Objection to commodity clearance of Corteva's MON 89034 x TC1507 x MIR162 x NK603 x DAS-40278-9 maize

August 2020

1. KEY CONCERNS

- The application fails to provide adequate information to facilitate public access to information, in an untransparent process that limits meaningful interrogation of the application. Attempts to gain further basic information from the applicant was rejected based on the inappropriate use of confidential business information by them.
- MON 89034 x TC1507 x MIR162 x NK603 x DAS-40278-9 has not been adequately assessed at the molecular level, raising concerns for unintended effects that may have adverse human health impacts. Parental varieties of this stacked variety have been shown in independent studies to have unintended molecular alterations that should be further investigated to rule out potential adverse effects on food safety.
- Food safety assessment of substantial equivalence was a failure, with less than half of the components measured being detected, and statistically significant changes being detected. Nonetheless, the applicant makes false claims of nutritional equivalence to conventional varieties of maize.
- The variety has not been assessed for food safety, with not a single toxicology assessment nor feeding study being performed.
- The GM maize is tolerant to three herbicides that have all been linked to serious human health illnesses including cancers, reproductive toxicity and infertility. The approval of MON 89034 x TC1507 x MIR162 x NK603 x DAS-40278-9 will increase exposure to toxic chemicals at a population level, further compromising the health of the population at a time of a global disease pandemic.
- The Westernisation of diets in South Africa, and globally, is associated with metabolic diseases such as obesity and diabetes, characterised by the rising incidence of the double burden of obesity and malnutrition. This is further exacerbated by environmental chemicals also linked to such health issues. The COVID pandemic has exposed the dysfunctions in food systems, and also the various improvements that can be made to reduce disease risks and save lives during this, and any future pandemics that may arise.
- The industrialised food model that has contributed to multiple shocks that threaten the health and wellbeing of the population; with the sole benefits being the corporations that stand to profit.
- We urge that the government rejects the approval of this GM maize variety and embarks on an overdue shift towards food systems that increase the resilience of the health and food systems of our country.

13 The Braids, Emmarentia, 2195
P.O. Box 29170, Melville, 2109, Johannesburg, South Africa.
Telephone +27 11 486 2701 – Fax +27 11 486-1156
https://acbio.org.za/
NPO No. 57324 Registration No. 2004/025/37/08
Directors: M S Mayet; F Diedhiou; R D Marema; J P W Wilson; M B Orovwuje; R J Partridge

2. INTRODUCTION

The African Centre for Biodiversity (previously 'Biosafety') (ACB) was established in 2003 and registered in 2004. ACB carries out research, analysis, capacity and movement building, and advocacy, and shares information to widen awareness and catalyse collective action and influence decision-making on issues of biosafety, agricultural biodiversity and farmer managed seed systems (FMSS) in Africa. The ACB's work both informs and amplifies the voices of social movements fighting for food justice and food sovereignty in Africa. The ACB has played an essential watch-dog role on new GMO permits in South Africa for more than a decade now, adding substantially to the discourse about the scientific assessment of GMOs, as well as issues of socio-economic impacts and democratic decision-making, through lodging substantive comments/objections on at least more than 50 permit applications.

The ACB objects the approval for commodity clearance of into the South African food system. While it appears to have been approved for commercial cultivation in Brazil according to the ISAAA database, it is unknown how widely cultivated it is, if at all. ACB contacted Corteva for information pertaining to this application including cultivation rates, but they declined to share any information on the application, making claims that such information was confidential business information (CBI) (see Section 4).

3. SUMMARY OF THE APPLICATION

MON 89034 produces two insecticidal proteins that protect against feeding damage caused by European corn borer (Ostrinia nubilalis) and other targeted lepidopteran insect pests. Cry1A.105 is a modified *Bacillus thuringiensis* (Bt) Cry1A protein, and Cry2Ab2 is a Bt (subsp. *kurstaki*) protein.

TC1507 produces both the insecticidal Cry1Fa2 Bt protein targeted at lepidopteran pests, and a phosphinothricin N-acetyltransferase (PAT) enzyme, conferring tolerance to glufosinate herbicides.

