**Monsanto's response to objections from the African Centre for Biosafety to Monsanto's application for field trials of drought tolerant GM maize MON87460**

For ease of reference, our responses are laid out as per ACB's conclusions.

1. **The possibility of any real yield benefit to be derived from the transformed plants is not rated very high by Monsanto. The risks of exposing the environment to such a product cannot be justified within this context.**

As stated in the application, studies conducted with MON 87460 have confirmed that this event is agronomically and compositionally equivalent to conventional maize and has no increased tendency towards weediness and no increased susceptibility or tolerance to insects normally associated with maize. Furthermore, detailed safety assessments have established that the proteins contained in MON 87460 are safe for human consumption (see below, point 5). Thus, based on the characteristics of the expressed protein products in MON 87460, there is no meaningful hazard present, and therefore, the planting of a field trial of MON 87460 poses limited risks to the environment and human health. Several seasons of field testing with MON 87460 in South Africa and USA, with no ecologically disruptive impacts or harmful effects recorded as a result of these trials, are evidence of this.

Monsanto's drought event MON 87460 will not able to grow completely without water, but rather, is designed to provide yield stability during periods when water supply is scarce by mitigating the effects of drought – or water stress – within a maize plant. Field trials with MON 87460 in the US met or exceeded a 6% or greater target yield enhancement compared to the average yield obtained during drought conditions. Moderate drought can be defined as a dry period of at least two weeks resulting in approximately a 33% decrease in maize yield compared to optimal water conditions. These conditions occur almost every year in some area at some time during the growing season.

MON 87460 is expected to provide significant value to maize producers and consumers due to reduced yield loss under water-limited conditions. Improved yields under water-limited conditions will help to ensure a stable grain supply, even in years with low rainfall. Higher maize yield per hectare may help conserve the total number of hectares needed to meet the needs for food, feed and biofuel uses or produce more maize grain on the same number of hectares already used for maize production. Positive impacts on yield and improved yield stability will provide value to producers, consumers and the environment.

While much progress has been made to improve maize yield in water-limited environments through breeding, selection, and agronomic management practices, there remains potential for additional improvement. Biotechnology provides additional tools that can be used in combination with breeding and agronomic practices to enhance productivity. A study with conventional maize hybrids that were commercially available between 1953 and 2001 estimated that conventional breeding under water-limited conditions provided levels of tolerance that led to yield increases of approximately 1% per year when those conventional hybrids were cultivated in water-limited environments (Campos et al., 2006). Biotechnology is expected to provide yield increases of 6% or more. This level of yield increase represents significant value to farmers.

Unlike previous insect-protected and herbicide-tolerant traits that have significantly improved agricultural practices and yields by protecting against losses associated with insect damage and weed pressure, MON 87460 will enhance yield under dry land conditions by improving grain production. A detailed assessment of the agronomic and phenotypic characterization of MON 87460, including yield, was carried out to demonstrate efficacy of MON 87460. Efficacy of MON 87460 can be demonstrated by directly comparing its grain yield to a conventional control under water-limited conditions.

**"Drought tolerance is complex, mediated by multiple genes and regulatory pathways. Not easy to engineer into plants"**

Developing MON 87460 has indeed required significant effort by Monsanto. The CSPB gene does, in fact, successfully allow MON 87460 to produce better yields than would otherwise be possible under water-limited conditions. Two recent publications (Nelson et al., 2007; Castiglioni et al., 2008) successfully demonstrated the utility of single gene approaches for imparting drought tolerance in maize.

**"Re-assess potential for proliferation and persistence". Cannot be considered to be limited to areas with a lower limit summer rainfall of 150mm.**

Maize does not possess attributes commonly associated with weeds, such as long persistence of seed in the soil, the ability to disperse, invade and become a dominant species in new or diverse landscapes or the ability to compete well with native vegetation. Modern-day maize cannot survive outside of cultivation (Gould, 1968). Although maize from the previous crop year can overwinter and germinate the following year, it cannot persist as a weed. The appearance of maize in soybean fields following the maize crop from the previous year is a common occurrence. Measures often are taken to eliminate the plants with mechanical or chemical means in soybean fields; plants that remain and produce seed usually do not persist in the following years.

