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ARTICLE

Efficacy, Economics, and Sustainability of Bio-based Insecticides from Thermochemical Biorefineries

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The scope of this work rests at the interface between food and energy sustainability. Thermochemical conversion of biomass is an attractive strategy for the production of low-cost biofuels, and bio-based insecticides are a more sustainable and often safer alternative for pest management in agricultural production. This work demonstrates a complimentary strategy to access both biofuels and a bio-based insecticide through a catalytic fast pyrolysis process. Technoeconomic modeling shows the bioinsecticidebio-based insecticide can be produced at a cost ≤ 1.7 $/kg while fully formulated bioinsecticidebio-based insecticides typically sell for ≥ 6 $/kg, which can significantly reduce the biofuel selling price. Supply chain analysis shows a 46 – 88% reduction in green-house gas emissions for this agrochemical can be achieved. By using insecticidal activity data from two well-known crop pests, spotted-wing drosophila (*Drosophila suzukii*, Matsumura) and oriental fruit moth (*Grapholita molesta,* Herbst), with an analytical analysis, which achieved ≥99% mass balance closure on the thermochemically derived distillate product, a structure-function relationship between phenol alkylation and insecticidal activity is proposed. An ecotoxicological assessment of the bio-based insecticide was performed using existing data and prediction tools across 18 metrics. It is estimated that a 2000 tonne/day biorefinery can supply 1 – 5 % of the market, which is typical for other moderately scaled chemicals. The mixture of alkylated phenols, used as a bio-based insecticide, is an ideal coproduct that overcomes separation challenges associated with thermochemical streams, such as heterogeneity and reactivity, while providing a more sustainable source for agrochemicals. Synergistic strategies for energy and food production, such as coproduction of bio-based insecticides with biofuels, can be a viable approach to improve sustainability in both sectors.

Introduction

Ecological damage from agricultural and petroleum-based fuel production represents a significant challenge in sustainability. By 2050 agriculture production must expand by 25 – 70% (2005 baseline) to meet the food needs of a projected 9.7 billion people while the transport sector must reduce carbon emission 20 – 45% (2010 baseline) to limit atmospheric GHG levels to a 430 – 530 ppm CO_2eq target.[1,2] Gains in short term agricultural production are often prioritized over longer term stability, putting food supply at odds with long-term security and sustainability.[3] Accordingly, sustainable use of pesticides is a key focus area for food production in major regions of the world as outlined in the EU with the New EU Green Deal and its Farm-to-Fork strategy.[4,5] Similarly, liquid biofuels are promising but commercial adoption is limited by high costs.[6] A synergistic strategy towards reducing biofuel costs and reducing environmental impact of food production is to produce bio-based pesticides and biofuels

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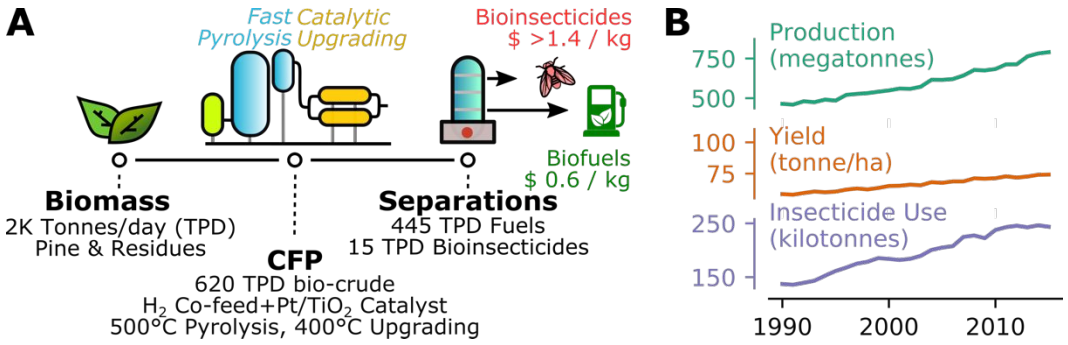

Figure 1: Sustainability considerations for bio-based insecticides. (A) Conceptional process for producing biofuels and bio-based insecticides from biomass using catalytic fast pyrolysis with minimum biofuel (green) and minimum bio-based insecticide (red) selling prices of each product shown.[35,36] **(B)** Annual growth for agricultural production (green), yield per unit of land (orange), and insecticide use (purple) continue to increas as population growth and technology development drive the agricultural sector.[6]

concomitantly in an integrated biorefining strategy, **Figure 1A**.

Pesticides, which broadly consist of herbicides, insecticides, fungicides, and rodenticides, benefit agricultural systems, but face major sustainability challenges. Between 1990 and 2015 food production and crop yields increased by 70% and 27%, respectively; however, these gains also corresponded to a 78% increase in global pesticide use, **Figure 1B**.[7] While benefits of pesticides include reduced land use that can offset water consumption and mitigate climate change, the global proliferation of pesticides has many undesired outcomes.[8] Negatives include non-renewable energy consumption, bioaccumulation of toxic compounds, detriment to beneficial insects, and increasing pest tolerance. The energy input to produce pesticides ranges from 6 to 16% of the total energy consumption of arable crops, thus contributing to GHG emissions.[9] Synthetic pesticides, especially insecticides, impact water quality when they are transported to reservoirs and streams where they can bioaccumulate.[10] Half-lives in the environment for organochlorines, many of which are now banned as insecticides, range from months to over a 100 years.[11] Pollinators, which provided €153 billion ($123 billion USD, 2005) in ecological services to the global economy, are under significant pressure leading to substantial annual colony losses, e.g. 40% loss in 2015 within the United States.[12–14] In 2018 the European Commission banned three major insecticides due to honeybee and pollinator harm.[15] Conventional insecticides are seeing increased pest tolerance.[16,17] The WHO has mobilized a concerted effort to deal with the health concerns from exposure to hazardous pesticides via unintentional or self-inflicted poisoning; such poisonings disproportionally affect low- and middle-income countries and account for 1 in 5 suicides globally.[18,19] For all of these preceeding reasons, alternative are needed that have reduced ecological impacts, are sustainable in the long term, and reduce risks to human health.[20] Biorefining is a viable strategy for making fuels and oxygenated chemicals. The U.S. Department of Energy identified over 1 billion tons of biomass that could offset 31% of U.S. energy consumption while maintaining food, feed, fiber, and timber needs.[21] Heavy-duty vehicle, marine, and aviation sectors will require energy-dense, liquid fuels even as electrification is decarbonizing light-duty vehicles. Selling chemical coproducts can can improve biofuel economics similar to the petrochemical industry where about 50% of profits come from the 15% of the oil barrel sold as chemicals.[22–24] Biomass derived molecules often contain oxygenated functionality that can provide performance advantages over existing materials.[25] The USDA has >20,000 biopreferred products registered, but there are >500,000 biobased chemical candidates available with unique, inherit chemical functionality that can drive innovation and sustainability.[26,27] This work is one venture to leverage this functionality by using biomass-derived, substituted phenols as the active ingredient in bio-based insecticides.

