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Til underretning for Folketingets Europaudvalg vedlægges Fødevareministeriets notater om ansøgning om fødevaregodkendelse i henhold til forordning 258/97 om nye levnedsmidler og nye levnedsmiddelingredienser af hhv. gensplejset (insektresistent) majs (linie MON863) og majshybriden (MON863xMON810).

Ministeriet for Fødevarer, Landbrug og Fiskeri
Fødevaredirektoratet/6. kontor
J.nr.: 2002-20-24-00304 og 2000-4230-0040
Den 21. juli 2003
FA3/ACD/THE
FVM 082
F:\FAELLES\TOETKOM\6-kontor\AKN+forklæde GMO-majs juni 2003.doc

NOTAT TIL FOLKETINGETS EUROPAUDVALG

om ansøgning om fødevaregodkendelse i henhold til forordning 258/97 om nye levnedsmidler og nye levnedsmiddelingredienser af hhv. gensplejset (insektresistent) majs (linie MON863) og majshybriden (MON863xMON810)

Dokument: Kommissionens skrivelse af 3. juni 2003

I overensstemmelse med den fastsatte godkendelsesprocedure i forordning 258/97 om nye levnedsmidler og nye levnedsmiddelingredienser har Kommissionen fremsendt den tyske vurderingsrapport vedrørende den genetisk modificerede - insektresistent – majs af linie MON863 og hybriden MON810xMON863. Det tyske vurderingsorgan vurderer, at fødevarer og ingredienser produceret af ovennævnte majs er lige så sikre som produkter produceret af konventionel majs.

Fra fremsendelsesbrevets dato har medlemsstaterne 60 dage til at tage stilling til ansøgningen og til at komme med bemærkninger eller begrundede indsigelser. Medlemsstaternes indstilling til ansøgningen skal således være kommissionen i hænde senest 2. august 2003.

Hvis ingen medlemsstater har indsigelser mod ansøgningen, vil den blive godkendt af Kommissionen. Hvis der fremsættes begrundet indsigelse mod ansøgningen, skal der træffes afgørelse om tilladelse til markedsføring efter proceduren i artikel 13 i forordning 258/97. Hvis der er kvalificeret flertal for Kommissionens forslag i Den Stående komité for Fødevaresikkerheden og Dyresundhed, udsteder Kommissionen beslutningen. Opnås der ikke kvalificeret flertal, forelægger Kommissionen sagen for Rådet, der kan vedtage forslaget uændret med kvalificeret flertal eller ændre det med enstemmighed. Handler Rådet ikke inden en frist på højst tre måneder, kan Kommissionen udstede beslutningen.

Fødevaredirektoratet, som er det kompetente fødevarevurderingsorgan for Danmark, har efter den sundhedsfaglige vurdering ikke grundlag for indsigelser mod ansøgningen. Da ansøgningen omfatter levende genetisk modificerede organismer skal der foreligge en miljømæssig risikovurdering, og der skal sideløbende gennemføres en godkendelsesprocedure efter bestemmelserne i udsætningsdirektivet.

En godkendelse af ansøgningen vurderes således ikke at berøre beskyttelsesniveauet i Danmark.

Regeringen agter på den baggrund at meddele Kommissionen, at Danmark finder, at en godkendelse bør følge det nye regelsæt, som Rådet opnåede politisk enighed om i november 2002. Danmark gør derfor begrundet indsigelse og fremsætter ønske om, at sagen tages op i komitéprocedure. Med hensyn til levende GMO kommer hertil, at der skal foreligge en godkendelse efter bestemmelserne i udsætningsdirektivet. Hvis det alligevel besluttes, at godkende linierne til fødevarer, bør det ske på betingelse af, at der fastsættes krav om mærkning af produkter, der indeholder eller er fremstillet af pågældende GMO-majs med en undergrænse på højst 0,9 procent, jf. den politiske enighed i Rådet herom i november 2002. Godkendelse til brug for fødevarer af levende GMO bør som nævnt under alle omstændigheder afvente en godkendelse efter bestemmelserne i udsætningsdirektivet.

Ministeriet for Fødevarer, Landbrug og Fiskeri
Fødevaredirektoratet/6. kontor
J.nr.: 2002-20-24-00304 og 2000-4230-0040
Den 21. juli 2003
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F:\FAELLES\TOETKOM\6-kontor\AKN+forklæde GMO-majs juni 2003.doc

AKTUELT NOTAT TIL FOLKETINGETS EUROPAUDVALG

om ansøgning om fødevaregodkendelse i henhold til forordning 258/97 om nye levnedsmidler og nye levnedsmiddelingredienser af hhv. gensplejset (insektresistent) majs (linie MON863) og majshybriden (MON863xMON810)

Dokument: Kommissionens skrivelse af 3. juni 2003

Resumé
I overensstemmelse med den fastsatte godkendelsesprocedure i forordning 258/97 om nye levnedsmidler og nye levnedsmiddelingredienser har Kommissionen fremsendt den tyske vurderingsrapport vedrørende den genetisk modificerede - insektresistent – majs af linie MON863 og hybriden MON810xMON863. Det tyske vurderingsorgan vurderer, at fødevarer og ingredienser produceret af ovennævnte majs er lige så sikre som produkter produceret af konventionel majs. En godkendelse af ansøgningen vurderes ikke at berøre beskyttelsesniveauet i Danmark.

Baggrund

Med skrivelse dateret 3. juni 2003 har Kommissionen til medlemsstaternes kompetente myndigheder fremsendt den første vurderingsrapport fra det tyske levnedsmiddelvurderingsorgan, Robert Koch Instituttet, vedrørende den genetisk modificerede - insektresistent – majs af linie MON863 og hybriden MON810xMON 863. Ansøgning om godkendelse er indgivet af Monsanto til de tyske myndigheder i august 2002. I april 2003 fremsendte de tyske myndigheder den første vurderingsrapport til Kommissionen.

Ansøgningen er indgivet i overensstemmelse med den fastsatte godkendelsesprocedure i forordning 258/97 af 27. januar 1997 om nye levnedsmidler og nye levnedsmiddelingredienser.

Fra fremsendelsesbrevets dato har medlemsstaterne 60 dage til at tage stilling til ansøgningen og til at komme med bemærkninger eller begrundede indsigelser. Medlemsstaternes indstilling til ansøgningen skal således være Kommissionen i hænde senest 2. august 2003.

Hvis ingen medlemsstater har indsigelser mod ansøgningen, vil den blive godkendt af Kommissionen.

Hvis der fremsættes begrundet indsigelse mod en ansøgning om godkendelse som nyt levnedsmiddel, skal der træffes afgørelse om tilladelse til markedsføring efter proceduren i artikel 13 i forordning 258/97. Afgørelsen træffes på grundlag af et forslag fra Kommissionen, som forelægges for Den Stående komité for Fødevaresikkerheden og dyresundhed (SCoFCAH). Forslaget behandles i en III a-procedure i SCoFCAH. Hvis der er kvalificeret flertal, udsteder Kommissionen beslutningen. Opnås der ikke kvalificeret flertal, forelægger Kommissionen sagen for Rådet, der kan vedtage forslaget uændret med kvalificeret flertal eller ændre det med enstemmighed. Handler Rådet ikke inden en frist på højst tre måneder, kan Kommissionen udstede beslutningen.

Nærheds- og proportionalitetsprincippet
Da ansøgningen ikke er en retsakt, skal overensstemmelsen med nærheds- og proportionalitetsprincippet ikke vurderes.

Formål og indhold
Ansøgningen vedrører enhver fødevareanvendelse af den gensplejsede majs (linie MON863) og majshybriden (MON863xMON810), dvs. såvel i rå som i forarbejdet tilstand.

På grundlag af datamaterialet konkluderer det tyske vurderingsorgan, at ansøgningen indeholder tilstrækkelige data om de molekylærbiologiske, ernæringsmæssige og toksikologiske aspekter til, at det kan anses for godtgjort, at den gensplejsede majslinie MON863 og hybriden MON810xMON863 kun afviger fra en konventionel majslinie ved de indsatte gener og deres produkter. Fødevarer og ingredienser produceret af ovennævnte majs vurderes til at være lige så sikre som produkter produceret af konventionel majs.

De danske myndigheders vurdering
Indledningsvis bemærkes, at Monsanto desuden har søgt om godkendelse til markedsføring (dog ikke dyrkning) i EU af den genmodificerede majs MON863 og hybriden MON863xMON810 i henhold til udsætningsdirektivet (direktiv 2001/18/EF). Den første vurderingsrapport er udarbejdet af de tyske myndigheder og rundsendt til de øvrige EU-landes myndigheder med henblik på bemærkninger. Fristen for bemærkninger var den 1. juli 2003.

Majslinjen MON863 har fået indsat et gen (cry3Bb1), der gør planterne tolerante overfor angreb af skadelige billelarver (majs-rodorm) og et gen (nptII), der giver tolerance overfor antibiotika (kanamycin). NPTII proteinet har flere gange tidligere været vurderet at være uden sundhedsmæssige problemer i gensplejsede fødevareplanter. Proteinet Cry3Bb1 har ikke tidligere været vurderet i relation til fødevarer.

Den genetisk modificerede majslinie MON863 x MON810 er opstået ved en traditionel krydsning af den ovennævnte majslinie og en majslinie MON810, som har fået overført et gen (cryIA(b)), der gør den resistent overfor angreb af skadelige sommerfuglelarver (af familien lepidoptera).

Det er Fødevaredirektoratets opfattelse, at der er foretaget alle de analyser og målinger, som er nødvendige for at bestemme mængden og arten af det indsatte DNA samt for at foretage en grundig sundhedsmæssig risikovurdering i forbindelse med anvendelse af de ovennævnte majs. For at kunne foretage denne sammenligning er analyser udført på såvel de gensplejsede majsplanter, som sammenlignelige konventionelle planter.

Ud over de sammenlignende kemiske analyser er foretaget en række undersøgelser i dyreforsøg. Dels er der lavet dyreforsøg (mus) med høje doser af de proteiner som gensplejsningerne giver dannelse af (Cry1A(b), Cry3Bb1 og NPTII) og dels er dyr (rotter og kyllinger) fodret med gensplejset majs. Tilsvarende er til sammenligning lavet undersøgelser med forskellige typer ikke-gensplejset majs. Ingen af undersøgelserne giver anledning til at ændre ved den konklusion, at de gensplejsede majs kan betragtes sundhedsmæssigt som svarende til konventionel majs.

