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POTENTIAL IMPACTS OF SYNTHETIC BIOLOGY ON LIVELIHOODS AND BIODIVERSITY: EIGHT CASE STUDIES ON COMMODITY REPLACEMENT
A SUBMISSION TO THE CONVENTION ON BIOLOGICAL DIVERSITY FROM ETC GROUP
JULY 2013

ISSUE: Due to problems with scale-up, some synthetic biology companies are shifting focus away from biofuels to high-value / low-volume products – especially compounds found in plants (e.g., essential oils, flavours, fragrances, colourants and pharmaceuticals) – which are traditionally cultivated by farming communities in the global South. In this submission, ETC Group presents a set of case studies outlining some specific ways that livelihoods from traditional agricultural production may be adversely affected as synthetic biology-based substitutes for plant-based commodities enter the market over the next few years. The engineering and patenting of metabolic pathways that could apply to a wide range of natural products is also a concern. Synthetic biology's potential impacts on biodiversity and the environment were detailed in the *International Civil Society Working Group on Synthetic Biology's* submission to SBSTTA in October 2011.[1]

METABOLIC PATHWAYS: Synthetic biology companies are engineering 'metabolic pathways' in microbes to act as 'biological factories' that produce desired compounds. According to current scientific understanding, as few as eight key pathways may be responsible for almost all of the 200,000 known natural plant compounds. Synthetic biologists are rapidly decoding, re-constructing and patenting these pathways. In the words of one synthetic biologist: "We ought to be able to make any compound produced by a plant inside a microbe."[2]

IMPACT: If commercially viable, synthetic biology's patented organisms have the potential to de-stabilize natural product markets, disrupt trade and eliminate jobs and livelihoods. New, bio-based substitutes deemed 'equivalent' to natural products could have far-reaching impacts on agricultural economies, especially for those producers without the information or resources to respond to sudden shifts in natural resource supply chains. Earlier efforts to use new technologies (e.g., plant cell culture and transgenics) to manufacture high-value natural products were largely unsuccessful. It is not known how well compounds produced through synthetic biology will compete in the marketplace with botanically-derived products; likewise, knowing precisely which products, which small farmers and whose economies will be most affected and how quickly is difficult, but some of the earliest impacts may be seen for growers of *Artemesia annua*, Coconut, Vanilla, Vetiver, Star Anise and Saffron, affecting livelihoods and associated traditional knowledge.

PLAYERS: The global market for plant-derived compounds has been estimated at $65 billion. The market for flavour and fragrance compounds alone is over $20 billion p/a (per annum). The natural fatty acids market alone was valued at $7.2 billion in 2011.[3] It is conservatively estimated that at least 50% of pharmaceutical compounds on the market come from plants, animals and microorganisms. The world's largest corporations are beginning to turn to synthetic biology for supplies of cheaper, more easily accessible high-value compounds traditionally sourced from plants.

PRODUCTS AFFECTED: Some biosynthesized compounds have already come to market and many others are in the pipeline. Among the near-term targets:

- Isoprene rubber: Could affect supply chain for both natural and synthetic rubber. The livelihoods of 20 million small holder families, mostly in Asia, depend on natural rubber. (The market for isoprene is $2 billion p/a).
- Coconut Oil: Natural fatty acids derived from coconut and palm kernel oil are a staple of the multibillion-dollar oleochemcial industry, supporting livelihoods of over 25 million people in the Philippines.
- Artemisia: Currently sourced from over 100,000 Asian and African farmers (~$90 million market p/a).
- Saffron: Iran produces an estimated 90% of the world's saffron, with export markets in over 40 countries ($660 million market p/a).
- Vanillin: An estimated 200,000 people worldwide are involved in the production of cured vanilla beans ($240 million market p/a).
- Vetiver Oil: In Haiti alone, 60,000 people depend on vetiver production ($10 million market p/a).

Case Study 1: Coconut Oil, Palm Kernel Oil and Babassu Oil
Case Study 2: *Artemesia annua* (sweet wormwood)
Case Study 3: Vanilla
Case Study 4: Rubber
Case Study 5: Star Anise (source of Shikimic Acid)
Case Study 6: Squalene
Case Study 7: Saffron
Case Study 8: Vetiver

Case Study 1: Coconut Oil, Palm Kernel Oil and Babassu Oil

PRODUCT: Industrially useful natural fatty acids known as 'lauric oils' – capric acid, lauric acid, myristic acid, palmitic acid – are currently derived from coconut oil, palm kernel oil and also babassu seed. So too are a suite of 'fatty alcohol' ingredients such as lauryl alcohol and myristyl alcohol. These are the key ingredients for common oleochemical products such as detergents, soaps and cosmetics.

Status: Three California-based companies are now producing fatty acids and fatty alcohols using synthetic biology. Solazyme has created a range of engineered algae strains whose oils are 'genetically tailored' to express high quantities of lauric acid, capric acid or myristic acid. Solazyme is also developing strains to produce high quantities of palmitic acid and oleic acid.[4] Codexis and LS9, Inc. have developed engineered microbes that produce fatty alcohols for detergents.[5]

AFFECTED COUNTRIES/REGIONS: 58% of global oleochemicals production is in Asia,[6] as is most production of coconut and palm kernel nuts. Babassu palm is grown in Brazil. Countries most affected will be the Philippines, Malaysia, Indonesia and India. Vietnam, Mexico, Nigeria, Thailand and Papua New Guinea also have sizable coconut and palm kernel production. In the Philippines, approximately one quarter of the population depends on coconut production – impacting as many as 25 million people.[7]

MARKET: The global market for natural fatty acids (primarily derived from coconut, palm and palm kernel oil) was valued at $7.2 billion in 2011 and is expected to reach $13 billion by 2017.[8] The market for lauric acid alone was estimated at about $1.4 billion in 2008.[9] The market for myristic acid is estimated at about $600 million.[10] In 2011 the market for palm kernel oil was estimated at $9.3 billion and coconut oil at $5.3 billion.[11] This is just part of a larger $206 billion plant oils market that the SynBio companies are eyeing up.[12] Detergent alcohols in particular are a $6 billion market worldwide, expected to reach $8 billion in a decade.[13]

COMMERCIALIZATION: Solazyme already has a production facility in the USA and has partnered with a number of key players to begin commercialization of its lauric oils. These partners include chemical giant Mitsui, household products transnational Unilever, grain traders Archer Daniels Midland and Bunge, as well as chemical firm AkzoNobel. Solazyme may have the technical capacity to capture up to 40% of global myristic acid production in the coming years with a new 100,000 MT/annum (metric tonnes per year) plant under construction in Brazil in collaboration with Bunge. Codexis is already selling small quantities of its CodeXol fatty alcohols and is hoping to have a 60,000 MT/annum commercial production plant running by 2015. In 2012, LS9 produced 135,000 litres of synbiotech-derived fatty alcohols and is now scaling to supply customers including Procter & Gamble.

BACKGROUND:

NATURAL OLEOCHEMICALS

Oleochemicals are those chemical products produced from oils, a large part of which is the 'natural oleochemical' market that refines vegetable oils into detergents, soaps, shampoos and other household goods. An important range of starter compounds for oleochemicals is the natural fatty acids known as 'lauric oils.' For these, coconut oil and palm kernel oil (different from palm oil, which comes from the pulp of the palm fruit) are the major raw material source for production – occasionally supplemented by small amounts of babassu oil, derived from the Brazilian babassu palm.

Coconut oil, produced from crushing the copra (flesh of matured coconut) of harvested coconuts is particularly rich in lauric oils and supplies much of the oleochemical market. Coconut oil consists of about 48% lauric acid, 16% myristic acid and 9% palmitic acid.[14] It is also a good source of capric or caprylic acid. Coconut and palm kernel oil are also the major industrial source for C12-C14 fatty alcohols (referring to the length of the chain of carbon molecules) such as lauryl alcohol and myristyl alcohol; these are used primarily for detergents. The largest users of natural coconut and palm kernel derived detergent alcohols are consumer products companies such as US-based Procter & Gamble, Netherlands-based Unilever and Germany-based Henkel.

