Production of γ-tocopherol Rich Mixtures

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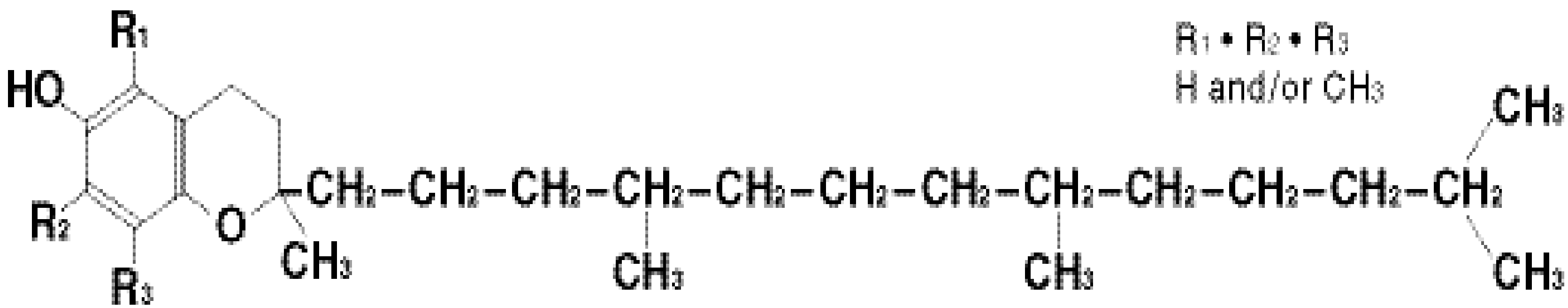
Introduction

- Soybean oil deodorizer distillate (SODD) is processed to produce mixtures of α, δ, and γ tocopherol
- Annual return on investments vary from \$3.18 - \$3.50
- Net Present Worth of \$3.80 - \$4.21 billion

Introduction

- Tocopherol-rich mixtures are used as dietary supplements
  - Fat soluble anti-oxidants
  - Neutralize free radicals
  - May help prevent chronic diseases
- Tocopherol mixtures contain homologues
  - α, γ, β, and δ-tocopherol

Introduction



Homologues	R1	R2	R3
Alpha- TOCOPHEROL	CH3	CH3	CH3
Beta- TOCOPHEROL	CH3	H	CH3
Gamma- TOCOPHEROL	H	CH3	CH3
Delta- TOCOPHEROL	H	H	CH3

Project Objective

- α-tocopherol linked to increased risk of heart disease
- Tocopherol mixture processed to produce various concentrations of γ and δ tocopherol
- γ-δ-tocopherol used for pharmaceuticals
- Pure γ utilized for research

Project Summary

Production Capacity

- 24,750 kg/day of a tocopherol-rich mixture to be separated into components or sold as produced
- 11,100 kg/day of γ-δ-tocopherol mixture
- 1,000 kg/year of pure γ-tocopherol

Raw Material

- Soybean deodorizer distillate (SODD)
  - 10% to 15% tocopherols
    - 60% are γ-tocopherol
    - 20% α-tocopherol and δ-tocopherol
- SODD can be purchased from numerous factories across the United States
- Shipped by truck loads
  - 48,000 lbs. for $0.14/kg.

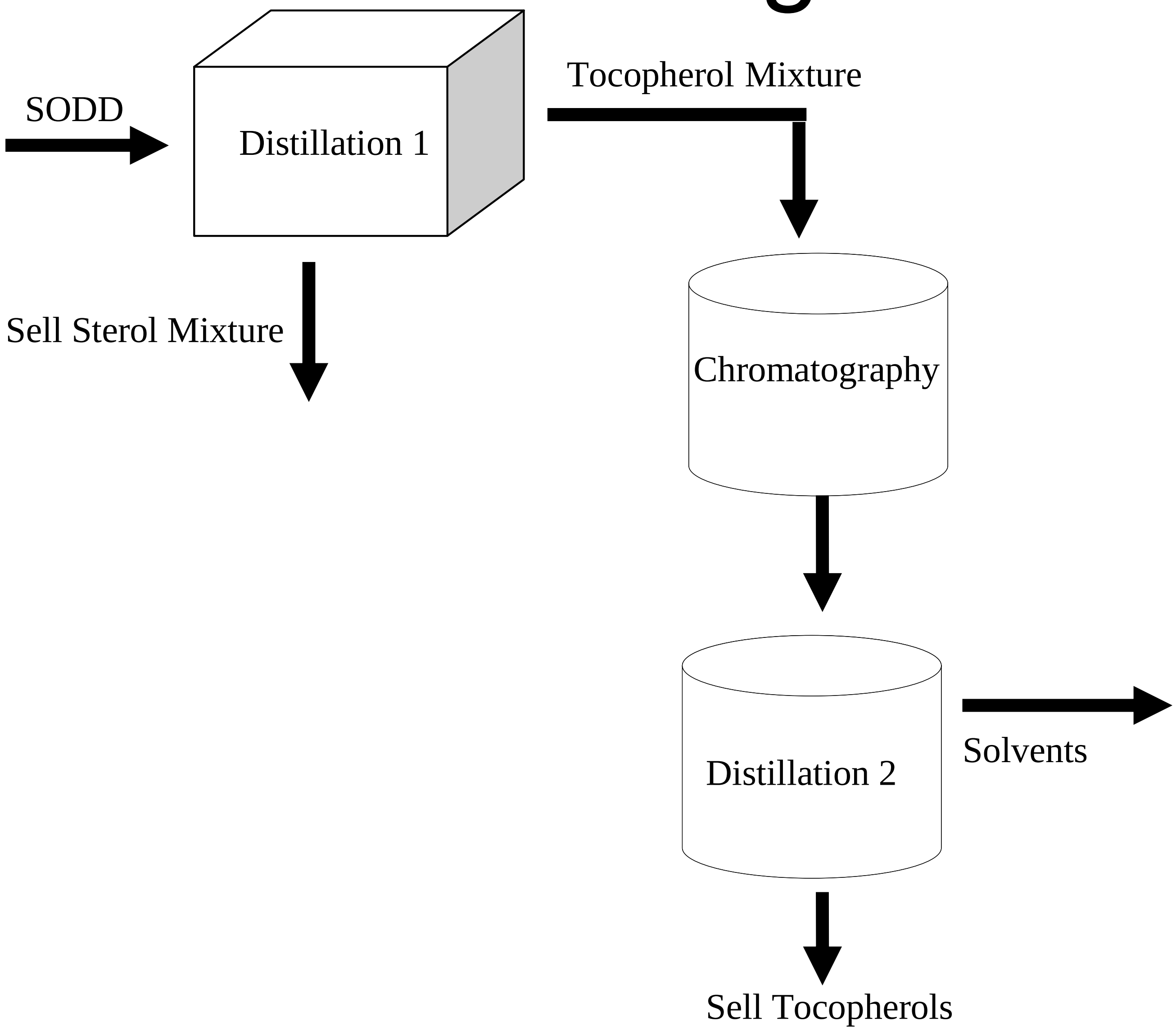
Processes Considered

- Distillation of SODD
- High Performance Liquid Chromatography (HPLC) to isolate γ-tocopherol
- Affinity chromatography for separation of γ-tocopherol
- Genetic engineering of soybeans to produce only γ-tocopherol

