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Unstable Transgenic Lines Illegal

Further evidence that most if not all commercially approved transgenic lines are genetically unstable and non-uniform has come to light. The transgenic lines fail to satisfy the current EU Directive requirements for proof of genetic stability and uniformity, and are hence illegal. Dr. Mae-Wan Ho *reports.*

In a recent study [1] on five commercially approved transgenic lines carried out by two French laboratories [2], all five transgenic inserts were found to have rearranged, not just from the construct used in transformation, but also from the original structure reported by the company. This was clear evidence that all the lines were genetically unstable.

Further evidence has come to light since. The Service of Biosafety and Biotechnology (SBB) of the Scientific Institute of Public Health (IPH) in Brussels has published on its website (http://biosafety.ihe.be/TP/MGC.html) reports on the molecular characterisation of the genetic map of six transgenic lines, four of which overlap with those analysed by the French laboratories: Bt 176 maize (Syngenta), Mon 810 maize (Monsanto), T25 maize (Bayer CropScience) and GTS 40-3-2 soybean (Monsanto).

The IPH is a Scientific Institute of the State, linked to the Belgian Federal Ministry of Social Affairs, Public Health and the Environment.

The Brussels reports are an overview of data presented at a meeting of the Belgian Biosafety Advisory Council. The data come from different scientific institutions, the applicants and from published papers. The reports found evidence of genetic instability similar to those described in the French study.

However, there are small and large discrepancies when the two sets of data are compared. In one case, Bt 176, there may even have been a misreporting or misidentification of the Bt transgene present, which the company claimed to be *crylAb*. Comparison with the public database revealed that the transgene has only 65% homology with the native *crylAb*, but 94% homology with *crylAc*. Bt toxins are potential allergens and immunogens; *crylAc*, in particular, was identified as a potent systemic and mucosal immunogen, as potent as cholera toxin [3].

The studies also revealed a discrepancy in regulatory practice. UK's Advisory Committee on Novel Foods and Processes (ACNFP) and the Belgian authority both appear to have allowed Monsanto to submit new molecular data on Roundup Ready soybean when independent analysis revealed its insert had rearranged.

Most of the discrepancies involve the structure of the insert, the number of insert(s) and locations within the genome; suggesting that the transgenic lines are not only unstable but also non-uniform. Consequently, the results of the molecular characterisation could differ from sample to sample of the same transgenic line. In other words, the transgenic lines may well not pass the DUS (distinctness, uniformity and stability) test, which is required by European legislation.

The new EU Directive 2001/18/EC on deliberate release of GMOs also requires information documenting *genetic stability* (Annex IIIB) as a condition for market approval. Genetic stability can only be demonstrated by 'event specific' molecular data of the kind carried out in the two studies. In view of the finding that practically every transgenic insert has rearranged from that reported in the company's original dossier, it would indicate that the transgenic lines have failed the test of genetic stability, and are no longer the same lines that were risk assessed, and in some cases, placed on the market. This has important safety implications. Rearrangements and deletions are signs of structural instability, which enhances horizontal gene transfer and recombination, with all the attendant risks [4]. This is particularly relevant as the molecular analyses have so far revealed a

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Questionable 'Stability' at JIC

strong tendency for transgenic inserts to land in mobile genetic elements, such as retrotransposons and repeat sequences. Four out of six transgenic inserts analysed for flanking sequences identified repeat or retrotransposon sequences.

For either or both those reasons, it would be illegal, under European legislation, to grant those transgenic lines commercial approval; and the lines that have been approved must surely now be withdrawn.

The detailed comparisons on the findings in the four transgenic lines from the two studies are presented below, followed by comments on the additional transgenic lines investigated separately in the two studies.

Transgenic lines analysed in both studies

Bt 176 maize (Syngenta)

The Bt176 maize dossier was first submitted in 1994 by Ciba Geigy (Novartis) and approved under the old EU Directive for growing, seed production, import, processing and food/feed purposes since 23 January 1997 [5]. It was modified for tolerance to the herbicide glufosinate, male sterility and insect resistance. Two constructs were used to transform maize (see below).

French study

Only the simpler construct was analysed. Company data showed single insert containing the cauliflower mosaic virus (CaMV) 35S promoter (hereafter referred to as P35S) driving the *bar* gene (glufosinate tolerance) terminated by the CaMV 35S terminator (hereafter referred to as T35S) followed by the ampicillin resistance (*bla*) gene plus a bacterial promoter, and the plasmid origin of replication, *ori*.