MIR162 produces the Bt Vip3Aa20 protein, which intends to protect against feeding damage caused by fall armyworm (Spodoptera frugiperda), corn earworm (Helicoverpa zea) and other targeted lepidopteran insect pests. MIR162 also expresses the phosphomannose isomerase (PMI) enzyme from *Escherichia coli*, as a plant selectable marker.

NK603 produces a 5-enolpyruvylshikimate-3-phosphate synthase protein from *Agrobacterium sp.* strain CP4 (CP4 EPSPS), which confers tolerance to glyphosate, the active ingredient in the Roundup® family of agricultural herbicides.

DAS-40278-9 produces the aryloxyalkanoate dioxygenase 1 (AAD-1) protein to confer tolerance to 2,4-D and quizalofop herbicides.

4. LACK OF ACCESS TO PUBLIC INFORMATION

Limited information contained in the redacted non-CBI version of the application restricts meaningful public participation in the decision-making process with regard to this transgenic event. As ACB has recently raised (ACB, 2020), the narrow opportunity for public participation in this format is very limited, with the applicant deeming what is considered CBI, preventing meaningful interrogation of the application.

Unfortunately, with regard to this application, further information was sought be ACB directly from the applicant but was also denied on the basis of CBI. ACB wrote to the applicant for further information on:

1. Whether any commercial cultivation has been undertaken to date involving these GM events?

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2. Who has been targeted for the commercial cultivation of these GM seeds from these GM events e.g. which farmers in terms of scale, turnover and in which areas of the country?
3. How much seed has already been distributed for commercialization in relation to question 1 and 2 above?
4. If no cultivation has yet taken place, which growing seasons has/ will the seed be cultivated?
5. What plans if any, does CORTEVA have to test for 2,4 residues in foodstuff bound for the local shelves in South Africa?

The response received was as follows:

> "*Please note that the information that you have requested is protected business proprietary and confidential information. As such, we are unable to share the same with you.*
>
> *Thank you for reaching out to us. Please feel free to contact me with any future enquiries*."

Such information is a matter of public interest, particularly since maize is staple crop consumed on a daily basis in this country. There is no justification for such information being withheld from the public. This inappropriate use of CBI fuels mistrust in this untransparent process, and implies the weaponization of CBI as a coverup for a lack of scientific rigour and/or corporate malpractice. Issues such as pesticide residues have legal limits to protect human and environmental health and thus declaring such information is of public interest to ensure safety and integrity of the food system. It is unclear how such information threatens business profits unless providing such information would reveal lack of regulatory oversight or breach of regulations in this regard.

Yet again, information that is very difficult to justify as CBI, is being withheld from the public on matters that have direct implications for their food systems and health, showing complete disregard for the concerns and welfare of the citizenry it is purported to be serving.

5. MOLECULAR CONCERNS

Lack of molecular characterisation to rule out unintended effects

Genetic modification is associated with unintended effects at the level of the genome, transcriptome, proteome and metabolome. For example, studies have shown that expression of Bt toxins Cry1A.105, Cry2Ab2 and EPSPS proteins in GM maize can cause changes in global proteome levels in GM maize varieties, resulting in impacts on metabolic pathways (Agapito-Tenfen et al., 2014). The NK603 parental line has also been shown to have altered proteome and metabolome profiles. Using unbiased 'omics' global profiling techniques to assess such changes, Mesnage et al., (2016) documented altered levels of proteins and metabolites indicative of oxidative stress, alterations in levels of enzymes involved in glycolysis metabolism, as well as TCA cycle involved in energy production in NK603 maize. Metabolome alterations also included a 28-fold rise in polyamines, which play multiple roles in cell growth, survival and proliferation; they can be either toxic in certain contexts.

The transgenic maize also carry genetic elements such as the t-nos terminator and the cauliflower mosaic virus 35S promoter that are associated with the production of novel RNA variants and genetic rearrangements respectively (Ho et al, 1999; EFSA 2009). Finally, the use of the vector *Agrobacterium tumefaciens* has been shown to induce genetic deletions, insertions, chromosomal rearrangements, translocations, scrambling of sequences and epigenetic (chemical modifications of DNA) perturbations (Jupe et al., 2019). This vector was used to develop NK603, and MON89034 parental lines.

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In summary, this transgenic variety has not been adequately characterised at the molecular level. The applicant should be asked to provide further data, including global 'omics' profiling data to ensure a lack of unintended molecular effects that may have health or environmental implications.