Majs er for en lille gruppe personer med gluten-intolerans en vigtig energikilde og der er således foretaget en *ernæringsmæssig* vurdering af både majs linie MON863 og hybriden MON863 x MON810 for at sikre, at de ikke adskiller sig væsentligt fra konventionel majs. Der ses enkelte signifikante forskelle i kemisk sammensætning mellem de gensplejsede majs og kontrolmajs. Forskellene viser dog ikke noget bestemt mønster og ligger inden for den naturlige variation i majs, hvorfor forskellene vurderes ikke at have ernæringsmæssig betydning. Den gensplejsede majs MON863 samt hybridmajsen MON863 x MON810 kan begge betragtes som ernæringsmæssigt "substantial equivalent" til konventionel majs.

I relation til kontrol angiver ansøger, at der er indsendt metode til entydig identifikation af MON863 og ansøger vil medvirke til afprøvning (validering) af metoden samt levere materiale til denne afprøvning. Tilsvarende er sket for MON810.

Konklusion: Samlet er det Fødevaredirektoratets vurdering, at der ikke er sundhedsmæssige betænkeligheder ved at anvende de omtalte majs til fødevarebrug.

Udtalelser

Ansøgningen og vurderingen skal ikke forelægges Europa-Parlamentet.

Gældende dansk ret

Markedsføring af nye levnedsmidler er reguleret af novel food forordningen nr. 258/97.

Konsekvenser

Forslaget har hverken lovgivningsmæssige, statsfinansielle eller samfundsøkonomiske konsekvenser. En godkendelse af ansøgningen vurderes ikke at berøre beskyttelsesniveauet i Danmark.

Høring

Forslaget har været sendt til høring hos en lang række myndigheder og organisationer, og der er indkommet følgende høringssvar:

Danmarks Jordbrugsforskning, Forskningscenter Foulum, har ingen bemærkninger til vurderingsrapport og resumé over ansøgningen.

Den Kongelige Veterinær- og Landbohøjskole (KVL) finder ingen anledning til betænkeligheder ved anvendelsen af de 2 genmodificerede majslinier til fødevarebrug, idet der ikke er tale om ansøgning vedr. dyrkning af disse majslinier indenfor områder i Europa, hvor majs dyrkes til såsæd.

Landbrugsraadet, Dansk Landbrug (fusionen af Landboforeningerne og Dansk Familielandbrug) og Danske Slagterier anbefaler, at Monsantos ansøgning imødekommes, idet den genmodificerede organisme ifølge vurderingsorganets rapport ikke giver anledning til sundheds- og ernæringsmæssige betænkeligheder. Det er dog en forudsætning, at det indsatte "antibiotikaresistensgen" efter de danske myndigheders vurdering ikke giver anledning til sundhedsmæssige betænkeligheder.

De samvirkende Købmænd har ikke bemærkninger til ansøgningen.

Økologisk Landsforening mener ikke, at der bør gives markedsføringstilladelse, da der ikke er nogle fordele ved de omtalte majs, der kan opveje betænkelighederne ved dem. Det anføres, at den ved gensplejsningen brugte CaMV 35s promoter, kan give ustabilitet og risiko for horisontal genoverførsel, hvilket giver grund til bekymring i forhold til både miljø og sundhed. Desuden er der betænkeligheder ved den indsplejsede Bt-egenskab (Bacillus thuringiensis; giver resistent overfor angreb af insektlarver), idet risikoen for at oparbejde resistens hos skadedyrene er væsentlig. Endelig anføres det, at konsekvenserne for sundheden ved brug af gensplejsede produkter som fødevarer generelt ikke er tilstrækkeligt belyst.

I forbindelse med høring i § 2 – udvalget (landbrug) og Det Rådgivende Fødevareudvalg er der indkommet følgende høringssvar:

Landbrugsraadet og Danske Slagterier anbefaler fortsat, at de to majssorter meddeles markedsføringstilladelse, idet de har noteret sig, at Fødevaredirektoratet har vurderet, at der ikke er sundhedsmæssige betænkeligheder herved.

FødevareIndustrien lægger i sin vurdering vægt på, at Fødevaredirektoratet ikke vurderer, at der er sundhedsmæssige betænkeligheder ved at anvende de omtalte majs til fødevarebrug, og der er FødevareIndustriens opfattelse, at ansøgningen om godkendelse af de to GMO-linier til fødevarebrug bør imødekommes.

Skov- og Naturstyrelsen ønsker, at godkendelsen af majslinierne afventer, at reglerne om sporbarhed og mærkning og om genetisk modificerede fødevarer og foderstoffer er endeligt på plads. Skov- og Naturstyrelsen mener, at afgørelse om tilladelse til markedsføringen skal træffes efter proceduren i art. 13 (komiteprocedure). Skov- og Naturstyrelsen vurderer i øvrigt, at det bør afklares, hvorvidt det iflg. Forordning 258/97 er tilstrækkeligt at indsende én ansøgning, når der som i dette tilfælde søges om godkendelse af to majslinier.

Skov- og Naturstyrelsen gør opmærksom på, at styrelsen den 5. maj 2003 modtog en ansøgning om tilladelse til markedsføring af samme to majslinier efter udsætningsdirektivet (2001/18/EF), og oplyser, at Danmark den 1. juli 2003 har givet følgende bemærkninger til Kommissionen vedr. denne ansøgning: Danmark tilkendegav, at da der er risiko for, at der i forbindelse med produktion i 3. lande sker en opblanding af majslinierne med konventionel majs til udsåning, bør disse majslinier indgå i den allerede eksisterende overvågning af importerede majspartier til udsåning fra 3. lande. Danmark kan i øvrigt ikke støtte en godkendelse til markedsføring af genetisk modificerede organismer, der indeholder gener, som giver resistens over for antibiotika, der anvendes i human- eller veterinærmedicinsk behandling. Danmark gjorde endvidere opmærksom på moratoriet og ønsker, at sagen tages op i komitéprocedure.

Tidligere forelæggelse for Folketingets Europaudvalg

Sagen har ikke tidligere været forelagt for Folketingets Europaudvalg.

EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL
Directorate D – Food Safety: production and distribution chain
D4 – Food law and biotechnology

SANCO

03. 06. 2003

Brussels,
SANCO/D4/AK/cw/D/440258(2003)

Note to the Permanent Representations of

Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden, United Kingdom

Subject: **Regulation (EC) N° 258/97**

Ref: **Grains and grain derived food ingredients from insect-protected Maize line MON 863 and Maize hybrid MON 863 X MON 810**

On 19 September 2002 you were informed of the request by Dr. B. Tinland (Monsanto) for an agreement for placing the above-mentioned product on the Community market. In application of Article 6.2, an initial assessment was carried out by the:

Robert Koch Institut (D).

On 8 April 2003 the competent authority of Germany forwarded the initial assessment report to the Commission services.

Please find attached for your consideration:

Erstprüfbericht des Robert Koch-Institutes (8. April 2003): Insektenresistenter Mais MON 863 und MON 863 X MON 810

Initial assessment report by the Robert Koch Institute (8 April 2003): Insect-resistant maize MON 863 and MON 863 X MON 810

The conclusion of the initial assessment report was that pursuant to Article 7 of the Regulation, an additional assessment is required.

Before proceeding with the additional assessment, I would like to receive your comments at your earliest convenience, preferably within 60 days following the transmission of this initial assessment report.

Patrick Deboyser

Enclosures

cc: Competent authorities, EFTA Secretariat, Dr. B. Tinland

Rue de la Loi 200, B-1049 Bruxelles/Wetstraat 200, B-1049 Brussel - Belgium - Office: F-101 8/70.
Telephone: direct line (+32-2)2953210, switchboard 299.11.11. Fax: 2960951.

COMMISSION EUROPÉENNE
DIRECTION GÉNÉRALE SANTÉ ET PROTECTION DES CONSOMMATEURS
Direction D - Sécurité alimentaire: chaînes de production et de distribution
D4 - Législation alimentaire et biotechnologi

SANCO

03. 06. 2003

Bruxelles, le
SANCO/D4/AK/cw/D/440258(2003)

Note aux Représentations permanentes

Autriche, Belgique, Danemark, Finlande, France, Allemagne, Grèce, Irlande, Italie, Luxembourg, Pays-Bas, Portugal, Espagne, Suède, Royaume-Uni

Objet : **Règlement (CE) N° 258/97**

Demande d'autorisation de mise sur le marché européen de graines et ingrédients alimentaires dérivés de graines de maïs des lignées résistantes aux insectes maïs MON 863 et maïs hybride MON 863 X MON 810 (Monsanto)

Le 19 septembre 2002, vous avez été informés à la demande de Dr. B. Tinland (Monsanto) d'un accord pour la mise sur le marché de la Communauté d'un aliment nouveau ou d'un ingrédient alimentaire nouveau mentionné ci-dessus.

En vertu de l'article 6.2, une première évaluation a été effectuée par:

Robert Koch Institut (D)

Le 8 avril 2003, l'autorité compétente d'Allemagne a transmis le rapport d'évaluation initial aux services de la Commission.

Veuillez trouver ci-joint à votre attention:

Erstprüfbericht des Robert Koch-Institutes (8. April 2003): Insektenresistenter Mais MON 863 und MON 863 X MON 810

Initial assessment report by the Robert Koch Institute (8 April 2003): Insect-resistant maize MON 863 and MON 863 X MON 810

La conclusion du rapport d'évaluation initial est qu'une évaluation complémentaire conformément à l'article 7 sera necessaire.

Avant procéder à l'évaluation complémentaire, j'apprécierais vos commentaires dans les 60 jours après la transmission du rapport.

Patrick Deboyser

Annexe

cc: Autorités compétentes, Bureau EFTA, Dr. B. Tinland

Rue de la Loi 200, B-1049 Bruxelles - Belgique - Bureau: F-[illegible] 8/70.
Téléphone: ligne directe (+32-2)2953210, standard 299.11.[illegible] Télécopieur: 2360951.

EUROPÄISCHE KOMMISSION
GENERALDIREKTION GESUNDHEIT UND VERBRAUCHERSCHUTZ
Direktion D - Lebensmittelsicherheit; Produktions- und Vertriebskette
D4 - Rechtsvorschriften des Lebensmittelbereichs und Biotechnologie

SANCO

Brüssel, den 03. 06. 2003
SANCO/D4/AK/cw/D/440258(2003)

Mitteilung an die Ständigen Vertretungen von

Österreich, Belgien, Dänemark, Finnland, Frankreich, Deutschland, Griechenland, Irland, Italien, Luxemburg, die Niederlande, Portugal, Spanien, Schweden, Vereinigtes Königreich

Betreff: **Verordnung (EG) N° 258/97**

Bezug: **Körner der vor Insekten geschützten Maislinie MON 863 und der Mais-Hybride MON 863 X MON 810 und daraus hergestellter Lebensmittel**

Am 19. september 2002 wurden Sie über den Antrag von Dr. B. Tinland (Monsanto) informiert das o.a. Produkt als neuartiges Lebensmittel oder neuartige Lebensmittelzutat in der Gemeinschaft in den Verkehr zu bringen.

