

3. RNA Interference for Next Generation Pest Control: Opportunities, Risks, and Paths to Adoption

Jyotirmayee¹

¹*School of Biotechnology, Institute of Science, Banaras Hindu University,
Varanasi, India, 221005*

Abstract

Escalating pesticide resistance, tightening regulatory pressures on conventional chemistries, and the need to protect biodiversity are pushing crop protection toward precision, biologically based tools. RNA interference (RNAi)—a sequence-specific gene-silencing pathway triggered by double-stranded RNA (dsRNA)—has emerged as a practical option for highly targeted pest control. Since late 2023, ledprona, a sprayable dsRNA active ingredient marketed as Calantha™ for Colorado potato beetle (CPB) management, has been registered in the United States, marking a milestone for exogenously applied RNAi products. This article synthesizes current knowledge on RNAi mechanisms relevant to pest control, compares delivery modes (host-induced gene silencing vs. spray-induced gene silencing), reviews the evidence base from laboratory and field studies—including the ledprona case—evaluates environmental fate and non-target safety, and summarizes the evolving regulatory landscape across OECD jurisdictions. Particular attention is

paid to resistance risk, product stewardship, formulation technologies that enhance stability and uptake, and integration into integrated pest management (IPM) strategies. The article concludes with a practical adoption roadmap for growers, advisors, and regulators. While RNAi products are not a panacea, the technology's specificity, short environmental half-life, and compatibility with IPM can help expand the sustainable control toolbox—provided stakeholders invest in careful design, resistance management, and transparent risk assessment.

Introduction

Modern agriculture faces a three-sided challenge: maintaining yield, minimizing environmental externalities, and slowing the treadmill of resistance to small-molecule insecticides. The Colorado potato beetle (*Leptinotarsa decemlineata*) alone has evolved resistance to dozens of active ingredients, repeatedly eroding control reliability and raising costs (Mishra et al., 2021). RNAi-based pesticides—engineered dsRNAs designed to silence essential pest

genes—offer species-level precision with limited non-target activity when properly designed and used. In December 2023, the U.S. EPA granted a three-year registration for products containing ledprona for CPB; product labelling and a 2025 supplemental label now guide field use (EPA, 2023, 2024, 2025). These actions signal regulatory willingness to evaluate and, where appropriate, authorize novel, sequence-specific biopesticides. Meanwhile, recent reviews document rapid growth in RNAi applications across insect orders and other pest groups, alongside the need for proportionate, evidence-based risk assessment (Germing et al., 2025).

RNAi: A concise mechanistic primer

In RNA interference, long dsRNA is processed by Dicer into ~21–25 nt small interfering RNAs (siRNAs). One strand loads into Argonaute within the RNA-induced silencing complex (RISC), which then guides sequence-specific cleavage of complementary mRNA, reducing protein expression and eliciting phenotypes that can include growth arrest or mortality in target pests (Hannon, 2002; Kim et al., 2016; Quílez-Molina et al., 2024). This core mechanism is conserved, but responsiveness varies across taxa and life stages; uptake and systemic spread can depend on gut physiology, pH, and dsRNA transporters. For agricultural use, design

focuses on highly conserved, essential genes with minimal homology to non-targets to confine activity.

Delivery modalities: HIGS vs. SIGS

Two practical routes exist for agricultural RNAi:

1. **Host-induced gene silencing (HIGS)** in genetically engineered plants that express pest-targeting dsRNA. HIGS has demonstrated efficacy (e.g., DvSnf7 in GM maize), but deployment depends on GM crop acceptance and regulatory frameworks (EFSA, 2017; Germing et al., 2025).
2. **Spray-induced gene silencing (SIGS)** applies formulated dsRNA exogenously, like a conventional foliar spray. SIGS avoids transgenics and can be used across cultivars; however, dsRNA is labile to UV and nucleases, so formulation is pivotal to persistence and uptake (OECD, 2020/2023; Vatanparast et al., 2024).

Recent polymer and nanoparticle carriers (e.g., chitosan complexes, core-shell systems) can shield dsRNA, facilitate cellular entry, and co-deliver synergists without altering the active's sequence-specificity (Quílez-Molina et al., 2024).

Case study: Ledprona (Calantha™) for Colorado potato beetle

Regulatory status and labelling. EPA registered ledprona products for CPB in December 2023 with time-limited registration typical for novel biopesticides; the federal label (EPA Reg. No. 94614-2) and a supplemental label (expiring December 30, 2026) specify target, rates, and stewardship (EPA, 2023, 2024, 2025). Extension materials (e.g., Cornell CALS) now list ledprona among new CPB options.

Mode of action and performance. Ledprona is a 490-bp dsRNA targeting *PSMB5*, encoding a proteasome β subunit essential for proteostasis. Following ingestion, CPB larvae generate 21-nt siRNAs and down-regulate *PSMB5* transcripts, producing dose-dependent mortality and reduced feeding (Rodrigues et al., 2021). Field and greenhouse trials show protection comparable to standard insecticides at much lower mass per hectare; low doses can still produce measurable behavioral and demographic effects that contribute to management (Pallis et al., 2022, 2023).

Program fit. As a precision tool with a distinct mode of action, ledprona can be rotated with conventional chemistries to diversify selection pressure. Its sequence specificity may be advantageous in conserving beneficials when deployed correctly (Rodrigues et al., 2021; Cornell CALS, 2025).