Description of the recombinant DNA before and after modification

The transgenic material has been generated synthetically and therefore has no history of safe use in nature. Determining the stability of the transgenic inserts also has safety implications, with genetic rearrangements and deletions being signs of structural instability, which enhances horizontal gene transfer and recombination, with all the attendant risks (Ho MW & Lim LC, 2003). Showing stability of the transgenes is thus important not only to confirm efficacy, but to also rule out potential unintended effects that may have occurred. This is particularly relevant as the molecular analyses have so far revealed a strong tendency for transgenic inserts to land in mobile genetic elements, such as retrotransposons and repeat sequences (Ho MW, 2003). Such instability and non-uniformity would not pass the DUS (distinctness, uniformity and stability) test and could not be considered legal under South African law, which requires proof of stability.

Despite no provision of data to support genetic stability, unsubstantiated claims are nonetheless made in Section 7.3 on the stability and molecular equivalence of the transgenic maize. The application states that the event was assessed by Southern blotting techniques, but no data is provided. It also appears that the lack of data is not due to being redacted from the non-CBI version. Further, Southern blotting techniques would not detect all potential events where the transgenes have been unstable, which would need to be confirmed with additional, more detailed analyses such as DNA sequencing of the insert and flanking genomic DNA regions.

This is particularly important claim to interrogate considering this transgenic event considering that independent analysis of data provided to Indian authorities for parental lines NK603 and MON 89034 found unintended modifications in the inserted transgenic DNA (Then, 2013).

The data provided does not confirm the integrity of the transgene sequences, not does it substantiate claims made by the applicant that the integrated DNA is stable. A detailed description of the sequence of the transgenes should therefore be provided prior to approval of this transgenic maize event.

6. HUMAN AND ANIMAL SAFETY ASSESSMENT

Establishing the food and feed safety of the transgenic maize event is essential considering that maize is not only consumed by humans and animals in South Africa, and is an important staple crop consumed on a daily basis.

A number of claims of safety are made in the safety assessment, that are questionable. For example, the applicant concludes that:
1) GM maize is compositionally equivalent to conventional varieties of maize
2) They proteins produced by the transgenes are not acutely toxic to mammals
3) Have a history of safe use.

However, no toxicology assessments have been performed on this stacked event to substantiate such claims.

Without thorough safety assessments such as chronic toxicological feeding studies, such claims remain unsubstantiated, as detailed below.

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Substantial Equivalence

The principle of 'substantial equivalence' for risk assessment has been criticised for being more of an analytical than scientific exercise that compares arbitrary comparators of GM crops to any variety or composite of varieties of conventional crops, such as levels of total fibre, limited number of minerals, fat and sugar (Ho & Steinbrecher, 1998). **Nonetheless, even this basic compositional analysis presented in the application was a technical failure, with the application stating in Section 8.6.1, that more than 50 % of a total of 63 analytes were below the levels of detection in the experiment and could thus not be measured.**

Further, a number of statistical differences were anyhow found, but the data was not provided in the application. The application states in section 8.6 that: "Although a limited number of statistically significant differences occurred between MON 89034 × TC1507 × MIR162 × NK603 × DAS-40278-9 (unsprayed or sprayed with glyphosate, 2,4-D, glufosinate, and haloxyfop) and the isoline in both combined site and individual site analyses these differences were not considered biologically relevant because the results were within ranges found in non-transgenic maize hybrids included in this study and/or within available literature ranges for non-transgenic maize.

The dismissal of statistically significant differences as not biologically relevant makes a mockery of the risk assessment process that requires such an analysis to inform on potential hazards. Compositional differences are indicative of unintended effects that should be further investigated, rather than conveniently dismissed. More detailed analysis should be performed as part of a precautionary approach to ensure the safety of this product. For example, 'omics' profiling techniques that look at thousands of genes, proteins and metabolite expression levels can provide a more detailed and unbiased analysis that can more adequately inform the risk assessment process. Indeed, substantial non-equivalence has been found with the parental line NK603, with levels of potentially toxic polyamines (Mesnage et al., 2016). Other GM crops have also been shown to be substantially 'non-equivalent' (Peng et al., 2019; Abdo et al., 2013; Bøhn et al., 2014; Agapito-Tenfen et al., 2013).

