Friends of the Earth

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Comments Submitted to the USMCA Secretariat on Behalf of Friends of the Earth
Transmitted via email to: ssmtlc@economia.gob.mx

Dear Secretariat,

We appreciate the invitation to provide comments assessing the environmental and human health impacts of the phaseout of glyphosate-based herbicides (GBH) and the GE White corn decree. Our comments are on behalf of Friends of the Earth United States (FOE). The authors are Dr. Kendra Klein, FOE Deputy Director of Science, and Dr. Charles Benbrook. No funding was received in support of these comments nor compensation paid.

Chronic Disease Concerns

Strong evidence confirms the rising frequency of serious adverse impacts on public-health in Mexico driven by declining food and diet quality. A global study of trends in ultra-processed food (UPf) sales from 2006 to 2024 reported a 38% and 32% increase in UPf and UP beverage sales in Latin America and the Caribbean. Chronic diseases trigger ~60% of deaths in Mexico, and account for 71% of disability-adjusted life years. The prevalence of overweight and obesity is among the best indicators of likely future health care costs. The rate of overweight and obesity among males over 20 years of age in Mexico ***increased from 29% in 1980 to 66.8% in 2013, and from 33% to 71.4% among females***.[1] Diabetes rose from 5.7% to 9.1% of the population from 2000 to 2012, or 60%.[2] Four chronic diseases linked to food quality and dietary choices[3] account for an estimated 88% of total chronic disease health-care expenditures in Mexico. Chronic kidney disease is the most expensive, leading to ~$9,000 in treatment costs per case. In 2012, arterial hypertension and gastritis were the two most common chronic problems, accounting for 32% and 22% of cases respectively.

In the U.S., glyphosate (GLY) exposures have been linked to fatty liver disease. A study by Mills et al. (2019) reported "a significant ***dose-dependent increase*** of glyphosate exposure with increase in fibrosis stages." Han et al. (2024) report an association between GLY and an index of the severity of fatty liver disease, especially among diabetic women. In a rat study testing very-low chronic doses of GLY, Mesnage et al. (2017) confirmed "substantial [glyphosate exposure] overlap with biomarkers of non-alcoholic fatty liver disease." The kidney is also a sensitive organ among people exposed to GLY (Wang et al., 2019). A 2022 study reported that people exposed to GLY and its metabolite aminomethylphosphonic acid (AMPA) face heightened risk of kidney damage at levels of exposure common in North America (media level in urine of 0.33 ug/g creatine adjusted GLY and 0.17 ug/g adjusted AMPA). The tubes in kidneys through which GLY passes on its way to excretion via urine are particularly sensitive to GLY-induced damage to DNA that can lead to cancer.

[1] Webtable 9, supplemental material in Ng et al, (2014) *Lancet*.
[2] Data on disease prevalence and costs from Figueroa-Lara et al (2016) *Plos One*.
[3] For the definitive analysis of food-diet-health risks, see the Institute for Health Metrics and Evaluation paper at https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)30041-8/fulltext

Core Elements in an Appropriate Risk Assessment of GE Corn

The three principal attributes of an "appropriate" genetically engineered (GE) food risk assessment are set forth in the WTO SPS Agreement, Article 5.7, as well as in the USMCA, NAFTA, and other agreements governing food safety. ***First***, an "appropriate" risk assessment must designate the food that is transformed and the purpose and nature of the transgene created to move novel traits into the food. ***Second***, it must accurately estimate human exposure levels to whatever toxins and chemicals are associated with a GE crop, taking into account dietary intake levels and variation in GE-trait expression. ***Third***, it must identify the hazards known or possibly associated with human exposures to a GE crop's toxins and associated pesticides, as well as the dose-dependent risks of adverse health impacts among the general public and vulnerable population cohorts (e.g. pregnant women, infants/children, people who are immunocompromised or battling chronic disease).

Limitations of Risk Assessments of Contemporary GE Corn Varieties

No existing GE corn risk assessment has assessed the adverse public-health impacts of concern in Mexico. An "appropriate" risk assessment would evaluate the individual and combined impacts of the specific herbicide-tolerant and *Bt*-transgenic or Vegetative Insecticidal Protein (VIP) (hereafter *Bt*/VIP) traits introduced in corn hybrids. Yet, existing GE-corn risk assessments focus predominantly on one event at a time. A total of 49 industrial GE corn cultivars are listed in the 2023 "Handy Trait Table" as shown in Table 1. On average, each expressed 2.5 herbicide traits and 3.6 *Bt*/VIP traits for control of insects. But varieties expressing 4-7 *Bt*/VIP traits now account for greater market share than those expressing 1-3 toxins, so the average number of *Bt*/VIP toxins expressed in today's varieties likely is around 4.5. Four cultivars were engineered to tolerate 10 herbicides, and 15 express five to seven *Bt*/VIP toxins. ***Two expressed a total of 17 GE traits***.

