



TOGETHER
for a sustainable future

OCCASION

This publication has been made available to the public on the occasion of the 50th anniversary of the United Nations Industrial Development Organisation.



TOGETHER
for a sustainable future

DISCLAIMER

This document has been produced without formal United Nations editing. The designations employed and the presentation of the material in this document do not imply the expression of any opinion whatsoever on the part of the Secretariat of the United Nations Industrial Development Organization (UNIDO) concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries, or its economic system or degree of development. Designations such as “developed”, “industrialized” and “developing” are intended for statistical convenience and do not necessarily express a judgment about the stage reached by a particular country or area in the development process. Mention of firm names or commercial products does not constitute an endorsement by UNIDO.

FAIR USE POLICY

Any part of this publication may be quoted and referenced for educational and research purposes without additional permission from UNIDO. However, those who make use of quoting and referencing this publication are requested to follow the Fair Use Policy of giving due credit to UNIDO.

CONTACT

Please contact publications@unido.org for further information concerning UNIDO publications.

For more information about UNIDO, please visit us at www.unido.org

ENVIRONMENT IMPACT ANALYSIS OF THE MANUFACTURE OF
PARACETAMOL (Acetaminophen)

1. INFORMATION SOURCES

- I. Technical information package on multi-product plant^{1/}.
- II. US Patent 4264525, example 11^{2/}.
- III. US Patent 4264526, example III^{3/}.
- IV. Technical information package on paracetamol and aspirin plant^{1/}, and operational formula for the manufacture of paracetamol^{4/}.

2. PROCESS INFORMATION

2.1 Schematic illustration of the syntheses

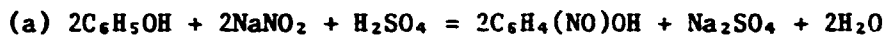
^{1/} NOBEL Chematur, Karlskoga, Sweden (1986).
^{2/} Huber, John, Sr., Stepwise reduction of p-nitrophenol (to Penick Corp., 1979).
^{3/} Ruopp, D.C.; Thorn, M.A., Borate reduction of nitrophenols (to Penick Corp., 1979).
^{4/} Sarabhai Research Centre (1981)

2.2 Definition of educts, intermediates and products

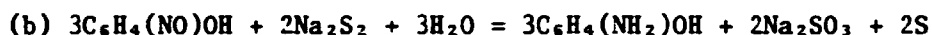
The common names, chemical formulae and molecular weights of reactants and auxiliary chemicals are listed in appendix 1.

2.3 Chemical reactions of the synthesis

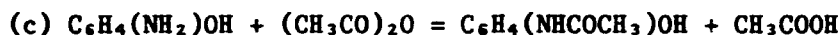
Source I



188.22 138.00 98.08 246.22 142.06 36.04

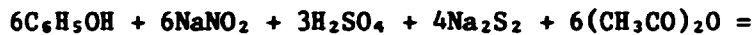


369.33 220.22 54.06 327.36 252.12 64.13



109.12 102.09 151.16 60.05

(d) Combined equation of the synthesis:

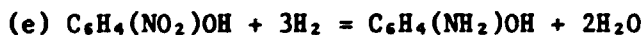


564.66 414.00 294.24 440.44 612.54

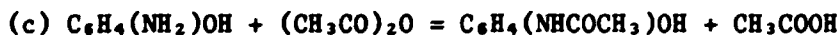


906.06 426.15 504.24 128.14 360.30

Source II



139.11 6.06 109.12 36.04



109.12 102.09 151.16 60.05

(f) Combined equation of the synthesis:

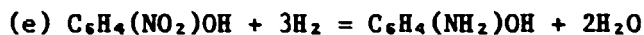


139.11 6.06 102.09 151.16 36.04 60.05

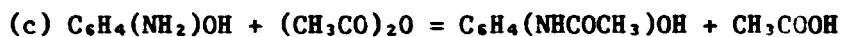
Source III



157.56 40.00 139.11 58.44

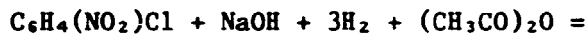


139.11 6.06 109.12 36.04



109.12 102.09 151.16 60.05

(h) Combined equation of the synthesis:



157.56 40.00 6.06 102.09



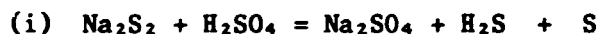
151.16 58.44 36.04 60.05

Source IV

Same as chemical reaction (c).

