

# NK603

## Roundup Ready<sup>®</sup> Corn NK603

Glyphosate tolerance

### Key Facts



Monsanto EMEA

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## NK603 - ROUNDUP READY® CORN NK603

### Maize, a key crop

After sugar cane, maize (*Zea mays*) is the second most frequently cultivated crop worldwide, followed by wheat<sup>1</sup>. Following European discovery of the Americas where this crop is indigenous, maize was rapidly adopted in Europe, Africa and Asia. Today, it is one of the few intensively cultivated crops in European agriculture. Significant areas of production include the Danube basin from southwest Germany to the Black Sea and southern France through to the Po Valley of northern Italy. In 2013-2014, approximately 988 million metric tons of maize were produced in the world. Significant areas of production included the US, China and Brazil, representing 35.6%, 22.12% and 8.03% of the global maize production, respectively (USDA, 2015).

As in other world areas, maize use in Europe is dominated by the demand for animal feed. Maize is also processed into valuable industrial and food products such as ethyl alcohol, maize meal, starch and sweeteners.

In 2014, the area of maize harvested in the European Union (EU) was approximately 10 million hectares, with a production of around 74.2 million tons. The EU is a large importer of maize, importing about 8 million tons of maize grain per year<sup>2</sup>. The major exporters of maize to the EU are Ukraine and Brazil, followed by Russia (European Commission, 2014)

### The development of herbicide tolerant maize

During its first growth stages (3 to 12-leaves), maize is very sensitive to competition from weeds for light, nutrients and water. Weed control in maize is usually started early in the growing season (pre- to early post-emergence of the crop) to remove small weeds that would soon compete aggressively with the crop. Generally, a tank mix of soil active and leaf-active herbicides is used.

Herbicide-tolerant (HT) crops were developed in the 1980's to respond to a demand from farmers for more environmentally friendly and flexible weed control methods with enhanced crop selectivity.

Today, the dominant biotech crops commercialized worldwide are those containing the herbicide-tolerant and pest resistant traits (James, 2014).

### Glyphosate: mode of action

Glyphosate, the active substance in Roundup® branded formulations, is a broad-spectrum herbicide that acts by inhibiting the enzyme (protein) "5-enolpyruvyl-shikimate-3-phosphate synthase" (EPSPS). This enzyme, found naturally in all plants, fungi and bacteria, is important in the production of the essential aromatic amino acids through a metabolic pathway that does not

exist in animals. Inhibition of EPSPS by glyphosate blocks the production of these amino acids, interfering with the plant's growth and ultimately leading to plant death (Alibhai and Stallings, 2001). When applied to weeds, glyphosate is taken up by the green leaves and is translocated to the growth points (meristems), present mainly in young shoots and root tips, where it blocks meristeme development.

Glyphosate is non-persistent and has limited mobility because it binds tightly to soil. It does not bio-accumulate and presents minimal risk to terrestrial and aquatic species including fish, birds, mammals and invertebrates. In addition, the compound presents very low toxicity to humans.

Glyphosate has been on the market for more than three decades and is registered in most countries around the world. Glyphosate is approved in the EU under Regulation (EC) 1107/2009, and glyphosate formulations are registered in all EU Member States.

### What is NK603?

NK603, which brand name is Roundup Ready® Corn NK603, is a genetically modified (GM) maize producing a glyphosate-tolerant EPSPS enzyme (CP4 EPSPS) derived from the CP4 strain of the common soil bacterium *Agrobacterium* sp. The glyphosate-tolerant EPSPS enzyme ensures the continued function of the aromatic amino acid pathway, even in the presence of the glyphosate herbicide (see Figure 1). As a result of this genetic modification, NK603 is tolerant to glyphosate, allowing its over-the-top use for selective weed control in the crop.

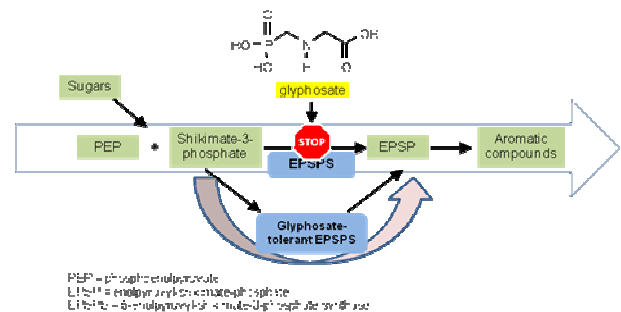


Figure 1: Schematic of the mode of action of the genetic modification in NK603

More information on this product can be obtained from the Center for Environmental Risk Assessment (CERA) GM Crop Database<sup>3</sup> and the EuropaBio website<sup>4</sup>.

