



## CONFERENCE/WORKSHOP ORGANISER'S REPORT

### *“Regulation of Externally Applied dsRNA-based Products for Management of Pests”*

The opinions expressed and arguments employed in this publication are the sole responsibility of the authors and do not necessarily reflect those of the OECD or of the governments of its Member countries.

#### **Brief Description of what the conference/workshop was about**

RNA interference (RNAi) is a biological process in which small ribonucleic acid (RNA) molecules inhibit protein expression, typically by causing the enzymatic destruction of specific messenger RNA (mRNA) molecules, which are the templates for the synthesis of proteins. This process is commonly referred to as post-transcriptional gene silencing (PTGS); that is, mRNA is transcribed from the DNA gene but before the message is translated into proteins by ribosomes, the mRNA is blocked or otherwise destroyed by an enzymatic process guided by a specific non-coding small interfering RNA (siRNA) or microRNA (miRNA).

In recent years, the application of double-stranded RNA (dsRNA) has been investigated in human and animal therapies, and in the development of agricultural products. Triggering RNAi, plant protection against pests may be achieved by topical application (e.g. spraying) of dsRNA molecules (with a nucleotide sequence specifically developed to target a pest species) onto the plant. The increasing development of these products has policy implications and guidance on regulating this technology is needed.

The OECD's two and a half-day Conference summarised the current state of knowledge and on-going developments that are relevant for the regulation of externally applied dsRNA-based products that are proposed for use as pesticides. Invited speakers included academic, industry and government experts in varying aspects of RNAi and their presentations summarised product developments, environmental fate, exposure to externally applied dsRNA in non-target organisms, lessons gathered from human therapeutic use of dsRNA, and key points from previous regulatory reviews of dsRNA-based crop traits.

#### ***Purpose and Scope of the Conference***

The main objectives of the OECD Conference were:

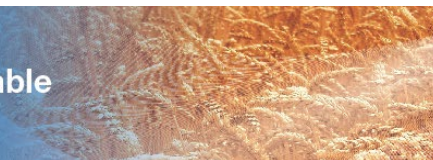
- to provide participants with a summary of the state of the art of dsRNA-based product used in agriculture;
- to exchange information on the current status and future possibilities for the regulation of externally applied dsRNA-based products that are proposed for use as pesticides;
- to facilitate exchanges on their implications in environment, health and regulation;
- to inform regulatory policy and facilitate harmonised approaches.

#### **Participation – details of total number of participants, countries they came from, backgrounds (academia, industry, etc.)**

Around 60 people from academia, government, industry and other stakeholders participated in this event. Countries they came from included: Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, France, Germany, Hungary, the Netherlands, Switzerland, the United Kingdom, the USA, and the European Union.

People attending the OECD conference included:

- members of the OECD Ad Hoc Expert Group on RNAi-based pesticides;
- invited experts from the pesticide industry (BIAC) and manufacturers of these products;
- invited experts from research institutes (academia), and
- regulators and evaluators from governmental or intergovernmental bodies.



### **Major highlights from the presentations**

The first session provided a background on the molecular mechanism of RNAi and relevant related pathways, reviewed the current understanding of cross-kingdom RNAi, examined the species-specificity of these dsRNAs on non-target species and discussed challenges related to the RNAi-efficiency in insects.

The second session dealt with the research to date that investigated the factors that affect insects' responsiveness to environmental dsRNA, covered approaches to assess biodegradation of dsRNA in different matrices and explored the role of certain technology to predict genetic changes and the impact in terms of efficacy of the RNAi products in target pests. It also summarised the published literature related to dietary uptake of external dsRNA in humans and addressed the lessons learnt from human therapeutic use of dsRNA.

The third and final session focused on how problem formulation can guide risk assessments for spray applications of pesticides containing dsRNA, and considered potential pathways and testable risk hypotheses in the context of environmental risk assessment. It also covered the experience of experts involved in the risk assessment of genetically-modified crop plants, which incorporate the machinery to synthesise RNA molecules specifically directed against a pest species feeding on the crop (so-called 'plant-incorporated protectants', or PIPs).