2.4 Other reactions considered in the analysis

Source I

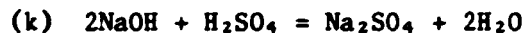


110.11 98.08 142.06 34.06 32.06



78.05 32.06 110.11

Source III



80.00 98.08 142.06 36.03

2.5 Chemical conversion efficiencies

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

Table 1. Overall nominal conversion factors of reactants to paracetamol

<u>Material input</u>	<u>F</u>
Acetic anhydride	0.675
p-Aminophenol	0.722
p-Chloronitrobenzene	1.042
p-Nitrophenol	0.920
p-Nitrosophenol	0.814
Phenol	0.623

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

Table 2. Paracetamol yields on feedstocks and acetic anhydride (percentage)

	I	II	III	IVa	IVb	IVc
Acetic anhydride	80	63	63	75	80	71
p-Aminophenol				75	90	80
p-Chloronitrobenzene			64			
p-Nitrophenol		66				
Phenol	69					

2.6 Brief description of the processes

2.6.1 Source I

Phenol is nitrosated in a multipurpose batch reactor by agitating the mixture of phenol, water and sodium nitrite and adding sulfuric acid under constant cooling. The produced crystalline p-nitrosophenol is removed by filtration and reacted with sodium polysulfide solution extemporaneously prepared from sodium sulfide and sulfur. The reaction is exothermic. The reaction mixture is filtered, the pH is adjusted, the precipitated p-aminophenol is crystallized and removed by filtration. The wet p-aminophenol is suspended in water and acetylated by acetic anhydride, used in excess, under constant cooling.

The precipitated paracetamol is removed by filtration and recrystallized from aqueous solution.

2.6.2 Source II

p-Nitrophenol is hydrogenated in aqueous solution at 65 to 70°C and 5-at pressure in two stages, in the presence of activated carbon and palladium-carbon catalyst. After about 50 to 60 per cent of the hydrogen has been added, the mixture is cooled, acetic anhydride is added and the reaction is completed until no more hydrogen is taken up by the reaction mixture. The acetylation is completed by acetic anhydride and the aqueous solution is

filtered while still hot. After cooling to about 5°C, the precipitated paracetamol is removed by filtration and dried.

2.6.3 Source III

p-Nitrophenol is prepared by the alkaline hydrolysis of p-chloronitrobenzene. The borate anion prevents the formation of by-products and enables the catalytic reduction of p-nitrophenol without separation from the reaction mixture. The process from the second step is basically the same as the one described under 2.6.2.

2.6.4 Source IV

This process is practically the same as the last step of processes 2.6.1 and 2.6.3.

ENVIRONMENT IMPACT ASSESSMENT

3.1 Material flow

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

3.2 Material requirement

3.2.1 Material consumption by nature of inputs

Source I

Reactants

Phenol	900 kg		
Sodium nitrite	820 kg		
Sulfuric acid	800 kg		
Sodium sulfide	1,080 kg		
Sulfur	90 kg		
Acetic anhydride	<u>840 kg</u>	4,530 kg	95.1%

Auxiliary materials

Carbon, activated	100 kg		
Sodium sulfite	115 kg		
Sodium bisulfite	<u>20 kg</u>	<u>235 kg</u>	<u>4.9%</u>
Total Source I		4,765 kg	100.0%

Source II

Reactants

p-Nitrophenol	1,389 kg		
Hydrogen	120 kg		
Acetic anhydride	<u>1,080 kg</u>	2,589 kg	98.1%

