NAVIGATING THE REGULATORY LANDSCAPE:

BIOPESTICIDE CASE STUDY

Context

Pesticides regulated under FIFRA by EPA include what may be considered "conventional" pesticides and pesticides derived from natural materials and microorganisms. Biopesticides are divided into three groups -- microbial pesticides, biochemical pesticides, and plant-incorporated protectants -- and are typically considered by EPA to be "reduced risk pesticides" because of their non-toxic mode of action. While EPA may have developed programs to encourage the registration of biopesticides, there are ongoing challenges in determining jurisdiction, assessing the safety of experimental trials, and ultimately determining that the biopesticide will not cause unreasonable adverse effects to human health or the environment.

Description of the technology

Pheromones are chemicals secreted by both humans and animals that trigger a social response from members of the same species (attracting potential mates or in ants being able to lead others to a food source). While they have long been used as effective attractants for traps, pheromones are often difficult and expensive to synthesize. In 2014, an International Genetically Engineered Machine Foundation (iGEM)[1] team from the National Chiao Tung University in Taiwan realized that if they could stimulate female

insects to overproduce pheromones, the females themselves could be the bait that lures males into a trap. In nature, female insects produce Pheromone Biosynthesis Activating Neuropeptide (PBAN) to stimulate the synthesis of pheromones to attract males for mating.[2] The iGEM team, which was a finalist for the grand prize in the international undergraduate student synthetic biology competition, developed a genetically modified strain of *E. coli* that produces PBAN. The team mixes the synthetically derived PBAN with a sugar solution, which is then placed in a trap as food. Female moths enter the trap and eat the sugar solution containing PBAN. The PBAN ingested by the female moths induces them to produce pheromones, which then attracts male moths into the trap. As long as the females ingest the sugar/PBAN mixture, they will continue to produce pheromones and attract males.

Discussion of the legal and procedural issues

Biochemical pesticides are among the biopesticides regulated by EPA. These pesticides are naturally-occurring substances that control pests by non-toxic mechanisms and include hormones, natural plant regulators, and pheromones. Substances or articles intended to control bacteria and fungi in or on living humans or animals are not intended for use against "pests" and thus are not pesticides regulated under FIFRA. Instead, such substances are regulated under FFDCA by FDA.

Under the controlling rules, EPA would take the position that the use of a biopesticide in a trap for purposes of mitigating (*i.e.*, interfering with the growth or mating of targeted pests) a pest *(i.e.*, moth) would require registration under FIFRA. On the other hand, EPA has determined that certain pesticides are not of a character requiring FIFRA regulation. Among those substances are "[p]heromones and identical or substantially similar compounds labeled for use only in pheromone traps (or labeled for use in a manner which the Administrator determines poses no greater risk of adverse effects on the environment than use in pheromone traps), and pheromone traps in which those compounds are the sole active ingredient(s)."[4] Synthetically produced compounds are considered "identical" to a pheromone when "their molecular structures are identical, or when the only differences between the molecular structures are between the stereochemical isomer ratios of the two compounds, except that a synthetic compound found to have toxicological properties significantly different from a pheromone is not identical."[5] There is an important, but subtle, distinction in this case: FIFRA exempts pheromones, but PBAN is not a pheromone. PBAN is a hormone that acts upon female moths to stimulate pheromone production, so PBAN itself is not eligible for the pheromone exemption and is regulated by FIFRA.

If use of PBAN were not regulated under FIFRA (*i.e.*, if it were a pheromone), it could be subject to the provisions of TSCA[6] or under the jurisdiction of other statutes, depending, among other factors, on the uses at issue. Note that if a pheromone is used in traps in conjunction with conventional pesticides, or in other application methods (other than traps), such that the exemption was no longer applicable, the pheromone would be subject to regulation under FIFRA. If the use of the pheromone was intended to control bacteria and fungi in or on living humans or animals, it would be subject to regulation under FFDCA. To complicate

this issue, whether the microbe or PBAN is considered a pesticide could well depend on which is introduced into the trap. If the microbe is used in the trap, it could likely be considered the active ingredient. If, on the other hand, the microbe is used only to produce PBAN and only the PBAN is used in the trap, PBAN would likely be the active ingredient regulated by FIFRA. In that case, the microbe could be considered a pesticide intermediate regulated by TSCA.

The legal and policy takeaway

EPA has acknowledged "that use of certain types of pheromone products presents lower risk than conventional pesticides and also acknowledges the unique properties of these niche-type products regarding their inherently narrow host range."[7] EPA's Biopesticides and Pollution Prevention Division (BPPD) focuses on all regulatory activities associated with biopesticides, with a particular focus on registering biopesticide active ingredients and end-use products, including certain benefits available to biopesticide registration applicants, such as reduced data sets, faster review periods, and lower fees compared to conventional registrations. BPPD also implements specific programs geared towards certain biopesticides. One example is its pheromones regulatory relief program that permits, in part, flexible confidential statements of formula for pheromone experimental use permits (EUP) to allow for active ingredient adjustments during the course of experimentation.

Even with the flexibility and benefits that BPPD products have, there nevertheless remain certain challenges and complications companies must navigate through the regulatory process. As the PBAN case above demonstrates, the same substance can potentially be subject to TSCA, FIFRA, or FFDCA depending on the intent and use of the technology at issue. In addition, although EPA's policies are intended to incentivize the registration of biopesticides, the registrant still needs to generate data, seek EPA's approval for experimental testing, and otherwise provide EPA with the information it needs to assess whether the biopesticide will cause unreasonable adverse effects on human health or the environment.

Endnotes

1 iGEM, *iGEM* Competition, available at http://igem.org/Main_Page.

2 National Chiao Tung University's iGEM Team, available at http://2014.igem.org/Team:NCTU_Formosa.

3 Wikipedia, *Pheromone biosynthesis activating neuropeptide*, available at http://en.wikipedia.org/wiki/Pheromone_biosynthesis_activating_neuropeptide.

4 40 C.F.R. § 152.25(b). A pheromone trap is "a device containing a pheromone or an identical or substantially similar compound used for the sole purpose of attracting, and trapping or killing, target arthropods. Pheromone traps are intended to achieve pest control by removal of target organisms from their natural environment and do not result in increased levels of pheromones or identical or substantially similar compounds over a significant fraction of the treated area." 40 C.F.R. § 152.25(b)(4).

5 40 C.F.R. § 152.25(b)(2).

6 15 U.S.C. §§ 2601-2695d.

7 EPA, *Pesticide Registration Manual: Chapter 3 -- Additional Considerations for Biopesticide Products*, available at http://www2.epa.gov/pesticide-registration/pesticide-registration-manual-chapter-3-additional-considerations#pheromone.

One Woodrow Wilson Plaza
1300 Pennsylvania Ave., N.W.
Washington, DC 20004-3027
T 202/691/4000
F 202/691/4001
www.synbioproject.org