It is difficult for maize to survive as a weed because of past selection in the development of maize. Plant breeders select against many traits associated wiht weediness (dormancy, lodging, shattering and dispersal of seed). In contrast with weedy plants, maize has a polystichous female inflorescence (or ear) on a stiff central spike (or cob) enclosed with husks (modified leaves) (Galinat, 1988). Consequently, seed dispersal of individual kernels does not occur naturally because of the structure of the ears. Individual kernels, however, can be distributed during grain harvest and transportation to storage facilities. In neither instance (natural or mechanical harvesting) does maize become a troublesome weed. Maize cannot survive without human assistance and is not capable of surviving as a weed.

2. **The application is silent on the measures to be taken to prevent pollen flow and makes assessment of the growing conditions impossible.**

In order to ensure that robust data is generated, it is in the best interest of Monsanto to ensure that no plants from the previous season remain, as this may interfere with accurate data analysis for the next season. Intensive management measures are therefore employed to ensure that volunteers are aggressively controlled.

Monsanto has been conducting maize field trials in South Africa in terms of the GMO Act for more than 13 years, with no ecologically disruptive impacts or harmful effects recorded as a result of these trials. Robust containment and isolation measures are in place to prevent pollen flow and in case of accidental release, Monsanto will take full responsibility to ensure appropriate mitigating measures are implemented.

The trials are conducted in a controlled environment and on completion of the trials, all material is rendered non-viable. All necessary isolation and seed dispersal control measures, as stipulated in the permits, are strictly adhered to. Inspections by the DAFF are carried out on all activities from planting to destruction of material. Therefore, the possibility of dissemination of transgenic maize from the site is virtually eliminated.

**Effect of wind speed and direction on cross-pollination (GM field upwind or down-wind) Example of canola pollen 3km away.**

Gene flow (often used synonymously with the term "outcrossing" or "cross pollination") is a natural biological process that occurs in most crop species, including maize. In order for successful cross pollination to occur plants must be sexually compatible, in close proximity for cross pollination to take place, and flower at the same time. Once in the atmosphere, pollen grains must remain viable long enough to be able to reach a viable silk to complete the pollination process. Average maize pollen completely loses viability after two hours of atmospheric exposure (Luna et al., 2001; Aylor, 2003).

3. **Incomplete molecular characterisation information and detail on subsequent genetic evidence to confirm the original transformation makes complete assessment of the transformation event impossible.**

Details of the molecular characterisation of MON 87460 were provided in the application. Where relevant, additional information has been provided below.

*Transformation method*

MON 87460 was produced by *Agrobacterium*-mediated transformation of maize with PV-ZMAP595, a binary vector containing a single transfer DNA (T-DNA) to express cold shock protein B (CspB) from *Bacillus subtilis*. The vector, PV-ZMAP595, contains both the left and right border sequences flanking the transfer DNA (T-DNA) to facilitate transformation. The T-DNA contains two expression cassettes. The first expression cassette produces *CspB* and the second expression cassette produces neomycin phosphotransferase II (*npt*II), a selectable marker that was used during product development. The *Agrobacterium*-mediated maize transformation to produce MON 87460 was based on the method described by Armstrong and Phillips (1988) and details were provided in the application.

*Characterisation of the inserted DNA*

The genetic elements introduced into the genome of MON87460 maize were analysed using established molecular biological techniques and included southern blot analysis, polymerase chain reaction (PCR) and DNA sequence analysis and flanking sequence bioinformatic analysis.

Molecular characterization of MON 87460 by Southern blot analyses demonstrates the insertion of a single functional copy of the *cspB* and *nptII* expression cassettes at a single locus within the maize genome. PCR and DNA sequence analyses provided the complete DNA sequence of the insert and confirmed the organization of the elements within the insert. The coding region of the *cspB* and *nptII* genes and their regulatory elements are intact and no plasmid backbone sequences are present.