Gemäß Artikel 6 (2) wurde die Erstprüfung vom

Robert Koch Institut (D)

durchgeführt.

Die zuständigen Behörden Deutschlands haben den Bericht über die Erstprüfung am 8. April 2002 an die Dienststellen der Kommission übermittelt.

Anbei finden Sie mit der Bitte um Stellungnahme folgendes Dokument:

Erstprüfbericht des Robert Koch-Institutes (8. April 2003): Insektenresistenter Mais MON 863 und MON 863 X MON 810

Initial assessment report by the Robert Koch Institute (8 April 2003): Insect-resistant maize MON 863 and MON 863 X MON 810

Der Erstprüfbericht gelangt zu der Schlußfolgerung, daß eine zusätzliche Prüfung gemäß Artikel 7 der Verordnung erforderlich ist.

Rue de la Loi 200, B-1049 Bruxelles/Wetstraat 200, B-1049 Brussel - Belgien - Büro: F-101 8/70.
Telefon: Durchwahl (+32-2)2953210, Zentrale 299.11.11. Telefax: 2980951.

Sobald wie möglich, vorzugsweise innerhalb von 60 Tagen nach der Übermittlung des Berichtes, bitte ich um Ihre Kommentare vor der Durchführung der zusätzlichen Prüfung.

Patrick Deboyser

Anlagen

cc: Zuständige Behörden, EFTA Sekretariat, Dr. B. Tinland

4

ROBERT KOCH INSTITUT

Initial assessment report
by the Robert Koch Institute
8 April 2003

Insect-resistant maize MON 863 and MON 863 X MON 810

Application by the Monsanto Company, USA, represented by Monsanto Europe S.A., Brussels, Belgium, to place genetically modified maize on the market pursuant to Regulation (EC) No 258/97

submitted by Bruno Tinland, Ph.D.

Contents:

1. Introduction

On 13 August 2002 an application was submitted to the Robert Koch-Institut (RKI) by the Monsanto Company, USA, represented by Monsanto Europe S.A., Brussels, Belgium, for approval of the placing on the market of genetically modified maize (Zea mays) MON 863 and MON 863 X MON 810 pursuant to Regulation (EC) No 258/97. In a letter from the Federal Ministry of Consumer Protection, Food and Agriculture (BMVEL) dated 28 August 2002, the European Commission was informed about the submission of the application and the RKI was appointed as the food assessment body responsible for conducting the initial assessment.

The subject of the application is the placing on the market of maize kernels from progeniture of the genetically modified maize line MON 863 with a resistance to certain coleoptera, especially larvae of maize root borers (*Diabrotica* sp.), and the placing on the market of maize kernels of the hybrid MON 863 x MON 810, which is produced by conventional cross-breeding of the two genetically modified maize lines MON 863 und MON 810 and combines the resistance to coleoptera with resistance to certain lepidoptera, such as the European corn borer (*Ostrinia nubilalis*). The maize kernels are intended to be used as foodstuffs both in unprocessed form and in the form of processed products.

The genetically modified maize line MON 810 (Notification C/F/95/12-02) was granted unrestricted authorisation to be placed on the EU market by Commission Decision 98/294/EC of 22 April 1998 and the publication of the corresponding decision of the competent French authority on 5 August 1998 on the basis of Directive 90/220/EEC. In addition, products made from MON 810 maize were recognised as substantially equivalent in accordance with an opinion of the ACNFP (the competent body in the UK) of 10 December 1997 pursuant to Article 5 of Regulation (EC) No 258/97 (published in OJEC No C200 of 26.06.1998, p. 16).

In accordance with §2 of the (German) Novel Foods and Novel Food Ingredients Order (*Neuartige Lebensmittel- und Lebensmittelzutaten-Verordnung*) (NLV), the Federal Office for Consumer Protection and Food Safety (*Bundesamt für Verbraucherschutz und Lebensmittelsicherheit*) (BVL, establishment of the agreement), the Federal Biological Institute for Agriculture and Forestry (*Biologische Bundesanstalt für Land- und Forstwirtschaft*) (BBA), the Federal Office for the Environment (*Umweltbundesamt*) (UBA) and the highest *Land* authorities responsible for monitoring of foodstuffs were given an opportunity to comment on the application. The opinions of these authorities and an opinion from the Central Commission for Biological Safety (*Zentrale Kommission für die Biologische Sicherheit*) (ZKBS) were taken into account in drawing up the initial assessment report.

2. Completeness and form of the application

The above-mentioned application was submitted by Monsanto on 13 August 2002. An initial examination by the RKI of the documents submitted with the application revealed that they were not complete, which meant that further documents would have to be submitted at a later date. Once the applicant had done this in December 2002 and January and February 2003, the application was declared by the RKI on 14 February 2003 to be complete pursuant to Regulation (EC) No 258/97.

2.1. Administrative data

The application was submitted by Bruno Tinland, Ph. D., on behalf of the Monsanto Company, represented by Monsanto Europe S.A., 270-272 Avenue de Tervuren, B-1150 Brussels.

2.2. General description (categorisation and scientific classification)

The subject of the application is the placing on the market of maize kernels from progeniture of the genetically modified maize line MON 863 and maize kernels of the hybrid MON 863 x MON 810 produced by conventional cross-breeding. The maize kernels are intended to be used as foodstuffs both in unprocessed form and in the form of processed products. These novel foods and novel food ingredients (NF) thus come under the scope of Article 1(2) a) and b) of Regulation (EC) No 258/97.

The application relates to products from genetically modified maize plants. The applicant provided evidence that the host plant used for the genetic modification had already been used in the EU as a food or a source of food under comparable conditions of preparation and consumption. Its classification by the applicant in Category 3.1 in accordance with the Commission Recommendation of 27 July 1997 (97/618/EC) is approved.

2.3. Determination of the main requirements for the information

On the basis of the classification in Category 3.1, the applicant took account of the following evaluation criteria for the application documents, in accordance with Table II in Commission Recommendation 97/618/EC:

I. Specification of the NF
II. Effects of the production process applied to the NF
III. Previous experience with the organism used as the source for the NF
IV. Effects of the genetic modification on the characteristics of the host organism
V. Genetic stability of the GMO used as the NF source
VI. Specificity of the expression of the novel genetic material
VII. Transfer of genetic material from GMOs
VIII. N/A
IX. Foreseeable consumption/extent of use of the NF
X. Information on previous exposure of humans to the NF or its source
XI. Nutritional information on the NF
XII. Microbiological information on the NF
XIII. Toxicological information on the NF.

2.4. Consideration of structured models (decision trees)

The comments on the structured models (evaluation criteria) made in the application documents were presented conclusively and convincingly in the light of the decision trees. The information is substantiated by data in annexes and by studies and references submitted with the documents or subsequently.

2.5. Applicant's assessment and conclusion

In the section "Conclusion of MON 863 and MON 863 X MON 810 Maize Safety Review", the applicant presented his conclusions after evaluation of the information submitted, taking account of the most important issues connected with the NF. The RKI endorses the applicant's conclusion that NF derived from MON 863 and MON 863 X MON 810 are to be regarded as equivalent to conventional maize from the point of view of nutritional physiology and that no harmful effects are to be expected from consumption of such products.

Additional information is given in this section on labelling, traceability, detection and identification methods, reference material and Unique Identifiers.

Labelling

The proposals are in keeping with Article 8 of Regulation (EC) No 258/97 and are guided by Regulations (EC) Nos 49/2000 and 1139/98. If necessary, the labelling "produced from genetically modified maize" or "genetically modified" is to be used. No labelling is necessary if the maize is present only as an accidental and technically unavoidable admixture and remains below a proportion of 1%.

Traceability

Regulation (EC) No 258/97 does not contain any specific traceability requirements for NF. The applicant assumes, however, that the provisions of the future EC Regulation on the traceability and labelling of GMOs and products made from them (proposal, see Official Journal of the European Union C 304 E, p. 327 of 30.10.2001) will apply to all NF.

Unique Identifiers

The applicant proposed the following as Unique Identifiers:

MON-ØØ863-5 for MON 863;

MON-ØØ81Ø-6 for MON 810.

For the hybrid MON 863 X MON 810 a combination of the two Unique Identifiers is proposed.

The information given by the applicant is in line with the "OECD Guidance for the Designation of a Unique Identifier for Transgenic Plants" of the Working Group on Harmonisation of Regulatory Oversight in Biotechnology of 19 February 2002.

Detection and identification methods, reference material

For the detection of MON 863 the applicant provided information on a PCR-based, "event"-specific method. The applicant explained further that he will be contributing to the development of a validated detection method by the EU's Joint Research Centre (JRC) by supplying MON 863 reference material, methods and sequence information on the associated PCR primers.

For MON 810 "event"-specific detection methods have already been published (2002/66/EC - OJEC No L 26 of 30 January 2002, p. 8). Further work on validation of methods is currently under way. The applicant has already made sufficient quantities of MON 810 reference material available to the JRC for this purpose.

In a covering letter regarding the subsequent submission of application documents (December 2002), the applicant stated that suitable reference material would be made available to the RKI.

2.6. Applicant's summary

An appropriate and adequate summary of the application dossier was submitted with the documents. In addition to a recapitulative description of the GMOs on which the NF is based and of the main aspects of the safety review, the summary contains the same data on labelling, traceability, detection and identification methods, reference material and Unique Identifiers as the section "Conclusion of MON 863 and MON 863 X MON 810 Maize Safety Review" (see above).

3. Appropriateness

In the RKI's opinion, the selection, presentation and quality of the data submitted with the full application are suitable and appropriate for an evaluation of the NF. Where available, the investigations were carried out in accordance with internationally recognised methods. A validity and plausibility test was conducted. The interpretations and assessments of the applicant and of the information and data of relevance for the safety assessment are shared.

4. Substantial equivalence

A determination of the substantial equivalence of products within the meaning of Article 5 of Regulation No 258/97 by the competent Federal Office for Consumer Protection and Food Safety (BVL) is not available.

For the purposes of assessing this application it was assumed, however, on the basis of the findings of ingredient analyses, animal feeding tests, characterisation of agronomic and morphological properties and determination of further phenotypic parameters that for the genetically modified organisms and products obtained from them, with the exception of the expression of the genes newly transferred to the host plants and the associated content of Cry proteins and NPT II, there is substantial equivalence with corresponding traditional products.

The RKI therefore considers that the testing and evaluation of the NF can concentrate on the newly transferred characteristics.

5. Evaluation of the data submitted

5.1. Data on the host organism and the use of maize

There is many years' experience of cultivating the host organism maize and using it as a raw material for animal feed and foodstuffs (evaluation grid III). The genetic modifications concern agronomic properties and are not aimed at altering nutritional and physiological characteristics of ingredients or at a different use of maize as a raw material.