Analysis revealed several fragments, all containing P35S: one with P35S joined to T35S, a second with P35S joined to an unknown sequence, and a third with P35S joined to the *bar* gene, with the T35S deleted (that means P35S could drive the expression of downstream maize genes).

At least three insertion sites were found for this construct.

Brussels study

This study [5] describes the line as being obtained by microprojective bombardment into immature embryos of inbred corn line CG00526 (*Zea mays* L.) using two different transforming plasmids. The plasmid pCIB4431 contains two copies of a synthetic truncated *crylA(b)* gene, having approximately 65% homology at nucleotide level with the native gene of *Bacillus thuringiensis* subsp. *kurstaki* strain HD1. The first copy is under the regulation of the maize phosphenlopyruvate caboxylase (PEPC) promoter (PPEPC) and the T35S. The second copy is under the regulation of the maize calcium-dependent protein kinase (CDPK) promoter(PCDPK), resulting in pollen-specific expression, and terminated with T35S. In addition, both copies were combined with the intron #9 derived from the maize PEPC gene to enhance expression in maize. The plasmid pCIB3064 contains the *bar* gene derived from *Streptomyces hygroscopicus* under the regulation of P35S and T35S. Both plasmids also contain a copy of the *bla* gene for amipicillin resistance under the control of a bacterial promoter.

There are still uncertainties about the copy number of the insert in event Bt176. Published results from Koziel et al [6] indicated that there may be as many as five copies of the *crylA(b)* gene present.

Data from Centrum Landbouwkundig Onderzoek, Mell, Belgium (CLO) revealed that the *cry* coding sequence showed 94% similarity with Genbank accession no. AF537267 for synthetic construct of *crylAc* gene. In comparison, the *cry* transgene showed only 65% homology at nucleotide level with the native gene of *Bacillus thuringiensis* subsp. *kurstaki* strain HD1. ***This suggests the company may have misreported or misidentified the transgene present.***

The company's dossier claimed one single copy of transgene insert (P35S-*bar*-T35S), and gave no information on 5' or 3' flanking sequences. For the second transgene insert (T35S-int#9-*crylAb*-PPEPC-PCPDK- *cry1Ab*-int#9-T35S), it claimed 2 to 5 copies were present, but no information on flanking sequences was provided.

Other sources report that first transgene insert is present in at least 4 truncated copies, ***and depending on the source***, the number of truncated copies differs.

This is an indication of non-uniformity of the transgenic line as well as genetic instability. The second transgene insert is present in at least 5 copies.

There are basic agreements between the two studies on the rampant rearrangements that have occurred. There is also evidence of non-uniformity from the Brussels study.

Mon 810 (Monsanto)

Mon 810, modified for resistance to lepidopteran insects (butterflies & moths), was submitted by Monsanto in 1995 and approved under the old Directive for growing, import, seed production and processing into animal feeding stuffs and industrial purposes since 22 April 1998 [7]. In December 1997 food and food ingredients derived from Mon 810 maize were notified under Article 5 of the Regulation (EC) 238/97 (for novel foods). Several hybrids of Mon810 are still pending approval for marketing:

- T25 x Mon810 submitted under the old directive in April 1999. The Scientific Committee gave a favourable opinion on 6 June 2000
- Mon810 x K603 submitted 15 Jan 2003 under the new Directive 2001/18/EC for import and use in feed and industrial processing.
- Mon863x Mon 810 submitted under the new Directive 7 Feb. 2003 for import and use of grain and grain products. On 29 August 2002, the application was submitted under Regulation (EC) 258/97.
- MaisGard/RR (Mon810and GA21) submitted under the new Directive 13 Feb 2003 for import and use in feed and industrial processing. On 16 March 2000, maize application was submitted under Regulation (EC) 258/97.

French study

Company data showed that the insert has a P35S driving a *crylAb* synthetic gene with terminator T-nos. Maize heat shock protein intron is located between P35S and *crylAb*. Analysis revealed however, that T-nos and part of the 3' (tail) end of the *crylAb* gene have been deleted. T-nos is detected elsewhere in the genome, indicating that it may have moved from its original position.

The 5' (head) end of the insertion site shows homology to the long terminal repeats (LTR) of the maize alpha Zein gene cluster, but no homology to the maize genome was detected at the 3' site, indicating that there had been scrambling of the maize genome at the insertion site. The strong P35S promoter could therefore be driving the transcription of an unknown gene downstream.