Overlapping regions spanning the entire insert and flanking genomic DNA were amplified by PCR using genomic DNA isolated from seed. The results confirmed the identity and arrangement of all of the genetic elements introduced into MON87460 maize and indicated that the DNA sequences flanking the 5' and 3' ends of the insert were identical to conventional maize.

*Genetic stability of the insert*

To determine the stability of the insert in MON87460 maize over multiple generations, DNA was isolated from seed from seven generations. Southern blotting indicated that: (1) the single copy of the insert introduced into MON87460 maize was stable over multiple generations; and (2) multiple generations of MON87460 maize contained no DNA sequence(s) from the backbone of plasmid PV-ZMAP595. The stability of the integrated DNA is demonstrated by the fact that the Southern blot fingerprint of MON 87460 was maintained for seven generations tested in the breeding history. Furthermore, these generations have been shown not to contain any backbone sequence from plasmid PV-ZMAP595. The stability was further confirmed by the fact that the inheritance of the T-DNA in MON 87460 follows Mendelian patterns of segregation.

**Do the inserts / fragments thereof lie on any transposons and what is impact of DNA insert on flanking sequences?**

Bioinformatic analysis of the flanking sequences were conducted to ascertain whether theoretical proteins generated from open reading frames (ORFs) at the 5' and 3' insert/maize junctions could be potentially toxic, allergenic or biologically active. None of the theoretical proteins exhibited any biologically relevant sequence homology with known toxins, allergens or biologically active proteins. The bioinformatic analysis undertaken was theoretical, with the results indicating that in the highly unlikely event that any ORF were to be translated or that the reverse complement strand of the *cspB* and *nptII* coding sequences were transcribed and translated, the translation product would not share a sufficient degree of sequence similarity or identity to indicate that it would be potentially allergenic, toxic, or have other health implications. The bioinformatic analysis of the insert junctions considered any sequence between two stop codons that would theoretically correspond with a peptide eight or more amino acids in length. This is a highly conservative approach that assumes transcription and translation are possible and does not consider whether such events are probable. Translation of these putative peptides is in fact improbable given that the sequence is located between two stop codons.

4. **The development of the MON 87460 event has not been optimised to minimise gene flow of ARMG and it is not clear why this was not done.**

*Horizontal gene transfer*

The factors affecting the potential for HGT between genetically modified plants expressing antibiotic resistance marker genes and microorganisms in the environment have been extensively studied (Nielsen *et al*., 1998; Smalla *et al*., 2000; Kay *et al*., 2002; Tepfer *et al*., 2003; Demanèche *et al*., 2008). HGT of *nptII* from transgenic plants to bacteria has been demonstrated in laboratory studies, but only under optimized conditions using a strong selection pressure and recipient bacterial strains harboring the *nptII* gene carrying deletions to produce high sequence homology (Gebhard and Smalla, 1998; Tepfer *et al*., 2003). HGT is known to be a rare event and has not been detected under field conditions (Nielsen *et al*., 1998; Demanèche *et al*., 2008). Transformation frequencies (the frequency of foreign DNA incorporation into the microbial genome) likely to be encountered in the field are low, representing environmental significance only on an evolutionary time scale.

The very low frequency of HGT from plants to bacteria needs to be placed in context with the widespread occurrence of resistance in bacterial populations, the ease with which genetic information is exchanged among bacteria, the high endogenous mutation rate of bacteria, and the importance of selective pressure. Resistance to kanamycin and neomycin is widespread, not only in pathogenic bacteria, but also amongst environmental organisms. If gene transfer from MON 87460 and juxtaposition to a bacterial promoter were to occur, this would not significantly add to the frequency of kanamycin and neomycin resistant microbes in the environment, since resistance to this class of antibiotics is already widespread in nature (EFSA, 2009; Demanèche *et al.*, 2008). When these factors are taken into consideration, the potential for *nptII* transfer from MON 87460 to soil microorganisms does not represent any meaningful risk.

