



DISCUSSION DIGEST

RNA Interference-Based Pesticides (RNAi): Exploring gene-silencing pesticides, their benefits & concerns

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This document summarises the University of Cape Town's (UCT) Division of Environmental Health's (DEH) Pesticide Community of Practice discussion held on the 25th of April 2024, titled 'RNA Interference-Based Pesticides (RNAi): Exploring gene-silencing pesticides, their benefits & concerns'. View the discussion [recording here](#), [presentation slides here](#), and [newsletter here](#). This digest presents the issues and points raised and the information shared by participants in response to questions prepared by the presenters:

- **Jack Heinemann** (University of Canterbury)
- **Magda Sachana** (Organisation for Economic Co-operation and Development - OECD)

Magda introduced the session providing the historical context of how an OECD ad hoc Expert Group was established in 2015 out of the **need to answer regulatory questions around ribonucleic acid (RNA) interference-based (RNAi-based) pesticides**. This included issues around **whether or not current risk assessment approaches and existing data requirements are applicable**. She pointed out to the participants the one-stop OECD webpage that contains all the material and documents that the Expert Group has produced.

Jack described how RNAi-based pesticides work. The key molecule in these pesticides is the **highly stable double-stranded RNA (dsRNA)**, which enters a target organism's cell following application, aided by a carrier, e.g. nanoparticles, viruses, and chemicals. RNAi causes gene silencing through either pre- or post-transcriptional processes. The former results in changes to deoxyribonucleic acid (DNA) that inhibit transcription of a gene and the latter results in changes to RNA that prevent production of protein. RNAi can create **smaller pieces of RNA, which may then produce secondary and tertiary RNA molecules which may independently induce RNA interference even though they do not share a sequence similarity with the original dsRNA**. Modified DNA in some cases can be **inherited** through cell division or reproduction. **Effects can vary** between organisms, species, and lineages, and in some cases **can last for an organism's lifetime and be inherited, sometimes for many generations**.

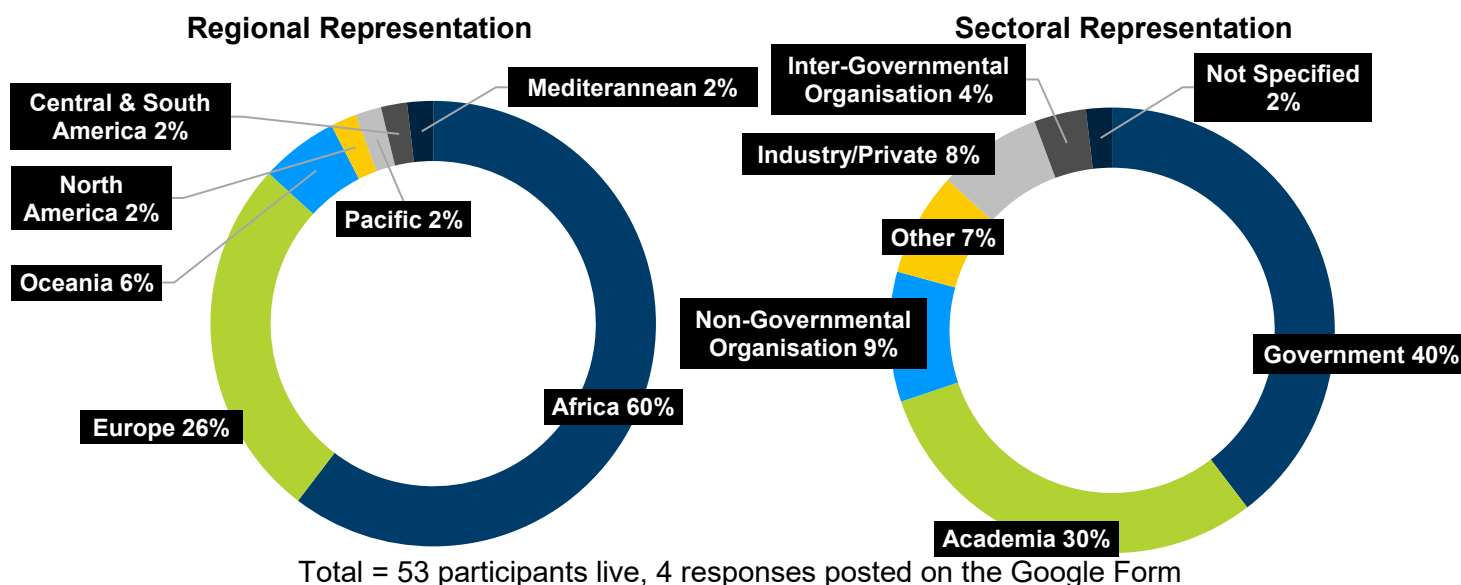
Jack also discussed mechanisms of action of RNAi-based pesticides that raise **concerns about off-target effects** (e.g., impacts on non-target organisms, unintended effects in target organisms, trophic transfer) and other issues from the use of RNAi-based pesticides. He explained the **difficulty of testing for and predicting both unintended and intended effects**.

