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October 1989

ENVIRONMENT IMPACT ANALYSIS OF
PRAZIQUANTEL SYNTHESIS

1. INFORMATION SOURCE

Dr. Seubert JÜRGEN, FRG Patent 25 04 250.6 to Merck Patent GmbH;

Priority date: 1 February 1975.

2. PROCESS INFORMATION

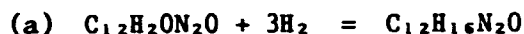
2.1 Schematic illustration of the synthesis

3185N

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.

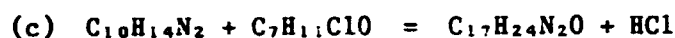
2.3 Chemical reactions



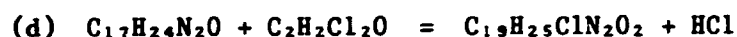
198.22 6.06 204.27



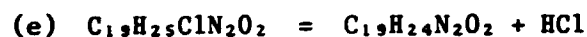
204.27 18.01 162.23 60.05



162.23 146.61 272.39 36.46

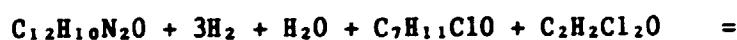


272.39 112.94 348.87 36.46



348.87 312.41 36.46

(f) Combined equation of the synthesis:



198.22 6.05 18.01 146.61 112.94



312.41 60.05 109.38

2.4 Other reactions considered in the analysis



60.05 40 82.04 18.02



40 36.46 58.44 18.02



112.94 18.02 94.50 36.46



112.21 = 36.46 74.12 74.55

2.5 Chemical conversion efficiencies

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

Table 1. Material requirements for praziquantel synthesis
(quantity/unit output)

Material input	F	f
1-Cyano-2-acetyl-1,2-dihydro-isoquinoline	0.634	1.921
1-Aminomethyl-2-acetyl-1,2,3,4-THIQ	0.654	
1-Aminomethyl-1,2,3,4-THIQ	0.519	
1-Cyclohexylcarboxamidomethyl-THIQ	0.872	1.189
1-Cyclohexylcarboxamidomethyl-2-chloroacetyl-THIQ	1.117	1.297
Cyclohexyl carbonylchloride	0.469	1.567
Chloroacetylchloride	0.362	0.546
Hydrogen	0.019	0.102
Ethyl acetate		2.621
Methylene chloride	6.336	
Raney nickel		1.455
Acetonitrile		1.781
Pyridine		0.844
Hydrochloric acid		4.422
Triethylamine		0.530
Potassium tertiary-butylate		0.520
Sodium hydroxide		5.041

Data in table 1 were calculated from examples 16, 26 and 28 of the FRG patent referred to in point 1. 90 to 95 per cent recovery and recycling was

assumed for solvents. When quantities were not given in the patent (dichloromethane, hydrochloric acid and sodium hydroxide) own estimations were included in the table.

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

Table 2. Praziquantel yields on feedstock intermediates and the main reactants (percentage)

1-Cyano-2-acetyl-1.2-dihydro-isoquinoline	33.0
1-Cyclohexylcarboxamidomethyl - T.H.I.Q.	73.3
1-Cyclohexylcarboxamidemethyl-2-chloro-acetyl - T.H.I.Q.	86.1
Cyclohexylcarbonyl chloride	29.9
Chloroacetyl Chloride	66.3
Yield of steps 1 to 3	45.0
Yield of step 4	85.1
Yield of step 5	86.1

The relatively low step-by-step and overall yields allow for two conclusions: first, the process of the laboratory scale synthesis is not optimized, therefore, the quantity of waste is not minimized; secondly, patent descriptions are written in such a way as to extend process protection to a maximum possible degree and to say only the necessary minimum about the process commercially used. As a result, process analyses from patent descriptions show a pessimistic view of economic feasibility and waste generation. Nonetheless, patent descriptions are the best sources of information at the opportunity assessment stage.

