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Barna MEZEY

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ENVIRONMENT IMPACT ANALYSIS OF THE MANUFACTURE OF ACETYLSALICYLIC ACID (ASA)

1. INFORMATION SOURCES

- Technical information package on multiproduct plant[1]
- Technical information package on paracetamol and aspirin plant [1]
- Operational formula for the manufacture of aspirin[2]
- Pharmaceutical manufacturing encyclopaedia[3]
- Gyógyszerek és gyógyszergyártás (Drugs and Drug Manufacturing)[4]
- Operational formula for the manufacture of ASA[5]

2. PROCESS INFORMATION

2.1 Schematic illustration of the synthesis

1/ NOBEL Chematur, Karlskoga, Sweden (1986)
2/ Sarabhai Research Centre (1981)
3/ Noyes Data Corporation, Park Ridge, N.J., USA (1979)
4/ Müszaki Könyvkiadó, Budapest, Hungary (1957)
5/ CHINOIN Chemical and Pharmaceutical Works Ltd.

3198N

2.2 Definition of educts, intermediates, and products

The common names, chemical formulas and molecular weights of reactants and auxiliary materials are listed in appendix 1.

2.3 Chemical reactions

(a) $C_6H_5OH + NaOH = C_6H_5ONa + H_2O$

94.11 40.00 116.10 18.02

(b) $C_6H_5ONa + CO_2 = C_6H_4(OH)COONa$

116.10 44.01 160.11

(c) $C_6H_4(OH)COONa + HCl = C_6H_4(OH)COOH + NaCl$

160.11 36.46 138.12 58.46

(d) $C_6H_4(OH)COOH + (CH_3CO)_2O = C_6H_4(OOCCH_3)COOH + CH_3COOH$

138.12 102.09 180.16 60.05

(e) $CH_3COOH + CH_2{=}C{=}O = (CH_3CO)_2O$

60.05 42.04 109.09

Combined equation of the synthesis

(f) Salicylic acid

$C_6H_5OH + NaOH + CO_2 + HCl = C_6H_4(OH)COOH + H_2O + NaCl$

94.11 40.00 44.01 36.46 138.12 18.02 58.4

(g) Acetylsalicylic acid

$C_6H_5OH + NaOH + CO_2 + HCl + (CH_3CO)_2O = C_6H_4(OOCCH_3)COOH +$

94.11 40.00 44.01 36.46 102.09 180.16

$+ CH_3COOH + H_2O + NaCl$

60.05 18.02 58.44

2.4 Other reactions considered in the analysis

(h) $C_6H_4(OOCCH_3)COOH + H_2O = C_6H_4(OH)COOH + CH_3COOH$

180.16 18.02 138.12 60.05

(i) $(CH_3CO)_2O + H_2O = 2CH_3COOH$

102.9 18.02 120.10

(j) $2NaOH + H_2SO_4 = Na_2SO_4 + 2H_2O$

80 98.08 142.06 36.04

(k) $CH_3COOH + NaOH = CH_3COONa + H_2O$

60.05 40.00 82.03 18.02

(1) $2CH_3COOH + Na_2CO_3 = 2CH_3COONa + CO_2 + H_2O$

120.10 105.99 164.06 44.01 18.02

(m) $NH_3 + HCl = NH_4Cl$

35.05 36.46 53.49

2.5 Chemical conversion efficiencies

The molar chemical input conversion factors, F, and the material input coefficients are summarized in table 1.

Table 1. Material requirements for the syntheses of salicylic acid and acetylsalicylic acid (in kg/1000 kg output)

Material input	F	f1	f2	f3	f4	f5	f6	f7	f8	f9
Phenol	681							806	927	717
Carbon dioxide	317							591	589	
Sodium hydroxide	290	34	16	5	4	53	112	398	394	450
Sulfuric acid		44			5			602	497	504
Fuel oil										330[a]
Salicylic acid	767	956	851	830	797	797	840			
Acetic anhydride 100%	567	945	720	733	126	660	750			
Ketene					208					
Sodium carbonate			23							
Carbon activated								37	184	10
Benzene			420	85						
Toluene					20					
Methylisobutylketone										2
Sodium dithionite								6		
Ammonia								150		
Hydrochloric acid								370		
Total		1,979	2,030	1,653	1,160	1,510	1,702	2,960	2,591	2,013

a/ Used for the preparation of carbon dioxide.