Brussels study

Mon 810 was produced by transforming maize genotype HiII with two plasmid vectors, pV-ZMBK07 and pV-ZMGT10. The plasmid pV-ZMVK07 contains the *crylAb* gene isolated from *Bacillus thuringiensis* ssp. *kurstaki*, placed under control of the enhanced CaMV 35S promoter (e35S) and the T-nos. An intron from the maize heat-shock protein (hsp70) is located between the e35S promoter and the *crylAb* gene. The second plasmid pV-ZMGT10 contains the CP4 EPSPS gene from *Agrobacterium* strain CP4 and the *gox* gene cloned from *Achromobacter* strain LBAA. Both plasmids contain the *nptII* gene under control of a bacterial promoter. Molecular analysis by Monsanto showed that the *nptII* gene and the backbone sequences of pV-ZMBK07 are not integrated and that none of the DNA sequences from vector pV-ZMGT10 are present.

According to the company dossier, Mon 810 contains a single copy of the e35S promoter, the hsp70 intron and the *crylAb* gene. The absence of the 3'T-nos sequence was confirmed by CLO.

CLO determined the 5' junction, upstream from the e35S, and found that the DNA shows 88% identity with the 22kDa alpha Zein gene of maize.

The rearrangement of the insert was confirmed in both studies. A potentially serious discrepancy is that the French study found the insert flanked by the LTR of the Zein gene cluster at its 5'end, and not by the Zein gene, as found in the Brussels study. A minor discrepancy is in the P35S reported in the French study as opposed to e35S in the Brussels study, and the detecting of T-nos elsewhere in the maize genome in the French study.

T25 maize (Bayer)

Liberty-link maize event T25, modified for tolerance to the herbicide glufosinate,

was submitted by AgrEvo (Bayer CropScience) in 1995 and approved for marketing since 22 April 1998 [8]. Products derived from T25 have been notified under Article 5 of the Regulation (EC) 258/97 on 21 October 1999.

A hybrid of T25, still pending approval for marketing, T25 x Mon 810, was submitted 29 April under the old Directive, and the Scientific Committee gave a favourable opinion on the dossier 6 June 2000.

French study

Company data showed that the insert includes a truncated ampicillin resistance *bla* gene in the plasmid vector pUC18, a P35S driving a synthetic *pat* gene (glufosinate tolerance) terminated by T35S. On analysis, the insert was found to have undergone further rearrangement, so that a second, truncated and rearranged P35S has been joined to the 5' (left, or head) end of the insert, while additional pUC18 sequences were found at the 3' (right, or tail) end.

Edges flanking the insert show homologies (similarities) with Huck retrotransposons (a class of mobile genetic elements) in the maize genome.

Brussels study

T25 was obtained by protoplast transformation of the parental line He/89 using plasmid pUC/Ac containing the *pat* gene from *S. viridochromogenes* Tu494 and controlled by P35S and T35S. The plasmid includes the *bla* gene for ampicillin resistance.

The company dossier claimed there was a single insert, and this was confirmed by CLO's analysis. The *pat* gene is "surrounded" by sequences from the plasmid vector pUC18. According to the dossier, a 2187 bp pUC fragment is present upstream of P35S. This fragment ends up in the *bla* gene followed by a 353bp fragment of the P35S, probably resulting from a duplication/recombination event. CLO confirmed these data, except that a shorter, 298 bp P35S promoter fragment was found. According to both the applicant and CLO, a fragment from pUC plasmid was found at the 3' end downstream of 35S terminator; but differences in length were reported.

Aventis submitted data that describe the host flanking sequences of the T25 line. A 151p(5') and a 121 bp (3') fragment show homology (94% identity) to maize alcohol dehydrogenase *adh*1 gene. ***This differs from the findings of the French study, which detected flanking sequences homologous with Huck retrotransposons***.

Apart from this discrepancy, the nature of the rearrangement in the insert was confirmed in both studies.

GTS 40-3-2 (Monsanto)

This line was modified for tolerance to the herbicide glyphosate (Roundup Ready variety). According to UK's Advisory Committee for Novel Foods and Processes (ACNFP) [9], the Committee considered Monsanto's RR soybeans line 40-3-2 under its "voluntary scheme" in 1994 and gave it clearance for food safety on 20 February 1995. The event has been approved for planting and/or consumption in a number of countries worldwide and products from it consumed for a number of years.

French study

The company's original data showed a single insert with P35S driving a composite gene containing the N-terminal chloroplast transit peptide (CPT4) joined to modified EPSPS gene with T-nos terminator. Analysis provided by the Ministry of Midclass and Agriculture, Belgium, published by Windels et al [10] revealed that a 254bp piece of DNA homologous to the EPSPS gene and 534bp of unknown DNA have been joined to the 3'end of the insert.

It was not possible to identify the insertion site, indicating that substantial genome scrambling or deletion had taken place at the insertion site.