Advancements in thermochemical processing of biomass is increasing access to bio-based chemicals. Distillation of biomass fast pyrolysis oils has historically been problematic due to water-generating condensation reactions, but catalytic fast pyrolysis (CFP), where biomass is pyrolyzed and the resulting vapors are upgraded over a catalyst, increases bio-oil

stability and enables downstream processing.[28] Specifically, the carbonyl content of the bio-oil, a key indicator of stability, can be reduced by ~50%.[29,30] Previous studies have shown that phenols in whole pyrolysis oils lead to moderate insecticidal activity, defined as the ability to kill or retard growth of insects.[28,31] This work builds on advancements in the catalytic fast pyrolysis of biomass and preliminary investigations of pyrolysis-derived insecticides to demonstrate how bio-based insecticides can be produced using scalable, economic, and industrially relevant processes. We demonstrate the separation of a catalytic fast pyrolysis oil fraction with high insecticidal activity, assess the technoeconomic viability and environmental impact of this bio-based insecticide relative to conventional insecticides through process modeling and life cycle inventory analysis, and perform a preliminary ecotoxicological risk assessment to identity any potential hazards posed by the compounds found in the candidate bio-based insecticides.

Results and Discussion

Experimental, modeling, and analysis efforts are combined to establish performance data and demonstrate the sustainability of this new source of insecticides. Production and testing data show that biomass can be converted to an intermediate bio-oil that is subsequently fractionated via vacuum distillation, and dose response curves were used to identify the fractions with the greatest insecticidal activity. Compositional analysis is combined with mortality data to hypothesize about structure-function relationships. Process modeling using Aspen Plus® and the Materials Flow through Industry (MFI) tool are combined to estimate production costs, GHG emissions, and supply chain energy of this bioproduct.[32] An ecotoxicological risk assessment that uses existing data and prediction tools is performed to determine if any components within the insecticide could be considered highly hazardous. Finally, the regulatory considerations and market demand are explored.

Production and Dose Response of Bio-Based Insecticides from Biomass

Bio-oil was produced by catalytic fast pyrolysis and separated into fractions to test insecticidal activity. The feedstock, pine, was converted via catalytic fast pyrolysis as described elsewhere.[33] Briefly, pine wood is first pyrolyzed at 500 °C, and the vapors are then upgraded over a platinum on titanium oxide (Pt/TiO_2) catalyst at 400 °C and near atmospheric pressure in a fixed bed reactor in the presence of H_2. The vapors are condensed into a bio-oil and then used to produce biofuels through hydrotreating and distillation. The catalytic fast pyrolysis process achieves a carbon yield of 38% to the bio-oil, which has an oxygen content of 16 wt%. For this biofuels process, a minimum fuel selling price of 3.33 $/gasoline gallon equivalent has been reported for the hydrotreated fuel products, which equates to the cost of biofuel production plus a 10% internal rate of return on 40% equity investment, and 60% debt financing at 8%.[34]

The economics of producing these renewable fuels can be improved by valorizing some of the carbon as chemicals. Previous work by others has shown activity of whole pyrolysis oils as insecticides. The hypothesis for this work was that enriching components within the oil would create a more potent bio-based insecticide while leaving the remaining bio-oil for further processing into biofuels. To test this hypothesis, the bio-oil was distilled into 4 fractions using vacuum distillation, of which three were tested as candidate bio-insecticides, **Figure 2A**. The first fraction was primarily an aqueous phase and

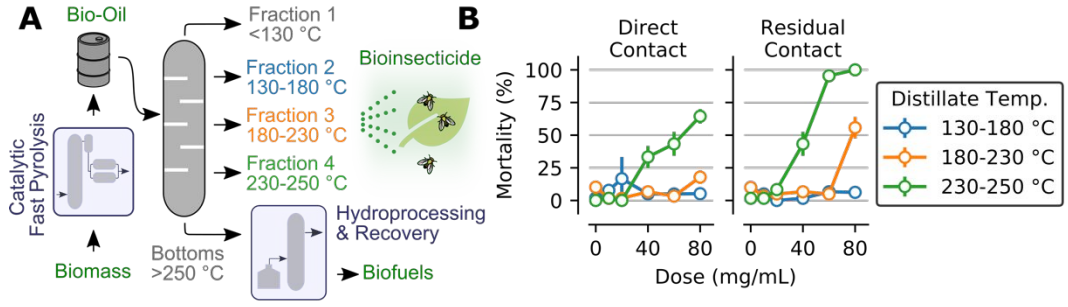

Figure 2: Production and efficacy of bio-based insecticides. (A) Process flow diagram showing the approach for producing candidate bio-based insecticides based on differences in boiling points **(B)** Residual and direct contact assays for three candidate fractions show the highest insecticidal activity in the 230 – 250 °C fraction. Error bars represent standard deviations.