The maize processing methods (evaluation grid II) do not have to be reassessed, since no modifications during processing and no new products are to be expected and there is many years' experience of using maize.

A change in the total quantity of maize consumption and/or significant changes in the composition of the batches of maize used for processing are not anticipated, since the genetically modified maize does not differ from conventional maize as regards its processing quality.

5.2. Description of the genetically modified organisms

5.2.1. MON 863

Using the particle acceleration method, the host maize line AT, cell line AT824, was transformed with the 4691 bp *Mlu* fragment PV-ZMIR13L of the pUC plasmid derivate PV-ZMIR13. The desired fragment was isolated by means of agarose gel electrophoretic purification. This fragment contains, in additon to a *nptII* gene from *E. coli Tn5* controlled by the 35S promoter of the Cauliflower Mosaic Virus (CaMV) and the terminator region of the *nos* gene from *Agrobacterium tumefaciens*, the gene that confers resistance to coleoptera, namely *MON 863 cry3Bb1*. This gene is a synthetic variant of *cry3Bb1* from *Bacillus thuringiensis* ssp. *kumamotoensis* with a DNA sequence deviating from the wild type. Compared with the amino acid sequence of the original protein Cry3Bb1, the version MON 863 Cry3Bb1 coded by the synthetic gene variant is distinguished by an additional alanin residue in position 2 and six further amino acid exchanges (D166G, H232R, S312L, N314T, E318K, Q349R), resulting in increased toxicity towards the target organisms.

The *MON 863 cry3Bb1* gene is under the control of a quadruple copy of a 21 bp section of the CaMV 35S promoter, designated by AS1 (activating sequence 1), in conjunction with a further part of the 35S promoter (4AS1 promoter). Next comes the 5´ non-translated leader area wt CAB of the chlorophyll a/b-binding protein from *Triticum aestivum* as translation enhancer, followed by the first intron of the *actin 1* gene from *Oryza sativa* as transcription enhancer. The *MON 863 cry3Bb1* gene is terminated by the 3´ non-translated region of the heat shock protein 17.3 from *Triticum aestivum* (see Fig. 1).

In the 3´ area of the *nptII* gene there is on PV-ZMIR13L a fragment which codes 51 aminoterminal amino acids of the *ble* gene (bleomycin binding protein, *Tn5*) out of a total of 121 amino acids. The open reading frame of the fragment begins 20 nt after the stop codon of *nptII*. Together with a polylinker and parts of the *nos* terminator, this fragment forms an open reading frame that could code for a total of 89 amino acids. This would result in a protein with a molecular weight of 10.25 kDa, designated in the application by BLE 10.25. The open reading frame for the *ble* fragment does not lie in the same frame as the *nptII* gene.

From a theoretical point of view, a translation of this open reading frame alone or as a fusion protein with NPT II seems unlikely. Natural ribosome binding sites such as IRES (Internal Ribosome Entry Sites) have not been identified and a readthrough of ribosomes from the *nptII* transcript into the open reading frame of BLE 10.25 is not to be expected, on account of different reading frames.

Western Blot analyses with antibodies against the BLE portion of the hypothetical protein did not give any indication of an expression of the ORF (detection limit of 1.7 µg/g fresh mass).

If despite the theoretical considerations and the ELISA results BLE 10.25 were to be formed on a small scale, a functionality, i.e. the ability to bind and therefore inactivate bleomycin (glycopeptide antibiotic from *Streptomyces verticillus*), seems unlikely. The natural protein BLE acts as a homodimer and does not have any enzymatic activity. The protein binds only bleomycin and thus inactivates its DNA-cutting effect. As the shortened BLE 10.25 does not have essential areas for dimerisation, a binding capacity for bleomycin seems unlikely.

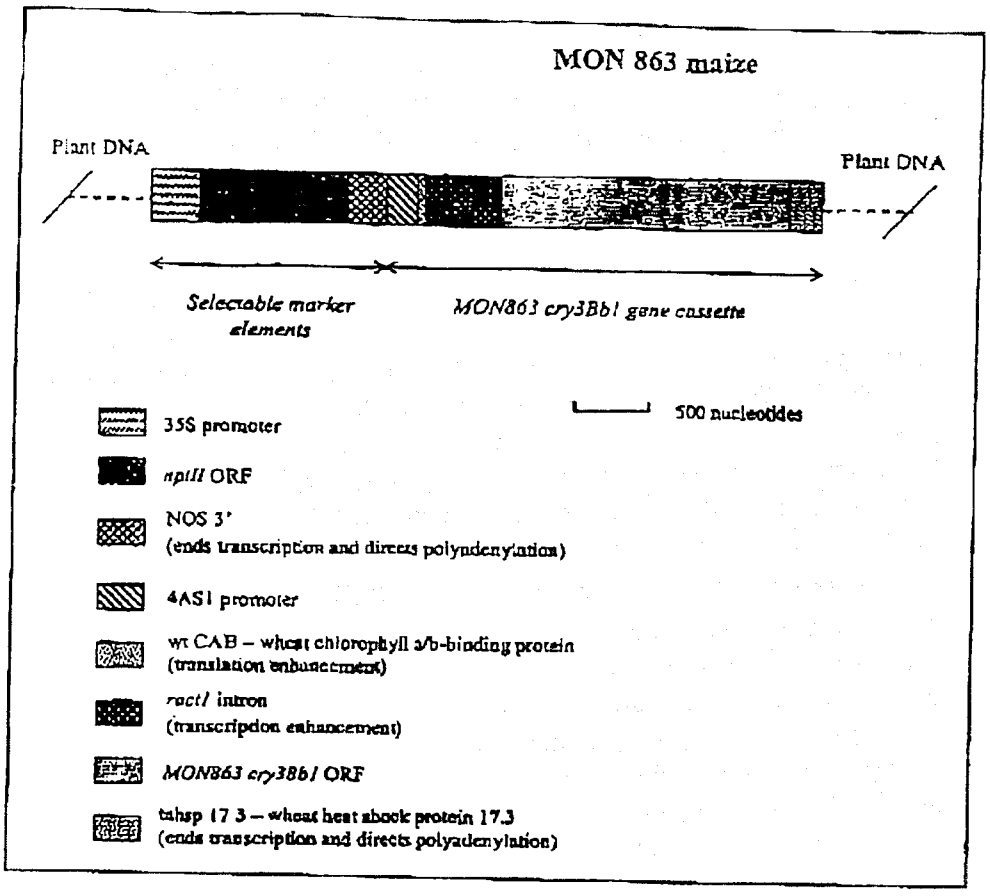

Figure 1: Diagram of the insert transferred to the host plants during transformation of MON 863 (source: application)

Segregation analyses and tests of the genomic DNA of MON 863 by means of Southern Blot analyses, PCR and DNA sequencing showed that one copy of the transferred fragment was integrated at one point into the maize genome and is passed down to the progeniture in a stable manner. Supplementary analyses using various restriction enzymes and probes confirmed that the genes are present on the transferred fragment in the predicted form. No further sequences, especially sequences of the pUC plasmid backbone, were found.

PCR amplicons from genomic DNA of the maize line MON 863, which represent overlaps of the two insert ends with the flanking sequences, were sequenced. At the 5' end, a 508 bp region was amplified with a flanking area 242 bp in length which did not belong to the insert. At the 3' end, 584 bp were amplified with a flanking area 224 bp in length. It transpired that the sequence of the insert in MON 863 tallies with the area from position 7 to 4681 of the *closed* fragment PV-ZMIR13L, so that all functional areas were transferred during the transformation. It can therefore be assumed that in the maize line MON 863 the genetic modification leads to the full-length expression of two new proteins, MON 863 Cry3Bb1 und NPTII (see expression analysis).

A sequence comparison of the flanking regions with public sequence databases shows for the 5' area a 99% homology with Exon 4 of the mitochondrially coded *Zea mays* NADH dehydrogenase subunit 4 (*nad4*). It is possible that mitochondrial sequences were integrated during the transformation.

For the sequences in the 3' flanking area, the public databases do not contain any marked homologies with stored plant DNA sequences.

A bio-informatics analysis of the amino acid sequences comparing all possible open reading frames of the transitional areas from the insert into the flanking regions and using appropriate protein databases did not give any indication of structural or immunological similarities with known allergens, toxins or pharmacologically active proteins.

5.2.2 MON810

Using the particle acceleration method, the host maize Hi-II, which is derived from the inbred lines A188 und B73, was transformed with the plasmid pV-ZMBK07, a pUC19 derivate. In addition to the replication origin (*ori*) and the *lac* sequences, it contains the *npt*II gene of the transposon Tn5 from *E. coli* under the control of its own promoter.

The plasmid pV-ZMBK07 also contains the gene *cry*IA(b) for a δ-endotoxin from *Bacillus thuringiensis* ssp. *Kurstaki* strain HD1. The *cry*IA(b) gene comprises 3 468 basic pairs and codes for a protein from 1 156 amino acids. In order to optimise expression in the maize, the gene was adapted to the codon application usual in plants and the intron sequence of the *hsp*70 gene (heat shock protein) from maize was inserted before the δ-endotoxin coding region. The expression of the δ-endotoxin gene is controlled in the genetically modified plants by a 35S promoter from CaMV with a doubled enhancer region (E35S). The non-translated DNA sequence (*nos* 3´) of the nopaline synthase gene from *Agrobacterium tumefaciens* was used as the transcription terminator.

In the transformant MON 810, of the described areas of the plasmid pV-ZMBK07 only one copy (shortened at the 3´ end) of the *cry*IA(b) gene with the E35S promoter and the *hsp*70 intron was integrated into the maize genome at one location (see Fig. 2). The amino acids 1 to 816 are coded by the shortened gene. The open reading frame continues in the adjoining area of the genome and codes for two further amino acids (phenylalanine and arginine) followed by a stop codon, so that a protein is formed from a total of 818 amino acids.

The stable chromosomal integration of the transferred *cry*IA(b) gene was confirmed by segregation analyses and tests of the genomic DNA of MON 810 by means of Southern blot analyses.

Southern blot analyses also showed that the *npt*II and *ori* sequences present on the vector used for the transformation were not transferred into the host plant. Moreover, NPT II could not be detected by means of Western blot analyses.

Since the shortened *cry*IA(b) gene from *Bacillus thuringiensis* ssp. *kurstaki* transferred into the genome of maize line MON 810 is transcribed by the effect of a 35S promoter, it can be assumed that there is a constitutive expression in the plant (see expression analysis).

DNA sequences of the overlaps of the two insert ends with the flanking areas were submitted by the applicant. At the 5´ end a 244 bp area of the flanking region was stated, at the 3´ end 195 bp.

