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Polyhydroxyalkanoate (PHA) Biopolyesters - Emerging and Major Products of Industrial Biotechnology

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Abstract
Background: Industrial Biotechnology ("White Biotechnology") is the large-scale production of materials and chemicals using renewable raw materials along with biocatalysts like enzymes derived from microorganisms or by using microorganisms themselves ("whole cell biocatalysis"). While the production of ethanol has existed for several millennia and can be considered a product of Industrial Biotechnology, the application of complex and engineered biocatalysts to produce industrial scale products with acceptable economics is only a few decades old. Bioethanol as fuel, lactic acid as food and PolyHydroxyAlkanoates (PHA) as a processible material are some examples of products derived from Industrial Biotechnology.
Purpose and Scope: Industrial Biotechnology is the sector of biotechnology that holds the most promise in reducing our dependence on fossil fuels and mitigating environmental degradation caused by pollution, since all products that are made today from fossil carbon feedstocks could be manufactured using Industrial Biotechnology – renewable carbon feedstocks and biocatalysts. To match the economics of fossil-based bulk products, Industrial Biotechnology-based processes must be sufficiently robust. This aspect continues to evolve with increased technological capabilities to engineer biocatalysts (including microorganisms) and the decreasing relative price difference between renewable and fossil carbon feedstocks. While there have been major successes in manufacturing products from Industrial Biotechnology, challenges exist, although its promise is real. Here, PHA biopolymers are a class of product that is fulfilling this promise.
Summary and Conclusion: The authors illustrate the benefits and challenges of Industrial Biotechnology, the circularity and sustainability of such processes, its role in reducing supply chain issues, and alleviating societal problems like poverty and hunger. With increasing awareness among the general public and policy makers of the dangers posed by climate change, pollution and persistent societal issues, Industrial Biotechnology holds the promise of solving these major problems and is poised for a transformative upswing in the manufacture of bulk chemicals and materials from renewable feedstocks and biocatalysts.

Keywords: Bioproducts; Industrial Biotechnology; Polyhydroxyalkanoates; Renewable Resources; White Biotechnology

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Introduction
The global public dialogue during the last 5 years is being shaped by four dominant threats: 1) Climate change, 2) Infectious diseases like SARS-CoV19, 3) Plastics pollution, and 4) Increasing geopolitical instability. All these threats are directly or indirectly tied to the ever-increasing consumption of and demand for fossil fuels. Since the late 1940's fossil fuels and access to them have caused the world economy to go through severe shocks that have negatively affected people and the planet, bringing us to our current state where these four major threats affect everyone, including those that are financially or politically profiting from it, although many do not realize that yet. The current shortage of fossil fuels – perceived or real – caused due to one or more of the above-mentioned threats have again disrupted our lives like it did in the 1970's and the early 2000's. The kneejerk reaction to each and every fossil fuel supply shock has been for governments to look for additional supplies of fossil fuels in the short-term, sacrificing many of their fundamental principles as a country or society, and instead of implementing long-term structural changes to their economies to reduce our dependence on fossil fuels. Our dependence on

fossil fuels is all pervasive and affects every facet of our lives and our livelihood, and now with climate change and plastics pollution it is beginning to threaten our very existence.

In keeping with the topic of this submission, the authors have focused on the threat caused by plastics pollution and to some extent climate change and how Industrial Biotechnology and products thereof reduces dependence on fossil fuels and in turn benefits humanity and our planet. Among the various bulk materials consumed today, those coming from fossil fuels such as fossil plastics stand out. Fossil plastics play a dominant role as demonstrated by their ever-increasing production and consumption (1). In the last 70 years we have increased our fossil plastics use from 1.5 million tons (Mt) in 1950 to 367 Mt in 2020, with half of all fossil plastics produced just in the last 15 years. Fossil plastics are ubiquitous, they are present in our food packaging to clothes and in our toys to automobiles. They are functional and easily discarded. Technology allows their production at low costs that the society has learned to accept and live with. However, society has yet to comprehensively deal with the end-of-life issues of fossil plastics, and the scale and costs of accumulation and persistence of these materials in nature paints a dire picture that has just begun to emerge. Comprehensive studies on all plastics ever produced and their fate show that until 2015 only 9% have been recycled and 12% incinerated for energy production out of a total of 8.3 billion tons produced, while 6.3 billion tons persist in our landfills and in the environment. This study also estimated that at the current rate humans would accumulate 12.3 billion tons of fossil plastics on earth by 2050 (2). Another comprehensive study on plastics consumption estimates that in 2050 we would produce over 1 billion tons (Gt) of plastics annually, use 15% of the fossil carbon used today solely for plastic production, and would have more plastics in our oceans than fish (3). In addition, incinerating one ton of fossil plastics, having a heating value of 23–42 MJ/kg, generates about 2.6 tons of CO_2, a greenhouse gas that fuels Climate Change and Global Warming (4). If production and use of fossil plastics increase as currently estimated, CO_2 emissions could reach 1.34 Gt per year by 2030, which corresponds to the emissions released by about 300 new 500-megawatt coal-fired power plants. By 2050, greenhouse gas emissions from fossil plastics could even exceed 56 Gt: 10–13 percent of the entire remaining carbon budget (5)! Disposal strategies like land filling cause littering of terrestrial and aquatic environments through macroplastic waste, while recycling contributes to microplastic formation with its generally acknowledged and scientifically well substantiated effects on biological systems and human health (6, 7).

This nexus of fossil plastics accumulation and persistence, emissions thereof and supply chain issues demonstrate the need for structural changes towards dramatic reduction in fossil fuel use and a transition to sustainable and circular production methods of materials both in the short and the long term. Indeed, the next decade will witness a fundamental transformation in the carbon resource base for industry, characterized by a rapid shift away from fossil fuels and a move towards renewable carbon resources (8). This transformation is where "Industrial Biotechnology" concepts are relevant and will play a major role (9).