was therefore not considered for use. The four fractions comprised 6, 6, 15, and 6 wt% of the feed CFP bio-oil. 64 wt% of the bio-oil remained in the bottom of the column, the distillate resid, as a viscous liquid. This demonstrates that polymerization reactions were sufficiently minimized, due in part to the stabilization afforded by the catalytic fast pyrolysis process, so as to not produce a carbonaceous solid. Physiochemical changes of the residual bio-oil and the bio-oil prior to distillation are provided in **Supplementary Table 1**. A decrease in carbonyl content is observed that is likely due to the removal of ketones by distillation rather than aging.[30] The most notable change is an increase in viscosity, which would need to be accounted for during process design. Metals and ash content remained low while elemental analysis demonstrated minor changes from the original Pt/TiO_2 oil. Future efforts will be required to demonstrate whether this residual material can be further processed into bio-fuels through hydrotreating routes or if additional steps, such as cracking, will be required. The 3% of the feedstock that was unaccounted for was assumed as losses likely held up in the bench scale equipment.

Dose response curves using spotted-wing drosophila, *Drosophila suzukii* (Matsumura) and oriental fruit moth, *Grapholita molesta* (Herbst), were used to identify the most active fractions. *Drosophila suzukii* is a serious pest of high value fruit crops in the America's, Europe and Asia, and *Grapholita molesta* is a cosmopolitan pest of stone and pomme fruit. [35–40] The three candidate fractions were subsequently tested for insecticidal activity using spotted-wing drosophila. These assays used both direct and residual exposure modalities where the insects were sprayed with a diluted solution of the candidate bio-based insecticide or the insects came in contact with residual bio-based insecticide after it had been applied to a petri dish and allowed to dry. After exposure, insect mortality was measured at 8- and 24-hour timepoints for each fraction. **Figure 2B**, which shows the 24-hr timepoint, is indicative of the observed trend that insect mortality increased as a function of dose and boiling point. For this timepoint the residual contact mortality was greater than the direct contact, which indicates that the duration of exposure may increase the efficiency. **Supplementary Figure 1** provides an annotated heat map of the aggregated spotted-wing drosophila data sets for all fractions, timepoints, and testing modalities. Dose response curves were calculated using 4 parameter log-logistic model and **Supplementary Table 2** presents the LC_{50} values, the concentration to achieve 50% lethality, for spotted wing drosophila direct and residual contact trials and diet assay performed for oriental fruit moth. The LC_{50} value of the most potent fraction for spotted wing drosophila was 62.46 ± 3.94 mg/mL. This is many orders of magnitude higher than the leading biopesticide for this pest, Spinosyn, estimated at 1.27 µg/mg, but it is more comparable to LC_{50} values reported for azadirachtin at 0.63 mg/ml.[41,42] Activity can potentially be improved through further separations or targeted catalysis.

Composition, Structure, and Activity

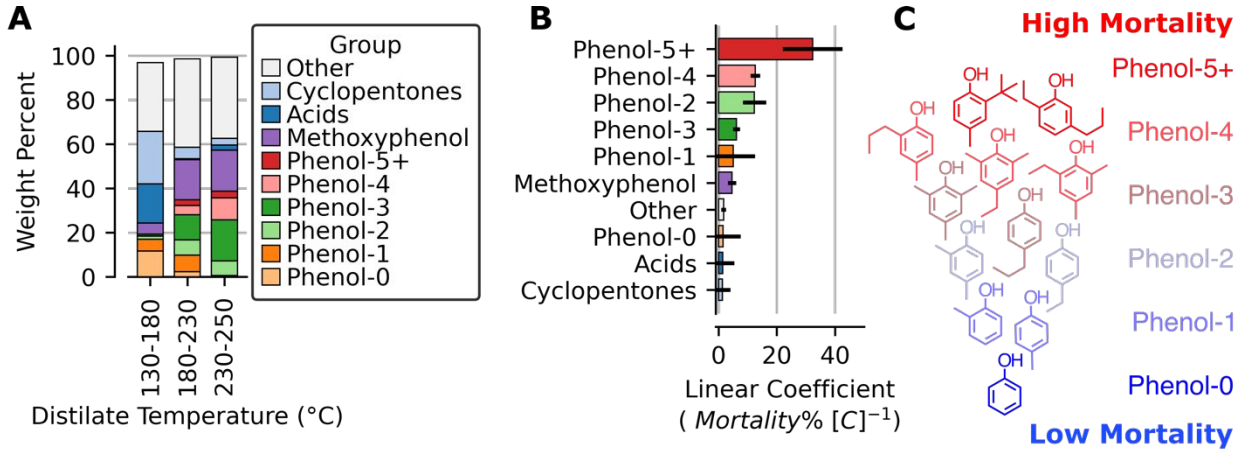

Figure 3: Structure-property relationships in bio-based insecticides. (A) Compositional analyses of distillate fractions from vacuum distillation of bio-oil show increased alkylation of phenols at higher boiling points. **(B)** Linear coefficients from correlating activity with concentration of chemical subgroups show highly alkylated phenols and methoxyphenols correlate with higher activity. **(C)** Structural depiction of increasing alkylation on phenols for both number of substitutions and number of carbons for each substitution, which is hypothesized to increase activity. The numerical value for each "Phenol" label indicates the number of substituted carbons from the ring.

