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ENVIRONMENT IMPACT ANALYSIS OF THE MANUFACTURE OF ISONIAZID

1. INFORMATION SOURCES:

Process I.1: ISONIAZIDE, Procédé de fabrication, F. Hoffmann-La Roche & Cie, Société Anonyme, Basel (1981).
Process I.2: UNIDO/ID/WG/267/5 (1978).
Process I.3: Unpublished UNIDO document.
Process II : Manufacturing process description of Isoniazid, G. Richter Pharmaceutical Works Ltd., Budapest (1980).
Process III: UNIDO document PC.14 (1981).

2. PROCESS INFORMATION

2.1 Schematic illustration of the synthesis

2.2 Definition of educts, intermediates and products

The common names, chemical formulae and molecular weights of reactants and auxiliary chemicals are listed in annex 1.

2.3 Chemical reactions

Process I.1

(a) $C_5H_4NCH_3 + 2KMnO_4 = C_5H_4NCOOK + 2MnO_2 + KOH + H_2O$

93.13 316.06 161.20 173.88 56.10 18.02

(b) $C_5H_4NCOOK + HCl = C_5H_4NCOOH + KCl$

161.20 36.46 123.11 74.53

(c) $C_5H_4NCOOH + CH_3OH = C_5H_4NCOOCH_3 + H_2O$

123.11 32.04 137.14 18.02

(d) $C_5H_4NCOOCH_3 + NH_2NH_2,H_2O = C_5H_4NCONHNH_2 + CH_3OH + H_2O$

137.14 50.06 137.14 32.04 18.02

Combined equation of the synthesis

(e) $C_5H_4NCH_3 + 2KMnO_4 + HCl + NH_2NH_{21},H_2O =$

93.13 316.06 36.47 50.06

$= C_5H_4NCONHNH_2 + 2MnO_2 + KOH + KCl + 3H_2O$

137.14 173.88 56.10 74.55 54.06

Other equations used in the analysis:

(f) $KOH + HCl = KCl + H_2O$

56.10 36.47 74.55 18.02

(g) $H_2SO_4 + 2NH_3 = (NH_4)_2SO_4$

98.08 34.06 132.14

(h) $4KMnO_4 + 2H_2O = 4MnO_2 = 4KOH + 3O_2$

632.23 36.04 347.76 224.40 96

Process I.2

(i) $C_5H_4NCH_3 + 2HNO_3 = C_5H_4NCOOH + 2NO + 2H_2O$

93.13 126.04 123.11 60.02 36.04

(c) $C_5H_4NCOOH + CH_3OH = C_5H_4NCOOCH_3 + H_2O$

123.11 32.04 137.14 18.02

(d) $C_5H_4NCOOCH_3 + NH_2NH_2H_2O = C_5H_4NCONHNH_2 + CH_3OH + H_2O$

137.14 50.06 137.14 32.04 18.02

Combined equation of the synthesis:

(j) $C_5H_4NCH_3 + 2HNO_3 + NH_2NH_{21},H_2O =$

93.13 126.04 50.06

$= C_5H_4NCONHNH_2 + 2NO + 4H_2O$

137.14 60.02 72.07

Other equations used in the analysis:

(k) $4HNO_3 = 4NO_2 + O_2 + 2H_2O$

252.08 184.02 32 36.04

Process I.3

(l) $2C_5H_4NCH_3 + 3O_2 = 2C_5H_4NCOOH + 2H_2O$

186.26 96.00 246.22 36.04

(m) $2C_5H_4NCOOH + 2NaOH = 2C_5H_4NCOONa + 2H_2O$

246.22 80.02 290.20 36.04

(n) $2C_5H_4NCOONa + H_2SO_4 = 2C_5H_4NCOOH + Na_2SO_4$

290.20 98.08 246.22 142.06

(c) $2C_5H_4NCOOH + 2CH_3OH = 2C_5H_4NCOOCH_3 + 2H_2O$

246.22 64.08 274.28 36.04

(d) $2C_5H_4NCOOCH_3 + 2NH_2NH_2H_2O = 2C_5H_4NCONHNH_2 + 2CH_3OH +$

$2H_2O$

274.28 100.12 274.28 64.28 36.04

Combined equation of the synthesis:

(o) $2C_5H_4NCH_3 + 3O_2 + 2NaOH + H_2SO_4 + 2NH_2HN_{21},H_2O =$

186.26 96.00 80.02 98.08 100.12

$= 2C_5H_4NCONHNH_2 + Na_2SO_4 + 8H_2O$

274.28 142.06 144.16

Process II

(p) $C_5H_5N + 2(CH_3CO)_2O + CH_3COOH + 2Fe = C_5H_4NC_2H_5 + 2(CH_3COO)_2Fe$

79.10 204.18 60.06 111.70 107.15 347.86

(q) $C_5H_4NC_2H_5 + 4HNO_3 = C_5H_4NCOOH + CO_2 + 4NO + 4H_2O$

107.15 252.08 123.11 44.01 120.04 72.04

(c) $C_5H_4NCOOH + CH_3OH = C_5H_4NCOOCH_3 + H_2O$

123.11 32.04 137.14 18.02

(d) $C_5H_4NCOOCH_3 + NH_2NH_2H_2O = C_5H_4NCONHNH_2 + CH_3OH + H_2O$

137.14 50.06 137.14 32.04 18.02

Combined equation of the synthesis:

(r) $C_5H_5N + 2(CH_3CO)_2 + CH_3COOH + 2Fe + 4HNO_3 + NH_2NH_{2.1},H_2O =$

79.10 204.18 60.06 111.70 252.08 50.06

$= C_5H_4NCONHNH_2 + 2(CH_3COO)_2Fe + CO_2 + 4NO + 6H_2O$

137.14 347.86 44.01 120.03 108.12

Other equations used in the analysis:

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

60.05 40.01 82.04 18.02

(t) $(CH_3COO)_2Fe + 2NaOH = Fe(OH)_2 + 2CH_3COONa$

173.93 80.00 89.86 164.08

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

98.08 80.02 142.06 36.04

Process III

(v) $C_5H_4NCN + 2H_2O = C_5H_4NCOOH + NH_3$

104.11 36.03 123.11 17.03

(d) $C_5H_4NCOOH + NH_2NH_{2.1},H_2O = C_5H_4NCONHNH_2 + 2H_2O$

123.11 50.06 137.14 36.03

Combined equation of the synthesis:

(w) $C_5H_4NCN + NH_2NH_2,H_2O = C_5H_4NCONHNH_2 + NH_3$

104.11 50.06 137.14 17.03

Other equations used in the analysis:

(g) $H_2SO_4 + 2NH_3 = (NH_4)_2SO_4$

98.08 34.06 132.14

2.4 Chemical conversion efficiencies

The molar chemical input conversion factors, F, are summarized in table 1.

Table 1. Overall stoichiometric conversion factors of reactants to isoniazid

Material input	F
Pyridine	0.580
Ethylpyridine	0.780
Acetic anhydride	0.740
4-Picoline	0.680
Potassium permanganate	2.300
Nitric acid	1.380
Oxygen	0.350
Isonicotinic acid	0.900
Methyl isanicotinate	1.000
Hydrazine hydrate	0.370
4-Cyanopyridine	0.760

The yields of the same processes are summarized in table 2.

Table 2. Yields of chemical conversions in isoniazid synthesis (percentage)

	Process				
Material input	I.a	I.b	I.c	II.	III
Pyridine				41.4	
Ethylpyridine				66.7	
Acetic anhydride				12.8	
4-Picoline	68.0	67.8	63.0		
Potassium permanganate	57.5				
Nitric acid		56.8		50.0	
Isonicotinic acid	81.8	81.8	81.8	a/	
Methyl isonicotinate	90.0	90.0	90.0	90.0	
Hydrazine hydrate	86.0	86.0	86.0	86.0	76.9
4-Cyanopyridine					63.3

a/ Not separated in the process

2.5 Brief description of the processes

2.5.1 Process I

4-Picoline is the feedstock in all the three variants of process I. But its conversion into isonicotinic acid (INA) is carried out by different oxidizing agents.

