THE COMMERCIALIZATION OF GUAYLE LATEX

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Commercialization of guayule latex

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Why do we need Alternative Rubber Crops?

• Natural rubber (NR) is a strategic raw material vital to developed countries – serious shortages are predicted by 2010, and 3 million tonnes per year by 2020 (International Rubber Study Group)

• The developed world is totally dependent upon NR imports from tropical countries – the U.S. consumes 14% of the world’s supply (China surpassed US consumption in 2004 for the first time)

• Thailand, Malaysia and Indonesia (72% of global production) formed a cartel in 2002 to control rubber production and drive-up prices – more countries have since asked to join

• NR production is dependent upon one genetically-narrow plant species, *Hevea brasiliensis* (clones) – we need biodiversity

• A natural solution to Type I latex allergy – high performance, low protein, no cross-reaction
The USDA Rubber Project – where it began (1989)

Biotechnological Production of Natural Rubber

Rubber biochemistry → Enzymes and structural proteins → Gene cloning → Transformation → New or modified rubber producer → Crop Development → Product Development

Guayule hypoallergenic latex

Growth and development
Strategic need is only a market driver in crises...

Emergency Rubber Project WWII

Tire made from guayule rubber
1991 - A commercial opportunity

Type I Tropical *Hevea* Latex Protein Allergy
Type I Tropical *Hevea* Latex Allergy Symptoms affecting up to 20 million Americans include:

- IgE antibodies
- Local urticaria
- Systemic urticaria
- Rhinitis
- Conjunctivitis
- **Asthma**
- Edema
- Bronchospasm
- Tachycardia
- **Anaphylaxis**

Ownby et al., *J. Allergy Clinical Immunology*, 1994
Type I *Hevea* latex allergy arose because of:

- Vastly increased usage of latex products in response to the AIDS epidemic (15-fold) – *Universal Precautions*
- Processing shortcuts led to products high in soluble protein
- Use of “green” latex (partially-hydrolyzed) latex
- Single-use powdered gloves aerosolized latex proteins
*Hevea* latex is a living cytoplasm containing rubber particles and is protein rich.
Hevea Latex

~50-75% hydrophilic protein in the cytosol

~10-25% hydrophobic membrane-bound protein

~10-25% hydrophobic protein bound to rubber particles

People became allergic to all protein groups
Hevea Allergy Summary:

To protect the normal folks from getting the allergy just leach the latex products properly – expensive treatments do not appear necessary.

To protect the hypersensitive use something else (natural or synthetic)
- both scientifically and litigiously trying to use Hevea latex for this subpopulation seems a “don’t even go there” proposition.
How to address Type I Latex Allergy

Circumvention?

- Use something else *i.e.* avoidance

- Synthetics

- Alternative natural rubber latex source
PROTECTIVE GLOVE MATERIALS

**Natural rubber** - best material, elasticity, tensile strength, fit, tactility and viral protection for surgical gloves (96%) and examination gloves.

**Synthetic surgical and examination glove materials**
Generally poorly elastic, with high break rates and viral penetration rates, expensive, but nonallergenic with respect to protein-mediated latex allergies

- Chloroprene (Neoprene)
- Nitrile rubber
- Styrene-butadiene (Elastyren)
- Styrene-ethylene-butadiene (Tactylon)
- Synthetic cis-polyisoprene
- Polyurethane
- EMA

ASTM standards were lowered to permit use of synthetics
Guayule Latex

Guayule had not been considered as a source of latex because it does not make its rubber in the form of a tapable latex.

However, guayule does still make its rubber in the form of rubber particles suspended in the aqueous cytosol.

Yulex® Natural Rubber Latex is made by extracting these particles while maintaining the suspension.
Parthenium argentatum Rubber Particles

Rubber particles are formed in parenchyma cells

Parthenium argentatum
Rubber Particle Preparation

Latex or homogenate in ice-cold buffer

Spin at 4000 xg for 10 min., 4°C

Rubber particles float into layer

Scoop off layer and resuspend

Spin at 3500 xg for 7 min., 4°C
Repeat as desired
Six-year Search for Commercial Partner
1991-1997

This included overcoming commercialization barriers and identifying potential partners

Greatly assisted by the USDA-ARS, especially
(1) Office of Technology Transfer
(2) Information Service
(3) Other research locations

And by USDA-CSREES
GUAYULE LATEX PRODUCTS

- Wet Mill
- Press
- Filter
- Clarify
- Separate liquid phases
- Concentrate
- Purify latex (light phase)
- Wash
- Bagasse
- Resins
- Biorefinery
- Cellulose
- Hemicellulose
- Lignin/Resin
- BIOFUELS
- BIOPRODUCTS

Aqueous extractant

Waste, Coproducts

0.2% Ammonia

LATEX

GUAYULE LATEX PRODUCTS
Latex extraction from guayule – scale-up

With the help of CSREES, U of AZ, USWCL
Guayule latex separation
Is guayule latex a safe alternative?