The OECD released two consideration documents on environmental (2020) and human health (2023) risk assessment approaches for regulating RNAi-based pesticides. Magda discussed several key conclusions within these documents. She highlighted that although **government agencies should regulate RNAi-based pesticides using the experience acquired from registering chemical and biological pesticides, some specific considerations apply to these pesticides**. She explained the concerns around using bioinformatics in isolation without testing to assess



potential non-target effects. It was highlighted that vertebrates have protective mechanisms that may prevent the uptake of exogenous RNAs, but **specific product formulations or chemical modifications may be designed to overcome these barriers. The risk assessment should go beyond assessing only the active ingredients to include product safety as a whole.**

Breakdown of Discussion Participant Demographics



PRESENTERS



Jack Heinemann: Professor Heinemann currently works at the School of Biological Sciences, University of Canterbury, as director of the Centre for Integrated Research in Biosafety. He previously worked at the United States National Institutes of Health. He holds a Bachelor of Science with honours from the University of Wisconsin-Madison (1985); a PhD from the University of Oregon (1989) and is a fellow of the Higher Education Academy. He was on the United Nations (UN) Roster of Biosafety Experts (until 2009), and the Cartagena Protocol for Biosafety's Ad Hoc Technical Expert Group (2009-2016, 2020). Professor Heinemann is an author for the International Panel

on Climate Change (6th report) on biotechnology for climate change mitigation and is an author for the United Nations International Assessment of Agricultural Science, Knowledge, and Technology for Development. He was an expert witness to the New Zealand High Court (gene technology) (2013-14) and the Employment Court (academic freedom) (2022-ongoing). He is also the proud mentor of many graduate students. His current research is on One Health, antimicrobial resistance in the environment, effective teaching practice, and biotechnology regulation and policy.

Magdalini Sachana: Dr Sachana has been a policy analyst within the Environment Health and Safety Division of the OECD's Environmental Directorate since 2015. She manages the development and implementation of policies in the field of chemical safety and contributes to the OECD Test Guidelines and the Pesticide and Hazard Assessment Programmes. Among other projects, Dr Sachana manages the OECD project on biological and RNAi-based pesticides. She is a trained veterinarian with a Master of Science in Biotechnology and a PhD in Toxicology.



CONTRIBUTIONS FROM PARTICIPANTS

Disclaimer: The information in this digest represents the opinions of members participating from different stakeholder groups expressed during the discussion. The views expressed in this document do not necessarily represent the opinion or the stated policy of the Swedish Chemicals Agency (KemI) or DEH UCT, nor does citing trade names or commercial processes constitute an endorsement

The key discussion points raised by participants are presented under each question. Throughout the discussion, informal polls were conducted to help encourage discussion among the participants. They do not provide any representative data but rather provide a snapshot of the participants' views.

QUESTION 1

What are your thoughts around RNAi-based pesticides? Are they a substitute for chemical pesticides?

Yes

- RNAi-based pesticides are a substitute for chemical pesticides
- They are a good substitute for chemical pesticides, considering human health and the environment
- RNAi-based pesticides are pesticides that target specific genes in pests. Because of this, they could be associated with having fewer negative externalities which essentially makes them a suitable substitute for chemical pesticides which often have negative effects on non-target organisms

Possibly/Maybe

- It's interesting to think that RNAi-based pesticides can target only the intended pests. This could very well be a good alternative to the traditional chemical pesticides
- They are promising, but more research needs to be done particularly bearing in mind our differing climatic conditions in Africa
- It is worth investigating RNAi-based pesticides further to substitute the use of chemical pesticides. More research especially on the specificity is needed

- There are areas that may need attention before scaling up such as the possibility of multiple targets and mutations

No/Unlikely

- They may be an expensive means of pest management for low and middle-income countries (LMICs) with the amount of research that has to be undertaken to understand their stability in African countries and to assist in sensitising adaptation to African people who are more used to conventional pesticides
- The limitations challenging greater adoption of RNAi based biopesticides include certain factors which influence efficacy. Effectiveness may be limited by the speed and persistence of pesticidal action as well as the significance of timing applications with respect to target pest life cycle and population dynamics

Other

- There are concerns surrounding RNAi-based pesticides, such as the potential for off-target effects and the development of resistance in pest populations
- This is a new approach, and we don't know much about it

Poll Questions

Poll 1. Have you ever heard of RNAi-based pesticides before this discussion?