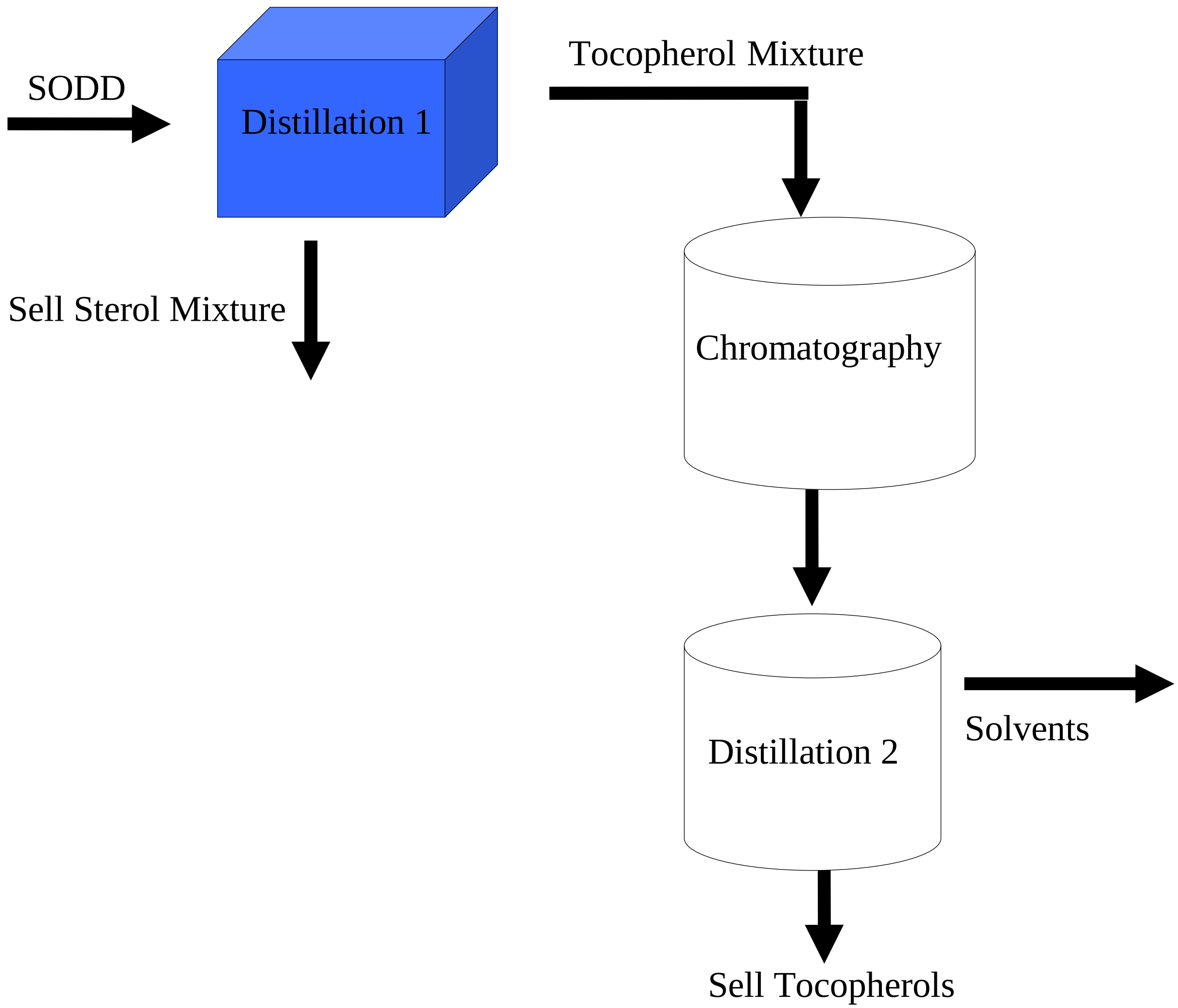
Processes Selected

- Enzymatic Distillation of SODD will be used to produce a tocopherol-rich mixture
- HPLC is used to separate γ-δ-tocopherol from the tocopherol mixture
- HPLC is also used to isolate γ-tocopherol from the mixture