Such new processes for large-scale production of biofuels, solvents, biopolymers, amino acids, enzymes, etc., that are based on inexpensive, abundantly and locally available raw materials need to be integrated into the "Biorefinery" concept, where the material cycle is a closed-loop process, and the footprint for carbon and greenhouse gas emissions are kept as small as possible. This means that the bio-industrial production processes need to be integrated into existing industrial production lines, where the substrates to produce these products come from today's waste carbon streams. Such concepts of upgrading waste to valuable bioproducts perfectly match contemporary ideas of the "Circular Bioeconomy" as a game changer towards a sustainable economy that is locally driven in contrast to the currently established fossil feedstock based and globally driven "linear economy" by a few fossil resource-rich countries (10). And governments, especially local and state, can play a major role in this transition away from the fossil fuel based global linear economy to a locally driven and sustainable bioeconomy that is based on agricultural and other feedstocks currently considered waste, through appropriate incentives to corporations and start-ups that possess the technology but lack financial and human capital.

Sustainability of "Industrial Biotechnology" concepts need to be further quantified, although they have already demonstrated their value despite being in their early stages of development, by the use of modern tools like the "Sustainable Process Index" (SPI). SPI is a measure to assess the viability of processes under sustainable economic conditions on a scientific basis. According to Krotschek and Narodoslawsky, the SPI concept assumes that the basis of any sustainable economy is the sustainable flow of solar energy. The conversion of the solar exergy to products, however, requires land area. Therefore, land area becomes the limiting factor for a sustainable economy. In this context, the SPI calculates the areas needed to provide the raw materials and energy demands and to manage and upgrade by-product flows from industrial processes in a sustainable way. Importantly, it also considers the areas needed for ultimate disposal of goods, such as plastics, since this concept embeds generated waste as raw materials into material cycles. This is exactly where Industrial Biotechnology, based on renewable resources, reveals its sustainability benefits: although fossil feedstocks are ultimately also based on solar energy and biomass, the have an extremely low rate of regeneration. For the stream of carbon present in products like plastics from the global carbon cycle to go back into its long-storage form (fossil feedstock) takes millions of years. This contrasts significantly to the raw materials and the life cycle for products of Industrial Biotechnology, where generation of renewable raw materials, converting them into renewable materials, their use, and then their conversion back to renewable raw materials such as complex biomass, methane or carbon dioxide has a life span of 6 years or less. And, then the cycle starts *de novo*, demonstrating the circularity of products of "Industrial Biotechnology". In the above cycle for products of Industrial Biotechnology, the use of these products takes up most of the 6 years while their regeneration takes up only a fraction of the time. Linear industry, based on fossil resources, differs drastically from this concept: fossil feedstocks are converted much faster for production of goods than the restoration of carbon back to fossil carbon storage or reserve can occur, but at much slower rate. Human intervention is then needed, and in most cases these spent products from fossil carbon either accumulate in landfills or in the environment or are incinerated to produce CO_2, thus resulting in significant alteration of the global carbon cycle. Coming back to the required land area as calculated by the SPI, one can estimate that the formation of 1 kg fossil compounds (calculated as "organic sediment" in the beds of oceans) requires about 500 m^2, while formation of 1 kg of renewables, such as carbohydrate-rich wheat, requires about 0.5 m^2, which gives renewables an SPI-factor of 1000 (11).

The Origin of Industrial Biotechnology

Originally called "White Biotechnology" and later renamed "Industrial Biotechnology", this field is not a new approach for manufacturing chemicals and plastics. The first large-scale biotechnological production of lactic acid dates back to 1881. In 1895, Boehringer Ingelheim discovered lactic acid production in large quantities by tailored application of selected bacterial production strains (12). At about the same time, in 1887, Buchner discovered the enzymes responsible in the yeast *Saccharomyces cerevisiae* for ethanol fermentation; this opened the door to understanding and optimizing industrial scale ethanol production based on scientific criteria rather than relying on ancient fermentation protocols that were based on trial and error. Moreover, in 1888 the Dutch scientist Martinus Willem Beijerinck discovered polyhydroxyalkanoates (PHA), which were subsequently identified by Maurice Lemoigne in 1920's. Biotechnological processes for a broad range of industrial products, such as solvents and energy carriers like acetone, isopropanol (2-propanol), 2,3-butanediol (2,3-BD), or 1-butanol were also discovered in the beginning of the 20th century. That time, it was already understood that facultatively anaerobic yeasts and bacteria (for production of ethanol or 2,3-BD) or strictly anaerobic Clostridia (production of 1-butanol, acetone, or isopropanol) can be applied as cell factories for "Industrial Biotechnology". Indeed, already at the beginning of the 20th century, biotechnological production of 2,3-BD, a precursor for 1,3-butadiene, the central compound in rubber production, was well researched, and Fulmer proposed a 2,3-BD production process based on "Industrial Biotechnology" in 1933 (13). In 1915, Chaim Weizmann, Israel´s first president from 1949-1952, patented a process for biotechnological production of acetone and alcohols (1-butanol and ethanol) from starch-based materials by a mixed microbial culture which mainly contained the species later known as *Clostridium acetobutylicum*. At that time (WWI), it was acetone, not 1-butanol, which was the product of major interest due to its military importance as essential compound to produce the explosive cordite, while 1-butanol was considered merely as an undesired by-product reducing the substrate-to-acetone yield in the process (14). After WWI, the need for explosives and thus for acetone suddenly decreased. Yet, this *Clostridium*-based Weizmann process experienced a revival when automotive production emerged in the USA, and amyl acetate was needed as component of car lacquers. Here, one needs to remember that amyl acetate production was highly dependent on the availability of alcohol amyl alcohol (pentanol), a by-product of bioethanol and spirit production ("fusel alcohol"). During the "Prohibition in the United States" (1920-1933), however, official ethanol fermentation processes became scarce, creating a shortage of amyl alcohol. As an alternative, butyryl acetate soon turned out as viable substitute in car lacquers, where the *Clostridium* product 1-butanol replaces amyl alcohol. Industry remembered that this alcohol can produced biotechnologically by the Weizmann fermentation process, and dug up the old fermentation protocols; indeed, in the early 1920's, biotechnological 1-butanol production became the second most important industrial fermentation process worldwide right after bioethanol production, while that time acetone became the product of minor interest of this fermentation process (15). During WWII, all these compounds became strategically important, but by then the production techniques changed from bioprocesses to the then emerging petrochemical approaches (16).

Finally, in the decades following WWII, petrochemical production processes for these compounds, high in their substrate-to-product yields and volumetric productivities, became well established, and fossil feedstocks were available at a low and stable price, which contrasted with the rather high costs for renewable feedstocks competing with nutritional purposes. Back then, biotechnological processes for producing 2,3-BD, 1-butanol, acetone, isopropanol and others were relegated to being scientific curiosities that only microbiologists persue in their laboratories (16).