Coconut oil production in the Philippines and beyond

Known in the Philippines as 'The Tree of Life,' the coconut tree is celebrated for its many uses from food and clothing to building materials. However, it is the copra (flesh of matured coconut) crushed into oil that is primarily sold as an international commodity both for food and more commonly for detergents, soaps, etc. Global production of coconut oil is estimated at 3,735,000 MT for 2013[15] with over 90% of that grown in Asia and the South Pacific. On average, 1000 coconuts yield 110 kg of oil.[16]

The Philippines is the world's leading producer of coconuts accounting for 46.2% of global coconut oil production and 59% of the world's coconut exports.[17] More than one quarter of the country's population is dependent upon coconut growing, transport, processing and trading for its livelihood. There are around 3.5 million coconut farmers and as many as 25 million people are directly or indirectly dependent on the coconut industry. Coconut farming is distributed across the entire country: of 79 provinces, 68 are coconut areas and coconut is grown on 26% of Philippine farmland (~324 million trees[18]). The coconut farms of the Philippines are relatively small – with an average area of 2.4 hectares and about two-thirds of the country's 1.4 million coconut farms are owner-operated. Coconut cultivation in the Philippines generally does not require chemical inputs and other crops are often grown together under the tall trees' shade. Despite their contribution to the country's annual GDP, poverty incidence among Filipino coconut farmers is about 62%, due to stagnation of copra prices since 2010 and low wages for coconut workers. Other major coconut producing countries include Indonesia (26.1% of world coconut oil production), India (12%) Vietnam (4.1%) and Mexico (3.9%).

Top 10 Coconut Oil Producing Countries / 2013 Estimate[19]

Country	Production 2013 (1000 MT)	Market Share (% of world production)
1. Philippines	1,725	46.2%
2. Indonesia	974	26.1%
3. India	447	12%
4. Viet Nam	153	4.1%
5. Mexico	145	3.9%
6. Papua New Guinea	63	1.7%
7. Thailand	46	1.2%
8. Sri Lanka	43	1.1%
9. Malaysia	35	0.9%
10. Mozambique	30	0.8%
Total top 10	***3,661***	***98%***

Estimated world coconut oil production for 2013: 3,735,000 MT

Palm kernal oil production

When the fruit of oil Palm trees are processed into palm oil, the kernel of the palm nut is kept aside and crushed separately into 'palm kernel oil' (PKO), which is high in lauric oils. As such, the palm kernel oil market is closely tied to the palm oil market. Currently 86% of the world's supply of palm oil[20] comes from large industrial plantations in Indonesia (7.65 million hectares)[21] and Malaysia (4.917 million hectares);[22] consequently, those two countries dominate palm kernel oil production. Much smaller amounts are grown in Nigeria, Thailand, Colombia and Papua New Guinea.

Replacing palm kernal oil with synbiotech substitutes

The past ten years have seen a significant increase in palm oil plantings because of the growth of support for biofuels, through direct and indirect subsidies. This has raised much concern about the accompanying destruction of forests, particularly ape habitats, release of carbon from cleared peatlands and the impact on migrant workers and forest communities. According to Friends of the Earth, some estimates show an area the size of Greece being cleared every year for palm oil plantations[23] and investigations by the CSO Grain uncovered land grabs (millions of hectares) for oil palm plantations across Asia, Africa and South America.[24] Because of the environmentally destructive profile of palm oil (including palm kernel oil), some of the corporate investments into producing lauric oils through synthetic biology have been promoted as environmentally beneficial. In 2010, Unilever, the world's largest user of palm oil, announced a multimillion dollar investment in Solazyme, signalling that the move was related to switching away from palm oil: "To Wash Hands of Palm Oil Unilever Embraces Algae: Consumer-Goods Maker Invests in California's Solazyme to Avoid Environmental Concerns," announced the Wall Street Journal.[25] While moving away from destructive palm oil is to be welcomed, any supposed environmental gain needs to be weighed against the following considerations:

1) Switching away from palm kernel oil to synthetic biology-derived fatty acids doesn't directly slow the market for palm oil. Indeed, given the ongoing interest in palm oil for biofuels and the highly concentrated nature of the market, the price of palm kernel oil may prove quite elastic. If so, it may be that the coconut oil market would suffer more.
2) The environmental gains of switching from monoculture palm may be offset by the increased use of sugars as feedstocks for the synthetic organisms producing the oil. Sugar production, like palm production, is associated with land clearance for intensive monocultures, large scale releases of greenhouse gases, significant agrochemical use and poor working conditions for sugar workers.[26] Sugarcane expansion in Brazil has been implicated in pushing the agricultural frontier deeper into the Amazon, begging the question of whether Unilever's investment in Solazyme ultimately implies only a change of scenery: forest destruction in Indonesia to forest destruction in Brazil.

Top 10 Palm Kernel Oil Producing Countries / 2013 estimate[27]

Country	**Production 2013 (1,000 MT)**	**Market Share (% of world production)**
1. Indonesia	3,588	52.8%
2. Malaysia	2,180	32.1%
3. Nigeria	305	4.4%
4. Thailand	190	2.8%
5. Columbia	100	1.4%
6. Papua New Guinea	60	0.9%
7. Ecuador	51	0.7%
8. Brazil	43	0.6%
9. Côte D'Ivoire	39	0.6%
10. Cameroon	32	0.5%
Total top 10	***6,588***	***96.8%***

Estimated world palm kernel oil production in 2013: 6,796,000 MT

BABASSU OIL PRODUCTION

Babassu oil is extracted from the kernels of nuts of the Babassu palm tree, which originates in the Amazon and is grown widely in the Brazilian states of Maranhão and Piauí.[28] The oil's properties are similar to coconut oil's and contains 50% lauric acid and 20% myristic acid.[29] Babassu palm is an aggressive weedy species able to flourish in different ecosystems and can form forest-like expanses of millions of hectares that look like plantations but are in fact naturally seeded. Removing Babassu kernels is a difficult task, usually carried out by women known as 'Babassu crackers' who sell the kernels to traders who in turn sell to industrial oleochemical processors.[30] According to *Biofuels Digest*, more than 400,000 women and their families traditionally process the palm for oil, soaps, flour and animal feed.[31] Babassu oil is generally not traded internationally; most of the oil produced is reserved for Brazilian cosmetics.

CURRENT STATE OF SYNTHETIC BIOLOGY ALTERNATIVES TO FATTY ACIDS AND ALCOHOLS

SOLAZYME: MAKING FATTY ACITDS IN ALGAE

Solazyme, Inc. of California, USA is a publicly-traded synthetic biology company whose business plan is to engineer algae in order to change the chemical profile of algal oil. Unlike most algae companies, Solazyme works with heterotrophic algae – strains that feed on sugar instead of sunlight and so can be grown in closed vats in an industrial facility rather than requiring shallow ponds.[32] While Solazyme was initially founded as a biofuels business, like many synthetic biology companies, it has shifted its business plan to produce natural compounds, flavours and food ingredients. Solazyme has engineered its algae to produce a range of "genetically tailored oils" which each express high levels of a particular fatty acid. The company claims it has developed algal strains that express up to 80% of their oil as lauric oils (cf. palm kernel oil's 55% lauric oils and coconut oil's 68%). Solazyme claims that an oleochemical facility utilizing its tailored oil rather than standard palm kernel oil could increase its output of the desired fatty acid components such as capric, lauric and myristic acid by more than 30%.[33]

In particular, Solazyme trumpets its ability to compete against natural coconut oil as a better source of myristic acid. According to Solazyme, coconut oil can sometimes reach concentrations of up to 15% myristic acid. By contrast, Solazyme's engineered algal oil currently boasts 60% concentration of myristic acid, almost four times more than in any widely available oil today.[34] As market analyst Kevin Quon points out:

> "This results in more than a 150% increase over that which is found in coconut oil. Through rough calculations, it would appear that in order to get 1 MT of myristic acid, it would either take 2.5 MT of tailored algal oil yielding 40% or it would take 6.67 MT of coconut oil yielding 15%. If we were looking just for myristic acid, it would therefore take 63% less oil in order to get it from Solazyme's tailored algal oil."[35]

Solazyme says their lauric oils will become commercially available toward the end of 2013.