The majority of contemporary GE corn events went through minimal food-safety regulatory reviews in the U.S. in the early 1990s through the 2000s. None were destined for direct human consumption, so there was no reason to conduct a thorough human dietary risk assessment. Tests that were done explored nutrient composition, stability and digestibility, and acute toxicity. The test substances were rarely the actual *Bt*/VIP toxins expressed in corn plants, but rather an alternate version extracted from GE cell cultures. Allergenicity was often the sole focus of human health risk assessments, especially after publication of a 1999 study that found IgE-antibodies against a *Bt* endotoxin in farmworkers exposed to *Bt* sprays. The majority of published studies focused on animal growth, feed efficiency, and reproduction related to corn as livestock feed. Corn oil and high-fructose corn syrup extraction essentially eliminates *Bt*/VIP toxins from the human food supply.

But corn is the caloric backbone of the Mexican food supply, accounting, on average, for ***50% of the calories and protein in the Mexican diet*** (Table 2, p. 18, MX Written Submission). Given these averages, it is near-certain a segment of the MX population consumes 70% or more of calories from corn on some days. Caloric intake from white corn in MX exceeds the level in the U.S. by 10-fold or more, based on Food and Agriculture Organization (FAO) data.[4] In addition, native corn consumption in MX is mostly minimally processed in ways

[4] FAOSTAT "Food balances" dataset, year 2021.

Table 1. Number of GE Traits in 49 Corn Cultivars in the 2023 "Handy Trait Table"			
	Number Cultivars	Percent of Total	Number Traits
Herbicide Tolerance			
No HT Traits	0	0%	0
Glyphosate (GLY) only	7	14.3%	7
GLY + Glufosinate	38	77.6%	76
GLY+GLUF+2,4-D+FOPS	4	8.2%	40
Total	49		123
Average per Cultivar			2.5
***Bt* /VIP Traits**			
One	4	8.2%	4
Two	12	24.5%	24
Three	14	28.6%	42
Four	4	8.2%	16
Five	6	12.2%	30
Six	4	8.2%	24
Seven	5	10.2%	35
Total	49		175
Average per Cultivar			3.6
Notes:			
1. Access "Handy Trait Table" at https://www.texasinsects.org/uploads/4/9/3/0/49304017/bttraittable_feb_2023.pdf			
2. "FOPS" is the aryloxyphenoxy propionate family of herbicides that contains 7 distinct active ingredients.			
3. Each herbicide that a cultivar is engineered to tolerate is considered a trait. The same applies to *Bt* and VIP toxins.			

that increase the bioavailability of nutrients overall,[5] but not all nutrients.[6] Minimal processing also increases the portion of the *Bt*/VIP toxins and herbicide residues in GE white corn that likely finds its way into corn-based human foods.

In MX, native corn has been selected over centuries on the basis of cooking qualities and compatibility with certain preparations, plus resistance to pests, local soils, elevation, and climatic conditions. In the U.S., farmers select industrial yellow corn varieties on the basis of yield and GE, pest-management related traits.

Prior to commercial sale, each GE corn event is subject to a limited, voluntary regulatory review by the US Food and Drug Administration (FDA). The FDA's "New Plant Variety Consultations" entail submission of data that:

- Characterizes the transgene and the intended effects of the DNA added to a non-GE corn isoline,
- Documents nutrient composition, stability, digestibility, and the possible presence of allergens, and
- Describes food and animal feed uses and/or industrial uses and attributes (ethanol, corn oil, high fructose corn sugar).