### Worldwide plantings and regulatory status of NK603

In 2014, 181.5 million hectares of GM crops were grown worldwide. Of the 184 million hectares of global maize planted in 2014, 30% or 55.2 million hectares were biotech maize (James, 2014).

The first commercial planting of HT maize plants was in the US in 1997. Planted surfaces increased rapidly, equalling approximately 99 million hectares worldwide in 2013 (as a single trait or stacked with insect tolerance trait) or approximately 57% of the total

<sup>0</sup> Roundup and Roundup Ready are registered trademarks of Monsanto Technology LLC

<sup>1</sup> FAOSTAT - <http://faostat.fao.org/site/339/default.aspx> (Accessed on 6 May 2015)

<sup>2</sup> Index mundi - <http://www.indexmundi.com/> (Accessed on 6 May 2015)

<sup>3</sup> CERA - <http://www.cera-gmc.org/GMCropDatabase> (Accessed on 6 May 2015)

<sup>4</sup> EuropaBio - <http://www.europabio.org/information-operators-product-information> (Accessed on 6 May 2015)

genetically modified (GM) plant acreage (James, 2014).

NK603 was first planted commercially in North America in 2001 after receiving authorization for planting in the US and Canada in the same year. Today, NK603 is approved for cultivation in Argentina, Brazil, Canada, Colombia, Honduras, Paraguay, the Philippines, South Africa, Uruguay, Vietnam and the US. Additionally, NK603 received regulatory approvals for import in Australia, China, the EU, Indonesia, Japan, Korea, Malaysia, Mexico, New Zealand, Russia, Singapore and Taiwan<sup>5</sup>.

### **A stringent regulatory system for genetically modified crops in the EU**

In the EU, the regulatory system for GM crops comprises several directives and regulations, including Directive 2001/18/EC for deliberate release of genetically modified organisms (GMOs) in the environment and Regulation (EC) No 1829/2003 concerning GM food and feed.

Regulation (EC) No 1829/2003 includes procedures for the authorisation of deliberate release (cultivation and/or import, and processing), in addition to food and feed use, according to the “one door, one key” principle.

A regulation on traceability and labelling of GMOs and products produced from GMOs (Regulation (EC) No 1830/2003) entered into force on 18 April 2004.

Furthermore, a regulation laying down the methods of sampling and analysis for the official control of feed as regards presence of genetically modified material for which an authorization procedure is pending or the authorisation of which has expired (Commission regulation (EU) No 619/2011) entered into force on 24 June 2011.

### **Regulatory status of NK603 in the EU**

#### ***Import, processing and animal feed use of grain***

In December 2000, Monsanto submitted an application for import and use of NK603 (excluding cultivation) under Directive 90/220/EEC to the Competent Authority of Spain, who evaluated the safety of NK603. The application was then amended to fulfil the new requirements of Directive 2001/18/EC. Spain issued a favourable Initial Assessment Report, which was forwarded to the EU Member States for further review in January 2003.

The European Food Safety Authority (EFSA) evaluated the notification as well as Monsanto’s responses to comments and reasoned objections from certain EU Member States. EFSA issued a favourable scientific opinion on 1 March 2004 (adopted 25 November 2003) concluding that *“NK603 maize is as safe as conventional maize and therefore the placing on the market of NK603 maize for food or feed or processing is unlikely to have an adverse effect on human or animal health or, in that context, on the environment.”* (EFSA, 2003).

After consideration by a Regulatory Committee composed of EU Member State experts and the Council of

Environment Ministers, NK603 was approved for import, feed and processing by the European Commission (EC) in July 2004 (Commission Decision, 2004) (Commission Decision 2004/643/EC).