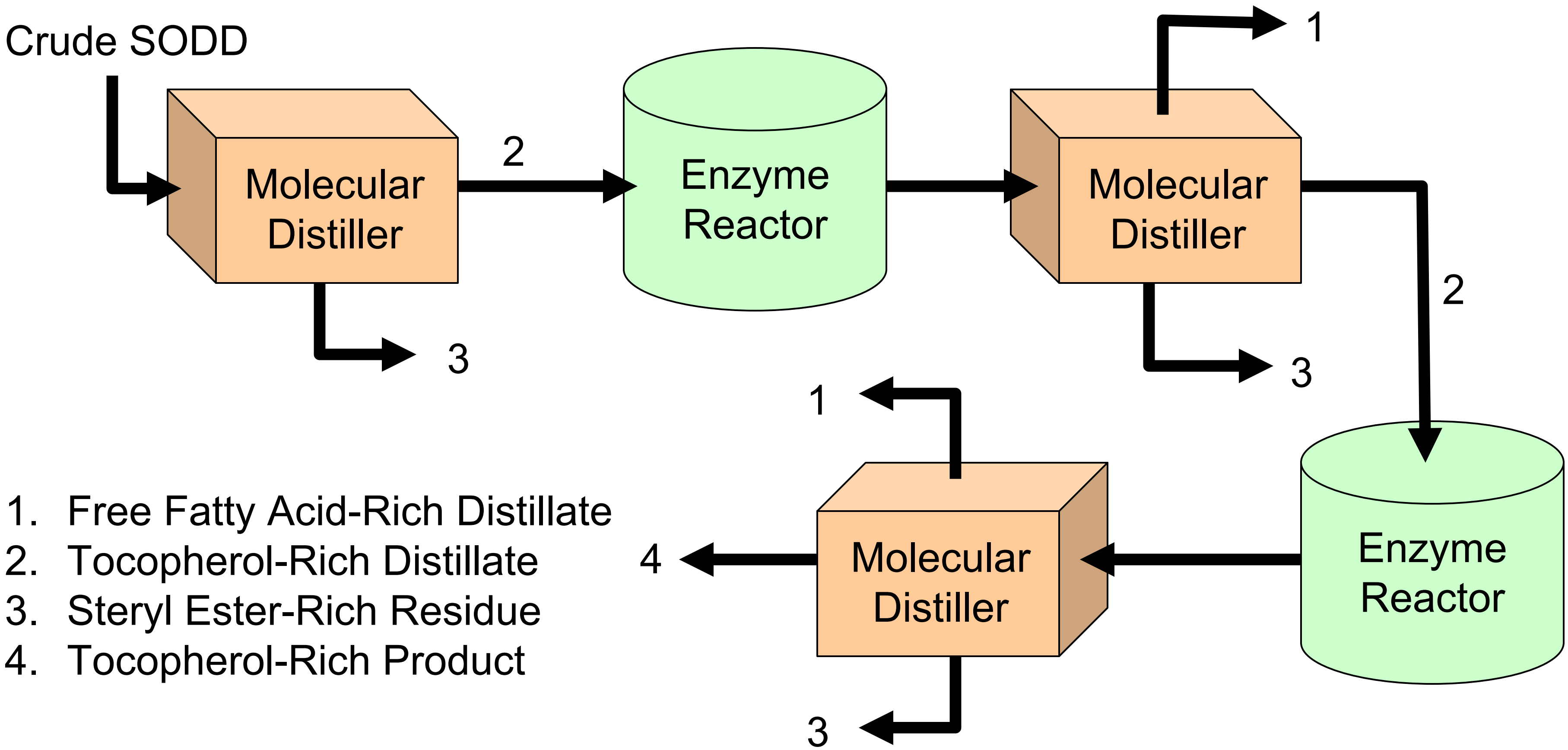
General Flow Diagram



Enzymatic Distillation



Enzymatic Distillation Flow Diagram

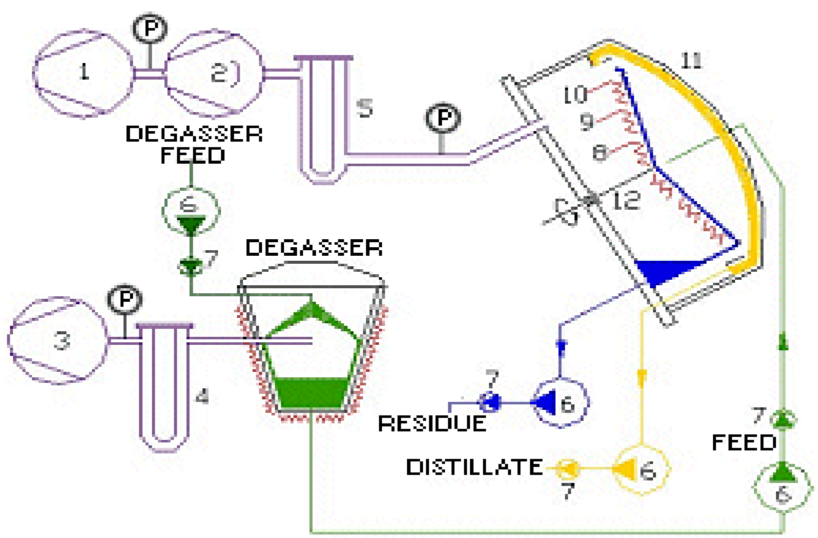


1. Free Fatty Acid-Rich Distillate
2. Tocopherol-Rich Distillate
3. Steryl Ester-Rich Residue
4. Tocopherol-Rich Product

Enzymatic Distillation

- Processes crude SODD into 65%-75% tocopherol mixture product
- Consists of two main stages
  - Molecular distillation
    - Removes unwanted components from mixture
  - Enzyme reaction
    - Converts unwanted components so they can be removed by molecular distillation

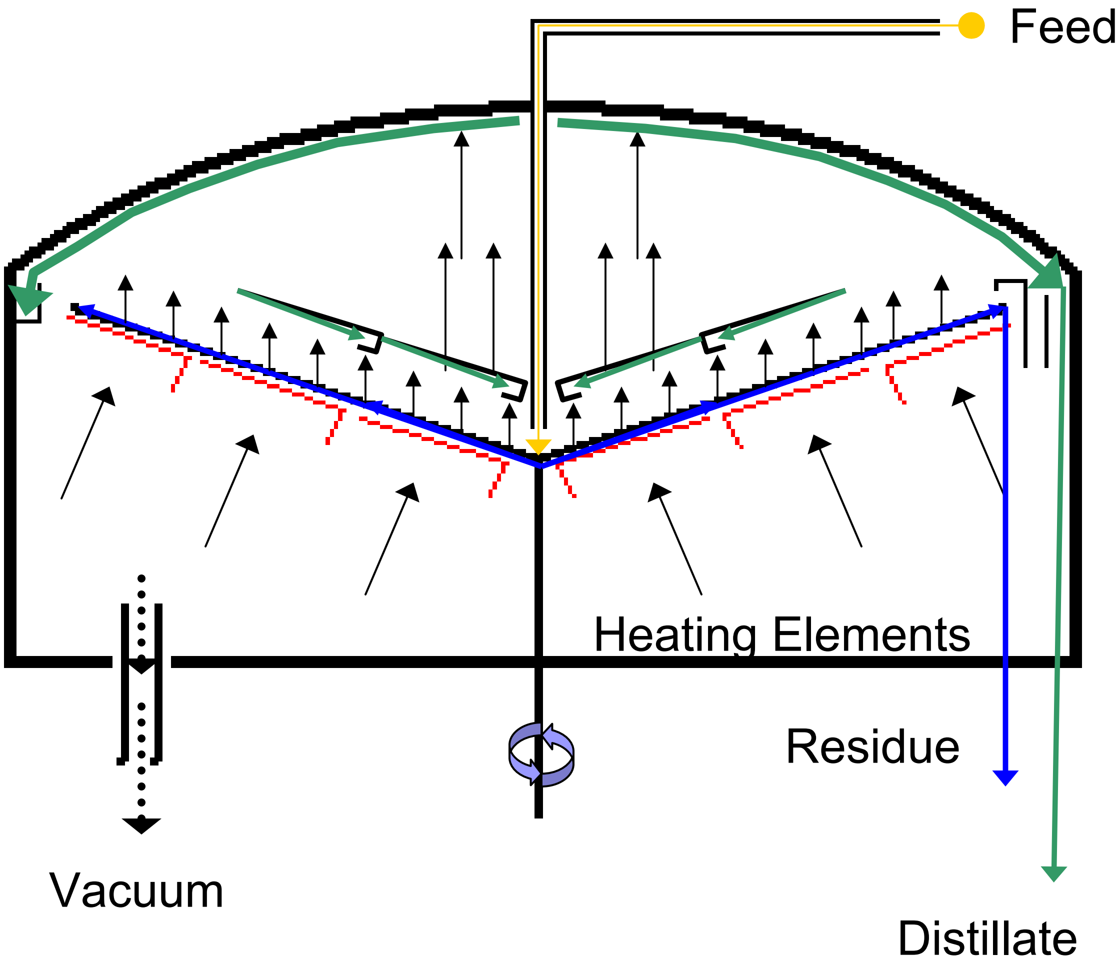
Molecular Distillation



Myers-Vacuum
Macro 36 Molecular Distiller

- Makes use of differing vapor pressures
- Low pressure system (~0.001 mm Hg)
- Commonly used to separate chemicals of high molecular weights
- Centrifugal model

Molecular Distillation Operation



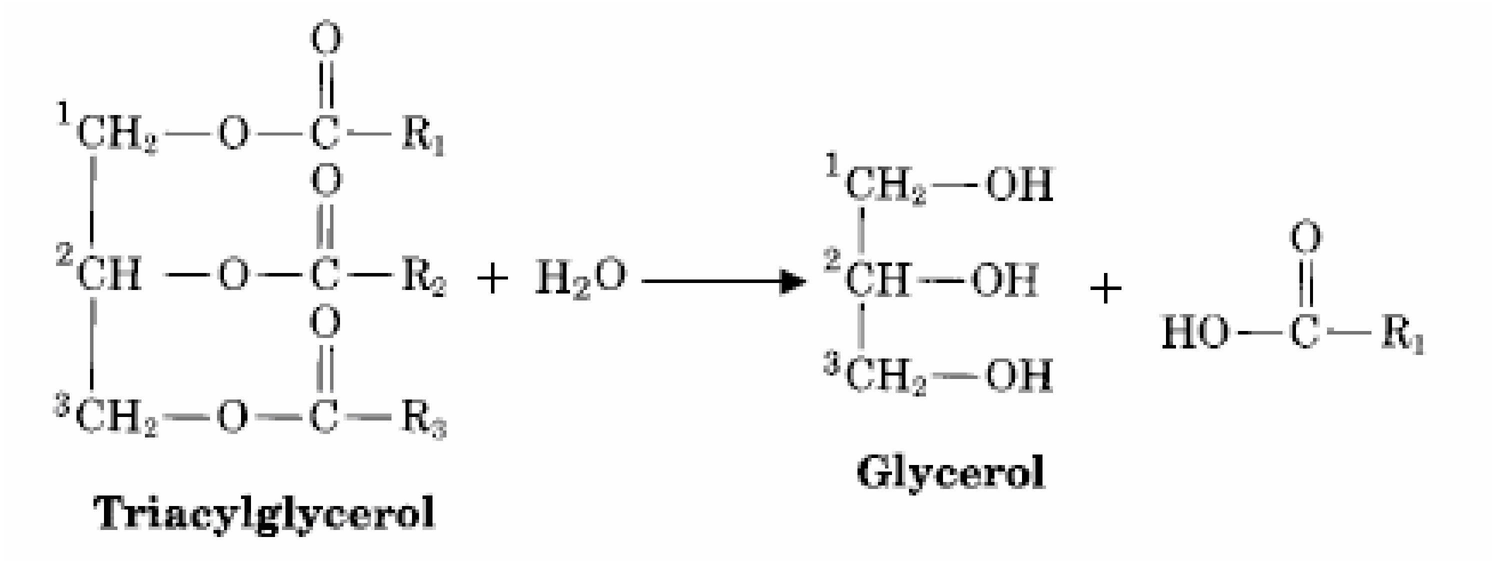
Enzyme Reaction

- Main purpose: to alter components structures and molecular weights to differ from that of the tocopherol's