Brussels study

This study merely referred out to the ACNFP website. It appears that Monsanto was allowed to submit new data in 2000, and again in 2002. The first confirming that a 254bp piece of the EPSPS gene has been joined to the 3' end of the insert, the second claiming that "large portions" (29bp + 420bp) of the 543bp of unknown

DNA found by Windels et al [9] was identical to soybean genomic DNA from the company's own "proprietary database", that has undergone rearrangement.

While the French study emphasized the rearrangement of the insert, both the UK ACNFP and the Brussel report have accepted Monsanto's new data and not questioned why they should differ so substantially from those presented in the company's original dossier.

Transgenic lines analysed in one study only

GA 21 maize (Monsanto) – French study

The line was modified for tolerance to the herbicide glyphosate (Roundup Ready). Company data indicated that the insert contains multiple copies of the cassette with the rice actin gene promoter (P-ract) driving the composite gene containing the N-terminal chloroplast transit peptide (CPT4) joined to modified EPSPS gene and T-nos. There were three complete cassettes flanked by a cassette with P-ract partially deleted at the 5' end, and one cassette with 3' deletion of EPSPS plus a lone P-ract at the 3'end. Analysis found partial deletion of P-ract and deletion of T-nos in *two* different cassettes.

The insertion site at the 3'end is flanked by sequences of *pol* polyprotein gene belonging to a PREM2-retrotransposon.

On 15 September 2003, Monsanto informed the European Commission that it was withdrawing its application for GA21 Roundup Ready maize and GA21 x MON810 MaisGard/Roundup Ready maize, for "commercial reasons".

Bt 11 maize (Syngenta) – Brussels study

This was notified in 1996 and approved under the old Directive for import and processing since 22 April 1998 [11]. The notifications for cultivation submitted in 1996 and 1998 are still pending. On 30 November 2000, the EU Scientific Committee on Plants gave a favourable opinion for cultivation. Up till now, the Commission has not received an updated version of these two notifications according to the requirements of Directive 2001/18/EC. In February 1999, Novartis submitted a new application, which is still pending. On 13 March 2002, the SCP gave a favourable opinion.

Food and food ingredient products derived from Bt11 crossed with the Northup King Company inbred line #2044 maize were notified on 20 Jan. 1998.

The plasmid used for transformation contains a synthetic truncated *crylAb*, isolated from *Bacillus thuringiensis* spp. *kurstaki* HDI, and a synthetic *pat* gene, isolated from *Streptomyces viridochromogenes* Tu494. Both coding sequences were placed under the regulation of P35S and the T-nos terminator from *Agrobacterium tumefaciens*. In addition, the promoter sequences of the *pat* and *cry1Ab* gene were combined with respectively intron Int II and Int VI derived from maize alcohol dehydrogenase *adh1S* gene to enhance expression. The event Bt11 maize was obtained by protoplast transformation with plasmid pZ01502 after digestion with restriction enzyme *Not*1 to remove the *bla* gene encoding ampicillin resistance.

The whole sequence of the insert was determined by TEPRAL, Strasbourg, France. The insert consists of a single copy of the vector fragment carrying both the *crylAb* and *pat* gene. "It was found that rearrangements have taken place into the insert compared to the original insert and that several parts of the plasmid have been truncated or unexpected inserted, e.g., t35S sequences….The presence of t35S fragments into the insert was confirmed by INRA."

Sequence analysis done by CLO with PCR using P35S specific primer in combination with a 3'T-nos specific primer, proved that the DNA segment present in between the two expression cassettes of the Bt11 insert is similar to the pUC vector backbone sequence.

Zimmermann et al [12] showed that next to the 5' P35S border of the *crylAb*, a maize 180bp knob-specific repeat sequence is present. In addition, CLO analysed the sequence that is present between the P35S sequence and the maize plant and demonstrated that a 1099 bp segment is present, homologous to the pUC backbone sequence and contains part of the *lacZ* coding sequence.

The junction regions at the 3' T- nos terminator border were amplified by CLO using a specific anchor primer. A 244 bp junction was amplified that contains 149 bp

plant DNA that on BLAST sequence analysis, showed similarity to the maize 180bp knob associated tandem repeat. Independently from CLO, the 3' T-nos border region was also amplified by Ronning et al [13], confirming this finding. The remaining part of the amplified 3'T-nos junction is homologous with the pUC backbone sequences.

These data provide evidence that the Bt11 insert is integrated in the *Zea mays* 180bp knob associated tandem repeat locus. At the P35S border, an extensive piece 1099 bp of pUC backbone DNA was observed between the plant DNA and the P35S promoter, while at the 3'nos border only a small stretch of pUC backbone DNA is present.

