Journal of Consumer Protection and Food Safety (2024) 19:127–129
https://doi.org/10.1007/s00003-024-01507-7

Journal of Consumer Protection and Food Safety
Journal für Verbraucherschutz und Lebensmittelsicherheit

EDITORIAL

RNA-based crop protection: potential, challenges, and practical examples

Aline Koch[1]

Received: 9 April 2024 / Accepted: 15 April 2024 / Published online: 12 June 2024

The growing need for sustainable food production in the face of multiple global crises such as climate change, biodiversity loss, and population growth require new crop protection strategies. The transformation of crop production is currently the subject of intense debate and a key topic at many crop protection conferences[1]. Many active ingredients are losing their registrations, exacerbating the situation for users who often lack suitable alternatives. Moreover, societal demands for pesticide-free agriculture to protect the environment and biodiversity are increasing the pressure on both the pesticide industry and applicators, since an overuse of synthetic chemical pesticides is a major cause for the decline of insect populations[2]. In the face of these challenges, there is a pressing call for innovative solutions aligned with the preservation of biodiversity. This need is anchored in both national and global initiatives such as the European Green Deal and the bioeconomy strategies advocated by Germany, the EU, and the UN. While the EU target of a 50% reduction of conventional pesticides by 2030 has been temporarily halted[3], the demand for a reduction remains, especially in Germany. Thus, the quest for promising and practical alternatives remains urgent to meet these challenges.

1 Harnessing RNA interference for targeted pest control

Compounds derived from double-stranded RNA (dsRNA) offer a promising alternative. Their mechanism of action is straightforward yet effective: these dsRNA molecules activate a naturally occurring mechanism within the cells of the target organism (in this case, the pest) known as RNA interference (RNAi). First, the dsRNA undergoes processing into small RNAs by specific Dicer enzymes and integrates into a silencing complex. This complex then specifically targets complementary messenger (m)RNA transcripts, binding to them and inhibiting the synthesis of essential proteins[4]. Due to the inherent specificity of this process, theoretically, only proteins from a singular pathogen or pathogen species can be impacted, rendering dsRNA compounds exceptional selective.

RNAi technology has been used in medicine since 2018, with 5 RNAi therapeutics currently approved in Germany[5]. For agricultural applications, sequence-based agents like dsRNAs offer a compelling (and likely superior) alternative to conventional synthetic chemical pesticides due to their high target specificity and consequent protection of non-target organisms, as succinctly articulated by Shaffer[6]: "Using RNAi versus conventional pesticides is the difference

[1] https://www.pflanzenschutztagung.de/dokumente/upload/9547f_Tagungsband_DPST_2023.pdf. Accessed 15 April 2024

[2] Wagner DL, Grames EM, Forister ML, Berenbaum MR, Stopak D (2021) Insect decline in the Anthropocene: death by a thousand cuts. Proc Natl Acad Sci USA 118:e2023989118

[3] https://www.euronews.com/my-europe/2024/02/06/von-der-leyen-announces-withdrawal-of-contentious-pesticide-law-the-first-defeat-of-the-gr. Accessed 15 April 2024

[4] https://www.uni-regensburg.de/biologie-vorklinische-medizin/cell-biology-and-plant-biochemistry/koch/index.html. Accessed 15 April 2024

[5] https://www.deutsche-apotheker-zeitung.de/news/artikel/2023/10/17/gene-per-rna-ausschalten. Accessed 15 April 2024

[6] Shaffer L (2020) Inner Workings: RNA-based pesticides aim to get around resistance problems. Proc Natl Acad Sci USA 2020 117:32823–32826

✉ Aline Koch
aline.koch@biologie.uni-regensburg.de

1 Institute of Plant Sciences Cell Biology and Plant Biochemistry, Plant RNA Transport, University of Regensburg, Regensburg, Germany

between using a pinch and a hammer." Over 100 scientific studies have already demonstrated the efficacy of RNAi-based crop protection technologies in controlling pathogens and insect pests in agriculture and horticulture. Particularly in Germany and Europe, there is a growing interest in non-GMO spraying (RNAi spraying) of RNAi active ingredients.

2 Recent developments and future prospects

Moreover, in December 2023, the first RNAi product, Calantha, developed by GreenLight Biosciences, was approved in the USA[7]. In 2007, scientists reported in Nature Biotechnology that the Colorado potato beetle can be effectively controlled using RNAi methods[8]. Field trials conducted by GreenLight Biosciences in the USA have confirmed that Ledprona[9] is as effective as conventional products such as spinosad and chlorantraniliprole[10]. In particular, Ledprona showed a significantly lower application rate of 9.9 g ai/ha compared with 88 g ai/ha for spinosad, underlining the potential of this technology[11].