- Sterols' properties are very similar to that of the tocopherol's making it the hardest of the substances to be removed from the tocopherols

Enzyme Reaction

- The enzyme *Candida rugosa* lipase catalyzes the hydrolysis of acylglycerols

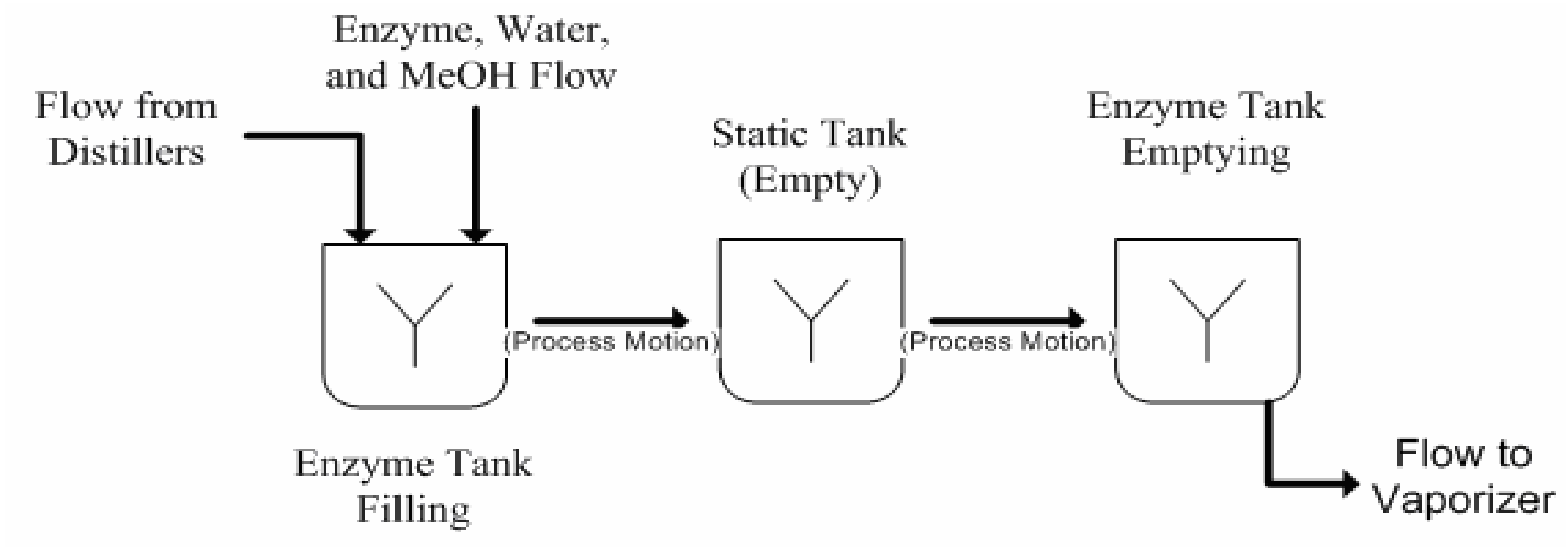


- R1, R2, and R3 are fatty acid residues

Enzyme Reaction

- *Candida rugosa* also catalyzes the esterification of organic acids and alcohols
- This is useful considering free fatty acids are organic acids and sterols are alcohols
  - This uses the components within the mixture in order to perform the reactions

Tank Flow



- In order to keep the process continuous the enzyme reactions take place in multiple tanks
- System of X+2 tanks
  - X is determined from available tank sizes and system flows

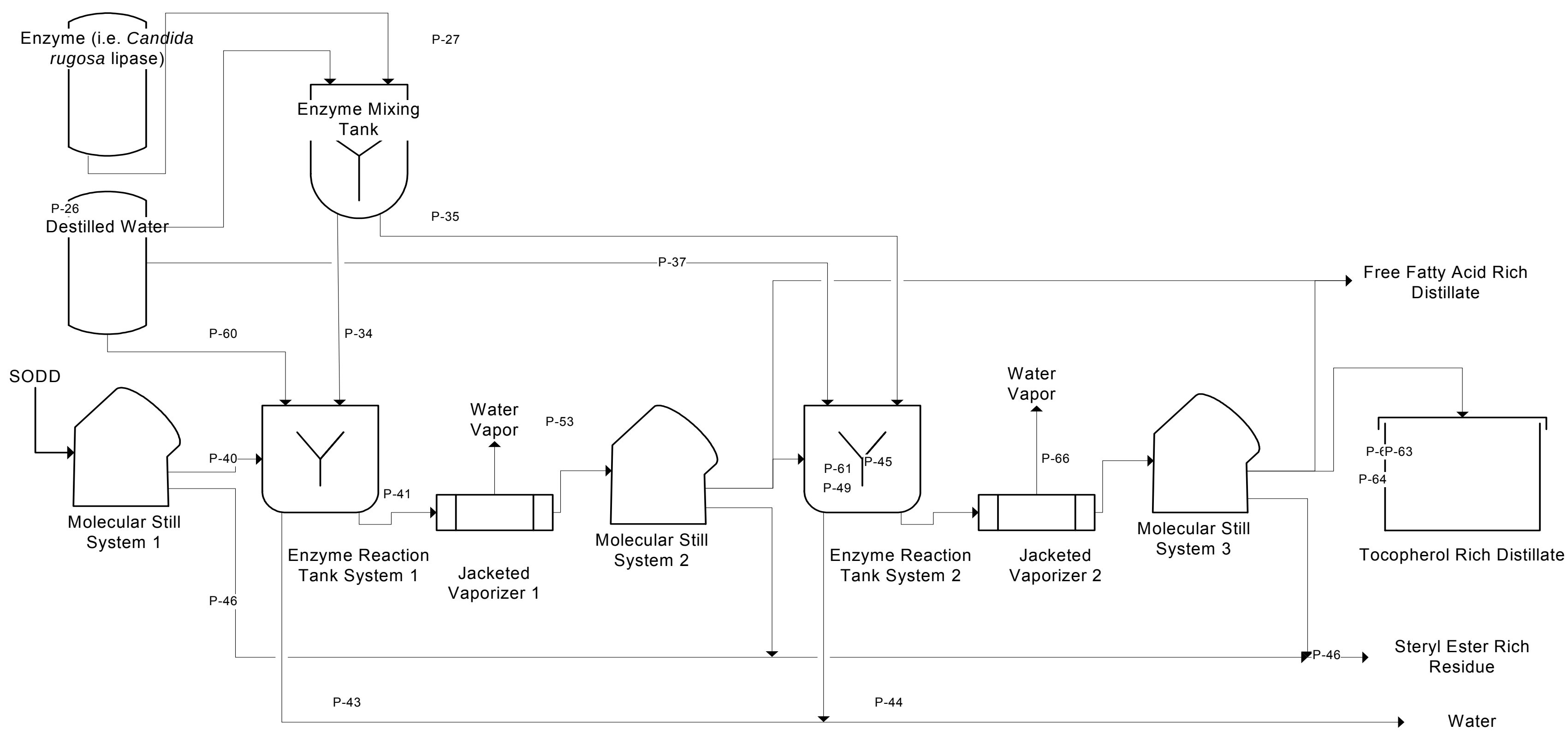
Tank Flow

System	Enzyme Concentration (U/mg)	Reactor Set	Fill/Drain time (h)	Size (m^3)	# of tanks	Batch time
Non-Methanol	700	1	0.5	13.8	50	24
		2	0.5	10.6	50	24
	1500	1	0.5	13.8	50	24
		2	0.5	10.6	50	24
Methanol	700	1	1.0	10.0	28	26
		2	1.0	3.9	28	26
	1500	1	1.0	10.1	28	26
		2	1.0	4.0	28	26