The documents and study results submitted by technology developers also state the company's conclusions regarding substantial equivalence, allergenicity, and food safety. Upon review of submitted data, approval is based on the FDA's ***acceptance of assertions and conclusions articulated by technology developers***. For example, an FDA "Note to the File" dated March 20, 2013 explains the basis for approval of Pioneer's yellow corn Event 4114. This event renders corn tolerant of glufosinate (via the PAT gene) and able to express Cry1F, Cry34Ab1, and Cry35AB1 targeting corn insects. The four-page FDA memo includes statements like:

- "Pioneer confirmed the genomic stability of the inserted DNA…",
- "Pioneer reports data on sixty-nine components…",
- "Pioneer concludes that this analysis supports the conclusion that forage from event 4114 corn is compositionally equivalent to conventional corn forage", and
- "Pioneer thus concludes that these differences [in certain nutrients, e.g. ash, phosphorous, potassium, and eicosenoic acid] are not biologically meaningful to food and feed safety."

In addition to FDA's "Note to the File" discussing submitted data, each GE event consultation concludes with a letter from the FDA. The first paragraph briefly describes the event, the transgene, and the purpose served via

[5] Fernandez-Suarez et a. "Importance of Mexico's native corn in the national diet. An indispensable review." *Mexican Phytotechnics Magazine*, 2013.

[6] De La Parsa et al. (2007) that report nixtamalization of corn reduces the concentration of some phytochemicals but increases phenolics, ferric acid, and some other nutrients.

insertion of foreign DNA. It states that the technology developer summarized a data package on the event and notes any additional information sought by FDA. Then, this key passage appears in essentially the same form in all event-specific FDA approval letters:

> "Based on the safety and nutritional assessment ***Pioneer has conducted***, it is our understanding that ***Pioneer has concluded*** that human and animal food from DP915635 corn are not materially different in composition, safety, and other relevant parameters...[and] does not raise issues that would require premarket review or approval ***by the FDA***."

The U.S. Department of Agriculture (USDA) review of Event 4114, and all other events, did not address food safety, and instead focused on whether it might become a "plant pest". The U.S. Environmental Protection Agency (EPA) addresses issues related to pest resistance management, food tolerance exemptions for GE toxins, and non-target impacts. Accordingly, the premarket reviews of all corn events now on the market have not included levels of human exposure to the associated herbicides and *Bt*/VIP toxins, nor animal studies designed to detect adverse health impacts of any sort. ***Such assessments were deemed unnecessary as long as technology developers asserted that foods derived from GE crops would be substantially equivalent in composition to non-GE foods.*** The short-term toxicology tests undertaken mostly in rodents were designed to detect significant impairment of growth or overt signs of acute toxicity. U.S. government agencies developed no data useful in assessing event-specific human health impacts.

Hence, the original approvals of GE corn events at issue in this dispute were conducted by and reflect:

- The scientific judgements of the companies developing the events and bringing them to market,
- Company decisions regarding what data to generate and share with government agencies,
- Each company's standards, thresholds, and statistical methods for delineating whether compositional differences exist (typically the case) and whether such differences are biologically meaningful (rarely the case, according to the companies), and
- Decisions by technology developers regarding which risks warranted assessment and by what testing methods and study designs, as well as the exposed populations and routes of exposure to be studied.

Several essential elements of an appropriate risk assessment were not included in the premarket testing and reviews of the GE corn events in question in this dispute. The adverse impacts of concern today in the wake of substantial human consumption of *Bt*/VIP toxins and herbicide residues – reproductive, developmental, neurological, metabolic, microbiome, GI tract-related – have not been addressed in a meaningful way in the FDA consultation process, or via any other process in the public or private sector.

Much has changed since the events in contemporary GE corn varieties were subject to the limited FDA consultation process. Most went through the process in the 1990s and 2000s before independent research had produced substantial data calling into question many of the core assumptions on which GE-event food-safety evaluations were grounded. Most events were evaluated as standalone genetic modifications, one event corresponding to a single trait. But as weeds resistant to GLY and glyphosate-based herbicides (GBHs) emerged and spread beginning in the early 2000s, and populations of insects became resistant to early *Bt* toxins, technology developers brought to market hybrids with stacked GE traits (see Table 1).

For years technology developers have asserted that if each single event was accepted by FDA as purportedly safe, then ***any combination of multiple events in a new hybrid would also be safe***. Remarkably, the FDA has simply assumed this assertion is valid, despite the fact that many scientists do not. In 2009, the EPA's Scientific Advisory Panel (SAP) held a meeting on "Data Required to Register Plant-Incorporated Protectants [PIPS, i.e. *Bt*/VIP toxins]". In its final report discussing "Charge Question C.1", the Panel concluded that "… testing for synergistic effects when two or more PIPs are combined is warranted … for human health and non-target organism effects." But still, in the U.S., no meaningful steps have been taken to develop such testing methods. To date, cumulative exposures to multiple toxins and herbicide residues associated with modern GE corn have not been explored in studies designed to assess possible adverse reproductive, developmental, neurological, or epigenetic impacts.