Guayule latex proteins do not cross react to *Hevea* latex protein antibodies in mice, rabbits or people.

Purified *Hevea* Latex

Purified *Guayule* Latex

<2% of the protein

Ber DJ, Munemasa KH, Hamilton RG, Cornish K, Howard BA, Klein DE, Settipane GA (1993) *J. Allergy and Clinical Immunology* 91: 271
Guayule latex product manufacture

Latex products made by Harry Bader at the Akron Rubber Development Laboratory, under a grant from Hercules Corporation.
Guayule latex glove and condom films provide an effective barrier to the transmission of human viruses.

Many different people and sectors helped!

USDA-ARS, WRRC, NCAUR, US WCL
USDA-ARS-NPS
USDA-ARS-OTT
USDA-ARS-IS
USDA-CSREES
DOE-NREL

Universities of Alberta, Arizona, California (Berkeley), Nevada (Reno), Utah, Colorado State, New Mexico State, Texas A & M

NIH, FDA, Cleveland Clinic, Scripps La Jolla, Johns Hopkins, Children’s Hospital, Woodland Clinic

Rubber Research Institute of India
South African ARC

Greece – Crete and Gaia Research Institute, Athens

Goodyear Tire and Rubber Company, Plantations Division.
Hercules Corporation
Yulex Corporation
Exclusive IP was essential to US business involvement and this was a solely ARS development – no CRADA umbrella

Patents:

Hypoallergenic Natural Rubber Products from *Parthenium argentatum* (Gray) and other non-*Hevea brasiliensis* species, by Katrina Cornish

U.S. Patent No. 5580942. 1996 *(the process)*

U.S. Patent No. 5717050. 1998 *(the product)*

Both patents were exclusively licensed to Yulex Corporation in 1997
So how is Yulex doing?
The guayule crop: Guayule natural rubber can substitute for *Hevea* rubber in products from tires to catheters
Guayule Cultivation Cycle

- Perennial crop
- Two years to first harvest, then annual harvests
- No pesticides
- Relatively little water
- Far more rapid response time to market demands than possible with *Hevea*
- Mechanized harvesting and processing
- Full range of NR products possible

Vice President of Agriculture (Mike Fraley) leading rapid acreage expansion
Mechanized harvesting using cotton equipment – a 21,540 lb module
Transportation
Delivery
Yulex Bioprocessing Plant (2005)
Ongoing Product Programs

Yulex ↔ Customers

Product Development

Scientific Advisory Board

Product Safety
Extractable protein
Surface antigens
Hevea Type I allergies
Potential guayule Type I allergies
Potential guayule Type IV allergies
Nitrosamines

New/Old Testing Methods
Increased test sensitivity
Guayule-specific immunochemical
Surface antigen
Animal trials
Yulex staff monitoring program
Live-subject skin
## Protein Content in Latex
(Modified Lowry, ASTM D5712-05)

<table>
<thead>
<tr>
<th>Sample</th>
<th>Protein (µg/g dry rubber)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Hevea</em>, sample 1</td>
<td>9,636</td>
</tr>
<tr>
<td><em>Hevea</em>, sample 2</td>
<td>9,196</td>
</tr>
<tr>
<td><em>Yulex</em>, sample 1</td>
<td>106</td>
</tr>
</tbody>
</table>

Protein assays by Wenshuang Xie and Colleen McMahan, USDA-ARS, Albany, CA
Yulex® exceeds the surgical glove standard, ASTM D-3577
- and beats NR for form, fit and feel
Connect 2005 Most Innovative New Product
Life Sciences – Medical Devices and Diagnostics
Yulex Corporation
for
Yulex™

[Image]
Yulex Distribution Agreement
2005 - 2010

Centrotrade Rubber USA, Inc.
Yulex & Centrotrade Partnership

On May 10, 2005 Yulex signed an exclusive five-year distribution agreement with leading international natural rubber supplier and distributor Centrotrade Rubber USA and Centrotrade Deutschland GmbH.