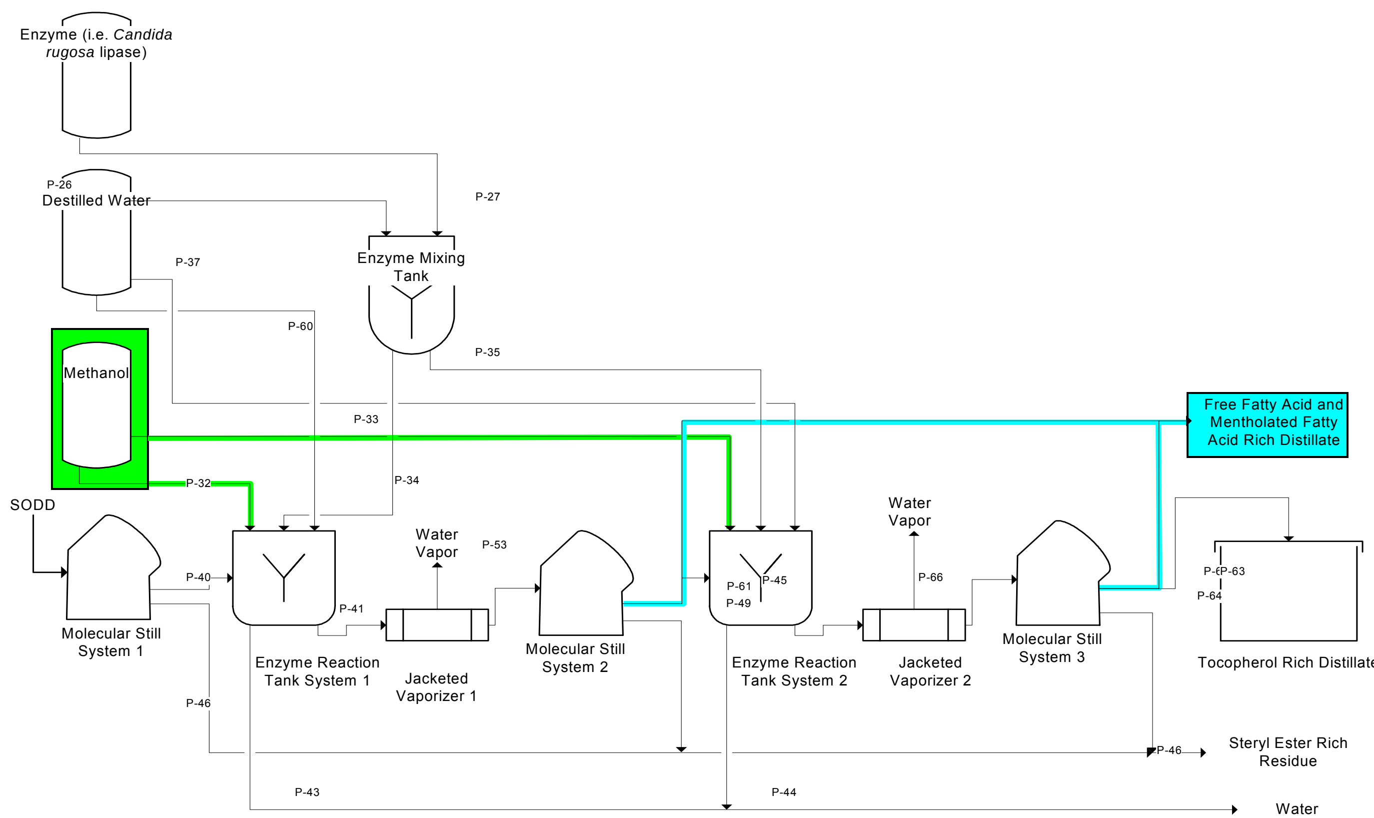
Process Setups

- Two different setups were looked at
  - With methanol
  - Without methanol
- When methanol is added to the process it bonds to the free fatty acids so that more can be removed
  - This creates a higher concentration (75%) in the tocopherol product

Enzymatic Distillation without Methanol



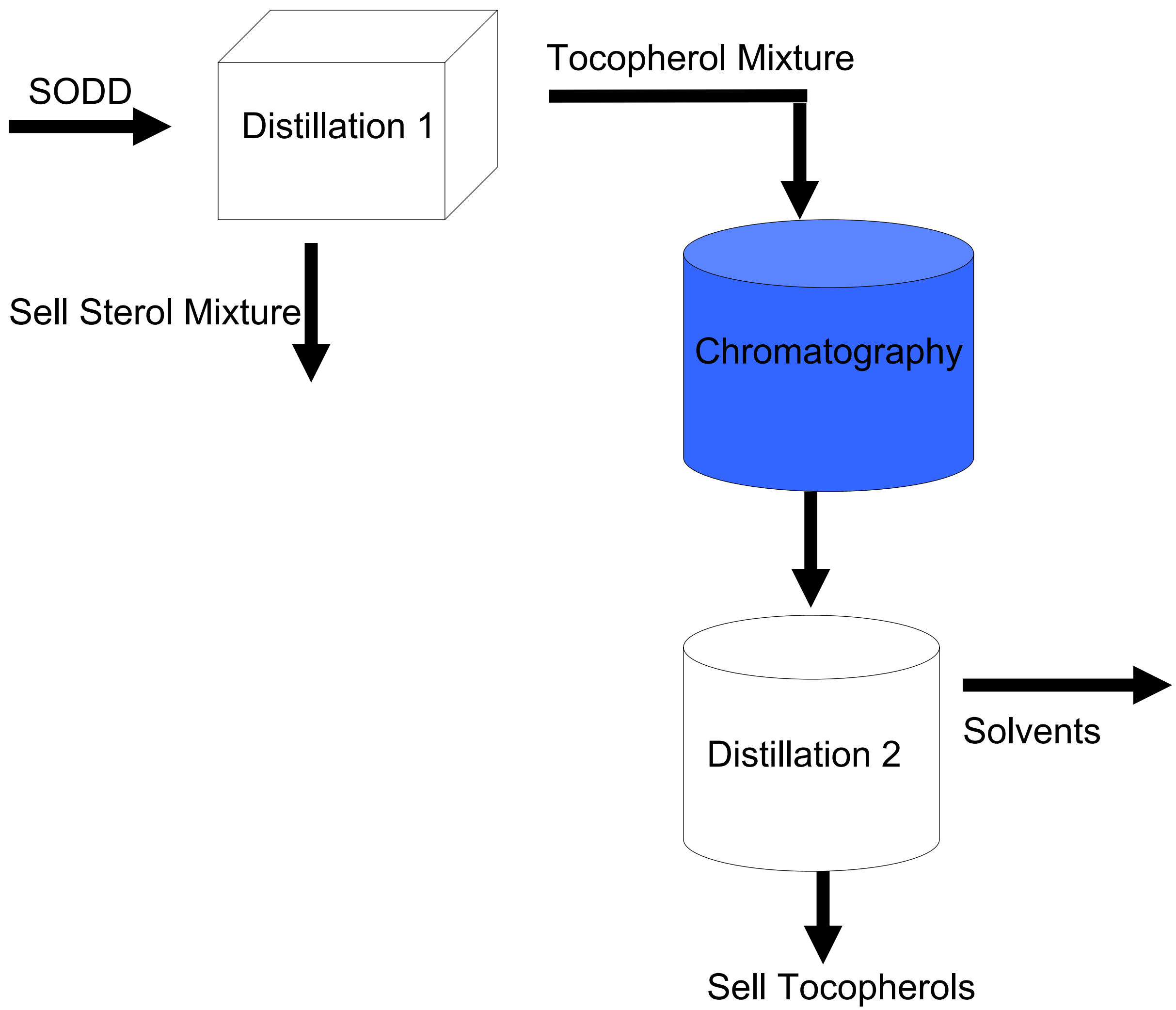
Enzymatic Distillation with Methanol



Enzymatic Distillation Products

- Steryl Esters
- Free Fatty Acids
- Mentholated Free Fatty Acids (methanol process)
- Tocopherol mixtures
  - Methanol process – 75% tocopherols
  - Non-methanol process – 65% tocopherols
- Water and water vapor