How Solazyme's algal myristic acid will fare against coconut-derived myristic acid in the marketplace depends in part on coconut oil prices and sugarcane prices (sugar is the feedstock for the engineered algae). Solazyme is keen to point out that while most coconut is sourced from the Philippines and takes several years to grow, sugarcane can be grown quickly in many locations, as well as in coconut producing countries, including the Philippines. In time, they hope to also be able to feed cheaper cellulosic sugars to their algae (e.g., grasses or wood pulp). As analyst Kevin Quon puts it: "…oil supply can be unlocked from a regional land restriction. Instead, the range is increased to include anywhere in which more-readily abundant sugarcane is grown. Once the ideal infrastructure is developed, it can even be produced at any location where cellulosic biomass is found."[36]

Solazyme has told investors that it would be able to manufacture oils at a cost below $1000 per MT if produced in a built-for-purpose commercial plant,[37] although they currently plan to sell their myristic acid for around $3000/MT.[38] Today myristic acid sells for more than $4200/MT.[39] Solazyme is moving ahead with building at least two large commercial plants: a facility in Illinois, USA producing approximately 500,000 gallons of oil/annum and a facility in Brazil able to ferment over 28 million gallons/annum. At 60% concentration, the Brazilian facility alone would theoretically be able to meet about 40% of global myristic acid market.[40]

Solazyme has signed a number of joint ventures and agreements with some of the world's largest sugar, chemical and oleochemical players, including Bunge, Archer Daniels Midland, Dow, Akzonobel and Mitsui. The $20 million dollar Mitsui deal is especially important to compete against coconut and palm kernel oil since it focuses specifically on myristic acid as well as additional oils that Solazyme is developing for the oleochemical and other industrial sectors.[41] Mitsui has been producing oleochemicals for 20 years through its subsidiary Palm Oleo and is a significant investor in Kuala Lumpur Kepong Berhad (KLK), which owns palm oil and rubber plantations and is the world's largest oleochemical company. On signing the multi-year deal, Mitsui stated that it "looks forward to strengthening its position in the oleochemicals industry through the successful development and commercialization of these novel products."[42] Solazyme also has an agreement with Unilever, one of the world's largest end-users of oleochemical ingredients for production of consumer soaps and detergents. In this way, Solazyme appears to have secured partners for each stage of production from initial sugar to final consumer product.

CODEXIS AND LS9: MAKING FATTY ALCOHOLS IN MICROBES

Codexis is a synthetic biology company using computer-based techniques to artificially 'evolve' and re-engineer enzymes and microorganisms.[43] LS9, founded by leading synbio researchers Jay Keasling and George Church, engineers microbes – primarily *E. coli* – to produce industrial compounds.[44] Both are based in California and both were initially focused on biofuels but are now moving into other markets. Both companies have developed the technology to produce fatty alcohols. According to Codexis, so-called "detergent alcohols" for use in household products represent a $6 billion market worldwide, expected to reach $8 billion in a decade.[45]

While there is a range of different fatty alcohols, identified by the 'chain length' of carbon molecules, the popular C12-14 alcohols, known as lauric alcohols, are usually derived from coconut oil and palm kernel oil. Codexis has developed a microorganism that produces a new lauric alcohol dubbed CodeXol and, in collaboration with Chemtex, a subsidiary of Italian chemical company Gruppo M&G, is scaling up production of CodeXol; they aim to reach full-scale commercialisation by 2015.[46] In June 2013, Codexis and Gruppo M&G announced that they had successfully scaled up a process that would transform cellulosic biomass into lauric alcohols.[47] In theory, this would allow Codexis to produce a competitor to coconut and palm kernel oil-derived detergents using agricultural and forest waste residues as feedstock.

LS9 has agreements with Procter & Gamble[48] and a facility in Florida, USA that produces 135,000 liters of fatty alcohols at a time and has reportedly been producing batches for commercial partners. LS9 plans three 750,000-liter fermenters in Brazil, which could produce 10,000-25,000 MT/year of fatty alcohols while a large-scale commercial facility is expected (in 2017-2018) to have a capacity of 200,000 MT/year.[49]

Case Study 2: *Artemesia annua* (sweet wormwood)

PRODUCT: Artemisinin, the key ingredient in the world's most effective anti-malarial drug, is extracted from *Artemisia annua,* commonly known as sweet wormwood. Today the pharmaceutical industry sources natural artemisinin from thousands of small farmers in Asia and Africa.
STATUS: Synthetic biologists at California-based Amyris, Inc. have inserted an engineered metabolic pathway in microbes to produce artemisinic acid, a precursor to artemisinin production.
AFFECTED COUNTRY/REGION: At the present time 80% of the *Artemisia*/artemisinin is produced in China, 15% in Vietnam and the reminder in Kenya, Tanzania, Uganda, Madagascar and a small amount in India. Trials of *Artemisia* are being grown in Zimbabwe, South Africa and Nigeria.[50] Those in the artemesinin trade estimate that approximately 10,000 farmers worldwide grow *Artemesia annua*.[51]
MARKET: In 2011, the average price of artemisinin was around $550/kg. The global market for the production and extraction of *Artemisia*/artemisinin was between $82.5 million and $93.5 million.[52]
COMMERCIALIZATION: Already commercial. Pharmaceutical giant Sanofi-aventis has now scaled up production of artemisinic acid in commercial fermentation tanks and, in April 2013, announced production of enough 'semi-synthetic' artemisinin to supply one third of the global market. In 2014, Sanofi claims it will produce enough to meet half of the market demand. While Sanofi initially claimed it was only interested in using synthetic artemisinin to fill in supply shortfalls and quell price volatility, the synthetic biologist most closely associated with the project, Jay Keasling, has since gone on-record saying that the aim is to take over 100% of the artemisinin supply with semi-synthetic artemisinin.[53]

BACKGROUND: The key ingredient in the world's most effective drug treatment for malaria – artemisinin – is extracted from an ancient medicinal plant, *Artemisia annua,* commonly known as sweet wormwood. According to the World Health Organization (WHO), artemisinin-based combination therapies (ACTs) provide the most effective treatment against malaria. Today, the pharmaceutical industry sources natural artemisinin from around 100,000 small farmers who grow *Artemisia annua,* primarily in China, Vietnam, Kenya, Tanzania, Uganda, Madagascar and India. The average crop area per farmer in China and Africa is around 0.2 hectares.[54]

Although the global supply of natural artemisinin has experienced boom and bust cycles and some say ACTs are priced out of reach for poor people. Because of the increased demand for artemisinin and the reinvigoration of anti-malaria campaigns, a supply chain initiative called A2S2 (Assured Artemisinin Supply System) has been underway for some years to bring levels of production up and to end price volatility. A2S2 has been largely successful in this goal.

CURRENT R&D: In 2006, Professor Jay Keasling of the University of California-Berkeley and 14 collaborators announced they had successfully engineered a yeast strain to produce artemisinic acid, a precursor to the production of artemisinin.