2.6 Brief description of process

1-Cyano-2-acetyl-1,2-dihydro-isoquinoline is hydrogenated in ethylacetate solution, under a pressure of 260 atm., in the presence of Raney nickel. The solvent is distilled off, and the 1-aminomethyl-2-acetyl-1,2,3,4-tetrahydro-isoquinoline, (from now on the last part is abbreviated as THIQ), is hydrolyzed in a 25 per cent hydrochloric acid solution, the pH of the reaction medium is made alkaline, and the 1-aminomethyl-1,2,3,4-THIQ is extracted with methylene chloride. The solvent is distilled off, the residue is dissolved in acetonitrile and acetylated by cyclohexylcarbonyl chloride in the presence of pyridine hydrochloride. Acetonitrile is distilled off, the residue is dissolved in dilute aqueous hydrochloric acid, the pH of the medium is made alkaline, and the reaction mixture is extracted with methylene chloride. The solvent is again distilled off. The obtained crude 1-cyclohexylcarboxamidomethyl-1,2,3,4-THIQ is recrystallized from acetone. The purified intermediate is dissolved in methylene chloride and reacted with chloroacetylchloride in the presence of triethylamine. The obtained 1-cyclohexylcarboxamidomethyl-2-chloroacetyl-1,2,3,4-THIQ is recrystallized and the ring-closure reaction is carried out with the aid of potassium tertiary-butyrate in acetonitrile solution. After the addition of water, acetonitrile is distilled off and the residue is dissolved in methylene chloride. The reaction mixture is dried with anhydrous magnesium sulphate, the solvent is distilled off and the crude praziquantel is recrystallized from acetone. The overall yield is 33 per cent.

Other reaction routes are also described in the patent however, they are not significantly different from the above-described synthesis as far as environment protection is concerned.

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 requirements

3.2.1 Material consumption by nature of inputs

Reactants:

1-Cyano-2-acetyl-1,2-dihydro-isoquinoline	1,921 kg		
Cyclohexylcarbonylchloride	1,567 kg		
Chloroacetylchloride	546 kg		
Hydrogen	<u>102 kg</u>	4,136 kg	14.7%

Reaction promoters

Raney nickel	1,455 kg		
Pyridine	854 kg		
Triethylamine	530 kg		
Potassium tertiary-butylate	<u>520 kg</u>	3,349 kg	11.9%

Solvents

Ethylacetate	2,621 kg		
Acetonitrile	1,781 kg		
Methylenechloride	<u>6,339 kg</u>	1,041 kg	38.0%

pH adjusters

Hydrochloric acid	4,422 kg		
Sodium hydroxide	<u>5,584 kg</u>	<u>10,006 kg</u>	<u>35.4%</u>

Total: 28,232 kg 100.0%

The high share of solvents in the total material requirement is explained by the frequently repeated extraction operation. Real solvent use is higher than the calculated figure because solvents used to recrystallize intermediates and the finished product (ethanol, acetone, perhaps methylethylketone) were not quantified in the process description.

The share of hydrochloric acid and sodium hydroxide in the total amount of waste is also relatively high because of the multiple extractions and of the fact that the intermediates are not separated from the reaction mixture in the first three steps of the synthesis.

The quantity of reactants is also high by industrial standards because the overall yield is only about 33 per cent. The combined yield of the first three steps is 45 per cent, whereas the fourth and fifth steps are carried out with 85 per cent and 86 per cent yields, respectively.

The quantities of reaction promoters do not include credits due to recovery, although this is both possible and routinely done in commercial scale processes.

3.2.2 Material consumption by process stage

The material requirement has also be analyzed according to the distinct steps in the chemical syntheses:

1-Cyclohexylcarboxamidomethyl-THIQ, (steps 1-3)	23,388 kg	82.8%
1-Cyclohexylcarboxamidomethyl-2-chloroacetyl-THIQ (step 4)	2,854 kg	10.1%
Praziquantel (step 5)	1,990 kg	7.1%
	<u>28,232 kg</u>	<u>100.0%</u>

About 83 per cent of the material inputs is consumed in the first three steps because their combined yield is only 45 per cent and the extraction operations are encountered in this stage.

3.3 Waste streams and treatments

The following wastes are generated during the manufacture of 1000 kg of praziquantel:

<u>Steps 1-3</u>	<u>kg</u>		
Material inputs, intermediates, non-defined by-products and wastes	1,598		
Hydrogen excess	44		
Raney nickel	1,455		
Pyridine	844		
Ethylacetate	2,621		
Acetonitrile	1,050		
Methylene chloride	3,861		
Sodium acetate	795		
Sodium chloride	<u>7,591</u>	19,859	79.8%
 <u>Step 4</u>			
Intermediates and non-defined by-products and wastes	270		
Triethylamine	530		
Hydrochloric acid	215		
Methylene chloride	1,739	2,754	11.1%
 <u>Step 5</u>			
Intermediates, finished product and non-defined by products and wastes	161		
Potassium tertiary-butylate	103		
Potassium chloride	277		
Tertiary butanol	276		
Acetonitrile	731		
Methylene chloride	<u>739</u>	2,287	9.1%
 <u>Summary</u>			
Material inputs, intermediates, and non-defined by-products and wastes	2,029		
Hydrogen excess	44		
Raney nickel	1,455		
Pyridine	844		
Sodium acetate	795		
Sodium chloride	7,591		
Ethylacetate	2,621		
Methylene chloride	6,339		
Acetonitril	1,781		
Triethylamine	530		
Hydrochloric acid	215		
Potassium tert. butylate	103		
Potassium chloride	277		
Tertiary-butanol	<u>276</u>	24,900	100.0%