Chromatography



Chromatography: HPLC

- High Performance Liquid Chromatography
  - Tocopherol homologues exhibit different acidities in weakly dissociating solvents
  - Uses anion exchange: elutes according to polarity

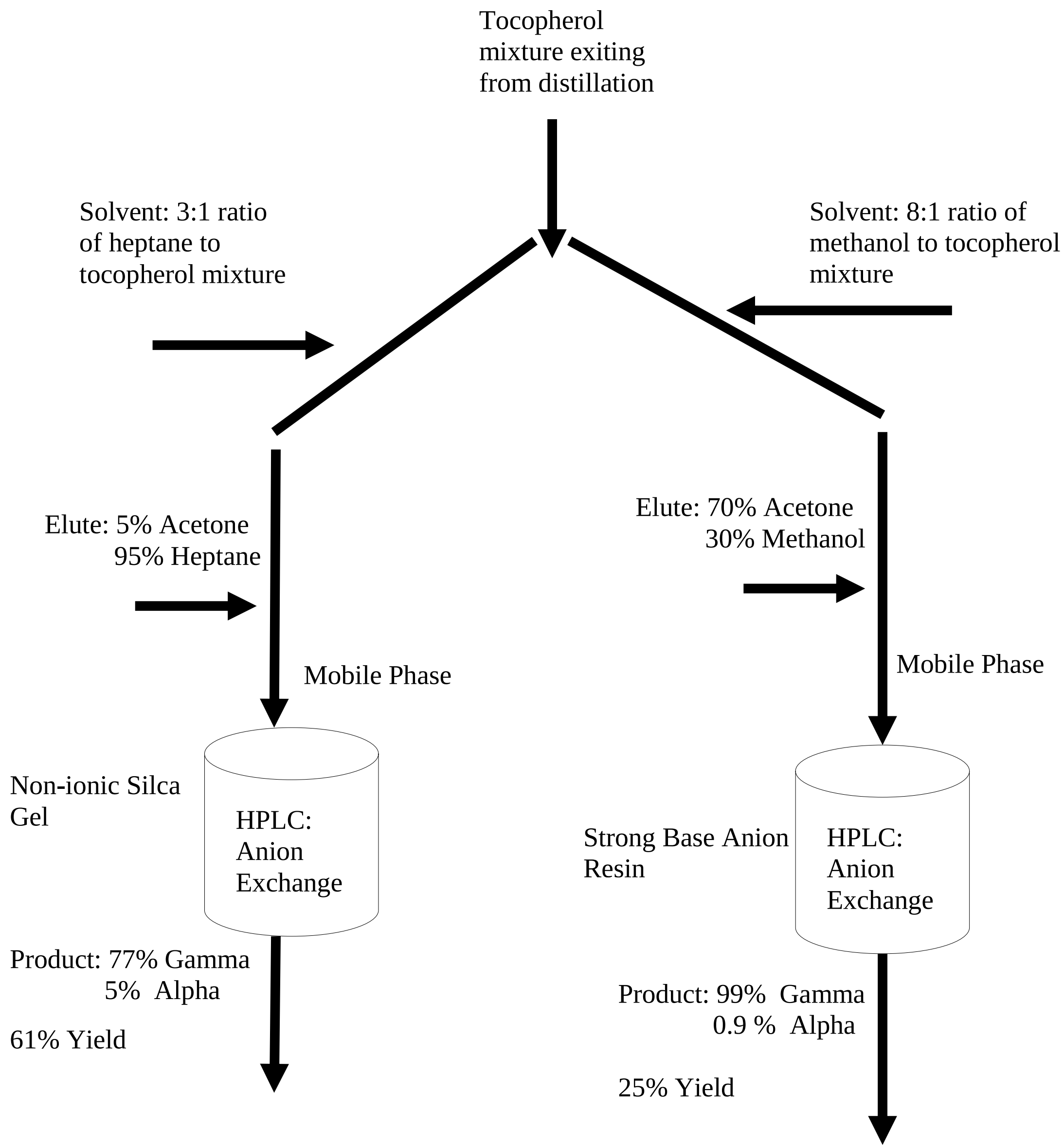
Chromatography: HPLC

- Gamma-delta-rich product
  - Non-ionic adsorbent resin
  - Load tocopherols mixed with alkane solvent (heptane) in a 3:1 ratio
  - Elute by adding small amounts of a ketone (acetone) to solvent (5% acetone & 95% heptane)
  - Ketone modifies polarity to suit desorption of gamma-tocopherol
    - ~77% gamma
    - ~17% delta
    - ~5% alpha
  - 61% yield