### **Major outcomes/conclusions in terms of policy relevance**

Below are listed the most significant considerations in terms of policy relevance. These considerations represent varied input from multiple participants during the conference and do not always reflect consensus views.

- The potential for exposure of non-target organisms as well as responsiveness to environmental RNAi were seen as the first parameters to consider in the risk assessment of external dsRNA applications before looking at sequence data.
- Sequence information alone should not and cannot be used as a stand-alone predictor of off-target effects.
- Protocols for addressing risk with dsRNA-based products require some revisions compared to how they are carried out for conventional pesticides because dsRNA-based pesticides often take longer to display efficacy. Any evaluation needs to account for this time lag by extending the study period. Additionally, any evaluation of a dsRNA-based pesticide should include monitoring for degradation of the dsRNA over time.
- Impact of product formulation on environmental persistence of dsRNA and uptake by non-target organisms requires consideration.
- The potential uptake of dsRNA by mammals is likely low due to substantial barriers in the oral and topical uptake pathways. Research on barriers to invertebrate oral and topical uptake is limited but the barriers limiting uptake in mammals may also hinder uptake in invertebrates.
- Evidence from human clinical studies suggest that systemic exposure of mammals to dsRNA when dsRNA is applied in the field as a pesticide is likely quite low.
- The use of established laboratory protocols for studying the persistence of Bt proteins from transgenic plants was proposed for evaluating the environmental fate and persistence of dsRNA.



- While it may be possible to generalise the applicability of barriers to dsRNA uptake identified in mammals to other vertebrates, it is currently not possible to predict responsiveness across invertebrate taxa to environmental dsRNA.

## **Relevance to CRP theme(s)**

### **I. MANAGING NATURAL CAPITAL FOR THE FUTURE**

#### **Integrated Agricultural Production Systems, Precision Agriculture**

Precision Agriculture is defined as a way to minimize the use of inputs and impacts on soil, while still seeking the highest possible growth rate of crops in economically, socially, and environmentally responsible ways. dsRNA-based products are designed to have a narrow mode of action against target pests which may result in reduced inputs and impacts to non-target organisms in comparison to other pest management technologies. RNA-based technologies offer additional tools for pest management via an alternative mode of action. Development of externally applied dsRNA-based plant protection products and their regulatory approach could further support the sustainability of crop production and augment the goals of integrated agricultural production systems.

### **II. MANAGING RISKS IN A CONNECTED WORLD**

#### **Risk assessment**

The conference has a direct impact on the work of the OECD Expert Group that is working on the data and risk assessment needs for externally applied dsRNA-based products, as it would inform the Working Papers on environmental fate and non-target organism assessment and human health assessment that this group is targeting for completion of the final draft by the end of 2019. The guidance from the Expert Group is aimed at providing support for OECD member countries as externally applied dsRNA-based products are expected to enter regulatory reviews in the coming years. Experts from a broad field of scientific areas were invited as presenters/participants at the conference, covering key areas of environmental fate, the potential for exposure to externally applied RNA for multiple categories of non-target organisms, the experience from previous risk assessment of dsRNA-based crops, and how the therapeutic use of dsRNA in humans can inform the human health assessment.

### **III. TRANSFORMATIONAL TECHNOLOGIES AND INNOVATION, Bioproducts and Bioprocesses, Precision Agriculture**

Regardless of the method of manufacture for externally applied dsRNA-based products to be effective for the management of pests, the active RNA component must engage the target pest's naturally occurring RNAi biochemical pathway. The conference informed and supported the development of a regulatory approach for these novel products, furthering the development of the bioeconomy.

Since externally applied dsRNA-based products may be designed in a manner that makes them very specific in their biological activity, these products may be a good fit for use in reduced-input and more sustainable agriculture.

## **Website for further details – please also indicate if the presentations are/will be available on the website**

Information about the conference, including the programme, speakers, abstracts, presentation files and other related material is available online (see below). The conference proceedings, including a meeting report and a



written version of each presentation, are expected to be published either as a special issue in a peer-reviewed journal or as an OECD document in 2020.

Website: <http://www.oecd.org/chemicalsafety/pesticides-biocides/conference-on-rnai-based-pesticides.htm>

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