

FACT SHEET

APPLICATION FOR APPROVAL FOR RELEASE OF PRODUCTS OF KK179 ALFALFA FOR SUPPLY OR OFFER TO SUPPLY FOR SALE OR PLACING IN THE MARKET

NBB REF NO: JBK(S) 600-2/1/18

The objective of the Biosafety Act 2007 is to protect human, plant and animal health, the environment and biological diversity. Under the Biosafety Act 2007, the National Biosafety Board (NBB) is currently assessing an application for approval submitted by Monsanto (Malaysia) Sdn. Bhd.

1. What is the application for?

This application is to import and release genetically modified KK179 alfalfa and its products.

2. What is the purpose of the import and release?

The purpose of the import and release is to supply or offer for sale/ placing on the market-for direct use as food, feed and for processing (FFP) of genetically modified KK179 alfalfa. KK179 alfalfa may enter Malaysia as hay to be used as feed meal for animals. The KK179 alfalfa is not intended for cultivation in Malaysia.

3. How has KK179 alfalfa been modified?

Genetically modified KK179 alfalfa was produced by insertion of caffeoyl CoA 3-O-methyltransferase (*CCOMT*) gene segments, derived from alfalfa, assembled to form an inverted repeat DNA sequence. The inverted repeat sequence produces double-stranded RNA (dsRNA) that suppresses endogenous *CCOMT* gene expression via the RNA interference (RNAi) pathway, leading to lower *CCOMT* protein expression resulting in reduced production of guaiacyl lignin subunits (G lignin), and thereby reducing accumulation of total lignin.

4. Characteristics of KK179 alfalfa

a. Details of the parent organism

The recipient or parental plant is *Medicago sativa* L., also known as alfalfa. Alfalfa (including both cultivated alfalfa and closely related subspecies) originated in Asia Minor, Transcaucasia, Turkmenistan, and Iran. Also known as lucerne, it has the longest history of any plant grown solely for forage. Due to its importance as an animal feed, it has spread globally and become acclimatized in Australia, New Zealand, North America, South America, and South Africa. Alfalfa is an important forage crop and as a legume, it is also desired for rotational use to improve soil characteristics such as nitrogen content.

b. Donor organism

The insert present in KK179 contains a partial gene segment of *CCOMT* from alfalfa (*Medicago sativa* L.).

c. Description of the trait(s) and characteristics which have been introduced or modified

The partial gene segment of *CCOMT* is configured into an inverted repeat sequence. The inverted repeat sequence produces dsRNA that suppresses endogenous *CCOMT* gene expression via the RNAi pathway. KK179 alfalfa reduces G lignin levels in forage through the suppression of *CCOMT*, a key enzyme in the lignin biosynthetic pathway. Suppression of *CCOMT* leads to decrease the amount of G lignin, leading to reduced total lignin levels in forage compared to conventional alfalfa at the same stage of growth.

d. Safety of the expressed proteins

The *CCOMT* suppression cassette encodes for dsRNA in KK179 alfalfa and is unlikely to encode for a protein. KK179 does not express a KK179 insert-derived protein (Kozak, 1989). RNA-based suppression of the *CCOMT* gene leading to the intended reduction of G lignin and total lignin in KK179 is mediated by dsRNA molecules. dsRNAs are composed of nucleic acids and are commonly found in plants and other eukaryotes for endogenous gene suppression. Nucleic acids have a history of safe consumption and are considered Generally Regarded As Safe (GRAS) by the U.S. FDA. There is no evidence to suggest that dietary consumption of RNA is associated with toxicity or allergenicity. Additionally, RNAi technique is a naturally occurring process that is believed to occur in all plants and animals (Dykxhoorn et al., 2003; Ivashuta et al., 2009; Parrott et al., 2010). KK179 alfalfa is unlikely to pose a risk as a result of exposure to expressed products of the DNA insert.

e. Utilization of alfalfa

Throughout history, the primary use of alfalfa has been as animal feed source for ruminant animals, including dairy cows, beef cattle, sheep, and goats, as well as for some non-ruminant animals, particularly horses. Greater than 95% of alfalfa used on farms is hay, silage, or haylage which is field dried or dehydrated hay. Other forms include greenchop or dehydrated pellets. Dairy producers are the largest purchasers of alfalfa hay in supreme and premium grades.