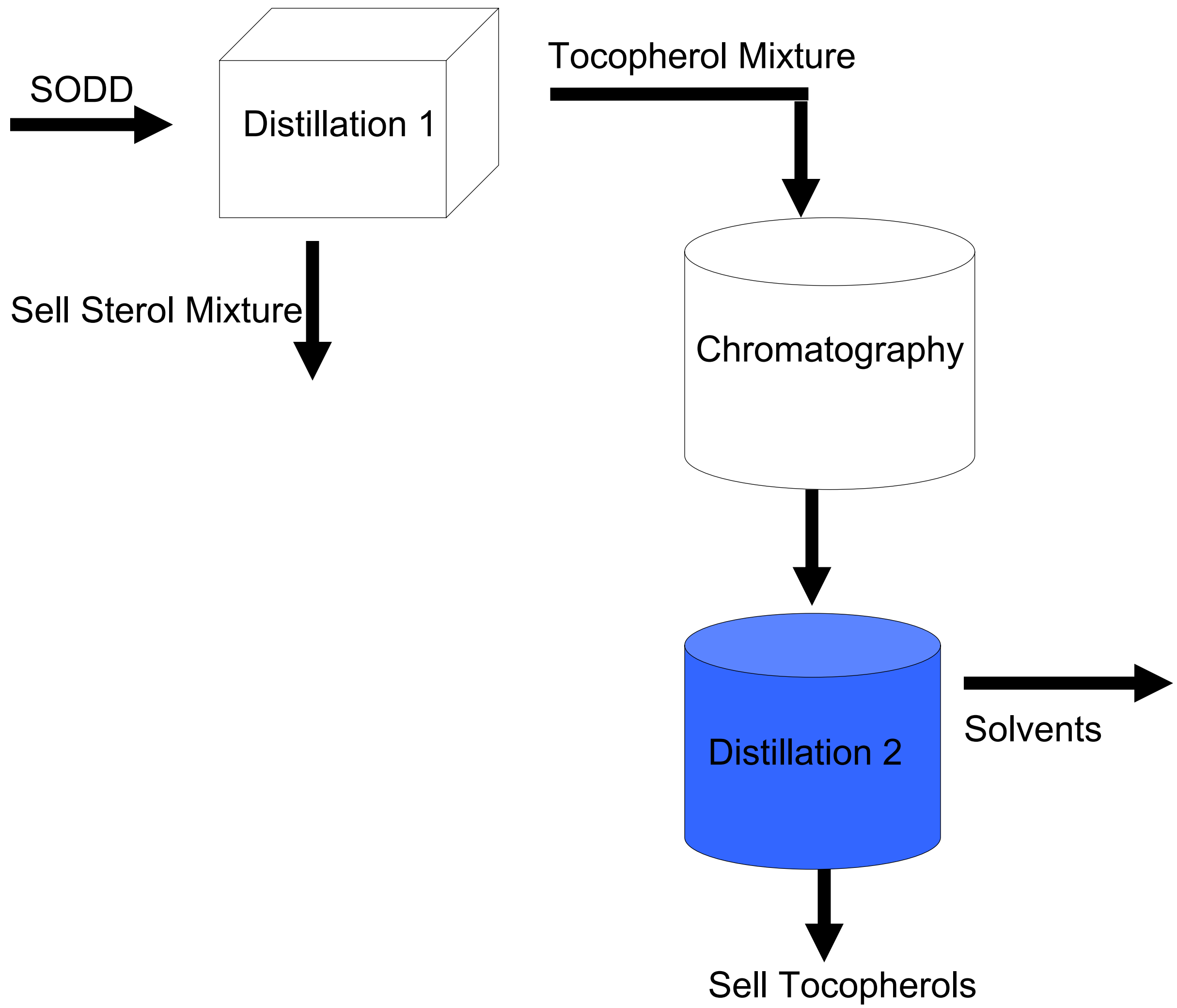
Chromatography: HPLC

- Pure gamma product
  - Strong basic anion exchange resin
    - Resins are sold in Cl form, converted to OH form using sodium hydroxide
  - Load tocopherols mixed with a polar solvent (methanol) in an 8:1 ratio
  - Elute by adding a ketone (acetone) to the solvent (70% acetone & 30% methanol)
    - 99% gamma
    - 0.9% alpha
    - 0.06% delta
  - 25% yield