Never heard of it	9
Have been approached about it	5
Have worked on regulating it	2
Have heard of it but have not needed to do any work on it	2



Poll 2. Regulating RNAi-based pesticides should be similar to:

Conventional chemical pesticides	0
Biological pesticides	8
Genetically modified organism	10
Something else (clarify in the chat)	3

QUESTION 2

What questions do you have in relation to RNAi-based pesticides, and/or to assessing their risks?

[Several of these questions were answered live (highlighted in grey) ([recording here](#)) or in the Q&A on page 6]

Assessments

- How are the approval assessments done regarding approval of these products especially in LMICs where capacity is considerably low?
- How can the off-target risks to humans, animals, and the environment possibly be tested or assessed, as there seems to be so many potential off-targets?
- Regarding predictability: dsRNA is quite stable as a compound but the effects on organisms (non-target also) are not necessarily predictable (e.g. abrasion effects and increasing exposure pathways). How will the regulatory framework deal with these unknowns? How do you do an adequate and robust risk assessment on these products?
- What methods can be used to assess the persistence and bioaccumulation of dsRNA molecules in the environment?
- How can long-term environmental impacts be assessed and mitigated?
- How can the potential for dsRNA molecules to enter food chains be evaluated in risk assessments for RNAi-based pesticides?

Issues for LMICs

- Are RNAi Pesticides affordable and easily accessible to LMICs?
- What is their use extent in Sub-Saharan Africa/SADC?
- Why should we commercialise a technology whose environment and human health effects are not fully known, especially for LMICs?

Other

- What are good databases to refer to for RNAi-based pesticides?
- If RNAi-based pesticides show some indicators of chemical pesticides and or risks, should they be registered as a biopesticide?

Poll Questions

Poll 1. Are you familiar with how the pesticides work and confident in your knowledge to be able to confirm or challenge claims of safety or efficacy?

Yes	8
Somewhat	8
No	2

Poll 2. Does the diversity of RNAi responses to active ingredients alter how you would regulate these pesticides?

Yes	9
Unsure	3
No	2



Poll 3. What type of testing methods for potential adverse effects (acute, chronic, NOEL, etc.) would best suit your needs?

- All 3 methods are necessary to do
- In vitro, in vivo, non-target organism testing, field trials
- Both acute and longer-term testing for human health and the environment should be conducted
- Acute, NOEL, ARfD, AOEL, OEL,
- Unsure
- Both but environmental issues are critical

QUESTION 3
How should RNAi-based pesticides be regulated in your country?

Tanzania

- RNAi-based pesticides are a new thing. Capacity-building to the regulatory authority is required before considering approval of these products

South Africa

- Based on the risks, as a chemical pesticide
- The RNAi-based pesticides should be regulated as any new protection product; the registration and approval should go through the risk assessment process. The risk assessment should assess the potential risks to humans, the environment and also the non-target organisms
- It should be considered an HHP until proven otherwise

Lesotho

- Regulations should be made based on well-collected evidence and well-studied effects of RNAi-based pesticides on the environment and human health. Should they be as minimal as possible, I don't believe they have to be regulated, but countries have to find ways of teaching their citizens about RNAi pesticides, their use and safe application

Nigeria

- RNAi-based pesticides will be new even to the regulatory authority, so they need to be educated on this first. Also, environmental, and human risk assessments should be done before regulating RNAi as a genetically modified pesticide

Country not Specified

- Beware! Some countries are deregulating at least some forms of dsRNA. Then, no matter what risk assessment framework you think is best, these actives may not be regulated. E.g. if naked dsRNA is deregulated and the formulation is water, then these pesticides might escape review
- To take the precautionary principle as the data is limited
- If the manufacturers remain responsible for assessing and providing safety information for their own products, we will be in the same situation as with the current pesticide paradigm
- Given the significant existing challenges with pesticide regulations in developing nations, the introduction of RNAi-based pesticides further complicates the situation

Poll Questions

Poll 1. Does your country have the expertise or capacity to regulate RNAi pesticides?

Yes (elaborate in chat)	0
Unsure	5
No	11



Poll 2. Are your safety concerns about RNAi based pesticides more related to human health or environmental issues and why?

- Both human health and environmental issues
- Both
- Both. The unknowns seem to outweigh the benefits
- Both
- Human health. The RNAi may be able to modify genes in human
- Both. The unknowns seem to outweigh the benefits
- Both are of great concern because there is inadequate data on the effects of such pesticides in Zambia
- Possible outcomes are more uncertain on biodiversity than on human health. Yet both are of concern
- Both, but environmental issues are critical
- Both. Human health and environmental health
- Both human health and the environment. There is need for more information on their impact so that there isn't a regrettable substitution
- Both human and environmental issues. No research has been presented to indicate the two have been addressed
- Both. Because the fate of these pesticides in the environment, like most pesticides, may have an effect on human health in the long run
- Chronic health issues and environmental fate and ecotoxicity
- Both
- Both, because they are interlinked

Q&A

Q: From research carried out on RNAi, do you think there are any chances of resistance in the future?