Auxiliary materials

Carbon, activated		49 kg	1.9%
-------------------	--	-------	------

Reaction promoters

Pd/C catalyst		<u>2 kg</u>	<u>-</u>
---------------	--	-------------	----------

Total Source II		2,640 kg	100.0%
-----------------	--	----------	--------

Source III

Reactants

p-Chloronitrobenzene	1,621 kg		
Sodium hydroxide	862 kg		
Hydrogen	120 kg		
Acetic anhydride	<u>1,078 kg</u>	3,681 kg	77.0%

Reaction promoters

Boric acid	62 kg		
Pd/C catalyst	<u>3 kg</u>	65 kg	1.4%

Auxiliary materials

Carbon, activated		30 kg	0.6%
-------------------	--	-------	------

pH adjuster

Sulfuric acid (also reaction promoter)		<u>1,005 kg</u>	<u>21.0%</u>
Total Source III		4,781 kg	100.0%

Source IV

Reactants

p-Aminophenol (a)	960 kg		
(b)	802 kg		
(c)	902 kg		
Acetic anhydride (a)	900 kg		
(b)	840 kg		
(c)	950 kg		
Total reactants:		(a) 1,860 kg	97.5%
		(b) 1,642 kg	97.5%
		(c) 1,852 kg	86.3%

Auxiliary materials

Sodium hydrosulfite (a)	18 kg		
Sodium bisulfite (b)	20 kg		
(c)	30 kg		
Carbon, activated (a)	30 kg		
(b)	100 kg		
(c)	150 kg		
Sodium sulfite (a)			
(b)	115 kg		
(c)	<u>115 kg</u>		
Total auxiliary materials:	(a)	48 kg	2.5%
	(b)	235 kg	12.5%
	(c)	295 kg	13.7%
Total Source IV:	(a)	1,908 kg	100.0%
	(b)	1,877 kg	100.0%
	(c)	<u>2,147 kg</u>	<u>100.0%</u>

The total material requirement for the production of 1,000 kg of paracetamol changes in the four sources, as follows:

Source I	4,765 kg
Source II	2,640 kg
Source III	4,781 kg
Source IV	1,877 - 2,147 kg

Total material consumption significantly increases with the degree of backward integration, e.g., the two additional steps between sources I and IV have changed total material consumption from 1,877 to 4,765 kg. The same data for a one-step difference between sources II and III are 2,640 kg and 4,781 kg, respectively. Reactants represent the highest share (77.0 to 98.1%) in total material consumption in all the analyzed processes. Each reaction is carried out in an aqueous medium, or the reactant is also the solvent. These facts reduce specific material consumption.

The specific material requirement is significantly lower with catalytic hydrogenation than with other methods of reduction.

Intermediates are generally not separated for purification during the synthesis. Additives are used to control side reactions. The main reactions are carried out under optimum conditions to guarantee both good yields and pharmacopoeial quality of the finished product.

3.2.2 Material consumption by process stage

The material requirement has also been analyzed according to the distinct steps in the chemical synthesis.

Source I

p-Nitrosophenol	Phenol	900 kg	2,303 kg	48.3%
	Sodium nitrite	820 kg		
	Sulfuric acid	<u>583 kg</u>		
p-Aminophenol	Sodium sulfide	1,080 kg	1,387 kg	29.1%
	Sulfur	90 kg		
	Sulfuric acid	<u>217 kg</u>		
Paracetamol	Acetic anhydride	840 kg	1,075 kg	22.6%
	Carbon, activated	100 kg		
	Sodium sulfite	115 kg		
	Sodium bisulfite	<u>20 kg</u>		
Total Source I:			4,765 kg	100.0%

Source II

p-Aminophenol	p-Nitrophenol	1,389 kg	1,530 kg	58.0%
	Hydrogen	120 kg		
	Carbon, activated	19 kg		
	Pd/C catalyst	<u>2 kg</u>		
Paracetamol	Acetic anhydride	1,080 kg	1,110 kg	42.0%
	Carbon, activated	<u>30 kg</u>		
Total Source II			2,640 kg	100.0%