Environmental fate, non-target safety, and human health

Consensus across OECD guidance indicates that unmodified dsRNA degrades rapidly in typical environments due to UV, nucleases, and microbial activity, leading to limited off-site persistence. Mammals and other vertebrates possess multiple barriers (e.g., gastric pH, nucleases) that severely limit uptake of dietary RNA, and nucleic acids are naturally occurring food components (OECD, 2020; 2023). That said, formulated products may alter stability and exposure, so risk assessments must consider the whole formulation—not just the naked dsRNA (OECD, 2020; RIVM, 2023).

Non-target organism (NTO) risk hinges on realistic exposure and sequence complementarity. Bioinformatic screens help prioritize taxa for testing, but cannot replace empirical data. Tiered testing and case-by-case evaluation remain the recommended approach across jurisdictions (OECD, 2020; Dalakouras et al., 2024).

The resistance question: Lessons and stewardship

Laboratory selection has produced CPB colonies with >11,000-fold resistance to dsRNA after repeated exposures, accompanied by cross-resistance to alternative dsRNA targets and a lack of

target-gene knockdown—implicating upstream uptake or processing changes (Mishra et al., 2021). This underscores the need for resistance management at commercialization, including:

- Rotating modes of action (MoA) across the season;
- Limiting consecutive dsRNA applications;
- Using label-specified rates/timings to avoid chronic low-dose selection;
- Deploying mixtures or sequences that target different non-overlapping genes when available;
- Integrating with non-chemical controls and biologicals.

Such measures parallel IRM best practices for Bt and chemical insecticides and should be embedded in labels and stewardship materials (Mishra et al., 2021; Pallis et al., 2022).

Formulation science: Making SIGS robust

Formulation is the technological fulcrum for SIGS. Protective carriers—polymer complexes, layered nanoparticles, or peptide vectors—can increase residence time on leaf surfaces, shield dsRNA from nucleases, and promote endocytosis in gut epithelia. Co-formulating dsRNA with conventional actives is being explored for complementary effects and logistics, provided regulatory and safety

considerations for co-formulants are met (Quílez-Molina et al., 2024; Dalakouras et al., 2024). Key design variables include dsRNA length and structure, release kinetics, and adjuvant compatibility.

Regulatory landscape: Convergence with room for nuance

- **United States.** EPA registered ledprona for CPB with a three-year term consistent with other novel biopesticides and published the corresponding labels (EPA, 2023, 2024, 2025). Ecological and human health problem formulations for dsRNA have benefited from FIFRA-aligned processes and OECD inputs.
- **OECD guidance.** The 2020 environmental and 2023 human-health monographs provide a harmonized scaffold for exposure assessment, fate testing, and NTO evaluation tailored to exogenously applied dsRNA (OECD, 2020; 2023).
- **European Union.** EFSA's corpus addresses RNAi primarily in GM plants (HIGS/PIPs), with 2025 guidance for RNAi-based GM plants and ongoing discussion about how best to adapt approaches for exogenous dsRNA; national authorities will likely expect

product-specific data packages (EFSA, 2017; 2025; Germing et al., 2025).

- **Canada.** Health Canada (PMRA) has issued public information notes outlining current regulatory approaches for dsRNA pesticides and points to OECD documents as technical references (PMRA/Health Canada, 2024).

Across regions, regulators stress that formulations (not just actives) must be characterized for fate, exposure, and NTO effects—especially when carriers could extend environmental persistence or broaden uptake.

Integration into IPM: Practical guidance for growers and advisors

1. **Positioning.** Deploy dsRNA products against pests with documented RNAi responsiveness (e.g., CPB) where precision is valuable for conserving beneficials and where resistance to other MoAs constrains options (Cornell CALS, 2025).
2. **Timing.** Target susceptible stages (often early instars for chewing insects) and align with degree-day models and scouting thresholds; adhere strictly to labeled intervals and spray volumes to avoid sublethal exposure.

3. **Rotation/mixtures.** Alternate with different MoAs; where permitted, sequence dsRNA with microbial or reduced-risk chemistries; avoid redundant back-to-back dsRNA sprays.
4. **Stewardship.** Preserve refuges when appropriate, document efficacy, and report performance shifts that could signal resistance.
5. **Compatibility.** Verify tank-mix and adjuvant compatibilities; check carrier interactions (pH, cations) that can affect dsRNA integrity.

Future directions and research needs

- **Multi-locus strategies.** Rotating or stacking dsRNAs that target unrelated essential genes may slow resistance, pending regulatory clarity on multi-target products.
- **Cost and scale.** Advances in microbial or cell-free dsRNA production and purification can reduce costs per hectare; techno-economic details remain a moving target and will influence adoption.
- **Environmental analytics.** Better field methods to measure dsRNA residues and degradation kinetics in real canopies will improve exposure models and support proportionate regulation (OECD, 2020/2023; RIVM, 2023).

- **Beyond insects.** Expanding SIGS to mites, nematodes, fungi, and viruses is active research; success will depend on host uptake biology and formulation innovation (Germing et al., 2025; Vatanparast et al., 2024).
- **Societal acceptance.** Transparent communication around mode of action, specificity, and residue profiles will be important for public confidence.

Conclusion

RNAi is not a silver bullet, but it is a sharp, smart arrow in the quiver. Ledprona's registration demonstrates that carefully designed dsRNA actives can meet regulatory standards and perform in the field against a hard-to-control pest. The technology's promise rests on three pillars: good design (specific targets, robust formulations), good stewardship (IRM-aware programs, data-driven use), and good governance (proportionate, science-based risk assessment). If these pillars hold, RNAi can help agriculture step off the resistance treadmill and toward a more resilient, biodiversity-aware pest management paradigm.

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