In variant Ia, 4-picoline is oxidized by potassium permanganate in aqueous medium at 85°C. The excess 4-picoline is removed by steam distillation, then manganese dioxide is removed by filtration. The alkaline filtrate is neutralized with hydrochloric acid, a part of the water is distilled off in vacuum, and INA is precipitated with excess hydrochloric acid. The mixture is cooled down, INA is removed by filtration and dried.

In variant Ib, 4-picoline is dissolved in concentrated sulfuric acid and oxidized with nitric acid. The nitrogen oxides are absorbed in a scrubber. The excess sulfuric acid is neutralized with sodium carbonate, the mixture is cooled down and INA is removed by filtration, it is washed with water and dried.

In variant Ic, 4-picoline is oxidized by air using vanadium pentoxide as the catalyst. INA is absorbed in an alkaline solution, from which it is precipitated with sulfuric acid.

The three process variants follow the same path from this stage onwards.

INA is esterified with excess methanol in the presence of sulfuric acid at the temperature of boiling. The cooled mixture is neutralized with ammonia solution, and the unreacted INA is removed by filtration. The pH is adjusted to 6.6 and INA is extracted with methylene chloride. The excess methanol and solvent are recovered by fractionated distillation and the residual INA is recycled into the process.

Methyl isonicotinate is reacted with hydrazine hydrate in an aqueous medium at 50°C. The mixture is cooled down, and the crude isoniazid is

removed by filtration and washed with water. Further crude isoniazid is recovered from the mother liquor by evaporation of water. The crude isoniazid is recrystallized, removed by filtration, washed with methanol and dried.

Anhydrous pyridine, the feedstock in process II, is ethylated with acetic anhydride and acetic acid in the presence of iron catalyst at the temperature of boiling. The crude ethylpyridine and excess pyridine are recovered by steam distillation. The aqueous solution is extracted with benzene. Benzene, pyridine and ethylpyridine are separated by fractionation. Ethylpyridine in concentrated sulfuric acid solution is oxidized with nitric acid at 140°C. The nitrogen oxides are removed from the reaction mixture by passing air through the reactor. INA is esterified by methanol, the mixture is cooled down, its pH is adjusted to alkaline and extracted with benzene. Benzene is distilled off and the residual methyl isonicotinate is purified by rectification. The synthesis proceeds further as in process I.

In process III, 4-cyanopyridine is hydrolized into INA in the presence of an anion-exchange resin at 60 to 80°C, and INA directly reacts with hydrazine hydrate.

3. ENVIRONMENT IMPACT ASSESSMENT

3.1 Material flow

The process flow schema and informative material balances are shown in annex 2 and annex 3, respectively.

3.2 Material requirements

3.2.1 Material consumption by nature of inputs

The following materials are used for the production of 1,000 kg of isoniazid:

	Process				
	I.1	I.2	I.3	II	III
	(in kilogrammes)				
Reactants					
4-Picoline	1,000	1,104	1,080		
Potassium permanganate	4,000				
Methanol	852	852	852	1,396	
Hydrazine hydrate	434	434	434	434	550
Nitric acid		2,429		2,758	
Sulfuric acid		1,656			
Oxygen			557		
Pyridine				1,395	
Acetic anhydride				5,792	
Acetic acid				3,013	
4-cyanopyridine					1,200
Sub-total	6,286	6,475	2,923	14.788	1,750
	61.1%	57.8%	41.6%	53.1%	51.9%
Solvents					
Methylene chloride	1,200	1,200	1,200		
Methanol	400	400	400	400	
Benzene				1,084	
Ethanol					1,600
Sub-total	1,600	1,600	1,600	1,484	1,600
	15.6%	14.3%	22.8%	5.3%	47.5%
pH adjusters					
Hydrogen chloride	923				
Sulfuric acid	1,200	1,200	1,769	2,678	
Ammonia	248	248	248		
Sodium carbonate		1,656		2,212	
Sodium hydroxide			464	3,710	
Sub-total	2,371	3,104	2,481	8,600	
	23.1%	27.7%	35.3%	30.9%	
Reaction promoters and auxiliary materials					
Vanadium pentoxide					
Iron filings				2,966	
Anion-exchanger					20
Carbon, activated	10	10	10	10	
Filtering aid	10	10	10	10	
Sub-total	20	20	20	2,986	
	0.2%	0.2%	0.3%	10.7%	
TOTAL	10,277	11,199	7,024	27,858	3,370
	100%	100%	100%	100%	100%