Table 1 contains technological data for six processes starting from SA and for three processes using phenol as the feedstock. The data came from different sources and different periods of time (sometimes from the same source), therefore, they reflect various levels of technical development. Some processes use a mixture of the reactant acetic anhydride and the produced acetic acid as the solvent, whereas others use mainlv benzene and toluene.

As regards environment protection, cne interesting process uses ketene to convert the by-product acetic acid into acetic anhydride which can again be used as reactant. The specific material requirement is the lowest with this process but ketene must be produced on the spot and its synthesis is dangerous (explosion risk). On the other hand, the by-product acetic acid can be recovered easily and used for industrial purposes.

Three processes use phenol as the feestock. Two of them purify the SA by sublimation, or crystallization, respectively. The third, modern process results directly in pharmacopoeial grade SA. Phenol and SA recovered from the mother liquor are recycled into the process.

The yields of the studied processes are listed in table 2.

Table 2. Acetylsalicylic acid yields on feedstock

Process	Yield (%)
1	86.0
2	93.0
3	94.7
4	97.5
5	96.2
6	91.3
7	84.5
8	73.5
9	95.0

The overall yields have been calculated with reference to SA (processes 1-6) and to phenol (processes 7-9), respectively.

2.6 Brief description of the processes

Processes 1-6 all acetylate SA with acetic anhydride at a temperature between 75 and 90°C. The differences between the individual processes are listed below:

Process 1 - Acetylation is carried out in acetic acid solvent, using sulfuric acid as the catalyst. The mixture is cooled down, the crystallized ASA is removed by filtration, washed with acetic acid, suspended in cold water, then filtered and washed again with water, and dried between 60 and 65°C.

An adequate amount of the mother liquor is recycled into the process and acetic acid is recovered by distillation from the remaining part of the mother liquor. After saponification, SA is also recovered, purified and recycled into the process.

Process 2 - SA is acetylated in acetic anhydride at a temperature from 74 to 79°C. After the acetylation has been completed, benzene is added, the mixture is heated up to 85°C and cooled down again to induce crystallization. ASA is purified by suspension in benzene, filtration and drying. Second generation ASA is obtained from the mother liquor by vacuum evaporation and cooling; ASA is then recrystallized from the mixture of acetic acid and benzene. Both acetic acid and benzene are recovered by distillation. Benzene is recycled into the process. Recovered acetic acid is used for other industrial purposes.

Process 3 - Acetylation is carried out by acetic anhydride in the mixture of acetic anhydride and benzene at about 85°C. The mixture is cooled, crystalline ASA is separated by centrifuging, washed with benzene, resuspended, filtrated and dried. The mother liquor is distilled off in vacuum to about one-fourth of its original volume, benzene is added, the mixture is cooled down, and the crystallized ASA is recycled into the next batch, without drying. Benzene and acetic acid are recovered from the distillate. Benzene is recycled into the process, whereas acetic acid is used in other processes. The mother liquor is also recycled until it becomes contaminated (with by-products). The contaminated mother liquor is saponified to recover SA.

Process 4 - Acetylation is performed with acetic anhydride in the mixture of toluene and acetic anhydride. The by-produced acetic acid is reconverted into acetic anhydride by ketene and recycled into the next batch. The toluene loss is made up simultaneously. Ketene must be produced in situ by cracking acetone. The mother liquor becomes contaminated after 6 to 10 batches, when acetic acid is recovered and recycled into the process; the ASA is saponified to recover SA.

Processes 5 and 6 use acetic anhydride as acetylating agent in acetic acid solution. The two processes differ from each other only in the treatment of the mother liquor. Only acetic acid is recovered in process 5, whereas ASA and SA are also recovered in process 6.

Processes 7 and 8 - SA is manufactured from phenol by the classical Kolbe-Schmidt synthesis: phenol is reacted with solid sodium hydroxide, the produced water is distilled off in vacuum. The dry sodium phenolate is gradually heated and carbon dioxide is introduced into the system to yield sodium salicylate. Normal pressure is restored and the unreacted phenol is distilled off. Phenol is recovered from its aqueous solution by extraction with organic solvents; it is recycled into the next batch.