The situation changed again with the Jom-Kippur-War in 1973, which was followed by the OPEC oil export embargo of 1973–1974 causing the first oil crisis and leading to a sudden increase of the crude oil price by about 70%. This first oil crisis demonstrated the extreme dependence of industrialized nations on fossil fuels. After the Iranian Islamic Revolution 1978-1979 and following the First Gulf War, the second oil crisis started, pushing crude oil price from 13 to 39 US-$ per barrel in 1979/80, thus ultimately showing the vulnerability of industrialized nations to the sudden shortage and price fluctuation of crude oil. This allowed the biotechnological processes for production of bioproducts like fuels, solvents, polymers, and other compounds to regain their importance, attracting the attention of large industrial companies; and now, the underlying bioprocesses for these products were no longer considered scientific curiosities. The late 1970's also exhibited the first examples of successful industrial-scale applications of biotechnology through the production and use of enzymes in laundry detergents, which replaced phosphates to better remove stains from textiles and helped eliminate the negative consequences of phosphate-caused eutrophication causing algal blooms (17). Industrial enzyme production and their use in laundry detergents and later in animal feed highlight some of the best examples of "Industrial Biotechnology" and their impact on society and the environment. In 2021, the global industrial enzyme market was estimated at more than $ 6 billion, an increase by 26% from 2016 (18). Numerous industrial enzymes each covering dozens of applications, from detergents, textile manufacturing, personal care applications, wood bleaching during pulp and paper production, leather treatment, baking, fruit juice clarification, brewery, to animal husbandry are industrially produced by the large-scale cultivation of microbes - bacteria, archaea, yeasts, or other eukaryotes (19).

The period spanning the first and second oil crisis also witnessed significant research and scale-up activities in polyhydroxyalkanoate (PHA) biopolyesters., although they had been first described by Maurice Lemoigne already in the 1920's and then relegated to being mostly a scientific curiosity until the 1970's. The factors motivating researchers to work on these strange microbial inclusion materials were indeed the fact that they were polymers and interesting from a material standpoint. Primary research focus, however, was dedicated to their metabolic functions in living cells and conditions stirring their biosynthesis and intracellular mobilization despite the prevailing notion at the time that "plastics are made from fossil sources such as petroleum, and not from bacteria". Shortly after this renewed interest in PHA, groundbreaking patents on first industry-fit PHA production processes were filed, e.g., the pioneering works of Holmes *et al.*, covering the fermentative production processes in bioreactors, downstream processing for product recovery, and, most of all, processing, blending and application of PHA biopolyesters as replacement for petrochemical polymers (20). Consequently, Imperial Chemical Industries (ICI), UK, started poly(3-hydroxybutrate-*co*-3-hydroxyvalerate) (poly(3HB-*co*-3HV)) copolyester production in 1976 using the soil bacterium *Cupriavidus necator* with an annual production capacity of 5,000 t; this PHA was commercialized under the trademark BIOPOL™, and used for manufacturing shampoo bottles, disposable razors, etc. Later, this technology was sold via Zeneca and Monsanto to Metabolix, who, in 2006 launched a joint venture (Telles) with Archer Daniels Midland (ADM) to commercialize PHA just as crude oil prices were again experiencing new peaks. Telles announced the commercialization of PHA biopolymers for injection molding, thermoforming, compression molding, and paper coating under the trademark Mirel™ touting at an annual capacity of 50,000 t. However, when the crude oil prices dropped again due to the economic crises in 2008/2009, PHA production again appeared sufficiently unprofitable since prices of renewable raw materials, such as sugar or starch, reached their relative peaks. The Telles joint venture was eventually terminated in 2012 and Metabolix resorted to contract manufacturing their products for sale. The price differential between PHA biopolymers from Metabolix and their fossil plastics counterparts remained sufficiently high between 2012 and 2016, ultimately leading to Metabolix terminating its PHA biopolymer activities. CJ CheilJedang, a Korean industrial Biotechnology/Food/Feed company was the beneficiary of Metabolix's demise when their PHA assets were sold to CJ CheilJedang. Noteworthy, also in the course of the second oil crisis in 1982, the company Chemie Linz, Austria, started large scale PHA production, producing about 1 t of this material per week in a 15 m^3 bioreactor with the bacterium *Alcaligenes latus* DSM 1124 (today: *Azahydromonas lata*) in a pioneering "Industrial Biotechnology" based process. The produced PHA was processed to manufacture prototypes of cups, bottles, syringes, bullets, pens, etc. Chemie Linz's original technology (fermentation conditions, composition of nutrient media, establishment of fermentation protocols, downstream processing) to manufacture PHA was originally developed at Graz University of Technology, Austria, and is today owned by the German company Biomer, which still manufactures the homopolyester poly(3-hydroxybutyrate) (P(3HB)) on industrial scale based on this process (21, 22).

Apart from the PHA sector, based on current crude oil prices far above 100 US-$ per barrel, we witness again a fundamental switch in manufacturing, evidenced, e.g., by the revival of the biosynthetic 2,3-BD production, which started in the USA, and, since the 2010's, is strongly emerging especially in PR China (23). Already in 2013, Savakis and colleagues estimated annual growth rates for biotechnological 2,3-BD production at 3-4% of total production (24). Currently, a small, but steadily growing number of companies such as LanzaTech and GS Caltex Corporation are producing bio-based 2,3-BD on an industrial scale (25).

A similar trend can be observed for 1-butanol; this important solvent and raw material in paints and coatings and in the textile industry is also being considered for scale-up. 1-butanol is a drop-in for gasoline and diesel fuel with high energy content (30% more than ethanol) and octane number similar to gasoline, and and is used as fuel additive. In 2007, the annual production of biomass-based 1-butanol ("biobutanol") was estimated at about 2.8 Mt (production capacity of 3.6 million tons), accounting for a market value of about 5 billion US-$ (26, 27). Currently, biobutanol production plants of are predominantly concentrated in Europe and North America exporting to markets in the Asia-Pacific region; the global biobutanol market was valued at 3.0 billion US-$ in 2013 and reaching US-$ 4.3 billion by the end of 2018 (27). Trends in biobutanol production are focused on moving from 1st generation feedstocks such as corn/starch to less expensive 2nd generation cellulosic feedstocks, which claims a reduction of raw material costs by about 50% (29). The next generation of biofuel might be produced from syngas or biogas, a material accessible from by conventional gasification or hydrothermal gasification of abundantly available lignocellulose waste materials (30).