#### ***Novel foods and novel food ingredients***

Monsanto submitted an application under the novel food and novel food ingredients Regulation (EC) No 258/97 to the Competent Authority of The Netherlands in April 2001. The Netherlands issued a favourable Initial Assessment Report, which was forwarded to the EU Member States for further review in January 2003 and, subsequently to EFSA, which issued a favourable scientific opinion on 1 March 2004 (adopted 25 November 2003) (EFSA, 2003).

After consideration by a Regulatory Committee composed of EU Member State experts and the Council of Agriculture Ministers, food and food ingredients derived from NK603 were approved by the EC on 3 March 2005 (Commission Decision, 2005).

#### ***Feed materials, feed additives and food additives***

In April 2005, existing feed materials, feed additives and food additives produced from NK603 were listed in the Community Register, according to Regulation (EC) No 1829/2003 concerning GM food and feed. Processed feeds such as maize gluten feed and meal are therefore approved in the EU<sup>6</sup>.

In August 2005, Monsanto applied for the renewal of the existing feed materials, feed additives, and food additives produced from NK603 listed in the Community Register, pursuant to Regulation (EC) No 1829/2003. A positive EFSA overall opinion, fulfilling the requirements of Articles 6 and 18 of Regulation (EC) No 1829/2003 and confirming the conclusions of the original safety assessment, was published 11 June 2009 (adopted 27 May 2009) (EFSA, 2009). According to the legal framework these authorised products remain lawfully on the market until a decision on re-authorization is taken by the EC.

#### ***Cultivation***

In August 2005, an application for use as any other maize, including the use for cultivation of varieties of NK603 in the EU was submitted to the Dutch Competent Authority, the National Institute for Public Health and the Environment (RIVM), which then transmitted the application to EFSA pursuant to Regulation (EC) No 1829/2003.

EFSA and the Spanish Competent Authority, appointed by EFSA as the EU Member State responsible for conducting the environmental risk assessment (pursuant to Regulation (EC) No 1829/2003) evaluated the application as well as Monsanto’s responses to questions. EFSA published a favourable scientific opinion on 11 June 2009 (EFSA, 2009), concluding that *“NK603 is as safe as its conventional counterpart with respect to potential direct effects on human and animal health and the environment”*, and recommending managing the use of glyphosate (which is regulated under Directive 91/414/EEC) on NK603 in regimes that have similar or reduced environmental

<sup>5</sup> Crop Life International - <http://www.biotradestatus.com/> (Accessed on 6 May 2015)

<sup>6</sup> Community register of GM food and feed - [http://ec.europa.eu/food/dyna/gm\\_register/index\\_en.cfm](http://ec.europa.eu/food/dyna/gm_register/index_en.cfm) (Accessed on 6 May 2015)

impacts compared with conventional maize cultivation.

On 17 October 2013, the split of the scope of the application was formally requested to the EC in order to facilitate continuation of the food and feed uses of NK603 in the EU. On 14 March 2014, the cultivation scope was formally withdrawn from the application. The authorization was finally granted by the EC on 24 April 2015 (Commission Decision, 2015).

### Traceability, labelling, unique identifier

Operators importing, handling or using NK603 grain and derived foods and feeds in the EU should be informed of the legal obligations regarding traceability and labelling, laid down in Regulations (EC) No 1829/2003 and 1830/2003 and in the conditions of placing on the market of the consent (Commission Decision 2004/643/EC). The unique identifier of Roundup Ready® Corn NK603 is MON-00603-6.

A NK603-specific PCR-based detection method allowing the identification and quantification of NK603 was provided to the Joint Research Centre (JRC), acting as the European Union Reference Laboratory (EURL). The validated methods, as well as the validation report for NK603 were published on 10 January 2005 on the EURL website<sup>7</sup>.

### Food, feed and environmental safety of NK603

#### Food and feed safety

The food and feed safety of NK603 was established based on:

- A detailed molecular characterization of the inserted DNA, where the results confirm that a single copy of the *cp4 epsps* expression cassette was integrated at a single locus within the maize genome;
- The long history of safe use of the CP4 EPSPS protein;
- The evaluation of CP4 EPSPS activity and its homology to EPSPS proteins present in a diversity of plants, including those used for foods;
- The rapid digestibility of the CP4 EPSPS protein by proteases found in the human gastrointestinal tract (pepsin and pancreatin);
- The lack of toxicity or allergenicity of the CP4 EPSPS protein generally and as demonstrated with bioinformatics as well as *in vitro* and *in vivo* safety studies of the CP4 EPSPS protein;
- A large margin of safety resulting from the low dietary exposure to the introduced CP4 EPSPS protein in NK603.