Source III

p-Nitrophenol	p-Chloronitrobenzene	1,621 kg	2,483 kg	51.9%
	Sodium hydroxide	<u>862 kg</u>		
p-Aminophenol	Hydrogen	120 kg	1,190 kg	24.9%
	Sulfuric acid	1,005 kg		
	Pd/C catalyst	3 kg		
	Boric acid	<u>62 kg</u>		
Paracetamol	Acetic anhydride	1,078 kg	1,108 kg	23.2%
	Carbon, activated	<u>30 kg</u>		
Total Source III:			4,781 kg	100.0%

Source IV

	a	b	c
Paracetamol			
p-Aminophenol	960 kg	802 kg	902 kg
Acetic Anhydride	900 kg	840 kg	950 kg
Sodium hydrosulfite	18 kg		
Sodium sulfite		115 kg	115 kg
Sodium bisulfite		20 kg	30 kg
Carbon, activated	<u>30 kg</u>	<u>100 kg</u>	<u>150 kg</u>
 Total Source IV:	 1,908 kg	 1,877 kg	 2,147 kg

3.3 Waste streams and treatment

The following waste streams are generated during the manufacture of 1,000 kg of paracetamol:

Source I

p-Nitrosophenol				
Phenol, p-nitrosophenol and by-products		170 kg		
Sodium sulfate		844 kg		
Nitrogen oxides		<u>88 kg</u>	1,102 kg	29.5%
 p-Aminophenol				
p-Nitrosophenol, p-aminophenol and by-products		90 kg		
Sodium sulfate		314 kg		
Sodium sulfite		687 kg		
Sodium sulfide, polysulfide		572 kg		
Hydrogen sulfide		<u>76 kg</u>	1,739 kg	46.6%
 Paracetamol				
p-Aminophenol, paracetamol and by-products		111 kg		
Acetic acid		547 kg		
Carbon, activated		100 kg		
Sodium sulfite		115 kg		
Sodium bisulfite		<u>20 kg</u>	<u>893 kg</u>	<u>23.9%</u>
 Total Source I:			 3,734 kg	 100.0%

Summary

Material inputs, intermediates, end product and by-products	371 kg
Sodium sulfate	1,158 kg
Sodium sulfite	802 kg
Sodium sulfide, polysulfide	572 kg
Sodium bisulfite	20 kg
Acetic acid	547 kg
Nitrogen oxides	88 kg
Carbon, activated	100 kg
Hydrogen sulfide	<u>76 kg</u>
 Total Source I:	 3,734 kg

Source II

p-Aminophenol			
p-Nitrophenol, p-aminophenol and by-products	217 kg		
Pd/C catalyst	2 g		
Carbon, activated	19 kg		
Hydrogen	<u>60 kg</u>	<u>298 kg</u>	<u>22.5%</u>
Paracetamol			
p-Aminophenol, paracetamol and by-products	208 kg		
Acetic acid	790 kg		
Carbon, activated	<u>30 kg</u>	<u>1,028 kg</u>	<u>71.5%</u>
Total Source II:		1,326 kg	100.0%

Summary

p-Nitrophenol, p-aminophenol, paracetamol and by-products	425 kg		
Acetic acid	790 kg		
Pd/C catalyst	2 kg		
Carbon, activated	49 kg		
Hydrogen	<u>60 kg</u>		
Total Source II:		1,326 kg	

Source III

p-Nitrophenol			
p-Chloronitrobenzene, p-nitrophenol and by-products	50 kg		
Sodium chloride	<u>602 kg</u>	652 kg	20.3%
p-Aminophenol			
p-Nitrophenol, p-aminophenol and by-products	212 kg		
Hydrogen	60 kg		
Sodium sulfate	799 kg		
Sulfuric acid	453 kg		
Boric acid	62 kg		
Pd/C catalyst	<u>3 kg</u>	1,589 kg	47.7%
Paracetamol			
p-Aminophenol, paracetamol and by-products	207 kg		
Acetic acid	788 kg		
Carbon, activated	<u>30 kg</u>	<u>1,025 kg</u>	<u>32.0%</u>
Total Source III:		3,206 kg	100.0%