Supported by a $42.5 million grant from the Bill & Melinda Gates Foundation, the researchers achieved the complex feat of engineering the metabolic pathway, which comprised 12 new synthetic genetic parts.[55] Inserted into yeast, the engineered pathway makes the yeast produce artemisinic acid, and a chemical process is then used to convert artemisinic acid to artemisinin. In 2008, Amyris granted a royalty-free license for its synthetic yeast to Sanofi-aventis for the manufacture and commercialization of artemisinin-based drugs, with a goal of market availability by 2013.[56] In April 2013, Sanofi and Amyris announced production of the first commercial batch of semi-synthetic artemisinin. Sanofi plans to produce 35 tons of artemisinin in 2013 and, on average, 50 to 60 tons/year by 2014, which will translate to between 80 and 150 million ACT treatments[57]– around half of current market demand. WHO approved a derivative of this semisynthetic artemisinin for use in May 2013.[58]

The companies claim that the new technology will diversify sources, increase supplies of high-quality artemisinin and lower the cost of ACTs. If microbial production of synthetic artemisinin is commercially successful, pharmaceutical firms will benefit by replacing a diverse set of small suppliers with one or two production factories. The Royal Tropical Institute of the Netherlands notes, "pharmaceutical companies will accumulate control and power over the production process; Artemisia producers will lose a source of income; and local production, extraction and (possibly) manufacturing of ACT in regions where malaria is prevalent will shift to the main production sites of Western pharmaceutical companies."[59] The Royal Tropical Institute asserts that insufficient supplies of Artemisia could be met solely by increasing cultivation of wormwood. Their report estimates that between 17,000-27,000 hectares of *Artemisia annua* would be required to satisfy global demand for ACTs, which could be grown by farmers in suitable areas of the developing world. Indeed, subsequent to the Royal Tropical Institute's report, farmers planted tens of thousands of additional hectares and in 2007, the artemisinin market became saturated with supply. Prices crashed from more than $1,100/kg to around $200/kg, driving 80 processors and many small farmers out of business. As a result, availability once again dropped below demand.[60] The 2007 production spike demonstrated the feasibility of meeting world demand for artemisinin with botanical supplies.

The international drug-purchasing facility, UNITAID, subsequently established the A2S2 initiative to provide loans and supply chain investment to increase the *Artemisia* harvest to sustainably high levels.[61] In 2011, artemesinin production from harvested crops was estimated at between 150-170 MT – close to 2007 levels. According to A2S2, "The present view is that artemisinin supply will be close to matching demand for 2012."[62]

The Royal Tropical Institute's report warned that the prospect of synthetic artemisinin production could further destabilise a very young market for natural *Artemisia*, undermining the security of farmers just beginning to plant it for the first time: "Growing *Artemisia* plants is risky and will not be profitable for long because of the synthetic production that is expected to begin in the near future."[63]

Case Study 3: Vanilla

PRODUCT: Natural vanilla flavour (vanillin) is sourced from the cured seed pod of the vanilla orchid.
STATUS: Switzerland-based synthetic biology company, Evolva, has constructed new metabolic pathways in microbes to produce several key flavour compounds found in vanilla and has partnered with International Flavors and Fragrances (IFF) to bring this product to market
AFFECTED COUNTRY/REGION: An estimated 200,000 people are involved in the production of cured vanilla beans per annum.[64] Madagascar, Comoros and Reunion historically account for around three quarters of the world's vanilla bean production. Other producers include Indonesia, China, Mexico, Uganda, Democratic Republic of Congo, Tanzania, French Polynesia, Malawi, Tonga, Turkey and India.
MARKET: Natural vanillin sells for $1,200-$4,000/kg. The world market for botanically-derived vanilla is approximately $240 million per annum.
COMMERCIALIZATION: Near-term. Evolva reports it is now scaling up production in collaboration with IFF and will launch a commercial product in early 2014.

BACKGROUND: Vanillin – the world's most popular natural flavor – is sourced from the cured seed pod of the vanilla orchid (*Vanilla planifolia*). Production of natural vanillin is time consuming and labour intensive: 1 kg of vanillin requires approximately 500 kg of vanilla pods and hand-pollination of approximately 40,000 flowers.[65] It is also regarded as an agro-ecologcial method of cultivation since vanilla beans must be shaded, usually by rainforest canopy, and require mixed planting of 'tutor' bushes on which they grow for support. Natural vanillin sells for $1,200-$4,000/kg. The annual world market for naturally-sourced vanillin is approximately $240 million; an estimated 200,000 people are involved in the production of about 2,000-3,000 MT of cured vanilla beans.[66] Madagascar and other island nations in the Southwest Indian Ocean (Comoros, Reunion) historically account for around three quarters of the world's vanilla bean production. Export earnings in the region are highly dependent on vanilla bean cultivation. An estimated 80,000 families cultivate vanilla orchids in Madagascar on approximately 30,000 hectares. In Comoros, an estimated 5,000-10,000 families depend on vanilla bean production. Approximately 4,000 farm families in indigenous communities of Mexico cultivate vanilla orchids; approximately 8,000 families in Central Africa (Uganda, Democratic Republic of Congo, Tanzania) depend on vanilla bean production. In recent years Indonesia and China have become major vanilla bean producers; other vanilla bean producers include French Polynesia, Malawi, Tonga, Turkey and India.

CURRENT R&D: In 2010, Switzerland-based synthetic biology company, Evolva, entered a 4-year agreement with the Danish government's Council for Strategic Research to develop a commercially viable and environmentally acceptable production route for biosynthetic production of vanillin. Scientists have already constructed a yeast-based fermentation route to both vanillin and other vanilla flavour components. In 2009, Evolva researchers described the creation of a *de* *novo* pathway to produce vanillin from glucose in two yeast strains; the new pathway involves bacterial, mold, plant and human genes.[67] In 2009 the global vanilla market, both natural and artificial, was valued at approximately $650 million. Evolva believes that its fermented vanillin can capture up to $360 million of the total global market.[68] The company claims it is now producing vanillin in engineered yeast at a price that is competitive with higher-priced artificial vanillin. In order to commercialize their synthetic biology-derived vanilla, Evolva have entered into a partnership with IFF and are currently in a scale-up process towards full commercial production. In late 2012 IFF told its investors that it would soon be sending out samples and expect to have commercial production start in mid-2014.[69]

The CEO of Evolva, Neil Goldsmith, acknowledges that the company's fermented vanillin is not equivalent to the cured vanilla bean, but he says that the taste profile of vanillin produced by engineered yeast is more complex and closer than artificial vanillin to the natural vanilla flavor.[70] Commercial viability ultimately depends on many factors; however, if Evolva succeeds in producing a vanillin flavour that can be scaled-up at a fraction of the cost of natural vanilla, it has the potential to provide a bio-based substitute for some portion of the natural vanilla bean flavour market. Evolva also believes that its synbiotech vanilla will be labelled as 'natural' in North America and in Europe.

Case Study 4: Rubber

Product: Rubber is the tropical plant-derived product receiving the most attention from synthetic biology companies seeking to manufacture biosynthetic substitutes of crucial building blocks. Companies are working to scale up production of biosynthetic isoprene, as well as butadiene and isobutene, all components in the manufacture of synthetic rubber. The goal is to manufacture commercial-scale quantities that will compete with both natural and synthetic rubber.
Status: Three different commercial teams are using synthetic biology to manufacture isoprene in microbial cell 'factories' via fermentation; DuPont and Goodyear have already produced a prototype tire using biosynthetic isoprene. France-based Global Bioenergies has produced both bio-butadiene and bio-isobutene using engineered metabolic pathways in bacteria.[71]
Affected countries/region: 20 million smallholder families rely on natural rubber (*Hevea brasiliensis*) for their livelihood. Cambodia, China, India, Indonesia, Malaysia, Papua New Guinea, Philippines, Singapore, Sri Lanka, Thailand and Vietnam accounted for about 92% of the global production of natural rubber during 2010. The global market for natural rubber was approximately $35 billion in 2010.[72]
Market: Current demand for isoprene: 850,000 tonnes per year,[73] with a market value of $2 billion.
Commercialization: Near term (2013 or 2014).

Background: Rubber is the tropical, plant-derived product receiving the most attention by synthetic biology companies. A major focus is *isoprene* – the molecule that is a crucial building block for making synthetic rubber. The gene encoding *isoprene* has been identified only in plants such as rubber trees (*Hevea brasiliensis*). In 2010, DuPont subsidiary, Genencor, announced that it had used synthetic biology to produce "BioIsoprene." The goal is to manufacture BioIsoprene cheaply and in commercial-scale quantities via fermentation to compete with both natural and synthetic rubber.[74]

Asia is by far the largest producer of natural rubber. In 2010, global natural rubber production was 10.4 million metric tons. Five Asian countries accounted for 83% of all natural rubber produced worldwide. According to the International Rubber Study Group 80% of all natural rubber is produced by small holders who farm an average 1 to 2 hectares.[75] Globally, an estimated 20 million small holder families rely on natural rubber for their livelihoods.