Material consumption for the manufacture of 1,000 kg of isoniazid changes within a wide range. The determinant factor is the number of steps involved in the different synthesis options:

4-Cyanopyridine (2 conversions combined in 1 step)..... 3,370 kg

4-Picoline (4 conversions in 3 steps) ..... 7,024-11,199 kg

Pyridine (4 steps) ..... 27,858 kg

The material consumption range of process I reflects the impact of the oxidation method on the preparation of isonicotinic acid.

Reactants play a dominant role (41 to 61 per cent) in the total material consumption, followed by pH-adjusters (23 to 35 per cent). The share of solvents is relatively low (5 to 23 per cent), except in process III where the quantity of ethanol represents nearly 50 per cent of the total material consumption.

3.2.2 Material consumption by process stage

The material requirement is analyzed also according to the distinct steps in the syntheses.

Process I	Variant					
	I.1		I.2		I.3	
	kg	%	kg	%	kg	%
Isonicotinic acid	5,923	57.6	6,845	61.1	2,670	38.0
Methyl isonicotinate	3,500	34.1	3,500	31.3	3,500	49.8
Isoniazid	854	8.3	854	7.6	854	12.2
Total	10,227	100.0	71,199	100.0	7,024	100.0

Process II		
Ethylpyridine	17,462 kg	62.7%
Methyl isonicotinate	9,542 kg	34.3%
Isoniazid	854 kg	3.1%
Total	27,858 kg	100.0%

Process III	
Isoniazid	3,370 kg

In variants 1 and 2 of process I, the highest amounts of materials are used in the oxidation step, partly because of the type of reactants involved and partly due to the low (about 68 per cent) weight conversion efficiencies.

In process II, the 41.4 per cent weight conversion efficiency of 4-ethylpyiridine synthesis plays an important role in the 62.7 per cent share of step one in the total material consumption.

3.3 Waste streams and treatments

The following wastes are generated during the manufacture of 1,000 kg of isoniazid:

	Variant					
	I.1		I.2		I.3	
	kg	%	kg	%	kg	%
Process I						
Isonicotinic acid						
Material inputs, intermediates, undefined by-products and wastes	218		355		324	
Manganese dioxide	2,200					
Potassium chloride	1,887					
Sulfuric acid			124			
Nitrogen oxide			1,394			
Sodium sulfate			2,219		824	
Sub-total	4,305	50.9	4,092	49.6	1,148	21.7
Methyl isonicotinate						
Material inputs, intermediates, undefined by-products & wastes	124		124		124	
Methanol	565		565		565	
Sulfuric acid	486		486		486	
Methylene chloride	1,200		1,200		1,200	
Ammonium sulfate	962		962		962	
Sub-total	3,337	39.5	3,337	40.5	3.337	63.0
Isoniazid						
Isoniazid, intermediates, undefined by-products and wastes	136		136		136	
Methanol	658		658		658	
Activated carbon and filtering aid	20		20		20	
Sub-total	814	9.6	814	9.9	814	15.4
TOTAL	8,456	100.0	8,243	100,0	5,299	100.0

Summary

Material inputs, intermediates undefined by-products & wastes	478		615		584	
Manganese dioxide	2,200					
Potassium chloride	1,887					
Sulfuric acid	486		610		486	
Nitrogen oxide			1,394			
Sodium sulfate			2,219		824	
Methanol	1,223		1,223		1,223	
Methylene chloride	1,200		1,200		1,200	
Ammonium sulfate	962		962		962	
Activated carbon and filtering aid	20		20		20	
TOTAL	8,456	100.0	8,243	100.0	5,299	100.0

