–20626

AGREE: Analytical GREEnness Metric Approach





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On line analysis: involves periodically sampling the reaction mixture and analyzing it. A portion of the main stream is diverted to a bypass line where the measurement takes place. The sampling is done automatically

AGREE: F. Pena-Pereira, W. Wojnowski, M. Tobiszewski, *Anal. Chem.* 2020, *92*, 10076–10082
Sampling and Analysis in Flow: M. A. Morin et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 20606–20626

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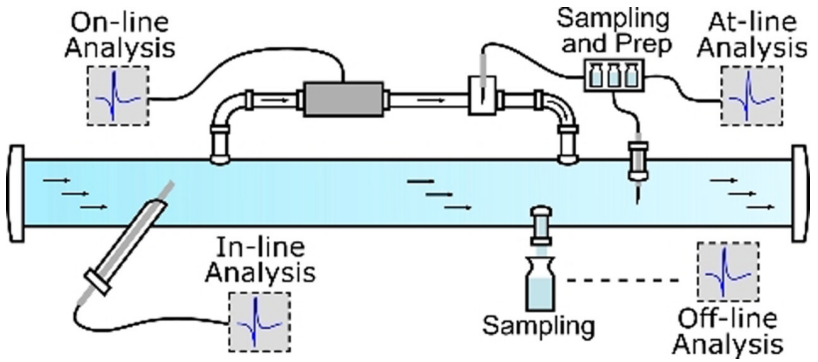

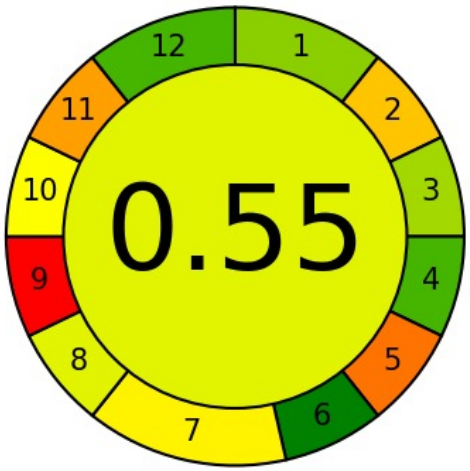

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At line analysis: requires automated removal and delivery of samples from the process line to an analyzer, with or without a sample preparation step between the process and the analysis.

AGREE: F. Pena-Pereira, W. Wojnowski, M. Tobiszewski, *Anal. Chem.* 2020, *92*, 10076–10082
Sampling and Analysis in Flow: M. A. Morin et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 20606–20626

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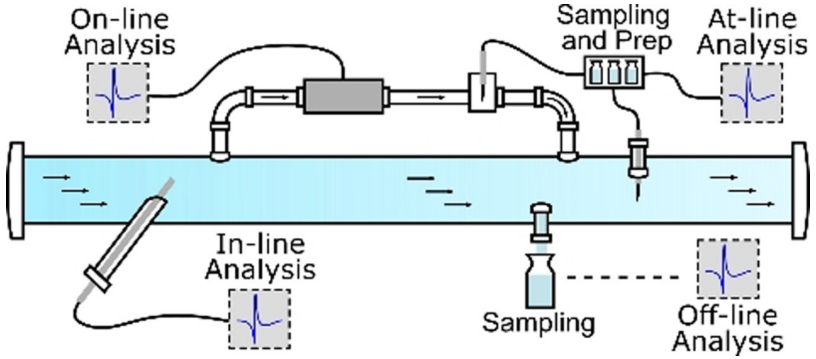

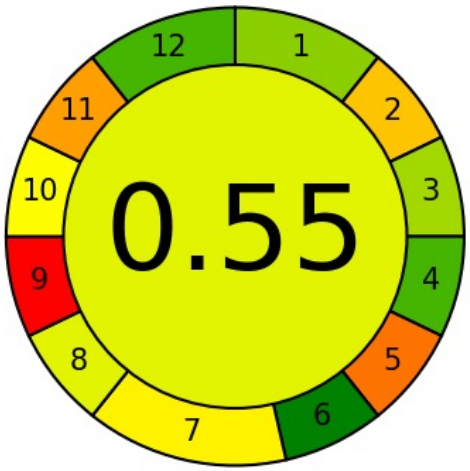

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Off-line analysis: involves analysis of samples at an offline analytical facility