To understand the relationship between composition and potency in bio-based insecticide fractions, samples were analyzed via GC×GC-MS/FID and compounds were grouped according to structure. The phenols were specifically grouped by degree of alkylation, meaning the total number of carbons within alkyl pendent groups from the phenol ring. Quantitative analysis, results provided in **Figure 3A** and **Supplementary Tables 3 and 4,** achieved near complete analytical mass balance closure, which is not commonly reported due to challenges in quantifying heterogenous streams from the thermochemical conversion of biomass. The first fraction, <130 °C, is largely comprised of water, and the organic material is primarily light organics and acids. The second fraction has a large cyclopentones (i.e., cyclopentanones and cyclopentenones) component, some acids, and a small number of other organics. The cutoff temperature, 180 °C, between fraction 2 and 3 was selected to split the fractions near the boiling point of phenol. The third fraction, 180 – 230 °C, is comprised primarily of phenols with a degree of alkylation of three or less and some methoxyphenols. The last fraction is comprised of alkylated phenols with a degree of alkylation of two or more and some methoxyphenols. Ordinary least squared regression was used to relate mortality and dose of each subgroup through linear coefficients. Fits and regression summaries are provided in **Supplementary Figure 2** and **Supplementary Table 5**, respectively. Linear coefficients, shown in **Figure 3B**, indicate that increasing degree of alkylation tends to correlate with increased activity, **Figure 3C**. Cyclopentanones have lower linear correlation with mortality and subsequently are less likely to be contributing significantly to the activity. It is proposed that the increasing degree of alkylation, and potentially the presence of methoxyphenols, explains the difference in potency observed for each fraction as shown in **Figure 2B**. These experiments were not designed to determine single component activity relationships so it is possible these correlations are spurious and the activity is due to other compounds within the fractions. However, this analysis provides a hypothesis underlying structure-function relationships which has some precedence in work by others and can be further explored.[43–45]

Understanding the relationship between specific chemical moieties and activity can enable process optimization for more active bio-based insecticides. Plants are well known to produce natural insecticides, namely pyrethins and monoterpenes, and natural phenols have demonstrated fungicidal activity.[46,47] Pavela found that phenols were generally the most active component of essential oils; analysis of the studied compounds indicates alkyl (e.g., thymol) over alkoxy functionality (e.g., guaiacol) contributes most significantly to the activity, which is in line with the results presented in **Figure 3B**. Further, 2-ethylphenol was found to be more active than 4-ethylphenol indicating substitution location can affect activity.[43–45] Several biochemical pathways have been identified that plant-derived insecticides act upon, which reduces likelihood of developed resistance. Modes of action, such as binding to gamma-aminobutyric acid (GABA) receptors to disrupt synapse functionality or activation of octopamine receptors, generally induce excitation or inhibition of the nervous system resulting in hyperextension of the legs and abdomen followed by immobilization and death.[48,49] As the links between activity and chemical functionality become more clear, targeted catalysis can be used to build on naturally occurring structures within biomass to increase lethality. Lignin contains alkyl groups in the *para* position and has a methoxy group in the *ortho* position. Based on the hypothesis that increasing degree of alkylation increases insecticidal activity, more potent bio-based insecticides could be accessed by promoting alkylation reactions that occur during pyrolysis and catalytic upgrading to modify lignin monomers. Others have demonstrated strategies for controlling alkylation by reducing the upgrading temperature, increasing N_2 pressure, or through catalyst selection.[50–52] This work identifies alkylated phenols and methoxyphenols as targets for which catalytic fast pyrolysis conditions, catalysis, and feedstocks can be tailored to improve yield and potency, but there is still much unknown about specific structure-function relationships. Identifying the specific proteins, pathways, and insect species that are affected by compounds in the mixed phenolic stream may be necessary to achieve the product performance and biorefinery process yields for this bioproduct to reach commercial maturity.

Technoeconomics, Supply Chain Analysis, and Biorefining at Scale

Technoeconomic models were used to estimate production costs from a thermochemical biorefinery and to compare the estimated productions costs with the sale prices of current commercial insecticides. The economics of bio-based insecticide production were explored by extending an existing Aspen Plus model for a catalytic fast pyrolysis biorefinery, **Supplementary Figure 3**, where the bio-based insecticide was separated from the bio-oil using fractional condensation followed

by two distillation columns.[34] The relationships between minimum product selling price, yield, and purity, defined as the amount of >2-carbon phenols and methoxy-phenols in the product fraction, were explored. Five cases were considered, as described in the methods, by operating the column at different conditions to affect purity and yield. For this process, where two distillation columns were used for separations, the purity of the bio-based insecticide ranged between 95.5 – >99.9 wt%, **Supplementary Figure 4**, and the achieved yields ranged between 5.2 – 9.6 kg / tonne-biomass, **Figure 4A**. The >2-carbon phenols and methoxy-phenols content in benchtop experiments, **Figure 3A**, did not achieve the same purity as the Aspen models, but even at the low observed experimental purity, high mortality was observed indicating the potency of the bio-based insecticide could be improved through further refining. The relatively lower concentration in the benchtop experiments can be attributed to using batch mode vs. steady state distillation in the model and non-optimized process conditions. For the five cases considered, the minimum product selling price ranged from 1.41 to 1.70 $/kg. This price range is lower than commoditized prices for cresols, 3 – 5 $/kg, and indicates that biorefining of highly alkylated phenols for use as bio-based insecticides should be cost competitive.[53,54] Additionally, fully formulated bio-based insecticides can command significantly higher market pricing, often selling for >$6/kg as shown in **Figure 4B**. Accordingly, it can be concluded that the net economic benefit to a biorefinery of this value-added coproduct could be significant.