Organic solvents account for the highest share, 43 per cent, of waste.

Salts rank second with a share of 36 per cent. Organic chemical inputs and outputs represent a relatively large amount, 10 per cent, of waste.

3.3.1 Liquid effluent

Water-soluble inorganic salts, left in the aqueous phase after extraction, can be discharged into the public sewage system. This effluent contains also a small portion of water-soluble organic solvents; its amount should not exceed the maximum allowable concentration in the public sewage water.

3.3.2 Air pollutants

The loss of organic solvents during the process contaminates the air. Hydrogen excess used for the reduction of p-nitrophenol is also an air pollutant.

3.3.3 Solid wastes

The exhausted Raney-nickel catalyst can be regenerated. The remnants of solvent recovery and mother liquors contain the major part of solid organic wastes which should be incinerated.

3.4 Industrial safety

3.4.1 Materials

All materials used in praziquantel manufacture are hazardous; chloroacetic acid is very toxic, whereas acetonitrile, chloroacetylchloride, Raney-nickel, sulfuric acid and sodium hydroxide are either toxic or dangerous to handle.

As regards fire and explosion risk, hydrogen is very dangerous, while acetone, acetonitrile, ethylacetate, pyridine, Raney-nickel and triethylamine are dangerous.

Round 35 per cent of the waste is non-poisonous inorganic salt, the rest is harmful to the human health or the external environment.

3.4.2 Chemical conversions

The chemical reactions involved in the synthesis of praziquantel are: catalytic hydrogenation, hydrolysis, acylation, chloroacetylation and cyclization.

The 1-aminomethyl-1,2,3,4-THIQ can also be synthesized from N-glycyl-beta-phenylethylamine by Bischler-Napieralski ring closure condensation followed by catalytic hydrogenation (schematic illustration of the synthesis, p. 1)

Backward integration can be increased with both synthesis routes, e.g., as follows:

The number of conversions would increase from five to eight, if the synthesis started from benzylicyanide which is easier to purchase than 1-cyano-2-acetyl-1,2-dihydroisoquinoline or N-glycyl-beta-phenylethylamine

4. SUMMARY EVALUATION

The environment impact analysis of praziquantel synthesis is based on a patent description. The data come from a laboratory scale process and the major objective is to extend process claims as much as possible without disclosing much about industrial know-how. Consequently, technical conclusions are semi-quantitative in character and the amounts of wastes from the laboratory scale synthesis reveal opportunities for process development. Both the kinds and amounts of organic solvents could be reduced; extraction operations can be eliminated. The solvents can be recycled and the efficiency of recovery can be improved. The manufacturing process should preferably be carried out in a closed system. Raney-nickel should be regenerated and recycled into the process.

The yields of steps 1-3 are very low and their improvement would result in a significant reduction of wastes. Organic solvents should be removed by heat or biological treatment from the effluents. Organic solid wastes can be incinerated. The control of air pollution by organic solvents requires above-the-average complementary investment.

The process starting from N-glycyl-beta-phenylethylamine was not been analyzed. Increased backward integration would start production from common petrochemical feedstocks (produced by low-waste technologies). This is important to mention because final environment impact analysis can only be made if all steps of the total synthesis have been evaluated.