AGREE: F. Pena-Pereira, W. Wojnowski, M. Tobiszewski, *Anal. Chem*. 2020, *92*, 10076–10082
Sampling and Analysis in Flow: M. A. Morin et al. *Angew. Chem. Int. Ed.* **2021**, *60*, 20606–20626

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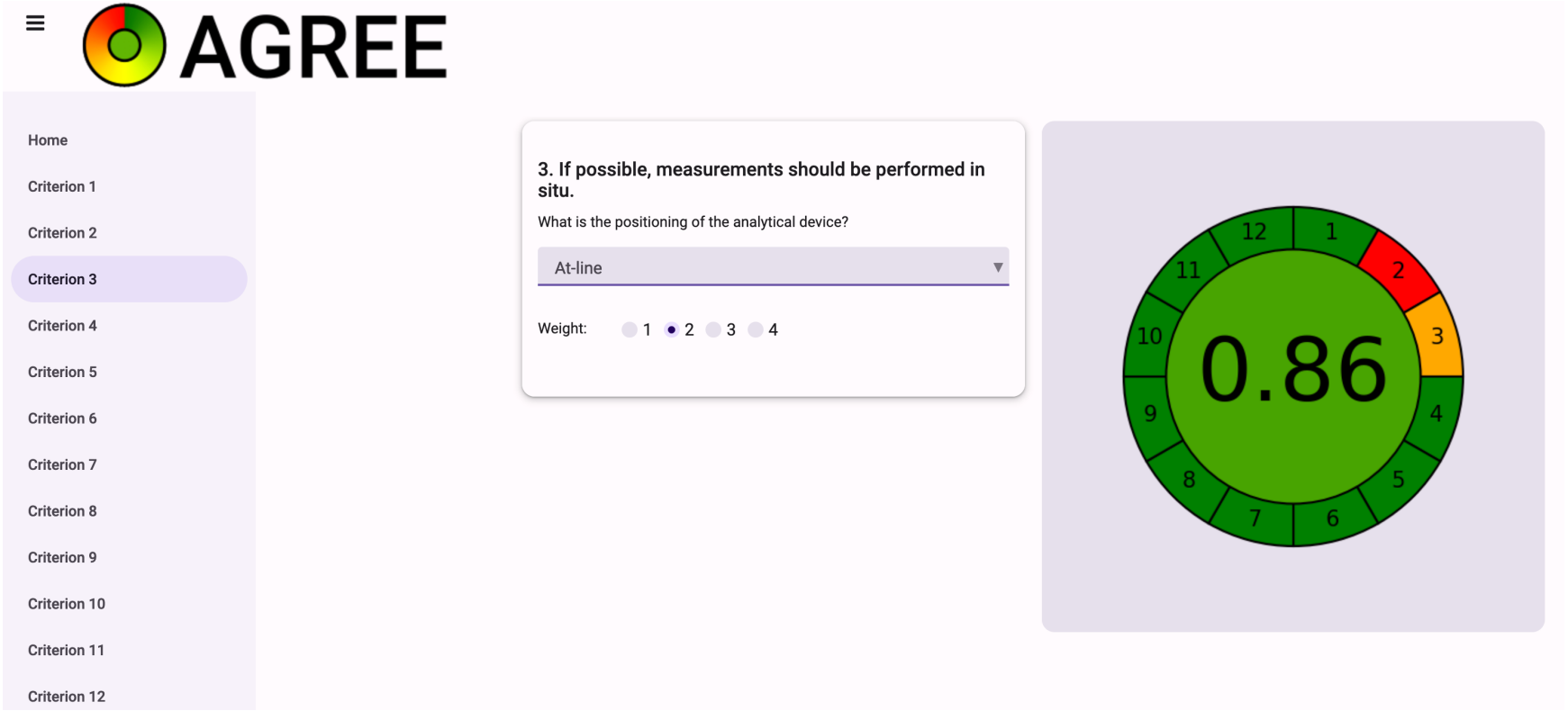
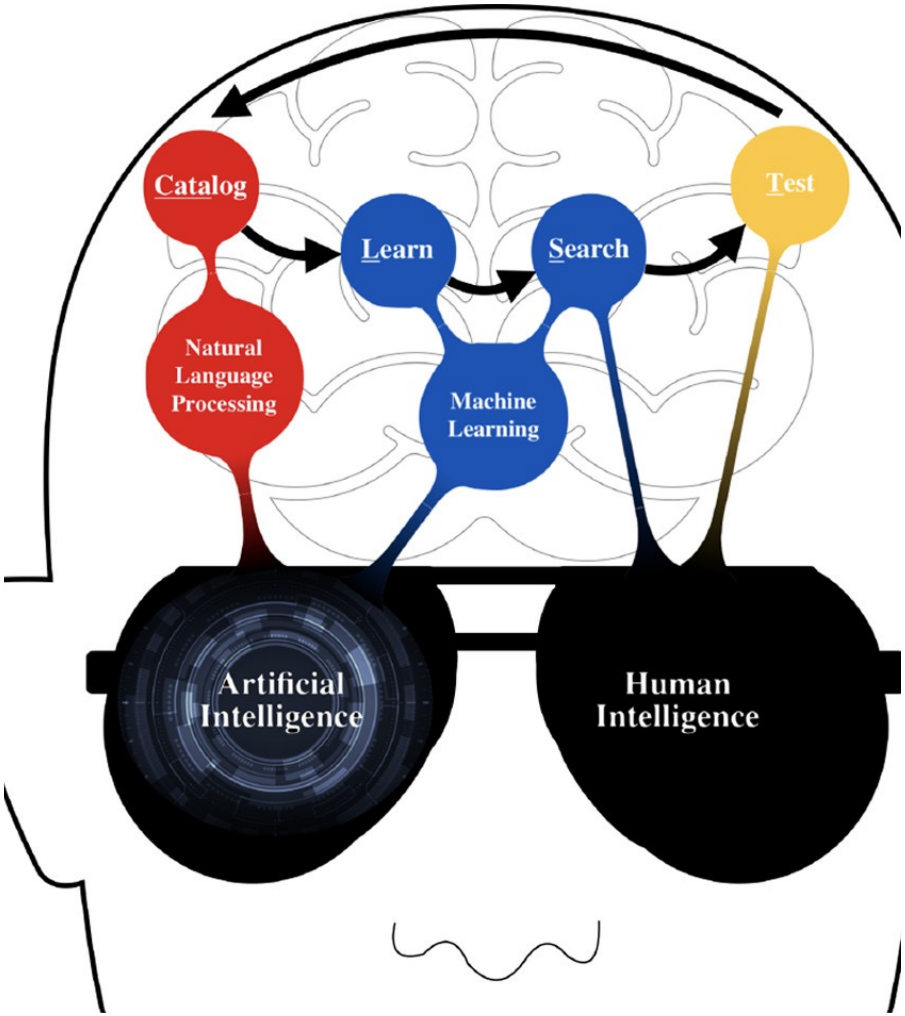