As new processes are proposed and developed, the environmental impacts should be benchmarked against current technologies. To compare biobased insecticide production to current insecticides, a supply chain analysis that considers the manufacturing of the insecticide starting from feedstock extraction to final production (cradle-to-gate) was performed on the bio-based insecticide cases using a mass allocation approach. The same approach was used for two established insecticides, organo-phosphates and pyrethroids, to serve as a benchmark. **Figure 4C** shows the aggregate supply chain energy requirements for the bio-based insecticides, which ranged between 38 and 60 MJ/kg while the modeled values for the organo-phosphates and pyrethroids were 148 and 443 MJ/kg, respectively. Supply chain energy correlates strongly with price, which is another indication for the economic competitiveness of these bio-based insecticides.[55] For the five bio-based insecticide production cases considered, there were significantly lower GHG emissions relative to the two established insecticides with the overall reduction in emissions that could be achieved ranging from 46 – 88%, **Figure 4C**. The main contributing source of GHG emissions is process fuel (e.g., burning natural gas to generate steam). The biorefinery route to insecticides has lower estimated supply chain energy and GHG emissions partially due to the byproduct credits for acetone and electricity.[56] Additionally, conventional pesticides have material inputs that result in greater transportation energy requirements than for the bio-based insecticides. The transportation contribution to the bio-based insecticides supply chain energy is negligible. Agricultural and petrochemical production account for approximately 14% and 4% of global GHG emission, respectively.[57] While insecticides sourced from biomass may have significantly lower emissions compared to conventional insecticides, the total reduction in GHG emissions from these sectors will likely be relatively minimal as insecticide production volumes are small compared to fertilizers or other commodity chemicals. Biomass derived herbicides have approximately an

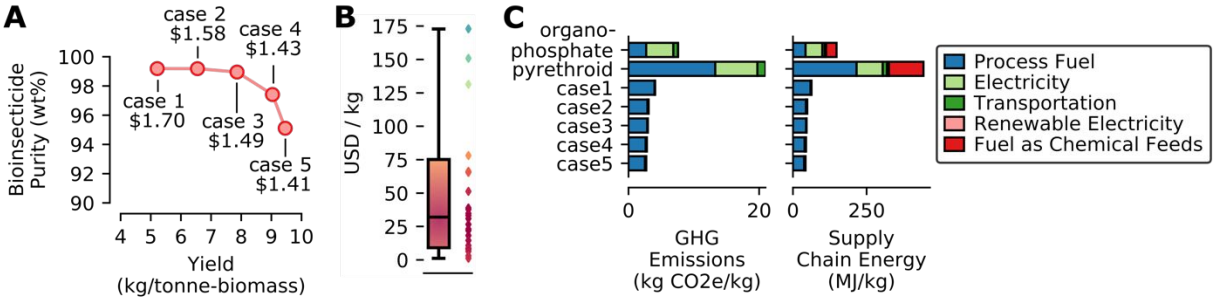

Figure 4: Sustainability metrics for bio-based insecticides. (A) Weight percent of alkylated phenols, or bio-based insecticide purity, in product fractions and minimum product selling price in $/kg as a function of yield based on Aspen Plus modeling for 5 different cases. **(B)** Whisker plot showing price range of 30 insecticides. Dots indicate individual data points.[56] **(C)** GHG emissions and supply chain energy of 5 bioinsecticde production cases and 2 currently approved insecticides.

order of magnitude larger production volume so pursuing other agrochemicals could have a greater absolute impact. Indirectly, thermochemically derived insecticides from biomass feedstocks could enable profitable production of biofuels, which have a significantly larger GHG reduction potential.[58]

Bio-based insecticides are a specific coproduct that offer unique advantages for thermochemical biorefineries at full scale. Selective production and isolation of a single compound from heterogeneous oxygenated bio-oils is difficult and will have limited production volumes. Mixed streams, such as oxygenated aromatics for resin production, have been previously pursued, but these mixtures often result in suboptimal performance.[59] They must also compete with highly refined, cheap, and pure commodity chemicals. Approved bio-based insecticides are often multicomponent plant extracts, and a mixture of compounds fractionated from a bio-oil rather than isolation of a single component will increase product volume, will reduce separations complexity, and could obtain regulatory approval if safety and efficiency of the product is demonstrated. Coproduct economics in a biorefinery are driven by the difference between the selling price of the fuel and coproduct. Fuels sell for <1 $/kg while pricing pressures from regulatory approval and limited production scales of bio-based insecticides results in prices above 6 $/kg to be common.[60] At 6 $/kg, this bio-based insecticide coproduced with a 3 $/GGE (1.06 $/kg) biofuel would account for 12 – 16% of the gross revenue but only 2 – 3% of the total product volume from a 2000 tonne/day biorefinery. In this scenario the biorefinery could sell the fraction as the active ingredient to an agrochemical company that would formulate the bio-based insecticide product, which have median sales pricing of 30 $/kg.

Market size, production volumes, and technical readiness of the biomass conversion technology will impact viability of this coproduct. Large chemical markets leverage economies of scale to reduce production costs, but these markets are challenging for biorefinery products due to scale limitations driven by feedstock logistics. Extremely small markets cannot absorb the production volumes of multiple biorefineries, and market saturation can drive pricing lower. The insecticide market is estimated at 100 – 250 kilotonnes annually and a single biorefinery can supply 1 – 5 %, which is in line with other moderately scaled chemical products.[61] Catalytic fast pyrolysis remains an emerging technology with pilot scale facilities, ≥0.5 ton per day, in operation and pathways to fuel prices of <$3.15 gasoline gallon equivalent (GGE).[56,62–64] The development of this bio-based insecticide help reduce biofuel prices, but commercialization of the bio-based insecticide is dependent on deployment of upstream conversion processes.[65] While compositionally different, commercial-scale non-catalytic fast pyrolysis facilities are currently in operation and may provide access to a bio-oil intermediate from which a bio-based insecticide fraction might be accessed.[66]