Centrotrade’s U.S. and European operations will distribute Yulex® Natural Rubber Latex worldwide to medical device manufacturers of surgical gloves, condoms, catheters and other latex-based medical products that are seeking an alternative to lower performing synthetic latex materials.
yulex® (guayule latex) first sales in 2005
Yulex has entered Revenue Phase

First Royalty Payment

(credited against licensing fees)
Regulatory Affairs

ASTM

FDA

ISO
Yulex® - Guayule latex

Modifications were made to the standard to accommodate the commercial introduction of guayule latex
- Introduction of a new Category 4.
The New Latex Category (not “Type”)

- **Category 4** — Centrifuged, or centrifuged and creamed, guayule latex, or other natural rubber latex, containing less than 200 micrograms total protein per gram dry weight of latex, with ammonia or other hydroxide, with other necessary preservatives and stabilizers.

- No detectable protein by D-6499, antigenic *Hevea* protein.

- Other changes to text in the body of the standard are included.

- Also, relevant changes to D1418 (nomenclature) and D1566 (standard terminology).
  
  - NR to remain term for Natural Rubber from *Hevea brasiliensis* NRG to be added to mean Natural Rubber from guayule (*Parthenium argentatum*)
## Dipped Medical Products

<table>
<thead>
<tr>
<th>COMMODITY</th>
<th>DIFFERENTIATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exam glove</td>
<td>Surgical glove</td>
</tr>
<tr>
<td>6 g</td>
<td>12 g</td>
</tr>
<tr>
<td>$0.035</td>
<td>$0.50</td>
</tr>
<tr>
<td>$2.65/lb</td>
<td>$19/lb</td>
</tr>
<tr>
<td>100-150,000</td>
<td>15,000</td>
</tr>
<tr>
<td>tons/yr US</td>
<td>tons/yr US</td>
</tr>
<tr>
<td>YULEX</td>
<td></td>
</tr>
<tr>
<td>Condom</td>
<td>Catheter</td>
</tr>
<tr>
<td>1-2 g</td>
<td>&lt; 0.5 g</td>
</tr>
<tr>
<td>$1-2</td>
<td>$8-10</td>
</tr>
<tr>
<td>$450/lb</td>
<td>&gt;$8,000/lb</td>
</tr>
<tr>
<td>7,000</td>
<td>&lt; 500</td>
</tr>
<tr>
<td>tons/yr US</td>
<td>tons/yr US</td>
</tr>
</tbody>
</table>
## Annual guayule acreage needed for different markets (at one ton latex per acre per year)

<table>
<thead>
<tr>
<th>Market</th>
<th>2005</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical and high-end consumer products</td>
<td>350,000</td>
<td>2,000,000</td>
</tr>
<tr>
<td>All NR latex</td>
<td>1,000,000</td>
<td>6,000,000</td>
</tr>
<tr>
<td>All NR products</td>
<td>8,000,000</td>
<td>12,000,000</td>
</tr>
<tr>
<td>All rubber</td>
<td>20,000,000</td>
<td>30,000,000</td>
</tr>
</tbody>
</table>

Demand is rapidly increasing as China and India industrialize – especially automotive and medical demands

*(International Rubber Study Group, 2005)*
Guayule growing region (ERP) - 124,540,000 acres
(probably more as climatic requirements may have shifted)

<table>
<thead>
<tr>
<th>State</th>
<th>Existing cropland</th>
<th>Guayule land</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA</td>
<td>10,628,000</td>
<td>47,000,000</td>
</tr>
<tr>
<td>AZ</td>
<td>1,254,000</td>
<td>29,000,000</td>
</tr>
<tr>
<td>NM</td>
<td>2,427,000</td>
<td>9,000,000</td>
</tr>
<tr>
<td>TX</td>
<td>40,040,000</td>
<td>39,540,000</td>
</tr>
</tbody>
</table>
Total Utilization of Guayule

Product .......... latex and rubber
   +
Coproduct ........ resin
   +
Byproduct ........ bagasse
Latex extraction by wet-milling guayule shrub also generates **bagasse** – a high energy “zero-cost” feed-stock of 9,720 Btu/lb and 15 lb/cu ft
Guayule can respond to market demands much more quickly than *Hevea*. If this isn’t met by guayule what *will* meet it?

**Projected NR growth**

- **3 million tonne/year**
- **NR shortfall**

### Guayule Production

- **Acreage**
  - $3 \times 10^6$
  - $10^6$
  - $10^5$
  - $10^4$
  - $10^3$

### Hevea Production

- **Acreage?**

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**Consumption**

- **Year**
  - 2005
  - 2010
  - 2015
  - 2020

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**Additional *Hevea* production acreage?**
Tropical *Hevea* protein-free, high quality Yulex® latex medical products can be manufactured, safe for use by people with Type I latex allergy.

Many other products, including tires, can also be made from guayule rubber.

Domestic rubber production provides non-subsidized agriculture, rural development, and raw materials security.