PHA biopolyesters are also on a new wave of industrialization; as recently reported, there is currently a steadily growing number of established companies producing PHA at large scale for production of bulk products (Biomer, Kaneka, Danimer Scientific, PHB/ISA, Tepha Inc., COFCO; TianAn Biopolymer, Ecomann, etc.) and emerging young companies with special focus on the use of inexpensive raw materials such as biogas (PHAXTEC, Mango Materials), Nafigate (waste cooking oil), Newlight Technologies (effluent gas – CH_4), RWDC Industries (waste cooking oil), or BluePha, ("alternative carbon source, incl. crops and kitchen waste"). Additional recent activities in PHA centers on the "Next Generation Industrial Biotechnology" (NGIB) concepts by engineered extremophilic microbes (BluePha, PhaBuilder, Medpha). Realistic estimates for the current annual quantities of PHA produced worldwide report about 10,000 tons, while combined announcements made by the companies listed in this paragraph report capacity expansion for the next decade of up to 1.5 Mt (22). Replacing this quantity of fossil plastics by PHA would save an annual amount of fossil feedstocks of approximately 3 Mt (based on the material balance for poly(ethylene) (PE): one PE plastic bag of 20 g requires an amount of crude oil of about 40 g or 50 mL, respectively), and roughly 3-5 Mt less CO_2 emissions into the atmosphere (31).

Definitions of Industrial Biotechnology, and Interrelation to other Branches of Biotechnology

"Industrial Biotechnology", also known as "White Biotechnology", describes industrial-scale implementation of biotechnology, namely the use of eukaryotic (fungi, algae) or prokaryotic (bacteria, archaea) cells where the industrial manufacturing processes are driven by "whole cell biocatalysis" or their components such as individual or a collection of enzymes that are used as biocatalyst(s) for manufacturing products in large scale using renewable carbon resources (32). Typically, industrial biotechnology describes production of bulk products required in large quantities. Important examples for highly demanded products produced by "Industrial Biotechnology" are enzymes for industrial applications such as amylases, lipases, proteases, and pectinases, often used as components of detergents or in the food processing industry, biopesticides such as *Bacillus thuringensis* toxin (Bt-toxin), and alternative energy carriers such as bioethanol, biobutanol, biogas, or biohydrogen. Finally, biopolymers to substitute fossil plastics such as PHA are a core field of "White Biotechnology".

There is some overlap of "White Biotechnology" and other biotechnological sections. For example, production of biopesticides like Bt-toxin serves to protect agricultural plants, hence, the products of "Industrial Biotechnology" are used in plant biotechnology, also called "Green Biotechnology". Fermentation with lactic acid bacteria (LABs) produces lactic acid, a bulk compound of "Industrial Biotechnology" of broad applicability, such as in cleaning supplies and detergents, as decalcification agent, and as biobased monomer to be used for production of poly(lactic acid) (PLA), a renewable polymer that can be industrially composted and is a substitute for fossil plastics. However, lactic acid is also of relevance in the food sector which is sometimes referred to as "Yellow Biotechnology", therefore lactic acid production at large scale traverses both "White Biotechnology" and "Yellow Biotechnology". Additional products belonging to more than one field of biotechnology are vitamins, used as food supplements (e.g., vitamin B12 (cyanocobalamin) produced at large scale by *Propionibacterium* ssp., or vitamin A (β-carotene) obtained from the halophilic microalga *Dunalliella salina*, a biocatalyst of Marine Biotechnology, also called "Blue Biotechnology"), antioxidants (various pigments accessible from diverse microorganisms), or essential amino acids and fatty acids of microalgal origin, also processes of "Blue Biotechnology". Technical enzymes produced via large scale fermentation, therefore also called "Industrial Enzymes", and used in food production are referred to as products of Food Biotechnology or "Yellow Biotechnology". One such notable enzyme that is used as part of animal feed is phytase (33). It helps pigs absorb and retain more of the phosphates contained in animal feed, thereby improving their growth and generating less phosphorous-based waste from pig farming. Enzymes for food and feed applications account for more than half of the global enzymes consumption, with an estimated 6%–8% annual growth rate (34).

Similarly, "White Biotechnology" also overlaps with "Red Biotechnology" (medicinal biotechnology), e.g., when it comes to bulk production of fungal antibiotics like penicillin. Moreover, PHA as a product of "White Biotechnology" can also be used in "Brown Biotechnology" (environmental biotechnology), which refers mostly to bioremediation processes, which in turn covers the remediation of ecological damage by the action of living organisms. On occasion plants are used for bioremediation, also called "phytoremediation" and in this case "Brown Biotechnology" overlaps with Plant Biotechnology or "Green Biotechnology". Bio-On, an Italian PHA producing company claimed that oil slicks on the ocean´s surface could be biodegraded by microorganisms if they were also given PHA powder as a co-nutrient ("Minerv Biorecovery technology"), thereby demonstrating that PHA, a product of "White Biotechnology", gets implemented in a "Brown Biotechnology" process (35). PHA can also be applied in water bodies polluted by nitrate, where PHA act as electron donors via the metabolic activity of denitrifying bacteria (36). This process is being practiced in PR China at waste water treatment plants and TianAn, a Chinese PHA producer, has successfully demonstrated this process (37). This illustrates how broad the range of products accessible from "Industrial Biotechnology" are; almost all products accompanying our daily lives, which are currently produced from fossil carbon chemistry can be produced by biotechnological means, or can be replaced by bio-inspired alternatives. For illustration, the PE plastic cup we used today for our coffee when commuting to work can conveniently be replaced by a cup made of PHA and its bio-composites, or through a PHA coating on paper cups instead of a fossil plastic coating; the fuel powering internal combustion engines are being produced by anaerobic Clostridia (biobutanol), and surgical wires and fibers typically consisting of fossil carbon derived poly(ε-caprolactone) sutures can be replaced by Tepha Inc.´s elastic and stretchable PHA biopolyester products, biosynthesized in bioreactors by engineered *Escherichia coli* cells.