Summary

Material inputs, intermediates, end products and by-products	469 kg
Sodium chloride	602 kg
Sodium sulfate	799 kg
Sulfuric acid	453 kg
Acetic acid	788 kg
Boric acid	62 kg
Pd/C catalyst	3 kg
Carbon, activated	<u>30 kg</u>

Total Source III: Total: 3,266 kg

Source IV

	a	b	c
p-Aminophenol, paracetamol and by-products	330 kg	111 kg	250 kg
Acetic acid	530 kg	547 kg	621 kg
Sodium hydrosulfite	18 kg		
Sodium sulfite		115 kg	115 kg
Sodium bisulfite		20 kg	30 kg
Carbon, activated	<u>30 kg</u>	<u>100 kg</u>	<u>150 kg</u>
Total Source IV:	908 kg	893 kg	1,166 kg

3.3.1 Liquid effluent

More than 90 per cent of the wastes is water-soluble and can be discharged into the public sewage system directly or after biological treatment in the production plant. Sodium sulfides are hazardous wastes and must be oxidized if their concentration is higher than 0.01 g/m³ in the public sewage system water. Phenol, p-chloronitrobenzene, nitrophenol and aminophenol waste waters deserve also special attention. Their maximum allowable concentration is 5g/m³ in the public sewage system water. The quantity of acetic acid is also high in the waste streams.

3.3.2 Air pollutants

Air pollutants are generated only during the nitrosation of phenol and the subsequent reduction. The nitrogen oxides and hydrogen sulfide represent 16.4 per cent of the paracetamol output.

3.3.3 Solid wastes

The exhausted catalyst can be regenerated, whereas used activated carbon should be incinerated. There are no other hazardous solid wastes.

3.4 Industrial safety

3.4.1 Materials

With a few exceptions (sulfur, activated carbon, boric acid, Pd/C catalyst, sodium chloride and sodium sulfate), all chemicals used in paracetamol manufacture are classified as poisons.

3.4.2 Chemical conversions

The chemical reactions involved in the manufacture of paracetamol are: nitrosation, reduction with sodium polysulfide, catalytic hydrogenation, alkaline hydrolysis and acetylation.

3.4.3 Alternative synthesis routes

Other processes described in the literature include also nitration (of phenol into p-nitrophenol), electrochemical reduction and Béchamp reduction (of p-nitrophenol or p-nitrosophenol into p-aminophenol), acetylation of p-aminophenol with keten, and bioconversion (hydroxylation of aniline or acetanilide into paracetamol).

4. SUMMARY EVALUATION

It is a common feature of all studied processes that organic solvents are not used and the chemical conversions are carried out in aqueous media. Feedstocks depend on the synthesis route or on the degree of backward integration. The last step is common in all the four technology sources.

Specific material consumption per unit quantity of finished product is 1.9 - 2.1 through 2.6 to 4.8, as the number of synthesis steps increases from one to three.

The reduction of p-nitrosophenol and p-nitrophenol is preferred by catalytic hydrogenation (round 85 per cent less waste, and also less hazardous waste streams).

Sources B and C reflect technical development efforts to increase yields and guarantee consistently good quality without the isolation and purification of intermediates.

The quantity of waste depends mainly on the degree of backward integration of the processes. 87 to 99 per cent of the waste is discharged diluted as waste water which can be best treated and controlled as regards environment protection. A large amount of inorganic salts and acetic acid can be recovered from the waste streams.

Air pollutants (nitrogen oxides and hydrogen sulfide) are encountered only in one process. They represent 4.4% of the total waste and must be absorbed in a scrubber. Solid waste consists of exhausted catalyst (always regenerated) and used activated carbon which is incinerated.

Reduction by catalytic hydrogenation, recovery of acetic acid after acetylation and the improvement of the step-by-step yields may decrease the amount of hazardous waste by about 50 per cent.