Sodium salicylate in the reactor is dissolved in water, the solution is decolorized by activated carbon and a reducing agent, then filtered. Dilute sulfuric acid is added to the filtrate to precipitate SA; the mixture is cooled, filtered and SA is dried. The crude SA is purified either by recrystallization from water or by sublimation.

<u>Process 9</u> - The modern carboxylator enables the preparation of pharmacopoeial quality salicylic acid in one step, with excellent yield. The system is completely closed, including the recovery of phenol and methylisobutyl ketone used as the solvent.

Salicylic acid (SA) from phenol
(kg/100 kg SA)

	Process 7	Process 8	Process 9
Reactants:			
Phenol	806	927	717
Sodium hydroxide	398	394	450
Carbon dioxide	591	589	
Sulfuric acid	602	497	504
Fuel oil (for the preparation of CO_2)			330
	2,397	2,407	2,002
Percentage:	81.0	92.9	99.4
pH adjusters:			
Ammonia	150		
Hydrochloric acid	370		
	520		
Percentage:	17.6		
Solvent			
Methylisobutylketone			2
Percentage:			0.1
Auxiliary materials			
Activated carbon	37	184	10
Sodium dithionite	6		
	43	184	10
Percentage	1.4	7.1	0.5
Total:	2,960	2,591	2,013

Acetylsalicilic acid from phenol (ASA)[a/]

Materials	Quantity		
Reactants			
Phenol	571		
Sodium hydroxide	359		
Fuel oil	263		
Sulfuric acid	402		
Acetic anhydride	660	2,255	97.3%
pH adjusters			
Sodium hydroxide		53	2.3%
Auxiliary materials:			
Carbon, activated		8	0.3%
Solvents:			
Methylisobutylketone		2	0.1%
	Total:	2,318	100.0%

a/ Process 5 and Process 9.

3. ENVIRONMENT IMPACT ASSESMENT

The total material requirement for the production of 1,000 kg of ASA changes between 1,160 kg and 2,030 kg if SA is the educt. This range extends from 2,013 to 2,960 kg when the synthesis starts from phenol.

3.1 Material flow and informative material balance

The material flow schemas and informative material balances are shown in appendices 2 and 3, respectively.

3.2 Material requirements

3.2.1 Material consumption by nature of inputs

Acetylsalicylic acid (ASA) from salicylic acid (SA)

	Process					
	1	2	3	4	5	6
Reactants:						
Salicylic acid	956	851	830	797	797	840
Acetic anhydride	945	720	733	126	660	750
Ketene	-	-	-	208	-	-
	1,901	1,571	1,563	1,131	1,457	1,590
Percentage:	96.1	77.4	94.6	97.5	96.5	93.4
pH adjusters:						
Sodium hydroxide	34	16	5	4	53	112
Sulfuric acid	44			5		
Sodium carbonate		23				
	78	39	5	9	53	112
Percentage:	3.9	1.9	0.3	0.8	3.5	6.6
Solvents:						
Benzene		420	85			
Toluene				20		
Percentage		20.7	5.1	1.7		
Total:	1,979	2,030	1,653	1,160	1,510	1,702

The majority of material requirements consists of reactants. Acetic anhydride is both a reactant and a solvent. Organic solvent is used only in the old processes. Benzene is avoided as much as possible nowadays because it is dangerous to health upon repeated exposure.

3.2.2 Material consumption by process stage

The material flow according to the chemical steps in the ASA synthesis from phenol is given below:

SA (Process 9)	1,605 kg	69.2%
ASA (Process 5)	713 kg	30.8%
	2,318 kg	100.0%

The effect of backward integration on total material requirement for the manufacture of 1,000 kg of ASA is illustrated below:

Salicylic acid, as educt (process 5)	1,510 kg
Phenol, as educt (process 9)	2,318 kg

3.3 Waste streams and treatments

The following by-products (a) and wastes (b) are generated during the manufacture of 1,000 kg of ASA from SA:

	1		2		3		4		5		6	
	a	b	a	b	a	b	a	b	a	b	a	b
Salicylic acid	61		26		20		10	4				
Acetic acid	189	535	294	144	376	124	80	25	350		350	
Acetylsalicylic acid by-products		167		76		58		21		40		96
Sodium sulfate		60						7				
Sodium acetate				69		12				108		229
Sulfuric acid		3										
Benzene				420		85						
Toluene								20				
Carbon dioxide				9								
	250	765	320	718	396	279	90	77	350	148	350	325

The quantities of recovered reactants and commercially saleable by-products (SA and acetic acid) are relatively high. Process development efforts have been concentrated on the elimination of organic solvents; the reactant acetic anhydride and/or the by-product acetic acid are used as solvents.