A highly complex and heavily used product such as the antibiotic tetracycline is exclusively produced via biotechnological means. This polyketide requires 72 chemical reaction steps when synthetically produced and has poor conversion yields, making it uneconomical to produce via chemical means. On the other hand, biosynthesis of this antibiotic inside living *Streptomyces* strains occurs via optimized and interconnected cascadic enzyme reactions yielding optimum conversion of the renewable carbon substrate into the desired product (38). Generally, enantiopure products are typically biocatalyzed enzymatically or through whole cell biocatalysis, in other words inside living microorganisms, since enzymes inside living cells or outside are highly stereoselective, while chemical processes often result in low enantiomeric excess. This is of importance for the production of pharmaceutical active compounds, where often only one stereoisomer displays the required biological activity (39). For example, the (*S*)-enantiomer of the β-blocker propranolol has a 100-fold higher antagonistic activity at the β-receptor than the (*R*)-enantiomer (40), while for the anti-malaria drug Resochin (Bayer AG), the racemate of chloroquine is applied (41); hence, stereoselectivity, as provided by biocatalysis, is of utmost importance for activity of pharmaceutically relevant products. Enantiopurity is also important for lactic acid production, where only the L-(+)-enantiomer is readily digested by humans, and enantiopure lactic acid is also needed for polymerization to PLA. Selecting appropriate LABs is, therefore, important to produce the appropriate lactic acid of high enantiopurity in anaerobic fermentation (42).

More recently, there is an increasing overlap of "Industrial Biotechnology" and "Blue Biotechnology", where biotechnological production processes have been tapping the wealth of marine microorganisms to use them as biocatalysts to produce various products. Microorganisms isolated from the oceans offer plenty of products of significance for industry, such as enzymes active at very high or very low temperature ("extremozymes"; used, e.g., for designing novel tensides), or ingredients of marine microalga and cyanobacteria that are the source of valuable nutrients or food additives such as pigments for coloring food, antioxidants for preserving food, and polyunsaturated fatty acids taken as supplements by humans as well as animals (43, 44).

Production of PHA which is an "Industrial Biotechnology" process, we witness a current trend towards using robust PHA producing strains that are adapted to high salinity and isolated from the ocean or salt lakes. Examples of such strains are the haloarchaeon *Haloferax mediterranei*, a strain growing at an optimum salinity as high as 200 g/L NaCl, or *Halomonas* TD01, a Chinese salt lake isolate. While *Hfx. mediterranei* cultivations are currently performed in laboratory and pilot scale (300 L working volume) (45), *Halomonas* TD01 and their genetically modified versions e.g., *Halomonas bluephagenesis*, are already being applied industrially in innovative biotech companies in PR China, such as PhaBuilder, where PHA is currently slated to be produced at an annual capacity of around 10,000 tons. BluePha and COFCO each have an annual capacity of about 1,000 tons (22). BluePha even emphasizes on their website that they industrially produce PHA via "Blue Biotechnology" (46). The high salinity requirements of these organisms necessitate cultivating them in hypertonic media, which in turn prevents other microbial species to contaminate the mono-septic culture, thus

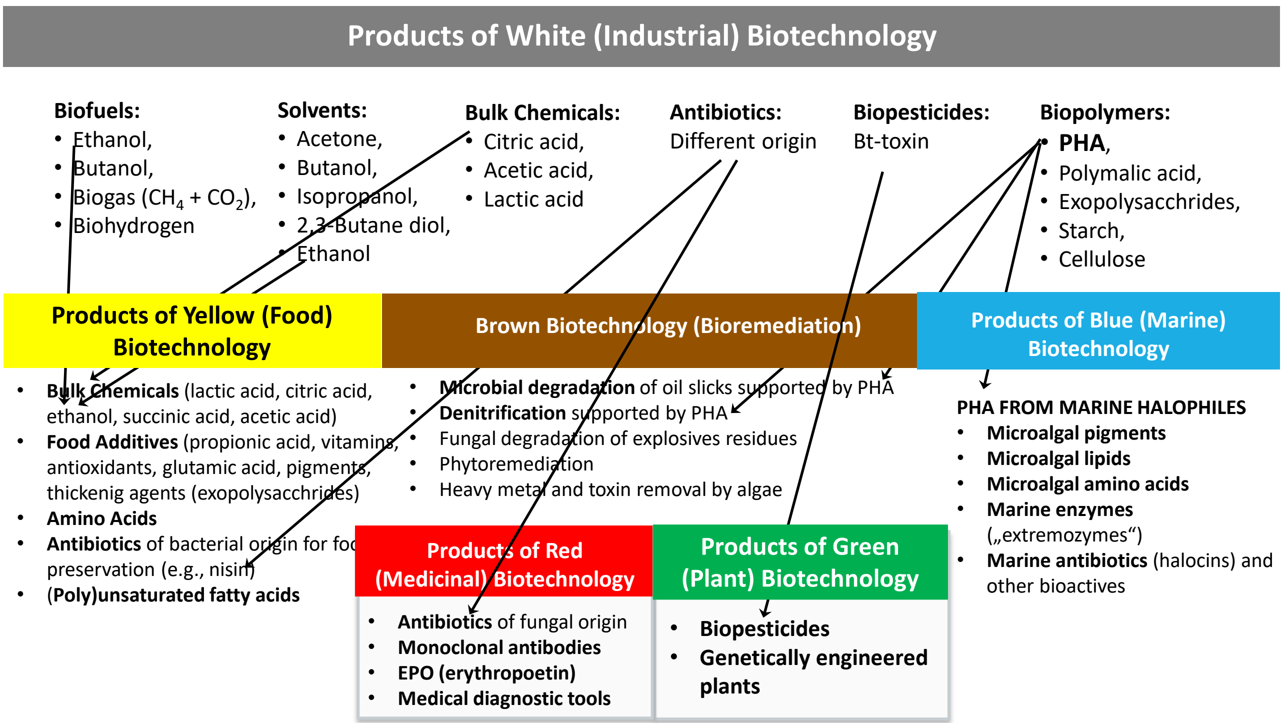

Figure 1. Examples of products of "White/Industrial Biotechnology", and its overlap with other sectors of biotechnology.

allowing fermentation and production of PHA with minor or no sterility precautions reducing production cost. In the case of *Halomonas* cultivations, fresh water is substituted by ocean water, which already contains the optimum salt concentration for cultivation. The combination of optimized and engineered marine production strains obtained by "synthetic biology", low or no sterility precautions, and inexpensive cultivation media is being called the "Next Generation Industrial Biotechnology" (NGIB), and holds the potential of being a viable route to producing PHA economically (47). Other auspicious halophilic PHA production strains that fit this NGIB concept are already waiting in the wings, such as the eubacterium *Halomonas halophila*, a strain with expedient PHA productivity from abundantly available inexpensive raw materials (48, 49).