Process II

4-Ethylpyridine	kg	kg	
Material inputs, undefined by-products and wastes	718		
Iron filing	997		
Benzene	586		
Ferrous hydroxide	777		
Ferrous acetate	4,631		
Sodium acetate	7,609	15,318	66.7%
Methyl isonicotinate			
Intermediates, undefined by-products and wastes	395		
Methanol	1,045		
Sulfuric acid	630		
Benzene	498		
Sodium sulfate	2,964		
Nitric oxide	1,314	6,846	29.8%
Isoniazid			
Intermediates, undefined by-products and wastes	136		
Methanol	658		
Activated carbon; filtering aids	20	814	3.5%
TOTAL		22,978	100.0%

Summary	kg
Material inputs, intermediates, undefined by-products and wastes	1,249
Iron filing	997
Benzene	1,084
Ferrous hydroxide	777
Ferrous acetate	4,631
Sodium acetate	7,609
Methanol	1,703
Sulfuric acid	630
Sodium sulfate	2,964
Nitric oxide	1,314
Activated carbon; filtering aid	20
Total	22,978

Process III

Material inputs, intermediates, undefined by-products and wastes	563
Ammonia	187
Ethanol	1,600
Anion exchanger	20
Total	2,370[a/]

[a/] Materials used for the regeneration of anion-exchanger are not included.

The five process variants are ranked by waste generation for the manufacture of 1,000 kg of isoniazid, as follows:

Process	Waste
III	2,370 kg
I.3	5,300 kg
I.2	8,240 kg
I.1	8,460 kg
II	22,980 kg

3.3.1 Liquid effluents

The majority of inorganic wastes is water-soluble and can be discharged, after appropriate treatment, into the public sewage system. Organic solvents are recovered, or recycled into the process, and only a minor fraction contaminates the industrial waste waters.

3.3.2 Air pollutants

Nitric acid is used for the preparation of isonicotinic acid in processes I.2 and II. Nitrogen oxides, by-produced during these oxidations, must be completely absorbed in a scrubber. This treatment is very expensive which makes the above processes technically and economically obsolete.

Organic solvents might pollute the air during the drying of solid products, and during the distillation or recovery of solvents.

3.3.3 Solid wastes

Manganese dioxide can be sold and iron filings are recycled into the process. The residues and tars, left after the evaporation of mother liquors and recovery of solvents, should be burnt in a special incinerator.

3.4 Industrial safety

3.4.1 Materials

The majority of the chemicals used in the manufacture of isoniazid, are poisonous and harmful to health. Methylene chloride, hydrazine hydrate, nitrogen oxides, sulfuric acid (98 per cent) and caustic soda are hazardous or very hazardous materials and wastes, respectively.

Benzene, ethanol, hydrazine hydrate, methanol and pyridine are inflammable.

High temperatures initiate vigorous reactions in hydrazine hydrate and sulfuric acid. Sulfuric acid reacts vehemently also with water.

3.4.2 Chemical conversions

The chemical reactions involved in the syntheses of isoniazid are: oxidation with potassium permanganate, or nitric acid, or oxygen over vanadium pentoxide catalyst; esterification; hydrazide formation; Wibaut-Arens reaction; hydrolysis; hydrazide formation on an anion-exchange resin.

4. SUMMARY EVALUATION

Processes I.2 and II are not used any more mainly due to economic reasons closely associated with environmental pollution problems (nitrogen oxides by-products during oxidation and need for repeated extractions with organic solvents to achieve pharmacopoeial grade product). Process I.1 represented the state-of-the-art at the time of its introduction into commercial use (1952) but it is less economic than process I.3 (Large volumes of organic solvents are used in both cases. The maximum recovery and recycling of unconverted reactants and solvents are integral parts of modern processes.

Process III is a low-waste technology with no hazardous by-products.