Top 5 Natural Rubber Producers

Country	Natural Rubber Production (million MT)
Thailand	3.3
Indonesia	2.7
Malaysia	0.9
India	0.9
Vietnam	0.8

Source: International Rubber Study Group

Current R&D: Synthetic rubber is typically made from chemical synthesis of petroleum-derived isoprene. Companies are now competing to develop the most efficient metabolic pathway for producing a cheaper version of isoprene via biosynthesis in engineered microbes. Global Bioenergies is developing bio-based isobutene and is collaborating with Poland-based rubber manufacturer Synthos to commercialize bacterial biosynthesis of bio-butadiene. The goal is to reduce the tire industry's dependence on petroleum-derived synthetic rubber, and, perhaps, to capture some portion of the market for natural rubber.

> "The BioIsoprene process being pioneered by Goodyear and Genencor finally offers the very real possibility for obtaining the quantities of low-cost isoprene needed to produce a meaningful large-volume alternative to Hevea natural rubber." – Frank J. Feher, *Rubber & Plastic News*, November 1, 2010.[76]

Three commercial teams are using synthetic biology to manufacture isoprene in microbial cell factories via fermentation:

- Genencor (now owned by DuPont) has been partnering with Goodyear Tire & Rubber since 2007 to develop BioIsoprene. Genencor predicts that its product will reach the commercial market in 2013. Prototype tires containing BioIsoprene have already been unveiled.
- In September 2011 Amyris, Inc. announced a partnership with French tire manufacturer Michelin to develop and commercialize isoprene.
- Texas-based GlycosBio announced in May 2010 a collaboration with Malaysia's Bio-XCell Sdn Bhd to build a biorefinery with a planned 20,000 tonne/year capacity to produce isoprene using glycerine (derived from oil palm) as a feedstock. The company plans to produce bio-isoprene for commercial rubber applications in 2014.

The tire industry is the driving force behind changes in demand for natural rubber. Although natural rubber is more easily replaced by synthetics in non-tire applications, natural rubber is still a vital – and thus far irreplaceable – component in tires. More than 60 % of all natural rubber is used for tires. (The content of tires is typically 50% natural rubber.)

BioIsoprene has already been used to manufacture prototype tires: According to a report in *Industrial Biotechnology*, "Current state-of-the-art technology has resulted in production, recovery, polymerization, and manufacture of tires with the isoprene component produced via fermentation. Continued improvements in both the cell factory and the production process are being actively pursued."[77] Genencor predicts that its product will reach the commercial market in 2013.

It is too early to predict if bio-isoprene has the potential to capture a portion of the market for natural rubber. But scientists who are working on BioIsoprene indicate that the product "has the potential to provide a large-volume alternative to Hevea natural rubber and petroleum-derived isoprene."[78]

Case Study 5: Star Anise (source of Shikimic Acid)

PRODUCT: Shikimic acid is the key raw material for the manufacture of oseltamivir (Tamiflu), an anti-viral drug. Shikimic acid is traditionally sourced from star anise, the pod of the Chinese medicinal plant, *Illicium anisatum.*
STATUS: After the outbreak of bird flu in 2005, demand for Tamiflu soared because countries began stockpiling the drug. Due to a shortfall in supplies of botanically-derived star anise, synthetic biologists began engineering the metabolic pathway of bacteria to produce shikimic acid via fermentation.
AFFECTED COUNTRIES/REGION: China produces about 80% to 90% of the world's star anise.
MARKET: In 2005, the price of Chinese shikimic acid derived from star anise soared to more than $400/kg, from $40/kg. Worldwide sales of the anti-viral drug fluctuate: in 2009 Tamiflu sales were $2.9 billion; in 2011 sales reached only $406 million.[79]
COMMERCIALIZATION: Most of the shikimic acid used by Roche to manufacture Tamiflu is now sourced from microbial fermentation. Roche has contracts with Sanofi-aventis (France) and others to provide the shikimic acid produced in 'cell factories.'

BACKGROUND: The production of a major anti-viral drug, Tamiflu, depends on shikimic acid, which is traditionally sourced primarily from star anise, the star-shaped pod of the traditional Chinese medicinal plant, *Illicium anisatum.* Roughly 80-90% of the world's star anise is grown in southwestern China, primarily in Guangxi and Yunnan provinces. An estimated 66% of China's star anise harvest is used to make Tamiflu.[80] (Star anise is also valued as a spice and for medicinal uses.) In Guangxi province alone, some 350,000 hectares of farmland are devoted to the star anise tree with an annual output of 80,000 MT.[81] After planting, it takes around six years for star anise trees to bear fruit. The process of extracting and purifying shikimic acid from star anise seeds is expensive. It takes about 30 kg of star anise to yield 1 kg of shikimic acid, enough to treat one person.[82] With the heightened threat of global pandemics (bird flu in 2005 and swine flu in 2009), demand for Tamiflu soared and drug company Roche (maker of Tamiflu) couldn't meet demand due to a shortage of star anise. Consequently, efforts to develop alternative production routes in *E. coli* intensified.[83]

Current R&D: Michigan State University professor, John Frost, founded a small start-up company, Draths Corp., in 2005 to produce building blocks for the chemical, pharmaceutical, and food industries – including shikimic acid. Frost and his co-inventor, Karen Draths, patented a technology for making shikimic acid in engineered *E. coli* that was subsequently licensed to Roche.[84] Today, the co-inventors hold a family of 14 patents and patent applications that cover methods and materials for the production of shikimic acid (see below). In November 2011, synthetic biology company Amyris, Inc. acquired Draths Corp. and its intellectual property.[85]

By the end of 2005, Roche was reportedly producing about one-third of its shikimic acid supply from the microbial fermentation process.[86] According to Roche, "a specific strain of *E. coli*, which, when overfed glucose, produces SA [shikimic acid]. During the process, the *E. coli* are fed, fermented, and broken down to extract the SA. Enormous vessels (each the size of 2 city buses) are required to accommodate the volume of *E. coli* mixture needed."[87]

Roche has continued to increase its fermentation capacity, suggesting that the microbial production of shikimic acid for Tamiflu production is competitive in price with shikimic acid derived from star anise. In March 2012, Roche told ETC Group: "For our Tamiflu production we mostly rely on the microbial fermentation process."[88] The company declined to specify the quantity or percentage of shikimic acid derived from microbial production.

Case Study 6: Squalene

PRODUCT: Squalane is a high-value, oil-free moisturizing ingredient used in a wide range of cosmetics that, until recently, was extracted primarily from the liver of deep-sea sharks.
STATUS: California-based synthetic biology company, Amyris, Inc., has engineered the metabolic pathway of yeast to produce a molecule called farnesene – an essential building block for a wide range of chemical products – including squalene.
AFFECTED COUNTRY/REGION: Instead of sourcing squalene from shark liver oil, the moisturizer can be extracted from botanical sources, including rice bran, wheat germ, amaranth seeds and olives. Refined olive oil is now the primary botanical source for squalene.
MARKET: Estimated demand for squalene is between 1,000-2,000 tons per annum. The livers of an estimated 3,000 sharks are typically required to produce 1 ton of squalene (that is, up to 6 million shark livers would be required to meet demand).[89]
COMMERCIALIZATION: Amyris, Inc. is selling commercial quantities of squalene to cosmetic ingredient buyer Soliance (France). Engineered microbes in Amyris' Brazil-based fermentation facility produce farnesene and byproducts such as squalene from up to two million tons of crushed sugarcane per annum.