Minor food uses include the consumption as dietary supplements, herbal remedies and sprouts in many countries. KK179 alfalfa may enter Malaysia as hay, or as feed meal for animals.

5. Assessment of Risks to Human Health

a. Nutritional Data

Compositional analyses confirmed that, other than the intended reduction in G lignin and total lignin, there is no meaningful effect on key nutrient, anti-nutrient, or secondary metabolite components in KK179 compared to a conventional alfalfa control. Of the 47 components statistically assessed, statistically significant differences were observed for three analytes in comparison to the control. However, the mean values were within the 99% tolerance interval determined from the conventional commercial alfalfa varieties and within the literature ranges. Hence, these differences are unlikely to be biologically meaningful. The applicant concludes from these results that, with the exception of the intended reduction in G lignin and total lignin, forage of KK179 alfalfa is comparable to forage of conventional alfalfa.

b. Toxicological Information

The *CCOMT* suppression cassette encodes for dsRNA in KK179 alfalfa, which is unlikely to encode for a protein that would raise a safety concern for humans (Kozak, 1989). There is history of safe consumption of RNAi-associated RNA molecules and apparent lack of toxicity of dietary RNA (FSANZ, 2013; Ivashuta et al, 2009; Jensen et al., 2013; Petrick et al., 2013; Rodrigues and Petrick, 2020; Snow et al., 2013; U.S. FDA, 1992).

c. Pathogenicity

The *CCOMT* suppression cassette encodes for dsRNA in KK179 alfalfa, which is unlikely to encode for a protein that would raise a safety concern for human (Kozak, 1989). KK179 alfalfa is unlikely to pose a risk as a result of exposure to expressed products of the DNA insert.

6. Assessment of Risks to the Environment

The application does not cover an environmental release. The application is intended only to cover the import of KK179 alfalfa products from countries where alfalfa is already approved and commercially grown, and that may enter Malaysia as hay or as feed for further processing. There are no viable alfalfa materials associated with the KK179 alfalfa products imported into Malaysia. Alfalfa hay does not contain viable plant materials.

7. What is the Emergency Response Plan?

KK179 alfalfa and food and feed products derived from it have been assessed as being as safe as its conventional counterparts and there are no reports of adverse effects since its commercialization. Should adverse effects be reported and verified, appropriate follow up action would be taken to investigate these, and if verified, appropriate actions taken.

a. First Aid Measures

No special first aid measures are required in response for exposure to this product.

b. Accidental Release Measure

No special measures are required in response to an accidental release. Nonetheless, spilled import forms such as hay or feed meals for further processing should be swept, scooped or vacuumed in a manner that avoids dust generation and dust-related hazards.

c. Handling and Storage

No special handling procedures are required for this product. KK179 alfalfa and its products may be handled and stored as any conventional alfalfa product.

d. Disposal Consideration

The same measures for waste disposal and treatment as for conventional alfalfa are valid for KK179 alfalfa.

8. How can I comment on this application?

Any member of the public may submit their comments or queries on publicly notified information about the application. Before submission of comments or queries, the person should review the information provided. Your comments or queries on any possible impacts/risks to the health and safety of the people and the environment that may be posed by the proposed release are appreciated. The submission of the comments or queries should be prepared carefully as it will be given the same scrutiny as the application by the NBB. The submission of comments and clarifications of queries should contribute to the NBB's assessment. Even if the submission is not science-based, and focuses on cultural or other values, it should still be developed in the form of a well-founded argument.

Please note that the consultation period closes on 25 March 2021 and written submissions are required before/by that date. Submissions must be addressed to:

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Please include your full name, address and contact details in your submission.