A well-known definition of "Industrial Biotechnology" is provided by EuropaBio - The European Association for Bioindustries, self-defined as "Europe's largest and most influential biotech industry group" dedicated to "promoting an innovative, coherent, and dynamic biotechnology-based industry in Europe" with most large and many midsized and small industry players among their members, such as BASF SE, Pfizer, DSM, etc. (50). They define "Industrial Biotechnology" as industry that "*uses enzymes and micro-organisms to make biobased products from renewable raw materials in sectors such as chemicals, food and feed, detergents, paper and pulp, textiles, and bioenergy*." Moreover, in a rather all-encompassing manner, they talk about "*biotechnological production of special chemicals and fine chemicals, food and food additives, agricultural and pharmaceutical precursors and numerous auxiliary materials*" for the processing industry as focus area of "White Biotechnology", hence, products of "Yellow", "Green", Brown" and "Red Biotechnology" are integrated in this definition (51).

The Germany-based Fraunhofer-Gesellschaft, arguably the world's leading applied research organization, defines "White Biotechnogy" as "*the industrial production of organic basic and fine chemicals as well as active ingredients using optimized enzymes, cells or microorganisms*" (52). This definition is noteworthy since "optimized" biocatalysts, that include tools such as genetic modification or engineering of production strains, synthetic biology, and enzyme design, are considered in this definition to be integral parts of industrial biotechnological processes of the future.

Finally, the definition used by Organization for Economic Cooperation and Development (OECD) distinctly mentions two hot spots of "Industrial Biotechnology": First, "Industrial Biotechnology" is dedicated to the replacement of finite (limited) fossil fuels with renewable raw materials, i.e., biomass. Second, "Industrial Biotechnology" enables replacing conventional industrial processes with biological processes that reduce energy requirements as well as "*reduce the number of process stages and thus reduce costs while creating ecological advantages at the same time*" (53).

The next section illustrates how PHA biopolyester production fits into these abovementioned hot spots in an expedient manner.

How does PHA Fit within Industrial Biotechnology?

Polyhydroxyalkanoates (PHA) are microbial storage compounds found in many prokaryotic species. In living cells, they serve as intracellular reserve materials helping cells to withstand periods of starvation, and contribute to protect the cells against various stress factors, such as heat, freezing, osmotic imbalance, UV-radiation or oxidation. Observing such cells under the microscope, PHA inclusions appear as light refracting granules of spherical to ellipsoidal shape. Chemically, PHA are polyoxoesters of hydroxyalkanoic acids (54, 55).

Being products of the microbes´ secondary metabolism, they are typically accumulated by cells during conditions of nutritional imbalance, characterized by surplus of exogenous carbon sources together with depletion of other nutrients pivotal for cell propagation, such as nitrogen or phosphate source. Under optimized cultivation conditions, mass fractions of PHA in producing cells can exceed 0.9 g/g. When nutritional conditions change again (such as the lack of exogenous carbon source), cells convert these reserve materials (the PHA) to supply their metabolism with carbon and energy. Importantly, carbon sources used as feedstocks for PHA biosynthesis are of renewable nature. Here, heterotrophic materials (sugars, lipids, alcohols) or their aerobic or anaerobic degradation products (CO_2 or CH_4, respectively) can be converted by various microbes to accumulate PHA. Hence, these materials are biobased (produced from renewable materials) and, at the same time, biosynthesized by living cells, which matches above-described definitions of Industrial Biotechnology when it comes to their industrial-scale manufacturing as bulk products (56). Indeed, there is a steadily growing number of companies producing and commercializing PHA on a small scale. Many of these companies target market segments where large quantities of fossil plastics are currently used and are coming under intense scrutiny due to their persistence in the environment. This covers especially plastics produced for single use applications, such as drinking straws, cutlery, plates, food packaging, hygiene articles, carrier bags, and diverse packaging materials (21). The need to substitute fossil plastics in these segments has already been regulated in Europe through the European Directive on Single-Use Plastics and elsewhere (57). This regulation implements the EU's plastic strategy (58), and took effect in the EU in summer 2021; it prohibits certain single-use plastics for which alternatives are already available. Such "single-use plastic products" are defined as products made solely or partly from materials or plastics that are the result of a chemical modification and which are not conceived, designed, or placed on the market to be used multiple times for the same purpose. For other single-use plastic items, EU member states must limit their use through national consumption reduction measures, a separate recycling target for plastic bottles, design requirements for plastic bottles, and compulsory labels for plastic products to inform consumers (57). This is exactly where PHA can play a key role in future as products made by "Industrial Biotechnology". However, The European Commission made a grave mistake of restricting the use of PHA in such segments by defining PHA