Appendix 1 to annex .. of the
 ENVIRONMENT IMPACT ANALYSIS OF THE MANUFACTURE OF
 PRAZIQUANTEL

Reactants, products and auxiliary materials
in Praziquantel manufacture

Compound	Chemical formula	Molecular weight
1-Aminomethyl-1,2,3,4-THIQ	C ₁₀ H ₁₄ N ₂	162.23
1-Cyano-2-acetyl-1,2-dihydroisoquinoline	C ₁₂ H ₁₀ N ₂ O	198.22
1-Cyclohexylcarbonylaminomethyl-THIQ	C ₁₇ H ₂₄ N ₂ O	272.39
1-Cyclohexylcarbonylaminomethyl- 2-chloroacetyl-THIQ	C ₁₉ H ₂₅ ClN ₂ O ₂	348.87
2-Cyclohexylcarbonylaminomethyl- 4-oxo-1,2,3,6,7,11b-hexahydro-4H- pirazino(2,1a)isoquinoline	C ₁₉ H ₂₄ N ₂ O ₂	312.41
Hydrogen	H ₂	2.02
Cyclohexylcarbonyl chloride	C ₇ H ₁₁ ClO	146.61
Chloroacetic acid	C ₂ H ₃ ClO ₂	94.50
Chloroacetylchloride	C ₂ H ₂ Cl ₂ O	112.94
Pyridine	C ₅ H ₅ N	79.10
Hydrochloric acid	HCl	36.46
Triethylamine	C ₆ H ₁₅ N	101.19
Potassium tertiary-butylate	C ₄ H ₉ KO	112.21
Sodium hydroxide	NaOH	40.00
Acetic acid	C ₂ H ₄ O ₂	60.05
Sodium acetate	CH ₃ COONa	82.04
Sodium chloride	NaCl	58.44
Butanol, tertiary	C ₄ H ₁₀ O	74.12
Potassium chloride	KCl	74.55

Appendix 2 to annex .. of the
ENVIRONMENT IMPACT ANALYSIS OF THE MANUFACTURE OF
PRAZIQUANTEL

Flow schemas of the manufacturing process of
Praziquantel

Appendix 3 to annex .. of the
 ENVIRONMENT IMPACT ANALYSIS OF THE MANUFACTURE OF
 PRAZIQUANTEL

Material balances
for the manufacture of 1000 kg of Praziquantel
 (kilogrammes)

	Inputs	Outputs
<u>Steps 1-3</u>		
1-cyano-2-acetyl-1,2-DHIQ	1,921	.
Raney-nickel	1,455	1,455
Hydrogen	102	44
Hydrochloric acid	4,384	
Sodium hydroxide	5,585	
Pyridine	844	844
Cyclohexylcarbonyl chloride	1,567	146
Ethyl acetate	2,621	2,621
Acetonitrile	1,050	1,050
Methylene chloride (dichloromethane)	3,861	3,861
Sodium acetate		795
Sodium chloride		7,591
Water	175	2,516
1-cyclohexylcarboxamide methyl-THIQ		2,641
Total steps 1-3:	23,563	23,564
Waste	23,564	
	-2,516	
	<u>-1,189</u>	19,859
<u>Step 4</u>		
1-cyclohexylcarboxamide methyl-THIQ	1,189	
Triethylamine	530	530
Chloroacetyl chloride	546	
Methylene chloride	1,739	1,739
Hydrochloric acid	39	215
Chloroacetic acid		44
Water	8	
1-cyclohexylcarboxamide methyl-2-chloroacetyl-DHIQ		1,523
Total step 4:	4,051	4,051
Waste	4,051	
	<u>-1,297</u>	2,754

Step 5

1-cyclohexylcarboxamid		
methyl-2-chloroacetyl-THIQ	1,297	
Potassium tert. butylate	520	103
Acetonitrile	731	731
Methylene chloride	739	739
Potassium chloride		277
Butanol tert.		276
Praziquantel		1,161
 Total step 5:	 3,287	 3,287
 Waste	 3,287	
	<u>-1,000</u>	<u>2,287</u>

Summary

1-cyano-2-acetyl-1,2-DHIQ	1,921	
Raney-nickel	1,455	1,455
Hydrogen	102	44
Hydrochloric acid	4,422	215
Sodium hydroxide	5,584	
Pyridine	844	844
Cyclohexylcabonyl chloride	1,567	146
Ethylacetate	2,621	2,621
Acetonitrile	1,781	1,781
Methylene chloride	6,339	6,339
Sodium acetate		795
Sodium chloride		7,591
Triethylamine	530	530
Chloroacetylchloride	546	
Chloroacetic acid		44
Water	183	2,516
Potassium tert.butylate	520	103
Potassium chloride		277
Butanol tert.		276
1-cyclohexylcarboxamide-methyl-THIQ		1,161
1-cyclohexylcarboxamido		
methyl-2-chloroacetyl-THIQ		226
Praziquantel waste		161
Praziquantel product		1,000
 Total:	 28,415	 28,416
 Waste	 28,416	
	<u>-2,516</u>	
	<u>-1,000</u>	<u>24,900</u>