The following wastes and by-products are generated during the manufacture of 1,000 kg of salicylic acid from phenol:

	Process		
	7	8	9
Phenol			
Sodium hydroxide			39
Sodium sulfate	706	700	729
Sulfuric acid	114	13	
Hydrochloric acid	49		
Phenol, salicylic acid and by-products	184	211	52
Ammonium chloride	471		
Methylisobutyl ketone			2
Carbon, activated	37	184	10
Sodium dithionite	6		
	1,567	1,108	832

The loss of organic solvents (benzene, toluene), used for the extraction of phenol from phenol-containing waste waters in processes 7 and 8, is not included in the table above. The modern process 9 recycles completely the unreacted phenol and uses such an organic solvent in such a closed system which permits recirculation with minimum loss. These improvements were achieved by a specially designed carboxylator wherein reaction conditions had been optimized to favour ortno-carboxylation, as indicated by the lowest quantity of "phenol, salicylic acid and by-products" row of the table.

3.3.1 Liquid effluent

The majority of wastes is water-soluble (inorganic salts, acetic acid or its sodium salt, phenol, acidic-type intermediates or by-products and their salts), and the pre-treated effluents (neutralization, solvent extraction and, if necessary, biological treatment) can be discharged through the public sewage network into the community waste water treatment plant. The maximum tolerated concentration of phenol and salicylic acid in the sewage effluent is 5 g/m^3. 811 kg of wastes are produced in process 9 during the manufacture of 1,000 kg of ASA; about 95 per cent of this total waste is discharged as a liquid effluent.

3.3.2 Air pollutants

Air pollutants come from processes 3 and 9 mainly as organic solvents, in particular benzene. The modern process 9 may produce some acetic acid and methylisobutylketone vapours, of which acetic acid can be absorbed in an alkaline stripper.

3.3.3 Solid wastes

From 10 kg to 184 kg of activated carbon, depending on the process, are used and collected during the manufacture of 1,000 kg of salicylic acid. Activated carbon is incinerated.

An evaporation residue is produced during the processing of contaminated mother liquor which is also incinerated.

3.4 Industrial safety

3.4.1 Materials

The majority of the chemical inputs is classified as toxic material, whereas the chemical outputs are practically non-toxic. Best industrial safety can therefore be achieved if the manufacturing process is carried out in a closed system.

3.4.2 Chemical conversions

The major steps in the synthesis of ASA are carboxylation and acetylation; other reactions are salt formation and acid liberation.

The processing of mother liquors involves saponification and, possibly, ketene addition on acetic acid.

4. SUMMARY EVALUATION

ASA is one of the oldest fine chemical products. It is a suitable model for the illustration of the economic motivation behind technical development to reduce material and energy costs. The reduction of waste was an extra profit already at an early stage of industrial development when environment protection in today's sense of the term did not exist.

Health and industrial safety criteria played also a role in the second stage of technical development when efforts were made to eliminate the use of organic solvents, especially benzene. The modern process 9 has integrated also the environment protection requirements into the manufacture of ASA.

ASA manufacture from phenol is also a good model to show that the economics of established processes can significantly be improved if the results of reaction kinetic, chemical engineering and chemistry research as well as modern process control techniques are put into practice. Process number 9 is a low-waste, so-called clean technology.

Appendix 1 to annex .. of the

ENVIRONMENT IMPACT ANALYSIS OF THE MANUFACTURE OF ACETYLSALICYLIC ACID

Reactants, products, and auxiliary materials in acetylsalicylic acid manufacture

Compound	Chemical formula	Mol. weight
Acetic acid	CH_3COOH	60.05
Acetic anhydride	$(CH_3CO)_2O$	102.09
Ammonia	NH_3	17.03
Ammonium chloride	NH_4Cl	53.49
ASA	$C_6H_4(OOCCH_3)COOH$	180.16
Carbon dioxide	CO_2	44.01
Hydrochloric acid	HCl	36.46
Ketene	C_2H_2O	42.04
Phenol	C_6H_5OH	94.11
Salicylic acid (SA)	$C_6H_4(OH)COOH$	138.12
Sodium acetate	CH_3COONa	82.03
Sodium carbonate	Na_2CO_3	106.00
Sodium chloride	$NaCl$	58.44
Sodium hydroxide	$NaOH$	40.00
Sodium sulfate	Na_2SO_4	142.06
Sulfuric acid	H_2SO_4	98.08