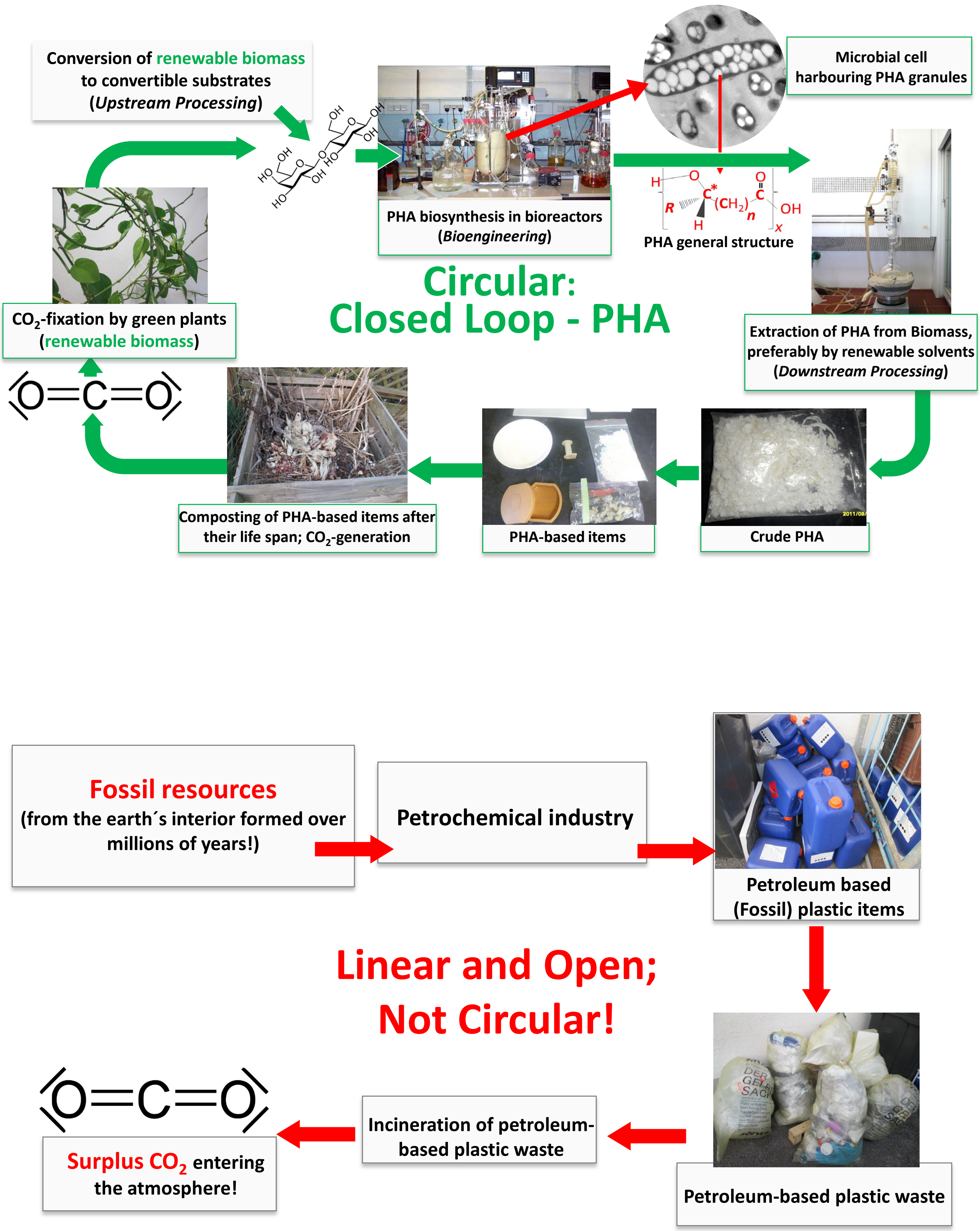

Figure 2. *Upper part:* Circularity of PHA biopolyesters produced from renewable feedstocks, produced as "bioplastics" by "Industrial Biotechnology". *Lower part:* Established, linear plastic production by industrial petrochemistry. Based on (60).

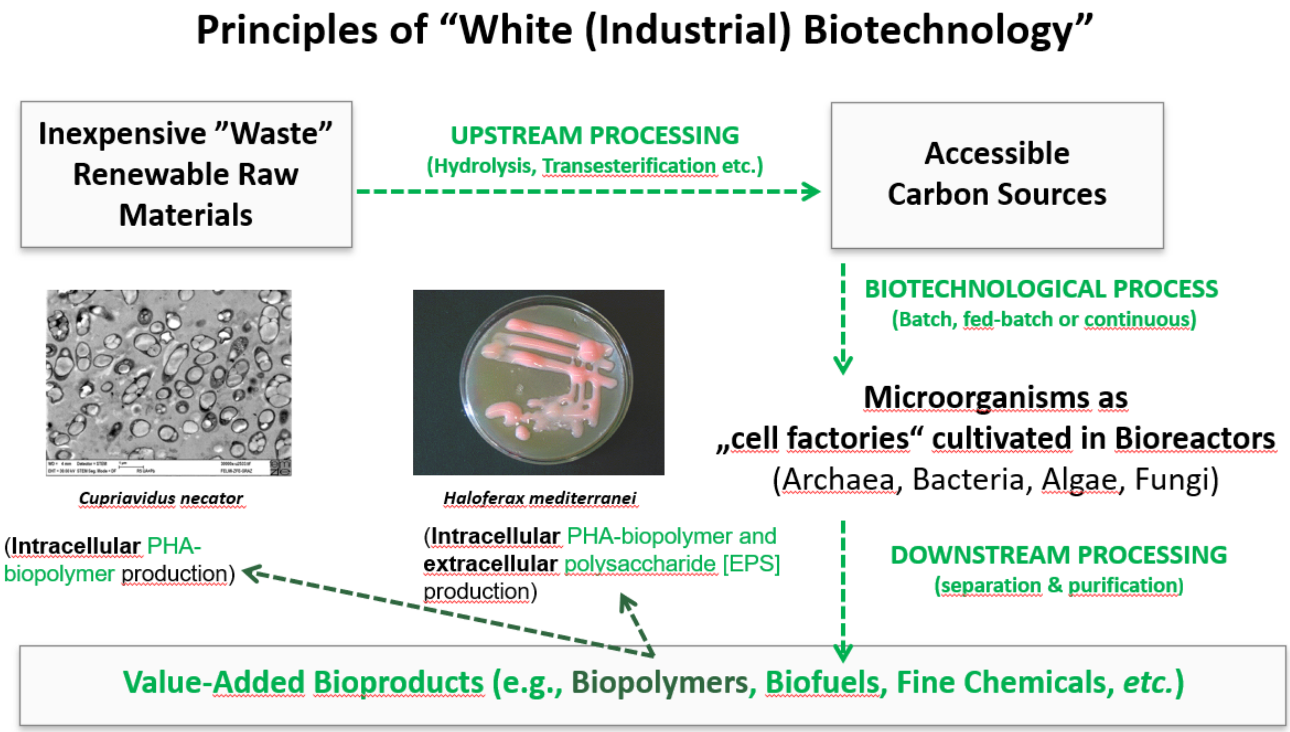

Figure 3. Schematic of "Industrial/White Biotechnology" for biopolymer (PHA and EPS) production.

as a "chemically synthesized product", thereby classifying it in the same category as fossil-plastics. The Commission ruled that fermentation is an industrial process and products of industrial processes are chemically modified products, thus implying that beer, wine, and cheese to be chemical products and non-natural. To add insult to injury, The Commission ruled that paper could be used for such applications although paper is cellulose that has been chemically modified.