Ecotoxicological Risk Assessment

Identifying and characterizing negative effects on off-target insects, vertebrates, and the environment are essential during the development of new insecticides. The Pesticide Action Network International (PAN) outlines a harmonized framework to identify highly hazardous pesticides based on aggregated guidance set by the Environmental Production Agency (EPA), the European Union (EU), the World Health Organization (WHO), and international agreements (i.e., Stockholm Convention, Rotterdam Convention, and Montreal Protocol).[67] This framework was applied to compounds detected within the most active candidate fraction, 230 – 250 °C, so risks related to acute and chronic toxicity, endocrine disruption, mutagenicity, carcinogenicity, bioaccumulation, environmental persistence, and off-target species toxicity could potentially be identified using existing data. **Supplementary Table 6** lists the 4 risk categories and provides a description of the 18 subcategories, the criteria as applied for each subcategory, and the data sources used. Out of the 115 compounds assessed, catechol and 4H-pyran-4-one were the only compounds that met any of the criteria to be indicated as a highly hazardous pesticide, **Supplementary Table 7**. Catechol has been indicated by the European Unions Global Harmonized System (EU GHS) as a compound that may cause cancer and 4H-pyran-4-one has a predicted LD_{50} of 100 mg/kg, which meets the WHO 1b criteria for acute toxicity. Both compounds could be removed through further separations, and experimental assays should be used to determine if the compounds, at the concentrations present in the 230 – 250 °C fraction, 0.1 and 0.4 wt% respectively, pose health risks. During the analysis, 2 compounds had information, guidance, or data that raised additional concerns, but did not meet the assessment criteria. A detailed explanation for each compound that met the assessment criteria or had reason for concern are found in **Supplementary Table 8**.

Understanding how structural motifs affects toxicity or environmental risk can help guide the development of

safer bio-based insecticides. To this end, the EPA Toxicity Estimation Software Tool (TEST), which provides experimental and generates predicted values, was used to relate the number of alkyl carbons, one measurement for the degree of substitution, to four different outcomes: rat oral LD_{50} as an indication for acute toxicity, Ames mutagenicity score as an indication for mutagenic potential, Daphnia Magna LC_{50} as an indication for aquatic organism toxicity, and bioaccumulation.[68] The linear and log-linear correlations are shown in **Supplementary Figure 5A-D** with insets providing whisker plots that include data for all compounds as the linear correlations are only for alkyl substituted phenols. From these correlations it can be seen that increasing alkylation has no correlation to oral acute toxicity, **Supplementary Figure 5A**. For mutagenicity, no correlation between alkyl substitutions and the Ames mutagenicity potential is apparent, **Supplementary Figure 5B**. Experimental data for the Ames mutagenicity assays are binary while the EPA TEST application generates a probability the compound will be mutagenic. **Supplementary Figures 5C and 5D** show increasing alkylation increases risk for aquatic organism toxicity and bioaccumulation. While this is true, daphnia magna LC_{50} and bioaccumulation values are at least one order of magnitude away from meeting criteria to be indicated as a highly hazardous pesticide. These 4 generated correlations show that increasing phenol alkylation can affect toxicological and environmental risks depending on the metric of interest. Overall, the compounds within the most active candidate bio-based insecticide, 230 – 250 °C, were found to be mostly benign, but this assessment highlights the need to carry out detailed testing within each category to prove the ultimate safety of the active ingredient.

Initial risk assessments for new insecticides can serve to identify early risks and mitigations strategies, but significant limitations exist in this approach, which were apparent in the assessment of this bio-based insecticide. Many compounds may not have existing data across the various risk categories to estimate potential hazards. For example, experimental data for bioaccumulation, environmental persistence, and toxicity to aquatic ecosystems were particularly limited, but tools such as the EPA's TEST or the EPA's Computational Chemicals Dashboard can provide some estimation of these risks, which is what was used for this analysis.[69] However, data or tools for assessing honeybee toxicity remain near non-existent despite high toxicity to bees, LD_{50} of <2 ug/bee, being the single most common reason for being listed as a highly hazardous pesticide by PAN. Here, analytical closure for candidate fractions was >96%, but chemical compositional analysis of biomass conversion streams has been historically challenging. Early toxicological and environmental screening as well as active ingredient identification of biomass conversion streams for agrochemical applications could be limited by analytical capabilities. Further, toxicological or environmental impact due to multicomponent interactions could increase risk and would not be captured in this approach as compounds are only being considered individually. Advanced computational tools and methods, such as the ability to use protein binding estimations in metabolic pathway models to ultimately predict toxic effects, could allow researchers to eliminate problematic compounds within the active ingredient early and accelerate the discovery of bio-based insecticides that are less hazardous to off-target species. As novel sources for agrochemicals are being explored in early-stage research, data gaps for the identification of toxicological and environmental hazards are apparent. Identification of these gaps can motivate the development of new methods and tools for early hazard detection, which can catalyze the development of safer pest management solutions.

Regulatory Pathway and Market Demand

Regulatory approval of a biomass derived insecticide is a major hurdle to commercialization, and developing a regulatory strategy early with knowledge of existing and emerging regulatory environment can increase the probability of commercial success. Two specific regulatory frameworks are considered, US and EU, which have significant differences specifically for bioderived active ingredients. In the US, pesticides are approved by the EPA as specified in Pesticide Registration Improvement Act of 2003 and are grouped into three categories: biochemical pesticides, microbial pesticides, and plant-incorporated protectants.[70] Biochemical pesticides are considered naturally occurring substances with a non-toxic mode of action against the target pest. The mode of action for this bio-based insecticide has not yet been established and will partially dictate the approval pathway. Regardless of classification, the EPA will consider the amount, the application frequency and timing, storage, and disposable of the pesticide to determine the likely hazard to humans, wildlife, fish, non-targeted insects, and plants as well as the contamination of soil and water. In the EU active ingredients and formulations are regulated on a case-by-case basis with no differentiation between bio- and conventional pesticides.[71] New pesticide formulations must follow the EU Reg. No.

1107/2009 and the Sustainable Use Directive. EU approvals are comparatively longer than the US, but recently the EU Commission is introducing a new regulation for low-risk substances to boost the biopesticide market. Further changes may be introduced through other legislation, such as the European Green Deal, that aim to zero net GHG emissions in the EU by 2050.[4] The EU commission explicitly states that strategic plans are to adopt strategies to drastically reduce the use and risk of chemical pesticides. For any regulatory body, the ability to manufacture a consistent product will be required. A quality-by-design approach that considers feedstock and process variability should be considered during development and scaleup of this bio-based insecticide to ensure chemical compositions remain within expected and approved ranges.