What's next ?

- What is the future of sustainable chemistry research? Interfacing artificial intelligence and human intelligence to (1) Catalog the literature with data mining, (2) Learn from this knowledge base using machine learning, and (3) use these insights to Search and Test new systems.

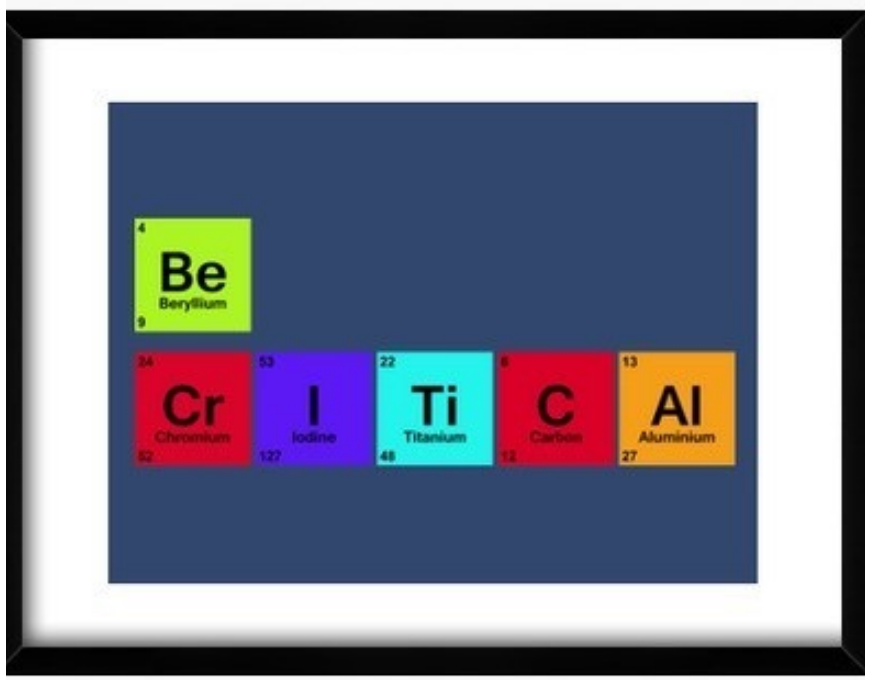


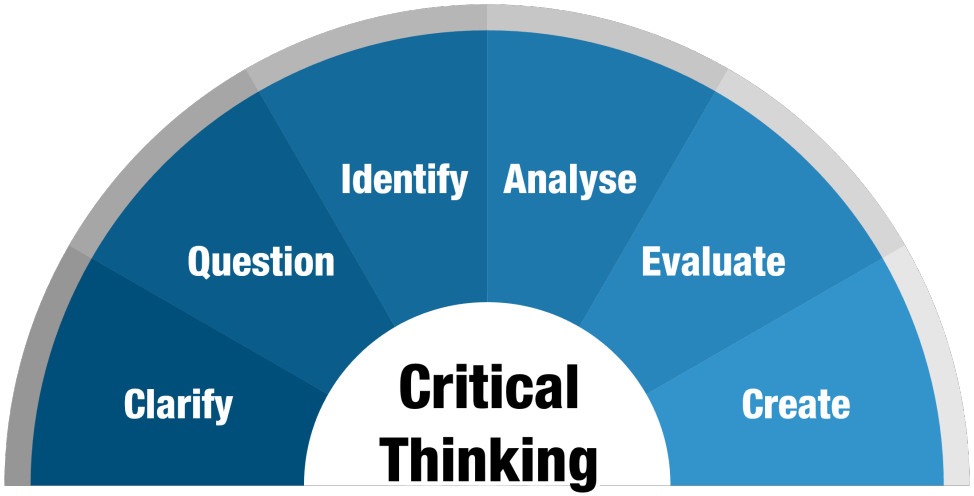
Can Artificial Intelligence and Machine Learning Be Used to Accelerate Sustainable Chemistry and Engineering?
K. C. Leonard et al. *ACS Sustainable Chem. Eng.* **2021**, *9*, 6126–6129

A Systematic Review on Intensifications of Artificial Intelligence Assisted Green Solvent Development
H. Wen, S. Nan, D. Wu, Q. Sun, Y. Tong, J. Zhang, S. Jin, and W. Shen *Ind. Eng. Chem. Res.* **2023**, *62*, 48, 20473–20491.

Opportunities and Challenges of Artificial Intelligence for Green Manufacturing in the Process Industry
S. Mao, B. Wang, Y. Tang, F. Qian, *Engineering* **2019**, *5,* 995–1002

The future of sustainable chemistry and process: Convergence of artificial intelligence, data and hardware
X.Y. Tai, H. Zhang, Z. Niu et al. *Energy and AI*, **2020***, 2,* 100036.





1.clarify your thinking purpose and context
2.question your sources of information
3.identify arguments
4.analyse sources and arguments
5.evaluate the arguments of others and
6.create or **synthesise** your own arguments.

https://www.monash.edu/student-academic-success/enhance-your-thinking/brainstorm-and-mind-map