BACKGROUND: Squalane is a high-value, oil-free moisturizing ingredient used in a wide range of cosmetics that, until recently, was extracted primarily from the liver of deep-sea sharks. Squalene is also used in the manufacture of vaccines. As a result of civil society campaigns to end the over-harvesting of shark livers as a source of squalene, the cosmetics industry has been forced to develop more sustainable, plant-based alternatives.[90] In 2008, L'Oreal and Unilever announced that they would remove shark-derived squalene from their cosmetic brands.[91] Squalene can be extracted from a number of botanical sources, including rice bran, wheat germ, amaranth seeds and olives.[92] Deep-sea shark catches are currently prohibited in many parts of the world and olive oil is now the primary plant-derived alternative source.[93]

CURRENT R&D: Amyris, Inc. has used synthetic biology to engineer the metabolic pathway of yeast to produce a molecule called farnesene – an essential building block for a wide range of chemical products (detergents, cosmetics, perfumes, industrial lubricants and transportation fuels) – including squalene. In February 2010, Amyris announced that it was selling its 100% bio-based Neossance™ Squalane – the company's first commercial product – to Soliance (a provider of ingredients to the French cosmetics industry).[94]

In November 2011, Amyris announced that the Brazilian Development Bank had approved $11.6 million financing for an industrial-scale facility to produce the company's farnesene product (Biofene™) and product derivatives, including squalene. According to Amyris, the Brazilian facility uses up to two million tons of crushed sugarcane annually as feedstock.[95] Amyris is reportedly scaling-up production of microbial-derived farnesene at other production facilities in the USA and Europe.[96] The company has not disclosed production costs or capacity related to squalene.

Case Study 7: Saffron

PRODUCT: Saffron, the world's most expensive spice, is derived from the crocus flower, *Crocus sativus.* Saffron is a food flavouring and colouring agent.
STATUS: Switzerland-based synthetic biology company, Evolva, has identified and built the metabolic pathways that result in three of saffron's key chemical compounds related to colour and flavour. The pathways are inserted into microbes to produce the compounds through fermentation.
AFFECTED COUNTRY/REGION: Iran accounts for over 90% of world saffron production. Spain, India, Morocco, Greece, Turkey, Kashmir and Afghanistan are minor producers.
MARKET: $660 million *per annum*.
COMMERCIALIZATION: Near-term (2015/16).

BACKGROUND: The world's most expensive spice, saffron is derived from the dried stigma of the crocus flower, *Crocus sativus.* Saffron is prized as a flavouring and colouring agent for food. Chemical constituents of saffron, including crocin and crocetin (colors), picrocrocin (bitter principle) and safranal (flavour), also have health benefits.[97] About 90-95% of the crocus flowers used to produce saffron are grown in Iran.[98] It takes 250,000 crocus flowers and 40 hours of labour to manually extract enough stigmas to yield 1 kg of saffron.

After pistachio, saffron is Iran's most important non-petroleum export product. During harvest, each hectare devoted to saffron provides jobs for up to 270 people per day.[99] Good quality saffron sells from $2,000 to $10,000/kg or more.[100] Annual worldwide sales of saffron are an estimated $660 million.[101] In 2009/2010, Iran's northeastern province of Khorasan Razavi exported 57 tons of saffron worth $156.5 million to 41 countries.[102]

CURRENT R&D: In 2010, Swiss-based Evolva, Inc. began working on a biosynthetic route to express saffron-derived genes in engineered microbes.[103] The goal is to build a novel metabolic pathway that instructs cells to produce key saffron compounds, which is then inserted into a microbial host for large-scale production in fermentation tanks. According to the company:

> "Producing the key saffron components by fermentation has three main benefits. Firstly, it will allow saffron to be available at a much lower price than currently, which will both expand existing markets and open new ones. Secondly it will eliminate the many complexities involved in the current supply chain. Finally by making each of the key components separately it will enable the production of customized forms that are for example particularly rich in aroma, taste or colour and that can be adapted to specific food formulations and regional preferences."[104]

Evolva conducts R&D on saffron at its location in Chennai. The company claims that it is now in the process of "pathway optimization" and predicts that a commercial saffron product will be available in 2015 or 2016.

Case Study 8: Vetiver

Product: Vetiver oil, a fragrance widely used in cosmetics and perfumes, is extracted from the aromatic roots of a perennial grass native to India (*Chrysopogon zizanioides)*, commonly known as vetiver.
Status: California-based synthetic biology company, Allylix, Inc., has engineered a metabolic pathway in microbes to produce a key fragrance compound found in vetiver oil.
Affected Country/Region: Farmers in Haiti, Indonesia, China, Japan, India, Brazil and Réunion grow vetiver for export. In 2007, small farmers in Haiti accounted for an estimated 60% share of worldwide vetiver exports.
Market: 250 tons *per annum*.
Commercialization: Near term. (In early 2012, Allylix announced plans to start commercial-scale production in late 2012, but no announcements have been made confirming start of production.)

Background: Vetiver, an essential oil with a rich, woody aroma widely used in cosmetics and perfumes, is extracted from the roots of a perennial grass native to India (*Chrysopogon zizanioides)*.[105] According to U.C. Lavania, a scientist at India's Central Institute of Medicinal and Aromatic Plants*,* vetiver is an essential oil used in 90% of all Western perfumes. Annual world trade of vetiver is an estimated 250 tons.[106] Major commercial producers include Haiti, Indonesia, China, Japan, India, Brazil and Réunion. For at least two island nations – Haiti in the Caribbean and Réunion in the Indian Ocean – the essential oil obtained from the roots of vetiver is a major source of foreign exchange earnings.[107] Haiti's share of worldwide vetiver exports grew from 40% in 2001 to over 60% in 2007.[108] In the wake of the worldwide financial crisis, Haiti has seen a sharp reduction in vetiver exports. An estimated 60,000 people in Haiti's Les Cayes region depend on vetiver as their primary income source; the crop is grown on 10,000 hectares.[109] The region also supports up to 13 distilleries that process and extract vetiver oil for export.[110] Before 2009, Haiti's vetiver crop was valued at approximately $15-$18 million per annum. In recent years Haiti's export earnings from vetiver have declined to around $10 million per annum.[111]

Current R&D: In March 2012, Allylix, Inc. announced that it would begin commercial-scale production of a new fragrance that the company calls "Epivone™" – which is structurally related to beta-vetivone, one of the key components of vetiver oil – in the third quarter of 2012.[112] (There have been no announcements that production has begun.) Epivone™ is produced via fermentation.

"Epivone is a highly valuable compound and because we own the patents claiming the fragrance and its novel production method, we expect to be the only commercial supplier."[113] – CEO, Allylix, March 12, 2012

At this early date, it is not possible to predict how or if Allylix's new biosynthetic product will affect demand for botanically-derived vetiver oil and the livelihoods of small-scale farmers who depend on it.