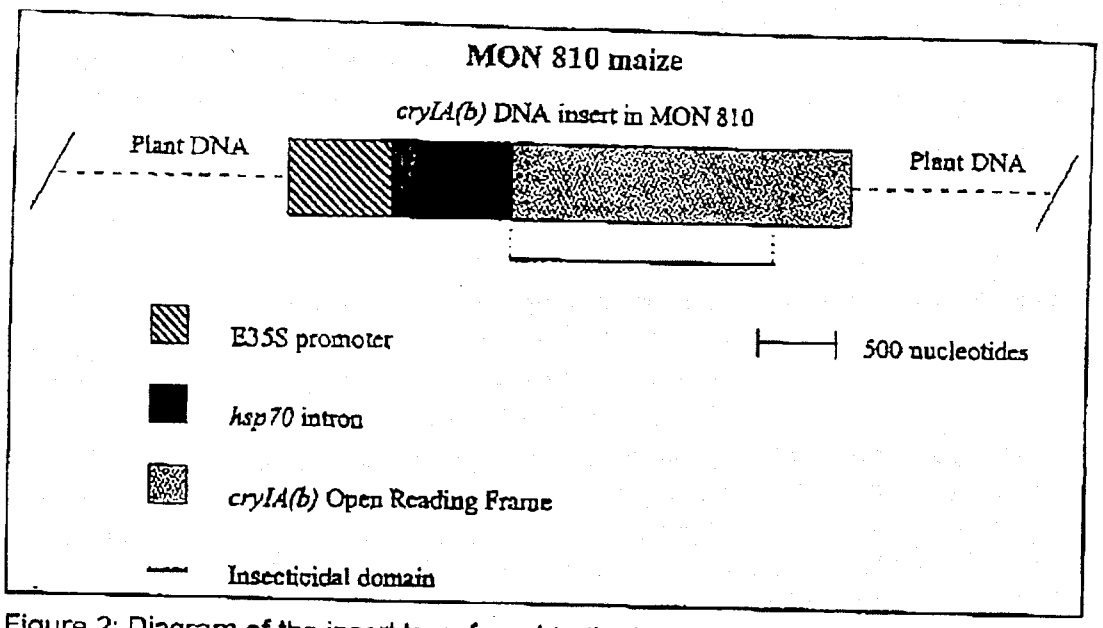

Figure 2: Diagram of the insert transferred to the host plants during transformation of MON 810 (source: application)

A sequence comparison of the flanking areas with public sequence databases shows for the 3' area homologies with the mitochondrially coded ribosomal protein 13 (*rps*13) and the closely linked gene in the mtDNA for the Fo ATPase subunit 9, whcih makes co-integration of mitochondrial DNA during the transformation seem possible.

For the sequences in the 5' flanking area the databases contain indications of homologies with various genomic maize DNA sequences, especially zein genes.

A bio-informatics analysis of the amino acid sequences comparing all possible open reading frames of the 3' transitional area from the insert into the flanking regions and using appropriate protein databases did not give any indication of structural or immunological similarities with known allergens, toxins or pharmacologically active proteins. Only for the reading frame in which Cry1A(b) is coded did the comparison with toxin databases reveal homologies with other Cry toxins.

5.2.3. Expression analysis of the Cry proteins and NPT II

Plant samples from a number of sites in the USA (1999) and Argentina (1999/2000) were tested by ELISA for levels of MON 863 Cry3Bb1, CryIA(b) and NPTII. The results are summarised in Tables 1 to 4. The highest expression mean values are shown in bold type. Studies on the expression of MON 863 Cry3Bb1 and NPTII in leaves, whole plants and roots during a vegetation period showed a reduction of protein levels in relation to fresh mass in all the tissues examined (data not shown).

Table 1: **MON 863 Cry3Bb1** and **NPT II** protein levels in µg/g fresh mass in plant tissues of MON 863 from outdoor experiments in the USA in 1999

Tissue Type	Days Post-Planting	Cry3Bb1 (range)	NPT II (range)
Young Leaf	21	81 (65-93)	0.98 (0.74-1.4)
Forage	90	39(24-45)	0.19 (0.17-0.23)
Mature Root	90	41 (25-56)	not done
Grain	125	70 (49-86)	<0.076 (LOD)
Silk	58	10 (1 sample)	not done
Pollen	60	62 (30-93)	not done

Table 2: **MON 863 Cry3Bb1** protein levels in µg/g fresh mass in plant tissues of MON 863 X MON 810 and MON 863 from outdoor experiments in Argentina in 1999/2000

Tissue Type	Days Post Planting	MON 863 X MON810	MON 863
Young Leaf	18	46.7 (35.5-53.2)	30.0 (21.3-47.2)
Pollen	60	79.6 (65.1-96.5)	60.4 (29.7-90.7)
Forage	90	23.6 (6.7-39.7)	12.8 (<0.22-28.8)
Grain	117	61.1 (38.5-83.1)	43.7 (<0.096-84.1)

Table 3: **Cry1A(b)** protein levels in µg/g fresh mass in plant tissues of MON 863 X MON 810 and MON 810 from outdoor experiments in Argentina in 1999/2000

Tissue Type	Days Post Planting	MON 863 X MON810	MON 810
Young Leaf	18	17.9 (14.1-27.5)	13.0 (1.5)
Pollen	60	<0.08 (<0.08-0.18)	<0.08 (<0.08)
Forage	90	7.9 (3.9-11.9)	5.6 (3.0-8.2)
Grain	117	0.84 (0.63-1.2)	0.46 (0.24-0.77)

Table 4: **NPT II** protein levels in µg/g fresh mass in plant tissues of MON 863 X MON 810 and MON 863 from outdoor experiments in Argentina in 1999/2000

Tissue Type	N	MON 863 X MON810	MON 863
Young Leaf	18	1.60 (0.53-2.32)	1.06 (0.58-1.56)
Forage	90	0.19 (0.13-0.27)	0.17 (<0.075-0.33)
Grain	117	<0.076 (LOD)	<0.076 (LOD)

5.3. Experience from previous outdoor experiments

In the European Union there have not so far been any releases with either MON 863 or the hybrid MON 863 X MON 810.

The genetically modified maize line MON 863 was released in the USA, Canada, Chile, Argentina and Japan. The hybrid MON 863 X MON 810 was studied in release experiments in the USA and Argentina.

The aim of the tests was in particular to produce data for authorisation procedures and to check the efficiency of the transferred insect resistance and other agronomic characteristics. For MON 863 there were no indications of metabolism-induced, phenotypic differences with respect to various agronomic parameters (plant development, bloom time, morphology, yield parameters, survival) between GMOs and controls. There are thus no indications of a modification of MON 863 with regard to survival, reproduction and propagation capacity.

For MON 810 it was stated in the application on the basis of outdoor experiments that the genetically modified maize has the same properties as non-transgenic maize lines, apart from the resistance to some species of *lepidoptera*.

On the basis of the respective experiments with MON 863 and MON 810, the application concludes for the hybrids of both that MON 863 X MON 810 too is probably not modified as regards survival, reproduction and propagation capacity.

The results of analyses of selected ingredients of MON 863 and the hybrid with MON 810 did not give any indication of an accidental influencing of the plant metabolism by the genetic modification along the lines of a so-called position effect or pleiotropic effects.

5.4. Authorisations issued to place products on the market outside the EU

The genetically modified maize line MON 863 was placed on the market in Japan and the USA. The genetically modified maize line MON 810 was placed on the market in the EU, Argentina, Australia, Canada, Japan, Korea, the Philippines, South Africa, Switzerland and the USA (source: AGBIOS database).

No information is available about the international authorisation status of hybrids produced by conventional cross-breeding. A separate authorisation for placing hybrids from authorised GMOs on the market is not, however, necessary in every country.

5.5. Assessment of use in foodstuffs

A risk assessment with regard to use of products of the genetically modified maize plants as foodstuffs requires evaluations of the changes caused by the transferred DNA segments in the composition of the genetically modified maize plants, including the newly formed proteins, a possible modification of the ingredients as a result of context changes and a possible horizontal gene transfer to micro-organisms of the gastrointestinal tract.

5.5.1. Assessment of the newly formed proteins

The assessment of the toxicological and allergenic properties of the novel food is made to a large extent on the basis of tests with the newly formed proteins. An assessment of this kind is possible because in the further tests with the composition of MON 863 and MON 863 X MON 810 there were no biologically relevant differences from conventional maize lines as regards the ingredients and both phenotypic and physiological parameters.

5.5.1.1. MON 863 (NPTII, MON 863 Cry 3Bb1)

In order to confirm the identity of the Cry3Bb1 expressed in MON 863 in comparison with the amino acid sequence derived from the DNA sequence, protein extract purified by immunoaffinity chromatography was examined by means of N-terminal sequencing and MALDI TOF mass spectrometry (carried out after ingestion of trypsin). This procedure facilitates on the basis of molecular mass determinations the comparison of theoretically derived fragments with fragments actually found. The fragments (molecule masses) identified by means of MALDI TOF MS tallied with postulated fragments of the MON 863 Cry3Bb1 protein. The results provide strong pointers that the Cry3Bb1 protein expressed in MON 863 corresponds to that predicted.

The N-terminal amino acid sequencing of the 74 kDa protein from MON 863 did not yield any usable results (blocking), unlike corresponding protein of microbial derivation. This is interpreted by the applicant as meaning that there could have been a post-translational modification in the aminoterminal area (N-terminal acetylation).

In a covering letter to an additional delivery of application documents (December 2002), the applicant stated that he did not know of any data and scientific publications which reported that non-toxic or non-allergenic proteins had developed toxic or allergenic potential as a result of N-terminal acetylation.

The RKI too considers that a significant influence of this protein modification on the physico-chemical proerties is unlikely. In connection with characteristics of allergens, post-translational N-terminal acetylation is not discussed (but glycosylation is).

The functional and biochemical equivalence between Cry3Bb1 protein in MON 863 produced bacterially in *E. coli* and that produced in plants was shown by means of MALDI TOF mass spectrometry, N-terminal sequence analysis (not blocked by N-acetylation because it begins at partially degraded N-termini), immunoblot, insect bioassay, SDS-PAGE, analysis of glycosylation and determination of the amino acid composition.

For the NPTII pfotein, the comparability with regard to molecular weight (approx. 29 kDa) and immunological reactivity to monoclonal antibodies for the proteins from MON 863 and *E. coli* was shown by immunoblot.

The results of studies carried out with the bacterially produced proteins can therefore be applied to the safety assessment of MON 863.

NPTII

Neomycin phosphotransferase is a type II aminoglycoside-3'-phosphotransferase (APH(3')II = NPT II) which catalyses the ATP-dependent phosphorylation of the 3'-hydroxyl group of the aminohexose ring of certain aminoglycoside antibiotics and thus inactivates them. The enzyme is characterised by a high substrate specificity (Nap *et al.*, 1992). A catalysing effect of the enzyme in the gastrointestinal tract of mammals depends on the availability of substrates (antibiotic and ATP) and on suitable reaction conditions.