As a result of misinterpretation of limited and incomplete substantial equivalence data, the applicant also failed to perform any animal feeding studies, claiming that there are no indications that the GM variety is not nutritionally equivalent. As such, there is basic information that would normally be supplied in a GM application that remains missing. This is a negligent approach from the applicant, with whom the burden lies to substantiate any claims of safety.

We urge that the applicant be asked to address failures to provide the required information demonstrating nutritional and compositional equivalence of this MON 89034 × TC1507 × MIR162 × NK603 × DAS-40278-9 maize event.

Toxicology

No data was provided by the applicant on any feeding studies performed in mammals. No data appears to exist for feeding studies using the whole plant.

The applicant justifies the lack of safety testing performed on the GM variety based on the prior regulatory approval of the parental varieties. For example, section 8.1 states "MON 89034 × TC1507 × NK603 × DAS-40278-9 maize has been granted both cultivation (2019) and commodity clearance (2016) approvals in South Africa. Additionally, MON 89034 × TC1507 × MIR162 × NK603 maize has been approved for commodity clearance in South Africa in 2018. Therefore, all the proteins expressed in MON 89034 × TC1507 × MIR162 × NK603 × DAS-40278-9 maize are already present in human and animal food chains."

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Independent research however challenges claims by the applicant that newly expressed proteins present in the transgenic variety have a 'history of safe use', based on empirical data gathered from *in vivo* animal studies, instead of untested assumptions made by the applicant. For example, studies have now linked Cry toxins to immunogenic reactions in mammals. Cry1Ac (which shows some similarity to Cry1A.105) is known to enhance immune reactions Vásquez-Padrón et al., 2000), and thus be potentially allergenic. Several Bt toxins have been shown to be haematoxic, and also to have potential impacts on human health (Shimada et al. 2003; Huffmann et al. 2004; Ito et al. 2004; Mesnage et al. 2012; and Bondzio et al. 2013). Cry toxins have also been shown to survive mammalian digestion, being detected in mice intestines, going against claims that exposure and thus toxicity, is limited (Vázquez-Padrón et al.,1999).

Combinatorial effects may also occur due to interactions between the novel transproteins and metabolites produced in the stacked variety. For example, having multiple Bt toxins may have cumulative or synergistic effects on non-target organisms. This is the basis for the EU regulation that requires risk assessment of stacked traits which defines a stacked event derived from conventional breeding of existing single event GM varieties as a "new entity" (Regulation (EC) No 1829/2003). It takes into account the possibility of stacked varieties showing disturbances in transgene and host genome stability, expression of novel proteins, and potential synergistic/ combinatorial interactions between the individual modifications. Such interactions in stacked events have been documented in stacked maize that carries both Bt toxins and glyphosate tolerance, showing alterations of transgene expression in the stacked versus single event lines (Vilberte et al., 2016).

Without chronic long-term feeding studies and more detailed toxicological tests that encompass parameters such as immune responses, reproductive toxicity, effects of pesticides, combinatorial effects of multiple transgenes, such conclusions of safety cannot be drawn for any of the three GM maize varieties.

7. HERBICIDE TOXICITY

As ACB has previously raised, there is wide scientific consensus on the human toxicity of herbicides, and their unsustainable use in agricultural systems. The failure of GM crops to perform their purported function of herbicide tolerance is now leading to ever increasing combinations of transgenic traits allowing for crops such as MON 89034 × TC1507 × MIR162 × NK603 × DAS-40278-9 to be tolerant to four herbicides at once. Not only is this a clear example of the futility of a GM approach to food production; their failure is having a direct adverse impact on the safety of our food.

Glyphosate herbicides have been widely associated with increased incidence of cancers, birth defects and reproductive toxicity. Toxicity is well documented in both industry and independent data. Most recently Bayer, formally Monsanto, lost two high profile court cases in the US where Monsanto was found guilty of not warning of the cancer risks of glyphosate herbicides that had resulted in two people suffering from NHL. Nearly 100,000 further cases are pending (Reuters, 2020). Just this month, new studies in major journals have been published showing reproductive toxicity effects including impairment of egg development in pigs (Spinaci et al., 2020), and impair female fertility in rats (Lorenz et al., 2020), both linked to hormone disruption.