In addition to being biosynthesized and biobased, PHA are also biodegradable and compostable, both via home and industrial composting as reviewed before (59). This biodegradability and compostability in turn underlines the circularity of PHA: Once disposed, items produced from spent PHA undergo aerobic or anaerobic degradation to CO_2 or CH_4, respectively and water, the very products used for their *de novo* biosynthesis by cyanobacteria (utilize CO_2 for PHA biosynthesis) and type II methanotrophs (utilize CH_4), or "Knallgas bacteria" (utilize CO_2 and H_2), for biosynthesis of heterotrophic feedstocks for PHA production by photosynthetic fixation of CO_2 by green plants (59). Figure 2 illustrates the circularity of PHA biopolyesters in comparison to established fossil plastics.

OECD´s definition of "White Biotechnology" referring to the "reduction of the number of process stages" in a production process (53) matches well with the biotechnological production scheme of PHA. For fossil plastics, feedstocks need to be fractionated and pure monomers need to be produced through numerous chemical steps. These monomers are then chemically polymerized by means of radical or condensation polymerization requiring complex and expensive catalysts as radical starters. In the case of PHA, renewable raw materials are directly converted by living organisms *in vivo* into PHA-precursors, namely hydroxyalkanoate monomers. The same microorganisms then polymerize the hydroxyalkanoate monomers into PHA polymer (20). This offers considerable advantage in the manufacture of PHA compared to PLA, another renewable polymers, where only the monomer (lactic acid) is produced biotechnologically, while dimerization of the monomer to dilactide and the subsequent challenging ring opening polymerization (ROP) of dilactide to PLA constitute separate, cumbersome and chemical production stages that need to be carried out consecutively in individual reaction vessels (61).

Figure 3 illustrates the principle of "White Biotechnology" when used for production of biopolymers like PHA or extracellular polysaccharides of that are of industrial and human relevance.

Future Trends and Outlook

Despite the embryonic nature of Industrial Biotechnology, the increasing awareness of the impact of climate change, environmental pollution, and the damaging effects of fossil fuels including global geopolitical instability caused by its use, industry, policy makers and the consumer are beginning to accept and even embrace their products. The European Commission has started the process to determine the benefits of biobased and biodegradable products and is on course to issue a new directive in 2022 to encourage and perhaps even mandate their use. California is revisiting its stance on the ban on using the term "biodegradable" on products, primarily due to the push from PHA producing and PHA based product manufacturing companies. Asian countries like Thailand, PR China and India are taking note, primarily due to the devastating consequences of environmental pollution and are mandating the use of biodegradable and biobased products, thus benefiting those that are already commercializing Industrial Biotechnology based products.

Therefore, this branch of biotechnology is poised to evolve rapidly in the next decade and take its place as the transformative driver in our move away from fossil fuels-based products into products that are closer to nature in their origin, functionality and in their end-of-life options. PHA is one such product that has the potential to replace more than 50% of fossil plastics used in packaging and personal care, and in textiles and durable products.

Industrial Biotechnology also holds the promise to offer novel products that could not have been thought of a few years ago. Industrial Biotechnology has the power to shorten and localize entire supply chains and benefiting all regions of the world. Industrial Biotechnology has the ability to allow the holistic development of a novel and innovative industrial economic system that would be multifaceted, starting from novel, non-pathogenic and powerful biocatalysts (production microorganisms), local and therefore far secure supply chains, the use of inexpensive raw materials including waste carbon sources that are not reused today. In order for Industrial Biotechnology to become more prevalent the acceptance by and the trust of the general public (consumers) and decision makers are crucial. The issues around genetic modifications of food producing plants and pesticides and the public's opposition to them in the past decades is still alive and there are disturbing trends of such opposition in the use of genetically modified organisms to manufacture materials and products that are not intended to be consumed. Here, Industry and Academia have a critical role to play by highlighting the benefits of products from Industrial Biotechnology, but also by promoting their safety during production, in use and at their end-of-life options. Surprisingly, issues surrounding the genetically modified organisms (GMO) and their use in medicinal biotechnology or "Red Biotechnology" are non-existent, since the consumer does not complain when genetically modified microorganisms are used to produce lifesaving medicines. For PHA in particular, acceptance will dependent on some essential questions, such as:

- Is the feedstock supply for producing the required amounts of biopolymers or bio-based polymers secure and not interfering with food supply?

- Do materials based on PHA match the product performance of fossil plastics, and importantly, do we need the performance offered by fossil plastics, and can we accept less?

- How would the waste management industry act or react to using home and industrially compostable products at their end-of-life, do we need major structural changes to accommodate these up-and-coming biopolymers?

- How would we educate the consumer about PHA, and win them over in order for PHA to thrive as an alternate to fossil plastics, and who should undertake such an endeavor?

- How would the co-existence of fossil plastics and the use of PHA biopolymer in large scale play out from their origin, during use and at end-of-life so that we can derive the benefits of both types of polymers?

- Are PHA sustainable in a holistic sense, such as, raw material use, energy requirement, downstream processing for product recovery, end-of-life options, and ethical aspects?

The trust and acceptance of the general public appears to be favorable within groups that are appropriately informed, and the same is true with policy makers. However, this information is not consistent and misinformation and disinformation is omnipresent. The issue of oxo-degradable polymers touted as materials that are biodegradable when they are not, is a case in point.

However, the overall benefits to the environment and to society from Industrial Biotechnology has been proven, and individual products that come from Industrial Biotechnology would likely require additional scrutiny as is the case with the European Commission's study on the benefits of biobased and biodegradable materials. Finally, the two most significant benefits of Industrial Biotechnology in the form of reduced fossil carbon use and local supply chains would benefit both the environment as well as society and those two together would help mitigate both climate change and environmental deterioration, thus elevating Industrial Biotechnology to the single most transformative change in the next decade and in this century.

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Conflict of Interest

No conflict of interest exists.

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