For NPT II the "Opinion of the ZKBS on the biological safety of antibiotic-resistant genes in the genome of genetically modified plants" issued in 1999 states: "The substrates of the APH(3')II enzyme include the antibiotics kanamycin, neomycin, geneticin, butirosin, gentamicin A and B and paromomycin. The therapeutically significant antibiotics used in human medicine amikacin, gentamicin (primarily C1, C1α and C2) and other aminoglycosides and aminocyclitols do not belong to the substrate spectrum of the APH(3')-II enzymes (Trieu-Cuot *et al.*, 1987; Davies, 1991; Simon and Stille, 1989)".

Although partly authorised in Europe, potential substrates of NPT II such as neomycin, kanamycin, gentamicin A and B and paromomycin still play only a minor part in human and veterinary medicine on account of their toxicity and/or the unfavourable resistance situation, and their use (paromomycin) is limited to very special infections (Kroker *et al.*, 2002).

Consequently, solely owing to the lack of substrates it is not to be expected that there is widespread formation of new potentially harmful reaction products in the gastrointestinal tract as a result of an enzymatic effect of NPT II protein ingested with feed.

In a **comparison of the amino acid sequence** of the NPT II protein **with known toxins and pharmacologically active substances** carried out through database searches, for a total of 4 677 protein sequences no biologically relevant similarities with mammal-toxic or pharmacologically active proteins were ascertained, so that on the basis of this study there is no indication that NPT II has a toxic potential.

The test of the **acute toxicity** of NPT II was carried out with protein produced in *E. coli* (Fuchs *et al.*, 1993). The protein was given in two successive oral administrations (interval of 4 hours) to albino mice in three doses (100, 1 000 and 5 000 mg/kg body weight) - 10 male and 10 female animals per dose. Clinical observations were made and the changes in body weight and the consumption of feed were determined. At the end of the test (days 8 and 9) the animals were killed and necroscoped.

No substance-related negative effects were observed on oral administration of NPT II protein up to a dose of 5 000 mg/kg body weight. The LD50 is therefore > 5 000 mg/kg body weight and the NOEL = 5 000 mg/kg body weight.

At an estimated proportion of 0.22 g maize kernels per kg body weight in the food of adults and 0.43 g/kg body weight in adolescents, a concentration of approx. $1x10^{-4}$ mg NPT II per g MON 863 maize kernels gives a daily intake of approx. $2x10^{-5}$ mg NPT II per kg body weight (adolescents: approx. $4x10^{-5}$ mg NPT II per kg body weight). Taking account of the NOEL (for mice) of > 5 000 mg per kg body weight, there is a sufficient safety factor of > $2.5x10^{6}$ for NPT II in the food of adults or > $1.25x10^{6}$ for adolescents.

However, since maize kernels are for the most part processed into maize starch, glucose/fructose syrup or ethanol prior to human consumption, resulting to some extent in a drastic depletion of the protein fraction, even higher safety factors are achieved for these products.

The **stability of the proteins vis-à-vis proteolytic enzymes** was tested *in vitro* in simulated mammalian gastrointestinal fluids (gastric fluid SGF and intestinal fluid SIF). A total breakdown of NPT II from *E. coli* occurred in SGF within 10 seconds. In SIF, within 2 to 5 minutes 50% of the enzyme was broken down. Enzyme tests showed an almost total loss of enzymatic activity after 2 minutes' digestion in SGF and 15 minutes in SIF (Fuchs *et al.*, 1993).

The results of the study showed that a rapid breakdown of the proteins under the conditions obtaining in the gastrointestinal tract of mammals can be assumed. It should be borne in mind, however, that NPT II in MON 863 maize can be enclosed in parts of plants on intake with food and can therefore resist digestion for longer than ascertained by these tests.

For further **assessment of the allergenic potential** of the NPT II protein, the amino acid sequence was compared with 567 protein sequences of known allergens and coeliac disease-triggering proteins (gliadins). No biologically relevant sequence homologies occurred. A comparison of all the possibilities of 8 successive amino acids of the Cry3Bb1 protein with the above-mentioned 567 protein sequences did not give any indication of similarities with epitopes of allergy-triggering proteins.

MON 863 Cry3Bb1

In a **comparison of the amino acid sequence** of the Cry3Bb1 protein expressed in MON 863 **with known toxins and pharmacologically active substances** by means of database searches, no biologically relevant similarities with mammal-toxic proteins were ascertained for a total of 4 677 protein sequences.

Sequence similarities of MON 863 Cry3Bb1 with other insecticidal toxins were ascertained. Almost all the toxins with sequence similarities belong to the group of the *B.t.*-delta-endotoxins. The further homologies found with sequences from *Clostridium bifermentans, Caenorhabditis elegans, Vibrio cholerae* and *Bacillus popilliae* were interpreted as biologically irrelevant on account of the lack of any indication of toxic effects in mammals.

The **acute toxicity** test was carried out with MON 863 Cry3Bb1 produced in *E. coli*. The protein was given in 2 successive oral administrations (interval of 4 hours) to albino mice in 3 doses (400, 1 100 und 3 200 mg/kg body weight) - 10 male and 10 female animals per dose. Clinical observations were made and the changes in body weight and the consumption of feed were determined (day 7/day 14). At the end of the test (day 14) all the animals were killed and necroscoped.

No substance-related negative effects were ascertained on oral administration of MON 863 Cry3Bb1 protein up to a dose of 3 200 mg/kg body weight. The LD50 is therefore > 3 200 mg/kg body weight and the NOEL = 3 200 mg/kg body weight.

At an estimated proportion of 0.22 g maize kernels per kg body weight in the food of adults and 0.43 g/kg body weight for adolescents, there is at a concentration of approx. 0.1 mg Cry3Bb1 per g MON 863 maize kernels a daily intake of approx. $2x10^{-2}$ mg Cry3Bb1 per kg body weight (adolescents: approx. $4x10^{-2}$ mg Cry3Bb1 per kg body weight). Taking account of the NOEL (for mice) of > 3 200 mg per kg body weight, there is a sufficient safety factor of > $1.5x10^5$ for Cry3Bb1 in the food of adults and > $7x10^4$ for adolescents.

Since, however, prior to human consumption maize kernels are mostly processed into maize starch, glucose/fructose syrup or ethanol, resulting to some extent in a drastic depletion of the protein fraction, even greater safety factors are achieved for these products.

The **stability of the proteins towards proteolytic enzymes** was tested in simulated mammalian gastrointestinal fluids (gastric fluid and intestinal fluid). MON 863 Cry3Bb1 protein from *E. coli* und from maize kernels of the transformant MON 863 is broken down rapidly in simulated human gastric fluid (SGF). A total breakdown occurred within 15 seconds. A low-molecular fragment of approx. 3 kDa was visible in the protein from MON 863 up to a maximum incubation period of 15 minutes as a weak strip in the SDS-PAGE (detection limit: 17 ng/track). The results of the study showed that a rapid breakdown of the proteins under the acidic conditions in the stomach can be assumed. In view of the small size of the 3 kDa fragment, which is broken down more slowly, no allergenic effect is to be expected because such small peptides are probably not in a position to present the two

epitopes, separated by a sufficiently large distance (spacer), needed to trigger an allergic reaction.

Digestion tests with simulated intestinal fluid (SIF) were not carried out with the Cry3Bb1 protein expressed in MON 863. Tests with a Cry3Bb1 protein of microbial origin, which was identical apart from two amino acids, showed that up to the end of the test after 24 hours a stable polypeptide of approx. 59 kDa was present and maintained its biological activity (detected by bioassay with potato beetle larvae). Given the considerable similarity of the Cry3Bb1 variants examined, it can be assumed that MON 863 Cry3Bb1 from the GMO, too, is broken down on digestion in the SIF only as far as a stable, insecticidal fragment.

In order to further **assess the allergenic potential** of the MON 863 Cry3Bb1 protein, the amino acid sequence was compared with 567 protein sequences of known allergens and coeliac disease-triggering proteins (gliadins). No biologically relevant sequence homologies occurred. A comparison of all the possibilities of 8 successive amino acids of the Cry3Bb1 protein with the above-mentioned 567 protein sequences did not give any indication of similarities with epitopes of allergy-triggering proteins.

All in all, the information available on the characteristics of the MON 863 Cry3Bb1 and NPT II protein and the results of the feeding studies involving mice, rats and hens (see below) give no reason to assume that intake of these proteins with food has harmful effects.

5.5.1.2. MON 810

From the production and use of conventional plant protection products on the basis of *B.t.* toxins there is many years' experience regarding the toxicological and allergological characteristics of the CryIA(b) protein too. In addition, the applicant submitted for the purposes of evaluating the CryIA(b) protein research and studies on stability, toxicity and allergenicity which had already been evaluated as part of the procedure for the placing on the market of the parent line MON 810 (Az.6788-02-13).

There is no indication of toxicity to birds, mammals and humans and none is to be expected either, since these taxa do not have the receptors needed to bind the CryIA(b) protein to gastrointestinal cells.

A **comparison of the amino acid sequence** of the Cry1A(b) toxin expressed in MON 810 **with known toxins** in the PIR, EMBL, Swissprot and Genbank databases did not show any biologically relevant similarities with known toxins, apart from homologies with other known *B.t.* proteins.

The **acute toxicity** test was carried out with Cry1A(b) protein produced in *E. coli*. Since it can be assumed that the protoxin is broken down in the course of digestion to the trypsin-resistant core protein, this core protein was used for the tests.

The protein was given orally in 2 successive administrations (interval of 3 hours) to albino mice in 3 doses (400, 1 000, 4 000 mg/kg body weight) - 10 male and 10 female animals per dose. Clinical observations were made and the development of body weight and feed consumption determined. At the end of the test (days 8 and 9) all the animals were killed and necroscoped.

No substance-related negative effects were detected on oral administration of Cry1A(b) protein (trypsinised core protein) up to a dose of 4 000 mg/kg body weight. The LD50 is therefore > 4 000 mg/kg body weight and the NOEL = 4 000 mg/kg body weight.

At an estimated proportion of 0.22 g maize kernels per kg body weight in the food of adults and 0.43 g/kg body weight in adolescents, there is at a concentration of approx. 0.01 mg Cry1A(b) per g MON 863 maize kernels a daily intake of approx. $2x10^{-4}$ mg NPT II per kg body weight (adolescents: approx. $4x10^{-4}$ mg Cry1A(b) per kg body weight). Taking account of the NOEL (for mice) of > 4 000 mg per kg body weight, there is a sufficient safety factor of > $2x10^{7}$ for Cry1A(b) in the food of adults and > $1x10^{7}$ for adolescents.