European Food Safety Authority (EFSA) recently affirmed its conclusion that the presence of *nptII* in biotechnology-derived plants does not pose a threat to human health or the environment (EFSA, 2009). Demanèche *et al.* (2008) also concluded that the risk that antibiotic resistance marker genes (ARMG) in biotechnology-derived plants can pose to commensal and clinical bacteria should be considered as almost null. In their study, fields were evaluated that were cultivated for 10 successive years with a *Bt* maize containing an ARMG. No change in the antibiotic resistant bacterial population was observed under these field conditions. The authors further concluded that even in the case that HGT would occur, the risk would be negligible since a plethora of ARMGs are already present in bacterial populations (Demanèche *et al.*, 2008).

Scientific evidence to date supports a conclusion that HGT is at most an extremely rare event in the environment. Even if it were to occur, the consequences would be negligible since the *nptII* gene introduced into MON 87460 is of bacterial origin and the protein produced would have no meaningful toxicity to humans and other non-target organisms under the conditions of use. In addition, the *nptII* gene is not expected to pose any additional risk of antibiotic resistance when MON 87460 is cultivated.

*EFSA Statement (2009)*

The ACB cites the EFSA Statement (2009): "Kanamycin and neomycin are both categorized by the WHO Expert Group on Critically Important Antimicrobials for Human Health as 'Highly Important Antimicrobial'… The increasing occurrence worldwide of "extensively drug-resistant" (XTB) isolates of MTB with resistance to second-line antibiotics such as kanamycin is a cause for global concern."
The EFSA statement concludes this paragraph with the following sentence: "**The *npt*II gene has not been implicated in such resistance.**"

Furthermore, in their letter of objection, ACB made reference to two panel members who expressed minority opinions on EFSA's statement (2009). Following adoption of the opinions, EFSA "consulted the Chairs of the GMO and BIOHAZ Panels as to whether the completion of the mandate would require a clarification of issues raised in the minority opinions of the joint scientific opinion… The Chairs responded by confirming that **the scientific issues related to the minority opinions have already been extensively considered during the preparation of the joint scientific opinion and the formulation of the conclusions therein and thus, from a scientific perspective, further clarification of the joint scientific opinion is not required, nor is further scientific work needed at this time**…". Monsanto therefore considers the EFSA statement and the conclusions reached therein to be trustworthy, and will cite it in context where relevant.

5. **No health and safety and human health impacts from possible consumption of MON 87460, in the event of gene flow and/or handling spills are included in the application. This hampers the public's ability to contribute or engage meaningfully in any discussions regarding GE foods or be able to make informed choices about matters that so closely impact on them.**

*Safety assessments*

This application is for a confined field trial and stringent confinement and management actions will be implemented to prevent dissemination (and hence unintentional consumption) of regulated maize grain. Nevertheless, safety assessments of CspB and nptII and their respective donor organisms establish that these proteins are safe for human consumption.

CspB has a history of safe consumption and nptII is present in several biotechnology-derived crops that have undergone previous safety assessments. The donor organism of the CspB protein, *Bacillus subtilis*, is not pathogenic, is present in many fermented foods, and has a history of safe consumption. Proteins containing cold shock domains are ubiquitous in nature, being present in many plants and common bacteria including species that are normally present in gastrointestinal flora. Cold shock proteins (CSPs) have no known toxicity and are not associated with pathogenicity. The CspB protein is homologous to the CSPs found in *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, and *E. coli*, which are normally present in gastrointestinal flora and, therefore, considered to be safe. The amino acid identity ranges from 35% to 98.5% across different plant and bacterial species. The strains of lactic acid bacteria, *Bifidobacterium* and *Lactobacillus*, are the most common type of bacteria used in the dairy industry for preparation of probiotic products containing live bacterial cultures. In addition, *Bacillus*, *Lactobacillus, and*

*Lactococcus* species containing CSPs are involved in many food fermentation processes of milk, meats, cereals, and vegetables.

Based on the characteristics of *cspB* and *nptII* and their expressed protein products in MON 87460, there is no meaningful hazard present, and as such, minimal risk is posed to the environment and human health. Both proteins are commonly found in the environment and have been shown to be nontoxic. Furthermore, using the guidance provided by the FDA, a conclusion of "no concern" was reached for the donor organisms and the CspB and nptII proteins.