The high level of efficacy against the Colorado potato beetle is not surprising from a scientific point of view, as the beetle order (Coleoptera) is one of the most sensitive insect pests to RNAi applications due to strong cellular uptake of dsRNA. It is therefore not surprising that the first approved product targets beetles; other products are expected to be developed soon against beetles, which include many important insect pests (corn rootworm, wireworm or rapeseed flea beetle). Pests from other insect orders are less responsive to dsRNA and further research and development is needed for these products[12]. However, promising approaches are being developed to control less sensitive pests such as butterflies (Lepidoptera) with RNAi.

3 Navigating challenges and opportunities in RNAi technology: overcoming hurdles for field application

The primary hurdle lies in protecting the RNA molecules from degradation by nucleases found in the saliva and gut of the pests. In principle, the use of RNAi sprays in the field requires stabilizing the active ingredient to protect it from environmental conditions. One promising approach is the encapsulation by using biodegradable chitosan-based microgels[13], which have been successfully used as formulations in biological crop protection. However, encapsulation of dsRNA in alginate capsules as part of an "attract and kill" strategy should also enable the transfer of RNAi technology to the field[14 15].

Overall, more basic research is essential to understand the uptake, transport and stability of RNAi in the environment, and its interactions with crops and pathogens, to optimize the technology for field application. This optimization will primarily involve the development of appropriate formulations. The selection of the formulation will be critical, particularly concerning regulatory approval and risk assessment during compound testing[16]. The issue of regulatory approval is pressing; as German regulatory authorities are expected to play a growing role in the testing of RNAi-based products in the near future.

For industrial applicants and users, it is crucial to know how the approval procedure for initial compound tests will be adapted (i.e., whether an abbreviated procedure will be considered). Science provides sufficient evidence for this, although further basic research is needed to progressively fill the existing knowledge gaps to provide a sound basis for risk assessment. The main advantage of RNAi technology lies in its selectivity, which makes the development of specific bioinformatic prediction tools crucial. These programs should already address potential off-target effects caused by random sequence similarity to RNA sequences in non-target organisms by using non-target organism sequence databases during the selection of RNA sequences. To achieve this, software must be developed that considers the differences in both the mode of action and specificity among different

[7] https://www3.epa.gov/pesticides/chem_search/ppls/094614-00002-20240229.pdf. Accessed 15 April 2024

[8] Baum J, Bogaert T, Clinton W et al. (2007) Control of coleopteran insect pests through RNA interference. Nat Biotechnol 25:1322–1326. https://doi.org/10.1038/nbt1359

[9] Rodrigues et al. (2021) dsRNA targeting the proteasome subunit beta type-5 gene in the Colorado Potato Beetle. Front Plant Sci 12:728652. https://doi.org/10.3389/fpls.2021.728652

[10] Pallis S, Alyokhin A, Manley B, Rodrigues TB, Buzza A, Barnes E, Narva K (2022) Toxicity of a novel dsRNA-based insecticide to the Colorado potato beetle in laboratory and field trials. Pest Manag Sci 78(9), 3836-3848. https://doi.org/10.1002/ps.6835

[11] Koch A (2023a) RNA-Wirkstoffe gegen den Kartoffelkäfer sind vielversprechend. Kartoffelbau 4/2023 (74. Jg.)

[12] Whyard S, Vélez AM, Smagghe G (2020) Double-stranded RNA technology to control insect pests: current status and challenges. Front Plant Sci 11:451. https://doi.org/10.3389/fpls.2020.00451

[13] https://www.uni-hohenheim.de/themenservice-artikel?tx_ttnews%5btt_news%5d=54063. Accessed 15 April 2024

[14] https://www.q-s.de/services/files/mediencenter/publikationen/FH_32_33_2023_Pflanzenschutz.pdf. Accessed 15 April 2024

[15] Koch A, Petschenka G (2022). Exogene Anwendung von RNA zur umweltfreundlichen Bekämpfung von Schadinsekten. J Kult 74:75–84. https://doi.org/10.5073/JfK.2022.03-04.05

[16] Koch A (2023b) Development of RNAi-based biopesticides, regulatory constraints, and commercial prospects. In: Koul O (editor). Development and Commercialization of Biopesticides: Costs and Benefits. Academic Press; 2023. pp. 149–171. https://doi.org/10.1016/B978-0-323-95290-3.00013-3

organism groups. If successful, the effort will simplify risk assessment procedures, facilitating quicker testing of active substances, ultimately benefiting both industry and applicators.

Funding Open Access funding enabled and organized by Projekt DEAL.