According to TEPRAL, it is not certain if only one copy of the insert is present.

Preliminary data of INRA showed that a set of primers designed on the edge fragment of Bt 176 amplified sequences from both Bt176 and Bt11. These data were obtained on six different Bt11 plant seeds received by Syngenta, suggest contamination of Bt11 by Bt176.

Bt 11 is therefore neither genetically stable nor uniform, and should on no account be approved.

Event Ms8xRf3 canola (Aventis, Bayer)

This 'event' is really a composite of two different transformations, and was first notified in 1996 (C/BE/96/01) from PGS (now Bayer Cropscience) under the old Directive 90/220/EEC for cultivation, import, seed production and processing into animal feed stuffs and industrial purposes [14]. On 24 Jan 2003, the European Commission received an updated version according to the requirements of the new Directive 2001/18/EC. Oil derived from Ms8xRf3 products has been notified under Article 5 of the Regulation (EC 258/97) on 21 October 1999.

It is not clear whether the company's data were provided in the original 1996 dossier or in the updated version submitted 24 January 2003.

Ms8 was produced by *Agrobacterium* mediated transformation using plasmid pTHW107. This plasmid contains the *barnase* gene derived from *Bacillus amyloliquefaciens* and the *bar* gene derived from *Streptomyces hygroscopicus*. *Barnase* under regulation of a tapetum specific promoter PTA29 isolated from *Nicotiana tabacum* and the T- nos terminator of *Agrobacterium tumefaciens*. The *bar* gene is regulated by the PSsuAra promoter isolated from *Arabidopsis thaliano* and by the 3' end of the T-DNA gene 7 of *A. tumefaciens*.

The transgenic fertility restorer line Rf3 was obtained using plasmid pTHW118 containing a *barstar* gene derived from *Bacillus amyloliquefaciens* under regulation of the PTA29 promoter and the T-nos together with the same *bar* cassette as described for pTHW107.

According to the company dossier, the Ms8 insertion contains a single T-DNA copy. At the left border (3'end of the T-DNA) a 357 bp host sequence was retrieved. At the right border junction (5' of the TDNA) an 864 bp host sequence was retrieved. PCR amplification from the parental line showed co-linearity with the sequences found on both sides of the T-DNA insert. Molecular analysis done by the CLO confirmed that the adjacent DNA is plant DNA. Search in the database showed that part of the 5' flanking regions has over 82% similarity with *Arabidopsis* sequences.

Determination of the pre-insertion site was done by the applicant using DNA isolated from wild type oilseed rape. Alignment of wildtype sequence with the Rf3 transgene locus revealed that a fragment of 51 bp is present at the wildtype locus but missing from the transgene locus. At the right border 5 nucleotides (filler-DNA) are inserted. Alignment of the wildtype sequence with the Ms8 transgenic locus revealed that 19bp are missing at the target site. At right border junction 3 nucleotides of unknown origin are inserted.

Both Rf3 line and Ms8 line transgene is integrated in a single genetic locus. But the Rf3 event resulted in the insertion of one-TDNA copy arranged in an inverted repeat structure with a second incomplete T-DNA copy. Event Ms8 contains an intact single T-DNA copy. During insertion, typical rearrangements have occurred at the pre-insertion site. In both lines, the dossier claimed, the inserts are flanked by plant DNA showing high similarity with Arabidopsis DNA.

CLO analysis confirms data in dossier (1996) for the right border (RB) of the Rf3 insert, but no data were available for the truncated left border (LB) and the plant DNA rearrangement. For Ms8, CLO confirms data in dossier.

I cannot ascertain from the report whether rearrangement had occurred in the original inserts in the two events Ms8 and Rf3, as it is unclear if the company's data were provided in the original 1996 dossier or in the updated version submitted 24 January 2003. The characteristic inversions, duplications and deletions, insertions and scrambling of host genome DNA at the sites of insertions are evident.

We have explained why this line is unacceptable in other respects [15] and should not be approved for commercial release. This is a 'terminator' crop, engineered for male sterility, ostensibly to prevent transgene escape, but in reality to protect patented herbicide tolerant trait. It also prevents farmers from saving seeds, compelling them to buy the fertile hybrid every year. In reality, the crop spreads both the male sterility 'suicide' gene *barnase* in its pollen – which is highly toxic to all cells, mammalian included - as well as the herbicide tolerance trait, with potentially large impacts on agricultural and natural biodiversity including the soil biota. The results of UK government-sponsored Farm Scale Evaluations, recently released, have documented negative impacts on biodiversity from growing this transgenic crop [16].

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