There is a growing and significant market pull for new, safer, and environmentally benign insecticides. Petrochemical based insecticides have been under growing public and regulatory scrutiny with the EPA systematically reviewing, and in some cases de-labeling, insecticides from the marketplace. [72,73] This trend has also been observed globally, which has left growers and agricultural stakeholders fewer pest management solutions to grow crops for the world's growing population. Access to effective insecticides has been further exacerbated by developed resistance to existing chemistries where 500+ species have developed resistance to 300+ insecticides.[74,75] The agriculture industry's reliance on bio-based insecticides has also been increasing. They can typically be brought to market more quickly than synthetic insecticides due to registration requirements within the US, and new regulations in the EU may expand upon this trend.[76] An average synthetic pesticide requires $250 million and a 10 year development timeline; conversely, a bio-based insecticide can take <$10 million with a 3 year development timeline.[77] A confluence of market forces have resulted in rapid growth of the biopesticide market, 8% CAGR, and bio-based insecticides are expected to benefit from this trend to become a major contributor in meeting food production needs.[78] While there exists a market-pull for bio-based insecticides, adoption of new products by end users remains challenging as historical perceptions of high cost and poor performance for bio-based insecticides may limit market penetration. Further, risks in moving from bench to production scale can pose a significant barrier to commercialization and profitability. For bio-based insecticides produced from the thermochemical conversion of biomass, research in the near term can focus on identification of the specific active components through orthogonal insect assays, development of the active ingredient into formulated product, field trials, mode of activity elucidation, and initial testing for regulatory approval packages. Any new pest management solution has inherent risks associated with wide scale adoption. With appropriate development and regulatory guidance, the benefits of bio-based insecticides, such as potentially more benign ecotoxicological profiles and reduced emissions, can outweigh these risks. The development of a global circular economy will require rethinking both energy and food production, and biomass derived insecticides represents an opportunistic strategy to positively impact both.

Conclusions

The results presented here provide work aimed at the development of new biobased insecticides produced through the thermochemical conversion of biomass. To consider how research and development of this bioproduct could move forward technical hurdles, economic and sustainability benefits, and commercialization barriers were discussed. Technical considerations explored how tuning chemical functionality during biomass deconstruction can improve insecticidal activity and how separations can address ecotoxicological risks. Technoeconomic modeling and supply chain emissions analysis showed the bio-based insecticide can improve biorefinery economics while reducing greenhouse gas emissions from agrochemical production. The pathway to commercialization was briefly considered through the lens of the regulatory environment and market demand for new agrochemicals. Renewable energy and sustainable agriculture will be a hallmark of a circular carbon economy, and the bio-based insecticide developed in this work is an opportunistic strategy for achieving this goal.

Methods

Production and Characterization of Bio-insecticides Active Ingredients

Bio-based insecticide fractions were generated from bio-oil that was produced using platinum on titanium oxide (Pt/TiO_2) to upgrade pyrolysis vapors generated from whole woody biomass.[33] The resulting bio-oil was vacuum distilled using a spinning band distillation column (model 800-SB-A, BR Instruments, MD) in a batch mode, **Supplementary Figure 6.** A Teflon band

was used which simulated 30 theoretical trays, and distillation was performed at 30 torr and with a reflux ratio of 10 – 60. The reflux ratio for the bench scale instrument is time based wherein a ratio of 10 indicates the reflux valve was closed for 10 seconds and opened for 1 second. Atmospheric equivalent temperatures (AET) were calculated using BR AET Utility software 1.0 and all reported temperatures are AETs.

Distillate cuts were analyzed by comprehensive two-dimensional gas chromatography with simultaneous time-of-flight mass spectrometry and flame ionization detection (GCxGC-MS/FID). Analysis was conducted using a LECO Pegasus 4D system (LECO Corp., St. Joseph, MI) equipped with liquid nitrogen cooled thermal modulator and a post column flow splitter. Inert capillary restrictors (0.1 µm ID) diverting column effluent from the flow splitter to the detectors were selected such that the TOF and FID signals produced nearly identical retention times. Method parameters are provided in Table 1. Samples were diluted gravimetrically ~1:10 in acetone for GC analysis. Compounds were identified using library matching and utilization of retention time regions in 2D chromatograms using LECO ChromaTof Software. The FID signal was calibrated using a series of representative compounds to establish instrument linearity and repeatability. All linear calibrations resulted in $R^2 \geq 0.995$. Compounds detected that were not directly calibrated were quantified from their theoretical response factors calculated via effective carbon numbers.[79] GC×GC method parameters provided in **Supplementary Table 9**.

Insecticidal Assays

We used adult spotted-wing drosophila, *Drosophila suzukii* (Matsumura) and first instar oriental fruit moth, *Grapholita molesta* (Herbst) a model insect for evaluating the direct, residual, and diet insecticidal activity of three pyrolysis distillate fractions. Following a preliminary range-finding experiment we evaluated 0 mg/ml, 10 mg/ml, 20 mg/ml, 40 mg/ml 60 mg/ml and 80 mg/ml of each of the three fractions with the balance of material made up of 70% acetone. Six replicates were performed for each dose and application condition.

Drosophila suzukii were sourced from laboratory colonies established from wild flies caught in 2018 and reared on a standard corn meal Drosophila diet.[80] For each dose and replicate, 5 males and 5 females were knocked out with CO_2 and stored at room temperature before use in trials. Insecticide applications were made to test subjects directly or to 9 cm petri dishes used in residual contact trials. For each replicate, 1.5 ml of the appropriate dose was loaded into a Potter spray tower (Burkard Manufacturing Co Ltd Hertfordshire, UK) and applied to flies on a 9 cm petri dish (direct mortality) or to a petri dish to which flies were added after dishes were dried in a fume hood for approximately 1 hour (residual mortality). The Potter spray tower was rinsed with 2ml of 95% acetone between each concentration. Flies in the residual mortality trial were provide with 1 ml of fly diet and left in the treated arena for the duration of the study. Fly mortality and morbidity were evaluated at 8- and 24- hours after direct application or placement into the treated dish. Flies were scored dead or moribund if flies showed no signs of movement or moved legs without locomotion when agitated with a small brush, respectively.