2,4-D, one of the two ingredients in 'Agent Orange' war chemical used to have a devastating effect in the Vietnam war, is also widely associated with adverse health effects including developmental and reproductive toxicity as a result of hormone disruption. 2,4-D has been linked to increases in birth abnormalities in high use areas in the US (Garry et al., 1996). Consistently, 2,4-D has been suggested to interfere with male reproduction, with effects including disrupted testosterone levels and spermatogenesis; reduced mortality of human sperm; and increased sperm abnormalities in farm workers (Swan, 2003; Lerda & Rizzi 1991),

13 The Braids, Emmarentia, 2195
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reduced testosterone and increased leutinising and follicle-stimulating hormones in male rats (both involved in male and female reproduction).

While glufosinate is claimed by the applicant to be included purely as a genetic marker used in the laboratory process, they also reveal that field trials did indeed test the use of glufosinate on this crop, suggesting it may also carry glufosinate residues. It's therefore is unclear what herbicides will be applied to thus crop and what the public will thus be exposed to if the crop is approved. Glufosinate has also been shown in many studies to have adverse effects on humans, with some government agencies including in the EU authorities, restricting its use since 2013 Herzine et al., 2002; Calas et al., 2008; Meme et al., 2009; Lantz et al., 2014; Laugeray et al., 2014; García et al., 1998).

Pesticides have also been linked more broadly to metabolic disease, including diabetes and obesity, thought to be at least in part linked to the hormonal disruption caused by pesticides, including herbicides such as glyphosate. The increased processing of foods also exposes people to endocrine disruptors in plastics, such as BPA. Indeed, there is increasing evidence that early-life exposure to environmental chemicals may play a significant role in the obesity epidemic (Hu et al., 2015; Rancière et al., 2015; James-Todd et al., 2016; Nelson et al., 2009; Grün et al., 2006). Such environmental chemicals are thus serving to exacerbate the deadliness of the current COVID-19 pandemic. Increasing the chemical burden of our foods is thus exactly the opposite direction we need to take for successfully recovering from the pandemic and ensuring long-term health resilience at a population level.

As widely acknowledged, the COVID-19 pandemic has laid bare societal dysfunctions including the underlying dietary and agricultural factors that contribute to disease risk and food insecurity. The pandemic has shone a light on the effects of sub-optimal nutrition fuelled by Westernised models of industrial agriculture and the concomitant inadequate nutrition it provides. Improving metabolic disease burden is urgently needed to avert further COVID-19 disease burden as well as the rising burden of non-communicable disease (Lancet, 2020). COVID-19 is a stark wake-up call to take action to change course with the models of food and agriculture that can promote health to not only combat communicable diseases such as COVID-19, but also the rising burden of non-communicable disease (NCD), with both tending to co-exist together. South Africa is increasingly suffering the double-burden of obesity and malnutrition. As reported by Tydeman-Edwards et al (2018), "The nutrition transition is characterised by a shift from traditional diets towards a more westernised diet. Although lower in variety, traditional diets tend to be higher in fibre and lower in fat, sugar and salt, resulting in a low prevalence of NCDs, whereas the Western diet is associated with an increased risk for developing NCDs". Such stark reminders brought to us by the COVID-19 pandemic provide the urgent opportunity to shift away from a food and agricultural model that serves no-one but private corporations, who continue to profit from furthering health, food and environmental crises that can and should be halted to support a healthy population that can withstand and combat the current shocks to our bodies and planet.

8. CONCLUSION

The ACB firmly rejects the approval of MON 89034 x TC1507 x MIR162 x NK603 x DAS-40278-9 to enter South Africa for commodity clearance, based on inadequate evidence of safety to human health.

We urge that the authorities take a precautionary approach in protecting reject these varieties to protect people and the environment.

Double burden of obesity and malnutrition. https://www.who.int/nutrition/double-burden-malnutrition/en/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6278724/ obesity/malnutrition in S Africa

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13 The Braids, Emmarentia, 2195
P.O. Box 29170, Melville, 2109, Johannesburg, South Africa.
Telephone +27 11 486 2701 – Fax +27 11 486-1156
https://acbio.org.za/
NPO No. 57324 Registration No. 2004/025/37/08
Directors: M S Mayet; F Diedhiou; R D Marema; J P W Wilson; M B Orovwuje; R J Partridge