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[1] International Civil Society Working Group on Synthetic Biology, *Potential Impacts of Synthetic Biology on the*
[2] Jay Keasling, quoted in Michael Specter, "A Life of its Own: Where will synthetic biology lead us?," *The New Yorker*, 28 September 2009, p. 59.
[3] BCC Research, "Global Market for natural Fatty Acids to reach 13 billion in 2017," 21 December 2012: http://www.bccresearch.com/pressroom/report/code/CHM062A.
[4] Doris De Guzman, "Solazyme files for IPO," *ICIS Green Chemicals*, 21 March 2011: http://www.icis.com/blogs/green-chemicals/2011/03/solazyme-files-for-ipo.html.
[5] Doris De Guzman, "Codexis Enters Detergent Alcohols Market," *ICIS Green Chemicals*, 5 March 2011: http://www.icis.com/blogs/green-chemicals/2011/03/codexis-enters-detergent-alcoh.html.
[6] Anon., *IHS Natural Fatty Acids Report*, July 2012: http://www.ihs.com/products/chemical/planning/ceh/natural-fatty-acids.aspx.
[7] 25% figure via Danilo Suarez, "Save The Coconut Farmer," *Manila Standard*, 7 May 2013: http://manilastandardtoday.com/2013/05/07/save-the-coconut-farmer/ . The population of the Philippines is currently around 103 million.
[8] BCC Research, "Global Market for natural Fatty Acids to reach 13 billion in 2017," 21 December 2012: http://www.bccresearch.com/pressroom/report/code/CHM062A.
[9] J.M. Dyer, S. Stymne, A.G. Green, A.S. Carlsson, "High-value oils from plants," *Plant J.*, 54, 2008, pp. 640–655.
[10] Kevin Quon, "Can Solazymes Potential Outweigh its Skeptics?" *SeekingAlpha.com*, 24 June 2013: http://seekingalpha.com/article/1518442-can-solazyme-s-potential-outweigh-it-s-skeptics?source=email_rt_article_readmore
[11] Doris De Guzman, "Solazyme production milestones," *ICIS Green Chemicals*, 6 July 2012: http://www.icis.com/blogs/green-chemicals/2012/07/solazyme-production-milestones.html.
[12] Solazyme Investor presentation: http://www.scribd.com/doc/111084056/110805-Solazyme-Investor-Presentation-Canaccord-Compressed.
[13] Codexis website: http://www.codexis.com/codexol.
[14] AOCS Lipid Library, "Oils and Fats in the Marketplace, Commodity Oils and Fats: Palm Kernel and Coconut (Lauric) Oils:" http://lipidlibrary.aocs.org/market/lauric.htm
[15] USDA figures indexed at http://www.indexmundi.com/agriculture/?commodity=coconut-oil.
[16] Feedipedia, "Copra meal and coconut byproducts:" http://www.feedipedia.org/node/46
[17] Philippine Coconut Authority, "Magnitude of the Industry:" http://www.pca.da.gov.ph/magnitude.html.
[18] Ibid.
[19] Indexmundi, "Coconut oil production by Country in 1000 MT, 2013 Estimate:" http://www.indexmundi.com/agriculture/?commodity=coconut-oil&graph=production.
[20] Mel White, "Borneo's Moment of Truth," *National Geographic,* November 2008: http://ngm.nationalgeographic.com/2008/11/borneo/white-text/4
[21] UNDP Green Commodities Facility, "Indonesia Sustainable Palm Oil Initiative:" http://greencommodities.org/index.php?option=com_content&view=article&id=166:indonesia-sustainable-palm-oil-initiative&catid=9:projects&Itemid=65.
[22] Malaysian Palm Oil Industry, "Oil Palm in Malaysia," *Palmoilworld.org*: http://www.palmoilworld.org/about_malaysian-industry.html.
[23] Friends of the Earth, "Palm oil: fueling landgrabs and climate change, not development," 4 Feb 2013: http://www.foe.org/news/archives/2013-02-palm-oil-fueling-landgrabs-and-climate-change-not-de.
[24] Grain, "Land Grabbing for Biofuels Must Stop," 21 Feb 2013: http://www.grain.org/article/entries/4653-land-grabbing-for-biofuels-must-stop.
[25] Paul Sonne, "To Wash Hands of Palm Oil Unilever Embraces Algae," *Wall Street Journal*, 7 September 2010: http://online.wsj.com/article/SB10001424052748703720004575477531661393258.html.

[26] Transnational Institute, Maria Luisa Mendonca,
"Impacts of Expansion of Sugarcane Monocropping for Ethanol Production," January 2009:
http://www.tni.org/sites/www.tni.org/archives/reports/landpolicy/mendoca_sugarcane.pdf
[27] Indexmundi, "Palm Kernel oil production by Country in 1000 MT, 2013 Estimate:"
http://www.indexmundi.com/agriculture/?commodity=palm-kernel-oil&graph=production.
[28] Wikipedia entry on Babassu Palm: http://en.wikipedia.org/wiki/Attalea_speciosa.
[29] Lauric oil composition from "Soap Making Oil Properties," Saratoga Scents:
http://www.saratogascents.com/soap_making_oil_properties.html.
[30] Patricia Shanley, Alfredo Celso Fantini (eds.), "Riches of the Forest: Fruits, Remedies and Handicrafts in Latin America," Center for International Forestry Research, p. 19.
[31] Anon., "Babassu Palm gets blame for Amazonian Destruction," *Biofuels Digest*, 25 August 2011:
http://www.biofuelsdigest.com/bdigest/2011/08/25/babassu-palm-gets-blame-for-amazonian-deforestation/.
[32] See Solazyme website, "Biotechnology that Creates Renewable Oils from Microalgae:"
http://solazyme.com/technology.
[33] Solazyme SEC Filings Form S-1 March 11 2011:
http://www.sec.gov/Archives/edgar/data/1311230/000119312511064209/ds1.htm.
[34] Anon., "Solazyme Management Discusses Q1 2013 Results - Earnings Call Transcript," *Seeking Alpha.com*, 8 May 2013:
http://seekingalpha.com/article/1417141-solazyme-management-discusses-q1-2013-results-earnings-call-transcript?page=2.
[35] Kevin Quon, "Solazyme Addresses The Limitations Of Oil Production - An Interview With Solazyme's Director (Part 2)," *SeekingAlpha.com*, 10 February 2013: http://seekingalpha.com/article/1170001-solazyme-addresses-the-limitations-of-oil-production-an-interview-with-solazyme-s-director-part-2.
[36] Ibid.
[37] Solazyme SEC Filings Form S-1 March 11 2011:
http://www.sec.gov/Archives/edgar/data/1311230/000119312511064209/ds1.htm.
[38] See Powerpoint slide: http://seekingalpha.com/article/1217241-partners-embrace-win-win-proposition-in-solazyme-s-tailored-oils.
[39] Kevin Quon, "Can Solazymes Potential Outweigh Its Skeptics?" *SeekingAlpha.com*, 24 June 2013:
http://seekingalpha.com/article/1518442-can-solazyme-s-potential-outweigh-it-s-skeptics?source=email_rt_article_readmore.
[40] Calculation for 40% figure: Solazyme's Brazilian facility has a projected capacity of 100,000 MT of algal oil – 60% concentration = 60,000 MT of Myristic Acid. According to Solazyme, the global market size is 150,000 Mt – see Powerpoint slide at http://seekingalpha.com/article/1217241-partners-embrace-win-win-proposition-in-solazyme-s-tailored-oils.
[41] Solayme press release, "Solazyme and Mitsui Enter into Multi-Year Agreement to Jointly Develop a New Suite of Tailored Algal Oils," 6 February 2013: http://solazyme.com/media/2013-02-06.
[42] Ibid.
[43] See http://www.codexis.com/technology.
[44] See http://www.ls9.com/technology/technology-overview.
[45] Anon., *Codexol detergent alcohol*: http://www.codexis.com/codexol.
[46] Doris de Guzman "Sugar Fatty Alcohols near commercialization," *ICIS Green Chemicals*, 20 April 2012:
http://www.icis.com/Articles/2012/04/20/9552164/sugar+fatty+alcohols+near+commercialization.html
[47] Codexis press release, "Codexis and Chemtex Achieve Key Milestone in Commercial Development of Bio-Based Chemicals from Non-Food Cellulosic Biomass," 14 June 2013:
http://ir.codexis.com/phoenix.zhtml?c=208899&p=irol-newsArticle&cat=news&id=1829906
[48] Doris de Guzman, "Sugar Fatty Alcohols near commercialization," *ICIS Green Chemicals*, 20 April 2012:
http://www.icis.com/Articles/2012/04/20/9552164/sugar+fatty+alcohols+near+commercialization.html
[49] Ibid.
[50] Personal communication with Malcolm Cutter, Director of FSC Development Services, UK and Project Manager of the MMV Artemisinin Programme, 24 April 2012.