Grapholita molesta were sourced from long time laboratory colonies reared on a pinto bean-based diet. Two oil fractions were evaluated, 180-230 °C and 230-250 °C, at the same 6 rates as evaluated for *D. suzukii*. Assays were performed in 24 well cell culture plates (Nunc non-treated multidishes, ThermoFisher Scientific) with 1.5 ml of moth diet loaded into each well. 35 µl of material (oil plus acetone) was added to each well and acetone allowed to evaporate under a fume hood. Ten newly emerged *G. molesta* neonates were placed in each well and wells capped with a perforated piece of parafilm to prevent larval escape. Larval condition (graded as either alive or dead) was recorded after 48 hours. Six replicates were conducted.

Dose response curves were calculated for both model insects with separate analyses conducted for contact and residually applied compounds for *D. suzukii* and the *G. molesta* diet assay. We used the "drc" package in the R computing environment using a four-parameter log-logistic regression where the minimum and maximum parameters were forced to 0 and 1 proportion mortality, respectively and the remaining parameters estimated using a binomial model. The "ED" function was used to provide estimates and standard errors for the LC_{50} for each model.[81]

Technoeconomic Analysis

In order to evaluate the economic impact of the coproduct valorization, a technoeconomic model was developed for the separation of mixed phenol fractions to be used as a bio-based insecticides. The 2019 state-of-technology catalytic fast pyrolysis NREL Aspen Plus® model was used and is described elsewhere.[34] Briefly,

the model comprises a catalytic fast pyrolysis plant with *ex-situ* upgrading of pyrolysis vapors and a throughput of 2000 dry tonnes per day of lignocellulosic biomass. Modifications to the fractional condensation train and the addition of two distillation columns were used to separate the targeted insecticide mixtures from the lighter bio-oil stream. The Dortmund-UNIFAC model was used for modeling the separation train.[82] The bottom fractions of both distillation units are then mixed back into the main bio-oil line and sent for hydro-processing into hydrocarbon fuels, **Supplementary Figure 3**. Five different simulations were generated by varying the split between bio-oil lights and heavies, and the lights were subsequently distilled to produce the bio-based insecticide fraction. These five cases were used to evaluate yield and purity of the insecticide mixtures. The feed stream used for modeling included the insecticidal species in experimentally measured proportions.

The economic analysis was completed using the same dataset for the capital and fixed operating expenditures as presented in Dutta et al.[34] The analysis used the derived bio-oil production cost from the model as a raw material cost for the bio-based insecticide. The portions sent to hydro-processing is assumed to be processable just like the whole stream prior to the separation of insecticidal compounds. The economic analysis was used to calculate the minimum product selling price (MPSP) of the bio-based insecticide, which represents the minimum price to sell the product to cover capital and operating expenditures to produce the co-product after separating the insecticides from bio-oil. The MPSP was calculated using discounted cash flow rate of return analysis, and 2016 dollars were used as the basis for the economic calculations.[34]

Life Cycle Assessment

The analysis utilizes NREL's Materials Flows through Industry (MFI) tool to estimate supply-chain level energy and GHG emissions.[32] The comparative analysis of conventional and bio-based insecticide supply chains relies on life cycle inventories of material and energy inputs to the final production process as well as manufacturing processes for the intermediate (upstream) inputs. For the bio-based insecticide processes, the technoeconomic models developed in this work provide the inventories, while for the conventional insecticides, inventory data was sourced from the ecoinvent database.[83] For a more complete discussion of the MFI tool methodology, refer to Hanes and Carpenter (2017).[32]

Risk Assessment

To assess toxicological and environmental risks a framework outlined by the pesticide action network (PAN) was used.[67] This framework uses a Boolean approach to risk assessment where a compound will receive a 1 in a specific subcategory if a certain qualitive (e.g. a regulating body has listed a compound as a carcinogen) or a quantitative (e.g. the bioaccumulation factor is greater than 5000) criteria was met. Where applicable and available, quantitative metrics (e.g., potential mutagen as determine prediction software) or other qualitative assessments (e.g., being list as potential rather than probable carcinogen by the EPA) were used to highlight compounds that may pose risk in a specific category even when the compound did not meet the strict threshold of the PAN framework. To improve the analysis, the EPA TEST application and EPA's Computational Chemicals Dashboard was used to generate additional quantitative data.[68,69]

Author Contribution

A.N.W. contributed to the separations and ecotoxicological analysis efforts. M.J.G. contributed to the insect bioassay experiments. R.J. contributed to the separations, chemical analysis, and process modeling efforts. S.D.O. contributed to the separations, chemical analysis, and process modeling efforts. J.H. contributed to the experimental bioassay efforts. J.A.P. contributed to the experimental bioassay efforts. S.R.N. contributed to the supply chain analysis effort. D.C. contributed to the market and regulatory analysis efforts. M.R.N. contributed to the separations and biomass conversion efforts. E.C. contributed to the bio-oil characterization and chemical analysis efforts. K.I. contributed to the bio-oil characterization and biomass conversion efforts. K.H. contributed to the technoeconomic analysis efforts. A.D. contributed to the technoeconomic analysis efforts. J.R.D. contributed to the separations and market analysis development. J.A.S. contributed to the market and biorefinery analysis. All authors contributed to the drafting and review of the manuscript.

Conflict of Interest

The National Renewable Lab has filed an international patent application under the PCT, application no. PCT/US20/66306. Authors associated with the application include A. N. Wilson, M. R. Nimlos, and J. R. Dorgan. The patent covers the use of compounds produced through the thermochemical conversion of biomass as bio-based insecticides. Marrone Bio Innovations has commercial rights to the

technology. The remaining authors declare no competing interests.

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