*Digestibility of DNA*

Studies conducted to determine if DNA in consumed feed can be found in milk or meat have shown that consumed DNA is not integrated into the genome of mammals (EFSA, 2007).

Cold shock proteins and other homologous proteins are ubiquitous in the environment by virtue of their presence in bacteria, plants and animals, including humans, where they function as nucleic acid chaperones (Karlson and Imai, 2003). The functional unit of cold shock proteins is the cold shock domain (CSD), which is a highly conserved nucleic acid binding domain. Humans consume numerous CSD-containing proteins in both the complexed and uncomplexed form, including bacterially-derived CSPB, and these would be subject to the same digestive processes as all dietary proteins and nucleic acids. Sources of CSPs include bacteria used to produce dairy products such as yogurt and cheese. *B. subtilis* itself is used to produce the Japanese soy food, natto. CSD-containing proteins are known to be present in a variety of food crops including wheat and rice.

With the exception of the single amino acid substitution at the N-terminus, the sequence of MON87460-derived CSPB is identical to the source organism (*B. subtilis*) and therefore its binding to single stranded nucleic acids would be no more stable (or unstable) to digestion, cooking or processing. Therefore, there is no reason to believe that CSPB:nucleic acid complexes derived from MON 87460 would behave differently to bacterially-derived CSPB:nucleic acid complexes that humans are already exposed to.

*Use of ARMGs*

NPTII is ubiquitous in *Escherichia coli,* and therefore, is normally present within the human gastrointestinal tract. NPTII is a commonly used antibiotic resistance marker present in several commercially grown biotechnology-derived crops including YieldGard® Rootworm maize (MON 863), Bollgard® cotton (MON 531), Bollgard®II cotton (MON 15985), and Roundup Ready cotton (MON 1445). NPTII is degraded in simulated gastric and intestinal fluids and is unlikely to survive digestive processes (Fuchs et al., 1993). NPTII is not detectable by western blot after 10 seconds of incubation in simulated gastric fluid (SGF) and is not detectable by western blot after 2.5 minutes of incubation in simulated intestinal fluid (SIF). The activity of NPTII is nearly undetectable following exposure to SGF for two minutes or SIF for 15 minutes (Fuchs et al., 1993). NPTII is also affected by heat treatment; therefore it is reasonable to expect NPTII to be denatured in any food produced from heat-processed MON 87460 grain. Additionally, the U.S. Environmental Protection Agency issued a tolerance exemption for NPTII on the basis of data

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demonstrating a lack of toxicity and rapid degradation in simulated digestive fluids (US EPA 1994).

The presence of nptII protein in maize is not expected to compromise the therapeutic use of aminoglycoside antibiotics in humans. NPTII confers resistance to neomycin and kanamycin but not to other aminoglycoside antibiotics with clinical applications. Neomycin has limited clinical applications because of side effects (renal and oto-toxicity) when administered systemically. It is minimally absorbed from the gut or skin and is administered topically for local antimicrobial effects (eye or skin) or orally to sterilize the gut prior to bowel surgery. Food ingestion is irrelevant to topical uses other than the gut, and concomitant ingestion of neomycin with food in the pre-operative setting is not expected as food consumption is not permitted. Kanamycin is rarely used as a result of higher renal and oto-toxicity relative to alternative aminoglycoside choices, but may be administered to treat multiple drug resistant tuberculosis (Goldstein et al., 2005). The aminoglycoside class of antibiotics is not effectively absorbed orally, and thus kanamycin is administered intravenously to treat systemic illnesses. Aminoglycosides like kanamycin are primarily excreted via the kidney, and they do not undergo entero-hepatic recirculation (excretion into the gut, followed by re-absorption). Thus, the presence or absence of NPTII in the gut is irrelevant to systemic use of kanamycin. In 2009, the European Food Safety Authority (EFSA) published its scientific opinion on the safety of antibiotic resistance markers. EFSA concluded that oral uses of aminoglycoside antibiotics would not be compromised by the presence of NPTII in food (EFSA, 2009).


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