[51] Personal communication with Charles Giblain of Bionexx, Inc., 16 April 2013.
[52] Ibid.
[53] Jim Thomas, "Synthetic anti-malarial compound is bad news for artemisia farmers," *The Guardian Poverty Matters Blog*, 12 April 2013.
[54] Assured Artemisinin Supply System (A2S2), *Production Cycle: from Artemisia to ACT,* 26 January 2012: http://www.a2s2.org/index.php?id=50.
[55] Withers, S. T. and J. Keasling, "Biosynthesis and engineering of isoprenoid small molecules," *Appl. Microbiol Biotechnol.*, 73(5), pp. 980-90.
[56] Details available on Amyris web site: http://www.amyris.com.
[57] Robert Sanders, "Launch of antimalarial drug a triumph for UC Berkeley, synthetic biology," 10 April 2013: http://newscenter.berkeley.edu/2013/04/11/launch-of-antimalarial-drug-a-triumph-for-uc-berkeley-synthetic-biology/.
[58] WHO Prequalification of Medicines Programme, "Acceptance of non-plant-derived-artemisinin offers potential to increase access to malaria treatment:" http://apps.who.int/prequal/info_press/documents/PQ_non-plant_derived_artemisinin_1.pdf.
[59] Heemskerk, W. *et al.*, *The World of Artemisia in 44 Questions*, The Royal Tropical Institute of the Netherlands, March 2006.
[60] Van Noorden, R., "Demand for Malaria drug soars," *Nature* 466, 3 Aug 2010, pp. 672-673.
[61] See http://www.a2s2.org/.
[62] A2S2, "Supporting Sustainable Artemisinin Supplies," Newsletter No. 1, July 2011.
[63] Heemskerk, W. *et al.*, *The World of Artemisia in 44 Questions*, The Royal Tropical Institute of the Netherlands, March 2006, p. i-ii: http://tinyurl.com/7zoazkh.
[64] Personal communication with Michel Grisoni, CIRAD (Centre de coopération internationale en recherche agronomique pour le développement), based in Reunion. All estimates for vanilla production and agronomic practices provided by Michel Grisoni.
[65] Hansen, E. H., B. L. Møller, G. R. Kock, C. M. Bünner, C. Kristensen, O. R. Jensen, F. T. Okkels, C.E. Olsen, M. S. Motawia and J. Hansen, "De novo biosynthesis of Vanillin in Fission yeast (*Schizosaccharomyces pombe*) and Baker's yeast (*Saccharomyces cerevisiae*)," *Applied and Environmental Microbiology*, 75, 2009, pp. 2765-2774.
[66] Personal communication with Michel Grisoni, CIRAD.
[67] Hansen *et al.*, "De novo biosynthesis of Vanillin"
[68] Personal communication with Evolva CEO, Neil Goldsmith, 5 October 2011.
[69] Anon., "International Flavors & Fragrances Management Discusses Q4 2012 Results - Earnings Call Transcript," *Seeking Alpha.com*, 7 February 2013.
[70] Ibid.
[71] Doris de Guzman, "Introducing Global Bioenergies," *ICIS Green Chemicals*, 19 July 2011: http://www.icis.com/blogs/green-chemicals/2011/07/introducing-global-bioenergies.html.
[72] International Rubber Study Group, "Statistical Summary of World Rubber Situation:" http://www.rubberstudy.com/documents/WebSiteData.pdf.
[73] http://www.glycosbio.com.
[74] Whited, G., Feher, F., Benko, D., Cervin, M., Chotani, G., McAuliffe, J., LaDuca, R., Ben-Shoshan, E. and K. Sanford, "Technology update: development of a gas-phase bioprocess for isoprene-monomer production using metabolic pathway engineering," *Industrial Biotechnology*, June 2010, 6(3), pp. 152-163.
[75] 2010 statistics on natural rubber production and exports provided by the International Rubber Study Group, Singapore. http://www.rubberstudy.com/
[76] F. Feher, "BioIsoprene for use in renewable alternatives," *Rubber & Plastic News*, 1 November 2010: http://www.scribd.com/doc/55461183/BioIsoprene-RPN-1Nov10.
[77] Whited *et al.*, "Technology update: development of a gas-phase bioprocess"
[78] Erickson, B., R. Singh and P. Winters, "Synthetic biology: regulating industry uses of new biotechnologies," *Science*, Vol. 333, September 2, 2011.
[79] See www.evaluatepharma.com.

[80] Zhuang Pinghui, "Drought hit harvest of star anise, vital to flu fight," *South China Morning Post* online, 29 March 2010.
[81] Ibid.
[82] Andrew Pollack, "Is Bird Flu Drug Really So Vexing? Debating the Difficulty of Tamiflu," *New York Times*, November 5, 2005.
[83] Saptarshi Ghosh, Yusuf Chisti, Uttam C. Banerjee, "Production of shikimic acid," *Biotechnology Advances*, 13 March 2012: http://dx.doi.org/10.1016/j.biotechadv.2012.03.001.
[84] Andrew Pollack, "Is Bird Flu Drug Really So Vexing? Debating the Difficulty of Tamiflu," *New York Times*, November 5, 2005. We do not know if Roche is currently using the proprietary fermentation method developed by Frost or an alternative method.
[85] Anon., "Amyris Acquires Draths," *Chemical Week*, 4 Nov 2011.
[86] David Bradley, "Star role for bacteria in controlling flu pandemic?" *Nature Reviews Drug Discovery* 4, Dec. 2005, pp. 945-946: doi:10.1038/nrd1917.
[87] Anon., "The Challenges of Tamiflu Manufacture:" www.roche.com/med_mb091105jvk.pdf.
[88] Email communication from Claudia Schmitt, Roche, March 21, 2012.
[89] Deep Sea Conservation Coalition website: http://savethedeepsea.blogspot.com/2011/08/save-deep-sea-sharks-squalene-and-trade.html.
[90] http://oceana.org/sites/default/files/spring08newsletterfinal.pdf
[91] Anon., "Unilever Eliminates Shark Squalene in Cosmetics," *Cosmetics and Toiletries,* 30 January 2008: http://www.cosmeticsandtoiletries.com/networking/news/company/15040046.html?page=1.
[92] Luis A. Brito et al., "An alternative renewable source of squalene for use in emulsion adjuvants," *Vaccine*, Vol. 29, Issue 37, 26 August 2011.
[93] Personal communication with Rebecca Greenberg, staff scientist, Oceana, 4 April 2007.
[94] http://www.amyris.com/en/newsroom/198-amyris-sells-first-renewable-product.
[95] Anon., "Amyris: Farnesene and the pursuit of value, valuations, validation and vroom," *Biofuels Digest,* June 25, 2010.
[96] Andrew McDougall, "Amyris receives multi-million dollar approval for first industrial-scale production facility in Brazil," *CosmeticDesign.com*, 28 November 2011. http://www.cosmeticsdesign.com
[97] J.P Melnyk, S. Wang and M. F. Marcone, "Chemical and biological properties of the world's most expensive spice: Saffron," *Food Research International*, Vol. 43, No. 8, October 2010, pp. 1981–1989.
[98] http://www.evolva.com/sites/default/files/attachments/eve-jan2012.pdf. See also: Anon., "Iran exports saffron to 41 countries," *Iran Daily*, 20 March 2010: http://www.irandaily.com/1389/2/5/MainPaper/3663/Page/5/Index.htm#.
[99] S. M. Javadzadeh, "Prospects and problems for enhancing yield of saffron (*Crocus sativus*) in Iran," *International Journal of Agriculture: Research and Review*, Vol. 1, No. 1, pp. 21-25, 2011.
[100] http://miss-swiss.com/2011/07/worlds-expensive-spice-10000-kilogram/
[101] Anon., Edison Investment Research, *Outlook: Evolva*, 4 April 2012: http://www.evolva.com/sites/default/files/attachments/edison-4april2012_0.pdf.
[102] Anon., "Iran exports saffron to 41 countries," *Iran Daily*, 20 March 2010.
[103] http://www.evolva.com/sites/default/files/press-releases/evolva-13september2010-halfyearresults_4.pdf.
[104] http://www.evolva.com. Confirmed in email communication with Stephan Herrera, Evolva, 29 March 2012.
[105] Aside from its aromatic and medicinal qualities, vetiver grass is highly valued throughout the global South as a traditional and effective soil and water management tool.
[106] U.C. Lavania, Central Institute of Medicinal and Aromatic Plants, Lucknow, India, *Other Uses, and Utilization of Vetiver: Vetiver Oil*, no date: http://www.vetiver.com/ICV3-Proceedings/IND_vetoil.pdf.
[107] Ibid.
[108] Caribbean Office of Trade Negotiations, CARICOM's Essential Oils Trade, *Private Sector Trade Note*, Vol. 9, 2009: http: www.crnm.org.
[109] Personal communication with Michel Apollon, General Manager, Unikodese, Port-au-Prince, Haiti, 23 April 2012.
[110] Ibid.

[111] Ibid.
[112] http://www.allylix.com/press/allylix-commercialize-novel-specialty-chemical
[113] Ibid.