NK603 was shown to be as safe and nutritious as conventional maize by analysis of key nutrients, including protein, fat, carbohydrates, amino acids, fatty acids and minerals.

Further details on the safety of NK603 are available in a product safety summary on Monsanto's website<sup>8</sup> and EFSA scientific opinion published on 11 June 2009 (EFSA, 2009).

#### Environmental safety

The environmental safety of NK603 was established through extensive laboratory and field testing conducted in the US in 1997, demonstrating that NK603 poses negligible risk to human health or to the environment.

Results from the phenotypic and agronomic assessments demonstrate that NK603 does not possess characteristics that would confer a plant pest risk compared to conventional maize. Data on environmental interactions also indicate that NK603 does not confer any biologically meaningful increased susceptibility or tolerance to specific disease, insect, or abiotic stressors, or changes in agronomic and phenotypic characteristics. This, together with the history of safe use of the CP4 EPSPS protein, demonstrates that the ecological interactions of NK603 with non-target organisms or soil processes are not different from conventional maize. Furthermore, the environmental safety of NK603 has been confirmed by 13 years of worldwide cultivation with no reported cases of harm to the environment.

Maize has no wild relatives in Europe to which the introduced trait could outcross. The likelihood of this maize spreading into the non-agronomic environment is negligible, since it is not more invasive in natural habitats than conventional maize. Moreover, the scope of the authorization covers the import, processing and all uses as any other maize, but excluding cultivation in the EU, and no deliberate release of the viable plant material in the EU environment is expected thereby limiting the environmental exposure to accidental spillage only.

In conclusion, the environmental impact of growing NK603 is not different from that of growing conventional maize, as stated in the June 2009 EFSA opinion (EFSA, 2009). The environmental impact of using weed control programs enabled by NK603 is further assessed in the following section.

### NK603, the benefits

NK603 provides the following benefits:

- Control of a wide spectrum of weeds using a smaller number of herbicides. This is particularly important since a number of active ingredients are being re-assessed for toxicological and environmental safety under Directive 91/414/EEC. Glyphosate has already been approved under this directive and can provide an environmentally sustainable, flexible, and profitable alternative to existing weed control programs (Dewar, 2009);
- Flexible broad-spectrum weed control options that allows over-the-top applications of glyphosate in maize on an "as needed" basis (Johnson *et al.*, 2000);

<sup>7</sup> EU-RL GMFF - <http://gmo-crl.jrc.ec.europa.eu/StatusOfDossiers.aspx> (Accessed on 6 May 2015)

<sup>8</sup> Monsanto - <http://www.monsanto.com/products/pages/product-safety-summaries.aspx> (Accessed on 6 May 2015)

- Contribution to achieve more consistency in the weed control results combined with the full and superior selectivity of Roundup® on NK603 hybrids to protect the yield potential of those hybrids;
- An excellent fit with reduced tillage systems, which are linked to many environmental advantages including improved soil and water quality, reduced soil erosion and runoff, improved wildlife habitat and reduced fuel use and CO<sub>2</sub> emissions (Brookes and Barfoot, 2014; Fawcett and Towery, 2002; Phipps and Park, 2002);
- The opportunity to replace several selective herbicides by a single broad-spectrum herbicide with a favorable human health and environmental profile. The active ingredient glyphosate is non-persistent and has limited mobility as it binds tightly to soil. The compound presents very low toxicity to humans. Furthermore, it does not bioaccumulate and presents minimal risk to terrestrial and aquatic species including fish, birds, mammals and invertebrates (Giesy *et al.*, 2000; Williams *et al.*, 2000);
- An additional mode of action within the weed control in maize contributes to proactive and sustainable weed resistance management in the crop rotation;
- The practical use of NK603 systems in several world areas has proven cost-effective weed control: in the US., data indicates estimated savings for maize growers of \$8/acre (Johnson and Strom, 2007 ; Marra *et al.*, 2002).

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