Since, however, prior to human consumption maize kernels are mostly processed into maize starch, glucose/fructose syrup or ethanol, resulting to some extent in a drastic depletion of the protein fraction, even greater safety factors are achieved for these products.

The *in vitro* **tests on stability to simulated gastric juices** (SGF, SIF) showed that the CrylA(B) protein *in vitro* reacts sensitively to proteolytic enzymes of gastric fluid (SGF) and is broken down within a few minutes (> 90% breakdown within 2 minutes). On the other hand, the protein was resistant to breakdown by intestinal enzymes (SIF) (no significant breakdown of the trypsin-resistant core protein after 19.5 hours), which can be attributed to the differing composition as regards the proteolytic enzymes in the simulated gastric juices.

For further **assessment of the allergenic potential** of the MON 810 Cry1A(b) protein, the amino acid sequence was compared with 219 protein sequences of known allergens. No biologically relevant sequence homologies occurred. A comparison of all the possibilities of 8 successive amino acids of the Cry1A(b) protein with the above-mentioned 219 protein sequences did not give any indication of similarities with epitopes of known allergy-triggering proteins.

All in all, the information available on the charcateristics of the Cry1A(b) protein and the results from the feeding studies and ingredient analyses (see next section) do not give any reason to assume that the use of the genetically modified maize kernels of the line MON 810 for the production of foodstuffs would have harmful effects on human health. The traditional agricultural use of *Bacillus thuringiensis* preparations consisting of a mixture of spores and parasporal crystals with δ-endotoxins, including Cry1A(b), did not give any indication of health risks either.

5.5.2. Feeding studies

As the further tests with the hybrid MON 863 X MON 810 do not give any indication that the genetic modifications of MON 863 and MON 810 influence each other, the results of the feeding studies with MON 863 and MON 810 maize can also be applied to the safety assessment of the hybrid MON 863 X MON 810.

5.5.2.1. Feeding studies with MON 863 maize kernels

In a **subchronic feeding study with Sprague-Dawley rats**, to which genetically modified MON 863 maize kernels in a proportion of 11% and 33% were fed over an exposure period of 90 days (20 male and 20 female animals per dose in each case), no substance-related, biologically relevant effects were detected compared with the non-transgenic control hybrid and with six other non-transgenic commercial hybrids. Clinical parameters of haematology,

clinical chemistry and urine chemistry were measured, changes in body weight and organ weight determined, histopathological examinations of various tissues carried out and feed consumption and mortality determined. It can be deduced from this extensive study that even with prolonged exposure to MON 863 maize kernels no harmful effects are likely.

The results of the evaluation of a **feeding test with chickens** (50 male and 50 female animals in each case) over a period of 42 days, whose feed contained up to about 60% genetically modified MON 863 maize, did not give any indication that the genetic modification caused any changes in the nutritional physiology properties of the maize. No biologically relevant modifications were ascertained on comparing MON 863 maize with the non-transgenic control (parent line) and six commercial hybrids as regards mortality, body weight, changes in body weight, feed intake, feed efficiency and various carcass parameters (weight of the various body parts such as thigh, leg, breast, wings) and in meat analyses (water content, protein, fat in breast and thigh) between the chickens which were given feed with a proportion of MON 863 maize and chickens which were given feed with a proportion of the non-transgenic comparable line and a further six different reference lines.

5.5.2.2. Feeding studies with MON 810 maize kernels

In a **subchronic feeding study** with Sprague-Dawley rats which were fed over an exposure period of 90 days with genetically modified MON 810 maize kernels with a proportion of 11% and 33% respectively (20 male and 20 female animals per dose in each case), no substance-related biologically relevant effects were revealed compared with the non-transgenic control hybrid and with six other non-transgenic commercial hybrids. Clinical parameters of haematology, clinical chemistry and urine chemistry were measured, changes in body weight and organ weight determined, histopathological examinations of various tissues carried out and feed consumption and mortality determined. It can be deduced from this extensive study that even with prolonged exposure to MON 810 maize kernels no harmful effects are to be expected.

5.5.3. Assessment of a possible modification of ingredients

Generally speaking, when genetic material is inserted into the genome of a host cell there is a possibility of the expression of genes lying directly at the point of integration or genetically paired genes being influenced, which can cause a change in the levels of ingredients in the genetically modified organisms as a result of metabolic processes being influenced. Context changes of this type can also, however, occur both under natural conditions (e.g. transposition, recombination) and as a result of the mutagenesis of plant material (e.g. UV light, gamma radiation, chemical mutagens).

5.5.3.1. Ingredients

Using material from four outdoor experiments in the USA (1999) and four outdoor experiments in Argentina (1999/2000), ingredient analyses were carried out on genetically modified maize MON 863 and MON 863 X MON 810 compared with isogenic, non-genetically modified maize lines and commercial hybrids. The parameters examined were: proximates (protein, fat, ash, moisture), ADF, NDF, amino acids (18), fatty acids (16:0, 18:0, 18:1, 18:2, 18:3, 20:0, 20:1, 22:0), vitamin B1, B2, E, folic acid, minerals(Ca, Cu, Fe, Mg, Mn, P, K, Na, Zn), phytic acid and trypsin inhibitor, together with ferulic acid, inositol, raffinose, p-coumaric acid, furfural in the kernels and proximates, ADF, NDF in the leaves. The carbohydrate levels in leaves and kernels were calculated from the measurement results for the proximates.

For some parameters the analyses showed statistically significant differences from the controls ($p=0.05$). Almost all the deviations found fall within the 99% confidence interval of the values that were determined for the commercial varieties, or lie in the intervals that are known for the corresponding parameters from the literature or are in line with the interval for other conventional varieties ("historical controls") which had been examined in earlier Monsanto studies. Exceptions to this are the values for vitamin B1 at two sites, one fatty acid (22:0 belenic acid), folic acid, ferulic acid and p-coumaric acid at one site, which lay slightly outside the possible comparative values; in some cases, there were no literature values or historical controls for these parameters. The deviations found were not detected across the board for all sites and are to be regarded as biologically non-relevant.

In the light of the results of the ingredient analysis it can be assumed that, apart from the synthesis of the newly expressed proteins, the maize kernels of the transgenic plants are substantially equivalent to traditional maize kernels.

5.5.3.2. Microbial metabolites

On the basis of the ingredient analyses the applicant states in the application that a different colonisation of the maize plants by micro-organisms and consequently new microbial metabolites in the plants are not to be expected as a result of the genetic modification. Over and above the applicant's assessment, the RKI assumes that in the case of kernels of the hybrid MON 863 X MON 810 there could, depending on the intensity of an infestation of maize root borers, be a reduction of Fusarium ear rot during cultivation and hence lower levels of fungal toxins (fumonisin B_1, DON, ZON) in the kernels (Munkvold *et al.* 1997 and 1999, Valenta *et al.* 2001). As causes of the reduction of Fusarium ear rot, reduced entry sites resulting from less damage and the disappearance of corn borer larvae as vectors for the penetration of fungal spores into plant tissue are mentioned.

Both for MON 810 and MON 863 and for the hybrid MON 863 X MON 810 it can be assumed that as a result of the expected reduction of entry sites for phytopathogenic micro-organisms there will at least not be any increase in colonisation. Accordingly, a higher concentration, compared with conventional varieties, of harmful microbial metabolites in the maize kernels of the GMOs is not to be expected.

5.5.3.3. Maize allergens

It has been known for some time that maize can cause food allergies (Pasini *et al.* 2002, Pastorello *et al.* 2000, Moneret-Vautrin *et al.* 1998). Patient reports and results of provocation tests with foodstuffs containing maize have been published (Tanaka *et al.* 2001, Pauls and Cross 1998). The prevalence of maize food allergies in the population is very low.
At international level, experts are currently discussing to what extent the testing of the allergen repertoire in genetically modified plants derived from a host plant species that is a known food allergen should be the subject of the GMO safety assessment (FAO/WHO 2001). The European Commission's Scientific Steering Committee recommends in its "Guidance Document for the Risk Assessment of Genetically Modified Plants and Derived Food and Feed" of 6-7 March 2003 that a decision be taken on a case-by-case basis in the light of the available information on the need for experimental investigations of the allergenic potential of GMO and parent plants.
A change in the allergen repertoire of genetically modified maize compared with the host plant as an accidental consequence of the genetic modification is very unlikely but cannot be ruled out. It is well-known that, even in conventional breeding, varieties with differences in the concentration of individual food allergens can occur. It can thus be stated that a potential change in the allergen repertoire does not represent a specific genetic risk.
On the basis of the available scientific information, the application procedure did not see any need for experimental comparative studies of the allergen repertoire in the genetically modified maize and conventional maize. This took into account that the maize proteins which were suspect on account of their IgE reactivity were only partly characterised in more detail (Pastorello *et al.* 2000) and that the RKI did not know of any findings of provocation tests with these proteins aimed at demonstrating their allergenicity.

5.5.4. Horizontal gene transfer in the human gastrointestinal tract

In view of the lack of selection advantage, a spread of the *B.t.* toxin genes incorporated in MON 863 and MON 863 X MON 810 and of the *nptII* gene from the genetically modified maize in micro-organisms of the gastrointestinal tract is unlikely. In its "Opinion on the biological safety of antibiotic-resistant genes in the genome of genetically modified plants" issued in 1999, the ZKBS classified the *nptII* gene present in MON 863 in Group I: "Group I includes antibiotic-resistant genes which (a) are already widespread in soil- and

enterobacteria and (b) whose relevant antibiotics are of no or only slight therapeutic significance in human and veterinary medicine, so that it can be assumed that - if at all - the presence of these antibiotic-resistant genes in the genome of transgenic plants does not have any effect on the propagation of these genes in the environment."

The assumption of the low probability of a horizontal gene transfer in the gastrointestinal tract is supported by studies in which DNA of the phage M13 was administered orally to mice and phage DNA could be detected in the faeces only up to a maximum of 7 hours after administration. There was no evidence of a colonisation of the intestinal flora with bacteria containing foreign DNA. Such DNA could be identified in the blood system in very small quantities (< 0.1%) over a short period (maximum 24 hours) (Schubbert *et al.* 1994).

With regard to the use of genetically modified maize for the production of foodstuffs it can be assumed that harmful effects on human health as a result of a horizontal gene transfer are unlikely.

5.6. Environmental risk assessment

As the cultivation of genetically modified maize is at present neither approved nor applied for in the EU, it can be assumed that genetically modified maize plants derived from the source line MON 863 or the hybrid MON 863 X MON 810 can reach open fields only accidentally and on a small scale.

5.6.1. Assessment of the ability of the genetically modified maize to survive or to establish itself and of the possibility of the imported genes being transferred to other plants by pollen

Maize is a pronounced domestication form which on account of, *inter alia*, the lack of seed losses can survive only through human cultivation. In addition, maize plants are not winter-hardy and cannot erstablish themselves in natural flora under the climatic conditions in Central Europe.