Chromatography Flow Diagram



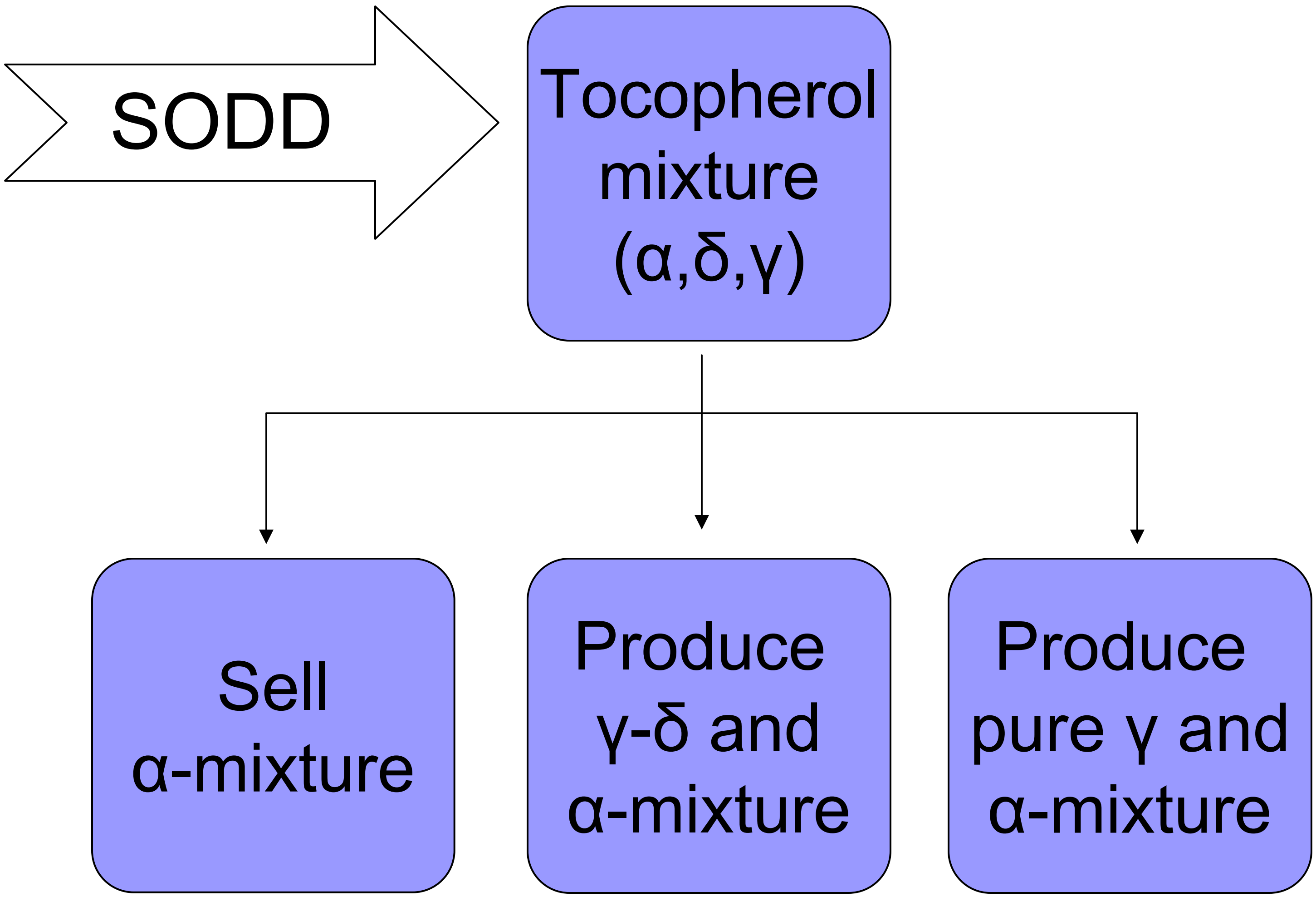
Distillation



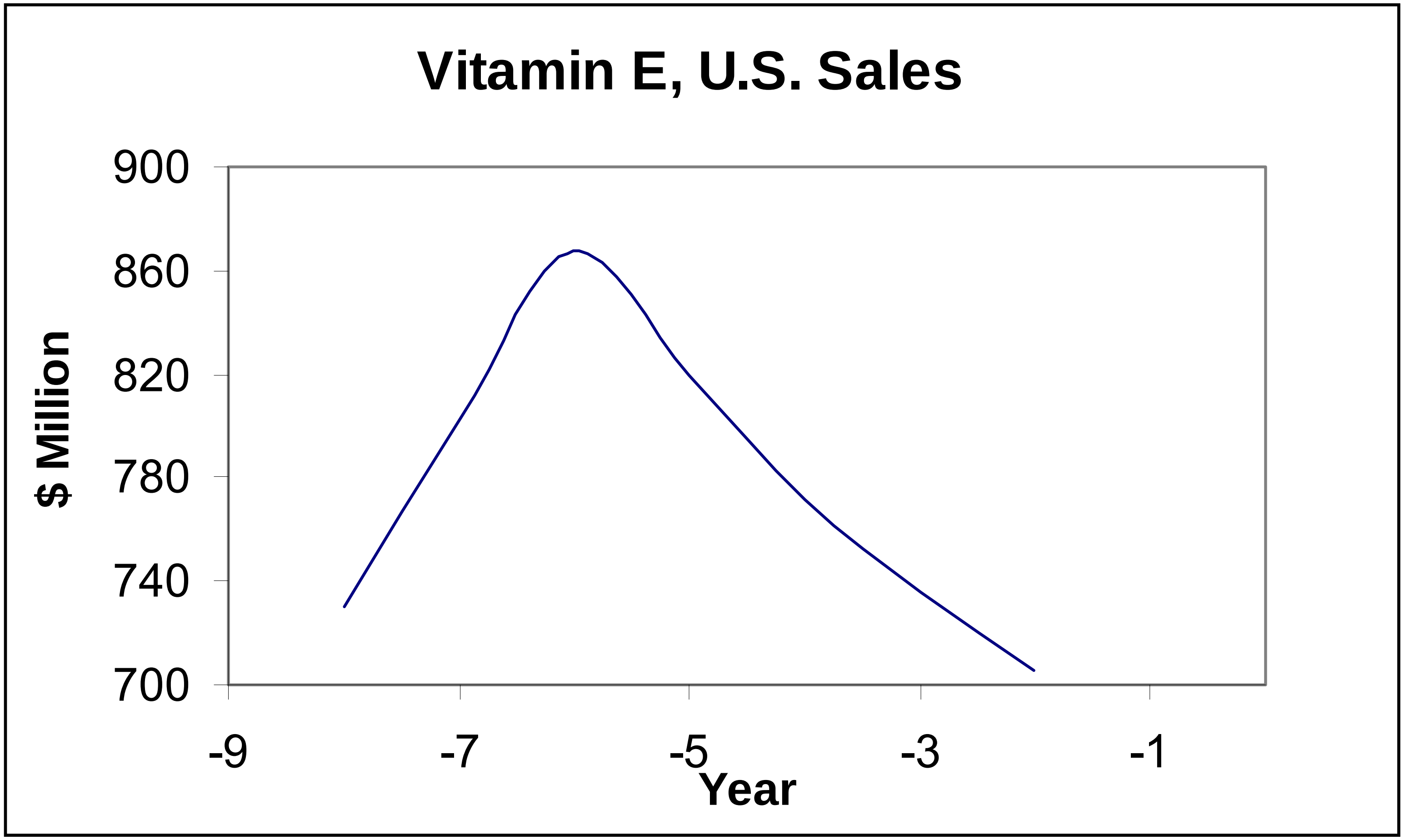
Distillation

- Evaporate the solvents leaving only tocopherols
  - Boiling points of solvents: 55-100^{o}C @ 760 mmHg
  - Boiling points of tocopherols: 200-220^{o}C @ 1 mmHg
- Solvents can be recycled

Production Options



Sales Price of α-tocopherol



Decision Factors

- Product Sale Price
  - α-rich mixture: $44/kg
  - γ-δ-rich mixture: $350/kg
  - 99% γ-tocopherol: $100,000/kg
- Current Market
  - Market for pure γ-tocopherol is relatively small
  - Market for γ-δ mixture is larger

Design Decisions

- Process all of the tocopherol mixture
  - Vary amount of γ-tocopherol produced
  - Remainder used to produce γ-δ mixture
- Byproducts of all processes are sold
  - Sterol Esters
  - Chromatography byproducts

Design Scenarios

Production Rates (kg/yr)			
Pure Gamma	Gamma-Delta	Alpha-Rich	Sterol Esters
0	5,510,588	3,523,163	90,337,500
1	5,510,585	3,523,164	90,337,500
10	5,510,563	3,523,177	90,337,500
100	5,510,344	3,523,307	90,337,500
1,000	5,508,148	3,524,603	90,337,500

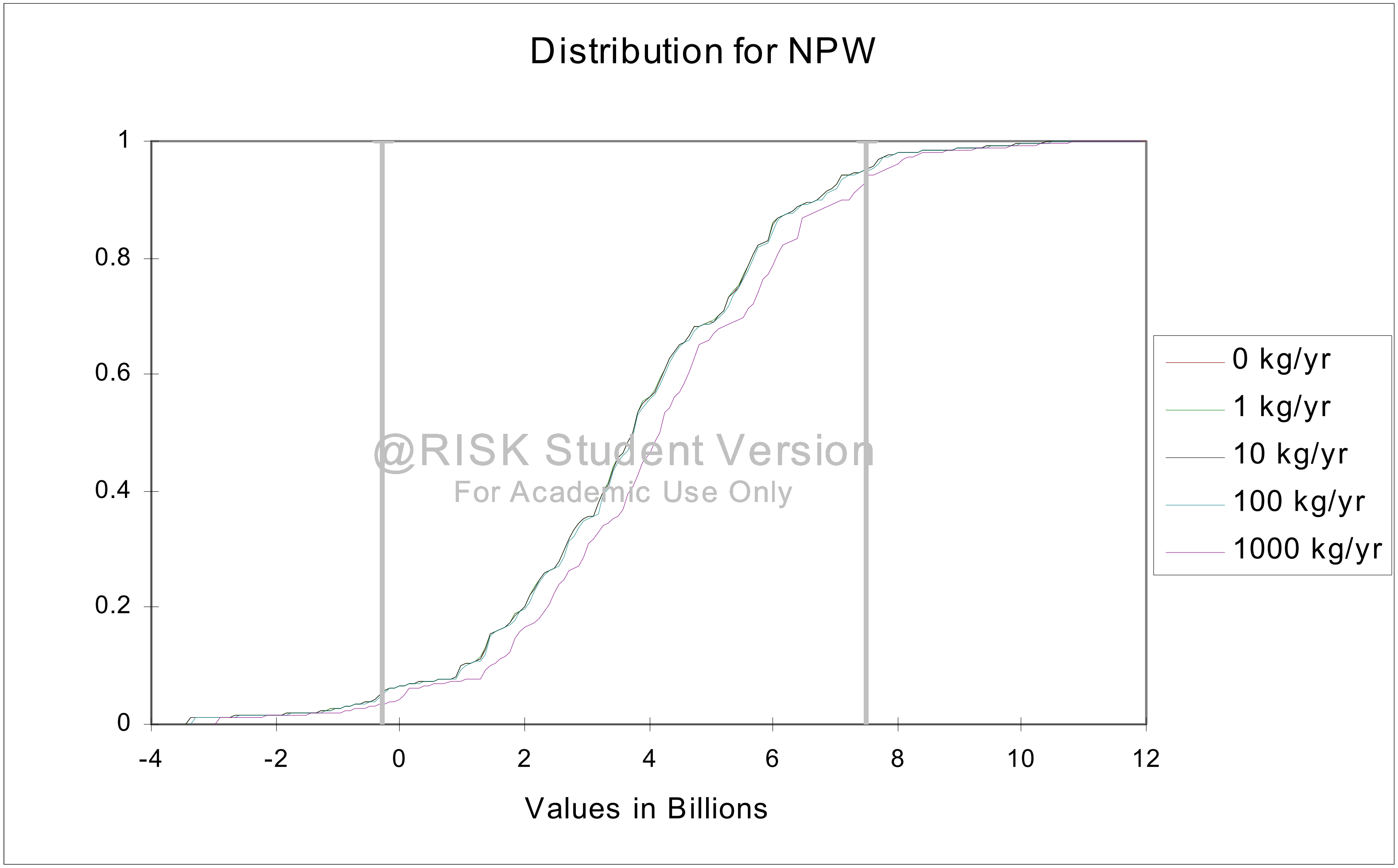
Economic Analysis

- Net Present Worth
  - NPW calculated for each scenario
  - Evaluated for 10 year period
  - Higher production rates of γ-tocopherol had higher NPW
  - Range from $3.80 to $4.21 billion

Economic Analysis

- Risk Analysis
  - 20% deviation for sale price
  - 10% deviation for equipment cost
  - Maximum, minimum and average NPW calculated for each scenario

Economic Analysis



Maximum and Minimum Profits

Pure Gamma Production kg/yr	NPW (Billions of Dollars) Minimum	Average	Maximum
0	-3.36	3.80	10.6
1	-3.37	3.80	10.6
10	-3.36	3.80	10.6
100	-3.32	3.84	10.6
1000	-2.95	4.21	11.1

Recommendations

- Produce maximum amount of γ-tocopherol
  - Increase current production to 4,000 kg/yr
  - Increase plant capacity as market for γ-tocopherol increases

FDA Regulations

Vitamins and other dietary supplements are regulated under regulations than standard over the counter and prescription drugs.

Dietary Supplement Health and Education Act of 1994 (DSHEA) states that dietary supplement manufacturer is responsible for ensuring the supplement is safe before it is marketed.

The FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market.

Post-marketing responsibilities include monitoring supplemental adverse event reporting, and product information such as labeling, claims, package inserts, and accompanying literature.

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Questions