A (Jack): Yes, I believe that resistance will be an issue with these as it is with any other pesticide

Q: Any study on human gene modification or mutation when exposed to RNAi?

A (Jack): There have been many studies of the type you suggest and many findings! Yes, there are some studies that find RNAi can be induced from ingestion exposures. But they are not uniform findings. That is up in the air. In my opinion, a very important exposure for people would be inhalation (for a systemic effect) and contact (for a local effect).

Q: Are there any studies on the long-term effects of exposure to RNA-based pesticides?

A (Jack): Not really, other than, for example, in *C. elegans* where heritable effects were measured for ~200 generations.

Q: Potential off-target effects of dsRNA pesticides could include lethality (death) to the non-target organism, including human or animal consumers of the plant. Is that correct?

A (Jack): Yes, non-target effects can be lethal. I showed examples in this workshop too. I'm also concerned about sub-lethal effects that undermine human health and environment health on broad scales but are weak on the individual scale.

Q: There are single-stranded stabilised RNAi like phosphorothioate antisense used in medicine. Has this been tested as a pesticide? A lot of people say it is safer than chemicals. Is it theoretical?

A (Jack): I'm not sure what chemical modifications and structures are in use or development other than those I've encountered in the literature.

Q: It would be nice to have the data on effects of RNA-based pesticides on the environment and humans. This would be very helpful when considering local registration of such pesticides.

A (Jack): I agree. This is the responsibility of the manufacturer to provide to regulatory authorities.



Q: It seems clear that there are many unknowns of RNAi technology, not only effects on target pests but also non-target organisms and ecosystem functions generally; to add, there is a lack of national capacity to conduct an adequate and robust risk assessment with different regulatory frameworks and sometimes weak. How do you suggest we actually assess the safety of and regulate the product? How do we ensure safety for our environment with so many unknowns? Do we have those tools, as Dr Magda claims? Are they exhaustive?

A (Jack): The US National Academies recommends detailed risk assessments for RNAi pesticides. We have also published on this. My reference paper has links to some of these.

Q: Do we know enough to have principles or general conclusions about where risks outweigh benefits?

A (Jack): Not in my opinion. Case by case.

Q: How many products have been already registered and where?

A (Magda): Just one in the United States.

RESOURCES

1. OECD Conference Dedicated webpage, including programme, speakers, abstracts, presentation files and other related material from the conference. <http://www.oecd.org/chemicalsafety/pesticides-biocides/conference-on-rnai-based-pesticides.htm>
2. OECD conference report containing a summary of input from presenters and participants. <https://www.frontiersin.org/articles/10.3389/fpls.2020.00740/full>
3. Heinemann, J. A. (2019). Should DsRNA Treatments Applied in Outdoor Environments Be Regulated? *Environ. Int.*, 132, 104856. DOI: 10.1016/j.envint.2019.05.050. <https://pubmed.ncbi.nlm.nih.gov/31174887/>
4. Frontiers Research Topic: RNAi Based Pesticides. <https://www.frontiersin.org/research-topics/11066/rnai-based-pesticides>
5. OECD considerations documents: Working Document on Considerations for the Environmental Risk Assessment of the Application of Sprayed or Externally Applied ds-RNA-Based Pesticides (No. 104) released in September 2020. [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2020\)26&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2020)26&doclanguage=en)
6. Working Document on Considerations for the Human Health Risk Assessment of Externally Applied ds-RNA-Based Pesticides (No.110) released in June 2023. [https://one.oecd.org/document/ENV/CBC/MONO\(2023\)26/en/pdf](https://one.oecd.org/document/ENV/CBC/MONO(2023)26/en/pdf)
7. US EPA's registration of Novel Pesticide Technology for Potato Crops released in December 2023. <https://www.epa.gov/pesticides/epa-registers-novel-pesticide-technology-potato-crops>

If you are not already a member, we invite you to join UCT's Pesticide Network to receive discussion updates and newsletters: <http://eepurl.com/ijR8DX>

The Division of Environmental Health (DEH) Pesticide Discussion Forum is a bi-monthly online seminar for pesticide regulators and resource persons, as well as students in the postgraduate Professional Masters in Chemical Risk Management (MCRM) and Diploma in Pesticide Risk Management (DPRM). Our aim is to provide support for managing pesticide risks and implementing risk reduction strategies.

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