Appendix 2 to annex .. of the

ENVIRONMENT IMPACT ANALYSIS OF THE MANUFACTURE OF ACETYLSALICYLIC ACID

Flow schemas
of the manufacturing processes of acetylsalicylic acid

Appendix 3 to annex .. of the

ENVIRONMENT IMPACT ANALYSIS OF THE MANUFACTURE OF ACETYLSALICYLIC ACID (ASA)

Material balances for the manufacture of ASA from SA and SA from phenol
(kg/1000 kg ASA)

Process 1 - From SA

	Inputs	Outputs	By-product	Waste
Salicylic acid	956	61	61	
Acetic anhydride	945			
Acetic acid		724	189	535
Sulfuric acid	44	3		3
Sodium hydroxide	34			
Water	51	15		15
Acetylsalicylic acid		1,167		1,167
Sodium sulfate		60		60
Total:	2,030	2,030	250	1,780

Waste 1,780
-15 1,765

Process 2 - From SA

	Inputs	Outputs	By-product	Waste
Salicylic acid	851	26	26	
Acetic anhydride	720			
Acetic acid		438	294	144
Sodium hydroxide	16			
Sodium carbonate	23			
Acetylsalicylic acid		1,076		76
Benzene	420	420		420
Water		11		11
Sodium acetate		69		69
Carbon dioxide		9		9
Total:	2,049	2,049	320	729

Waste 729
-11 718

Process 3 - From SA, 8-batch system

	Inputs	Outputs	By-product	Waste
Salicylic acid	830	20	20	
Acetic anhydride	733			
Acetic acid		500	376	124
Sodium acetate		12		12
Benzene	85	85		85
Sodium hydroxide	5			
Acetylsalicylic acid		1,058		58
Water	21			
Total:	1,674	1,675	396	279

Waste 279

Process 4 - From SA

Salicylic acid	797	14	10	4
Acetic anhydride	126			
Ketone	208			
Acetic acid		105	80	25
Sulfuric acid	5			
Sodium sulfate		7		7
Sodium hydroxide	4			
Water	7			
Toluene	20	20		20
Acetylsalicylic acid		1,021		21
Total:	1,167	1,167	90	77

Waste 77

Process 5 - From SA

Salicylic acid	797			
Acetic anhydride	660			
Sodium hydroxide	53			
Acetic acid		350	350	
Sodium acetate		108		108
Water	12	24		
Acetylsalicylic acid		1,040		40
Total:	1,522	1,522	350	148

Waste 148

Process 6 - From SA

Salicylic acid	840			
Acetic anhydride	750			
Acetic acid		350	350	
Sodium hydroxide	112			
Water	23	50		50
Acetylsalicylic acid		1,096		96
Sodium acetate		229		229
Total:	1,725	1,725	350	375

Waste 375
-50 325

Process 7 - SA from phenol

Phenol		
Sodium hydroxide	398	
Carbon dioxide	591	214
Sulfuric acid	602	114
Activated carbon	37	37
Sodium dithionite	6	6
Ammonium hydroxide (100% HCl)	150	
Hydrochloric acid (100% HCl)	370	49
Water		180
Sodium sulfate		706
Salicylic acid		1,184
Ammonium chloride		471
Total:	2,960	2,961

Waste 2,961
-180
-214
-1,000 1,567

Process 8 - SA from phenol

Phenol	927	102
Sodium hydroxide	394	
Carbon dioxide	589	203
Sulfuric acid	497	13
Activated carbon	184	184
Salicylic acid		1,211
Water		178
Sodium sulfate		700
Total:	2,591	2,591

Waste 2,591

Process 9 - SA from phenol

Phenol	717	
Fuel oil	335[a]	
Sulfuric acid 100%	504	
Methylisobutylketon	2	2
Activated carbon	10	10
Sodium sulfate		729
Salicylic acid		1,052
Water		182
Total:	2,013	2,017

Waste 2,017
-185 832

a/ 335 kg/1000 kg SA