Crossing with indigenous wild plants is not possible because maize does not have any cross-breeding partners in central European flora. The imported genes could therefore be transferred only by pollen transfer to plants of other maize field crops. As a rule, harvested maize is not used for resowing, which means that the new properties will not be transferred in this way to cultivated maize varieties.

It is unlikely that the above-mentioned properties of maize are influenced by the genetic modifications described in the application. In release experiments with the genetically modified plants the applicant has carried out studies on various ingredients, vegetative development, blooming, seed maturing, the behaviour of the plants vis-à-vis diseases, and yields. These experiments have confirmed that in respect of these properties the genetically modified plants do not differ significantly from non-transgenic maize lines. The possibility of the survival, propagation, naturalising and pollen transfer of accidentally released genetically modified plants is not be evaluated any differently than that of traditionally cultivated maize.

5.6.2. Assessment of the changes to the environment brought about by the transferred genes

The effects of the Cry proteins and NPT II formed in the genetically modified plants are unlikely to cause any risk to the environment if the products applied for are placed on the market.

5.6.2.1. *MON 863 cry3Bb1* and *cry1A(b)*

Both genes code for protein toxins. There is no evidence of any enzymatic activity of the proteins expressed in the GMO. It can therefore be assumed that apart from the formation of the Cry toxins in the genetically modified plants there will be no other effects on plant metabolism. This assumption is supported in particular by the results of the ingredient analysis. However, the evaluation of the agronomic parameters and the phenotypic characterisation of the GMO also reveal no influences on plant development and metabolism from the expression of the Cry toxins.

If genetically modified maize plants were to enter the environment on a small scale, it is not likely, given the selective effect mechanism of Cry toxins, *inter alia* through specific receptor binding in the intestinal tract of sensitive insects, that there would be any permanently harmful effects on the environment.

5.6.2.2. *nptII*

More detailed information on the characterisation and action of NPT II (aminoglycoside-3'-phosphotransferase II - APH(3')II) and on potential effects of a horizontal gene transfer is given elsewhere in the initial assessment report.

5.6.3. Assessment of a horizontal gene transfer from the GMOs to micro-organisms

A horizontal gene transfer from plants to micro-organisms in the environment cannot be ruled out but, *inter alia* in view of the fact that the maize described in the application is not to be grown in Europe, is to be regarded as unlikely.

Effects of such a gene transfer would only to be expected if there were a selection pressure in favour of the transferred gene. The assessment must also consider whether the gene in question is one that is already present in corresponding populations or a new one.

The ***MON 863 cry3Bb1*** gene was derived from the naturally occurring *cry3Bb1* gene from *Bacillus thuringiensis* ssp. *kumamotoensis* and optimised with regard to toxicity on target organisms. The ***cry1A(b)*** gene was derived from the naturally occurring *cry*IA(b) gene from *Bacillus thuringiensis* ssp. *kurstaki* and optimised for expression in plants. *Bacillus thuringiensis* strains containing such δ-endotoxin genes often occur on plants and therefore in animal feed too. It is therefore also more likely that these genes could enter the intestinal micro-organisms or the environment by horizontal gene transfer from non-transgenic *Bacillus thuringiensis* strains. A selective advantage would not be associated with this.

The remarks made above also apply to an assessment of potential effects of a horizontal gene transfer from *nptII* to micro-organisms in the environment. In view of the widespread nature of kanamycin and neomycin resistances in environmental organisms and the lack of selection pressure, harmful effects are not be expected in the unlikely event of a horizontal transfer of the *nptII* gene.

The other genetic elements introduced into the genetically modified maize plants are derived from rice, wheat, CaMV, *Tn5* and *Agrobacterium tumefaciens*. They often occur in the environment in any case and could therefore also with greater probability enter micro-organisms in the environment through horizontal gene transfer from non-transgenic organisms.

6. Summary, conclusions

The application documents submitted by Monsanto contain the information needed for a safety assessment.

On the basis of studies on the chemical composition and the agronomic, morphological, phenotypic, nutrition-physiological and toxicological characterisation of the GMO and novel foods and novel food ingredients produced from them, it can be assumed as a starting point for a safety assessment that there is substantial equivalence, except in the case of the new properties. Conventional maize, for which there is many years' experience of cultivation and use as a raw material for food and feed, is used for comparison purposes.

As the genetic modification was aimed at improving the agronomic properties, no influence on the further use of this maize as a raw material for the production of foodstuffs with regard to processing methods and the quantity used is expected.

The safety assessment does not give any indication of harmful effects on human health or the environment.

The molecular biology analysis of the genetically modified plants yields comprehensive information on the genetic modification made. This does not give any indication of risks with regard to their use as food or to the environment.

The applicant submitted appropriate information about detection and identification methods. The question of the availability of reference material has been settled.

The applicant assumes that the provisions of the future Regulation on the traceability and labelling of GMOs and products made from them will apply to all NF.

In addition, products have to be labelled in accordance with the provisions of the future EC Regulation on genetically modified food and feed in order to ensure that consumers are given comprehensive information and have freedom of choice.

In the light of current knowledge, the RKI considers that foodstuffs or food ingredients produced from MON 863 maize or from the hybrid MON 863 X MON 810 are just as safe as products produced from conventional maize.

Additional assessment in accordance with Article 6 (3) of Regulation (EC) No 258/97

In accordance with Article 9(2) of Regulation (EC) No 258/97, a decision on the approval of the placing on the market of NF,containing or consisting of GMOs shall respect the environmental safety requirements laid down by Directive 90/220/EEC to ensure that all appropriate measures are taken to prevent the adverse effects on human health and the environment which might arise from the deliberate release of GMOs.

Directive 90/220/EEC on the deliberate release into the environment of GMOs for the purpose of placing GMOs on the market as a product or in products was repealed with the entry into force of the new Directive 2001/18/EC on 17.10.2002. References to the repealed Directive are regarded as references to Directive 2001/18/EC (Article 36(1) and (2)).

Article 4(2) of Directive 2001/18/EC stipulates that GMOs which contain genes expressing resistance to antibiotics in use for medical or veterinary treatment must be taken into particular consideration when carrying out an environmental risk assessment. This requirement is applicable to the *nptII* gene present in the line MON 863. Article 4(2) of Directive 2001/18/EC also stipulates that antibiotic resistance markers in GMOs which may have adverse effects on human health and the environment must be phased out by 31 December 2004 in GMOs that are to be placed on the market. The competent body in the Commission has set up a working group to devise a system for evaluating antibiotic resistance markers (Working Group on Antibiotic Resistance Marker Genes - Article 4 (2) of

Directive 2001/18/EC, 1st meeting, 2 April 2004). The results of the deliberations of this working group and the competent body in the Commission should be taken into account in the safety assessment of the NF. The RKI therefore considers pursuant to Article 6(3) of Regulation (EC) No 258/97 that the NF must be subjected to an additional assessment in accordance with Article 7.

7. Bibliography

AGBIOS database - http://64.26.159.139/dbase.php.

Davies, J. E. (1991) Aminoglycoside-aminocyclitol antibiotics and their modifying enzymes, in: Lorian, V. (ed.) Antibiotics in Laboratory Medicine, 3rd edition, Williams and Wilkins, Baltimore.

FAO/WHO, (2001) Evaluation of Allergenicity of Genetically Modified Foods. Report of a Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology, Rome, Italy.

Fuchs, R. L., Ream, J. E., Hammond, B. G., Naylor, M. W., Leimgruber, R. M., Berberich, S. A. (1993) Safety assessment of the neomycin phosphotransferase II (NPTII) protein. BioTechnology, 11, 1543-1547.

Kroker, R., Scherkl, R., Ungemach, F. R. (2002) Chemotherapie bakterieller Infektionen. In: Lehrbuch der Pharmakologie und Toxikologie für die Veterinärmedizin, 2nd edition (H.H. Frey, W. Löscher, ed.), Enke-Verlag Stuttgart, 353-393 (2002).

Moneret-Vautrin, D. A., Kanny, G., Beaudouin, E. (1998) L´allergie alimentaire au mais existe-t-elle?, Allergie et Immunologie, XXX, No 7, 280.

Munkvold, G. P., Hellmich, R. L., Rice, L. G. (1999) Comparison of Fumonisin Concentrations in Kernels of Transgenic Bt Maize Hybrids and Nontransgenic Hybrids. Plant Disease, 83(2). 130-138.

Munkvold, G. P., Hellmich, R. L., Showers, W. B. (1997) Reduced Fusarium Ear Rot and Symptomless Infection in Kernels of Maize Genetically Engineered for European Corn Borer Resistance. Phytopathology, 87, 1071-1077.

Pasini, G., Simonato, B., Curioni, A., Vincenzi, S., Cristaudo, A., Santucci, B., Dal Belin Peruffo, A., Giannattasio, M. (2002) IgE-mediated allergy to corn: a 50 kDa protein, belonging to the Reduced Soluble Proteins, is a major allergen. Allergy, 57, 98.106.

Pastorello, E. A., Farioli, L., Pravettoni, V., Ispano, M., Scibola, E., Trambaioli, C., Giuffrida, M. G., Ansaloni, R., Godovac-Zimmermann, J., Conti, A., Fortunato, D., Ortolani, C. (2000) The maize major allergen, which is reponsible for food-induced allergic reactions, is a lipid transfer protein. JACI, 106, 744-751.

Pauls, J. D., Cross, D. (1998) Food-dependent exercise-induced anaphylaxis to corn. JACI, 101 (6), 853-854.

Schubbert, R., Lettmann, C., Doerfler, W. (1994) Ingested foreign (phage M13) DNA survives transiently in the gastrointestinal tract and enters the bloodstream of mice. Mol. Gen. Genet. 242, 495-504.

Simon, G. W., Stille, W. (1993) Antibiotikatherapie in Klinik und Praxis. Schattauer, Stuttgart, New York, 8th edition.

Tanaka, L. G., El-Dahr, J. M., Lehrer, S. B. (2001) Double-blind, placebo-controlled corn challenge resulting in anaphylaxis. JACI, 107 (4), 744.

Trieu-Cuot, P., Arthur, M., Courvalin, P. (1987) Origin, evolution and dissemination of antibiotic resistance genes. Microbiol. Sciences, 4: 263-266.

Valenta, H., Dänicke, S., Flachowsky, G., Böhme, T. (2001) Comparative study on concentrations of deocynivalenol and zearalenone in kernels of transgenic Bt maize hybrids and nontransgenic maize hybrids, Proceedings of the 23rd Mycotoxin Workshop, 2001, Vienna, Mycotoxin Research 17 A, 15-17.

Berlin, 8 April 2003

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The Agriculture and Fisheries Council will start on 26 May at **11:00** and not at 15:00 as indicated on the agenda I sent earlier.

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