Intensification of Industrial GE Corn Production

The scope of GE-corn human health risk assessments have failed to evolve in step with the intensification of industrial corn production, and in particular, changes in the mix of *Bt*/VIP toxins and herbicide-tolerant traits in specific cultivars. The near-doubling of average corn seeding rates since the late 1980s from ~20,000 to nearly 40,000 seeds per acre has been among the most consequential changes in terms of yields, pest pressure, the need for fertilizers, and plant health problems.

An important 2023 academic paper assessed 73 cases of *Bt* resistance in insects targeted by *Bt*/VIP transgenic crops over the last 25 years. The team identified just 3 insects with *Bt*-induced resistance in 2005, but 26 in 2020, plus another 17 displaying early signs of resistance. The authors conclude that *Bt* corn and cotton varieties have "produced some spectacular successes and ***disappointing failures in terms of durable success***." There is only one GE corn event (Vip3Aa) that is still fully or mostly effective against corn earworm. Accordingly, if MX were to widely plant GE corn, ***insect control benefits would likely be short-lived, but the contamination of germplasm would be essentially permanent***.

The emergence and spread of weeds resistant to GLY was predicted upon commercialization of Roundup Ready crops in 1996. By the mid-2000s, several resistant weeds had emerged, plaguing US farmers. A seminal December 2023 paper by 26 US-based weed scientists identified 354 confirmed cases of 57 GLY-resistant weed species "primarily confined to GR [glyphosate resistant] crop systems." As a direct result, the number of herbicides applied on GE corn acres has risen more than 50% since the 1990s, and nearly doubled in terms of acre-treatments.[7] Corn herbicide costs often now exceed $100 per acre in the U.S. Total seed-plus-chemical costs in GE-based systems have ~tripled since 1996. Fortunately, alternatives to herbicide-centric weed management systems have thrived for centuries in Mexico, and more are emerging. The decree phasing out use of GBHs has played a role. On farms, necessity is indeed a mother of invention.

Because of slipping plant health and heightened disease pressure, fungicide use on corn in the U.S. has also risen sharply. Prior to 1997, less than 1% of corn acres was sprayed with a fungicide. By 2009 about 10% was treated and today, around 40% is sprayed with one or more fungicides. In addition, reliance on pesticidal seed

[7] For a given corn-pesticide combination, acre-treatments are calculated by multiplying the percent of corn acres treated by total corn acreage planted, and then by the average number of applications made with a given herbicide.

treatments targeting fungal pathogens and soil-borne insects has markedly grown from, on average, ~1 per acre in 1996 to ~4.5 today. Table 2 draws upon USDA data to estimate the number of pesticides and GE toxins used to bring a corn crop to harvest from 1971 to 2023.

Table 2. Number of Pesticides and Pesticidal Compounds Used per Hectare/Acre to Manage Corn Pests in the US: 1971-2023

	1971	1990	1995	2000	2005	2010	2015	2020	2023
Herbicides	1.09	1.82	2.31	2.73	2.60	2.69	4.21	3.68	3.8
Insecticides	0.37	0.25	0.31	0.34	0.29	0.14	0.39	0.15	0.2
Fungicides			0.00	0.04	0.07	0.11	0.20	0.36	0.4
Bt/VIP toxins				0.19	0.47	1.37	2.43	3.68	4.5
Insecticide Seed Treatments	0.30	0.50	1.00	1.40	1.90	2.00	2.00	2.11	2.2
Fungicide Seed Treatments			0.30	0.80	1.20	1.50	2.00	2.17	2.3
All Pesticides and Toxins	1.8	2.6	3.9	5.5	6.5	7.8	10.2	12.2	13.4

Notes:

1. Use data is from the "Pesticide Use Data System" (PUDS; https://hh-ra.org/projects/measuring-pesticide-use/pesticide-use-data-system/). Data in PUDS is from the U.S. Department of Agriculture.
2. Data for 2023, seed treatments, and *Bt* /VIP toxins are projected by Benbrook Consulting Services.

In the 26 crop years since the introduction of GE-based industrial corn production systems in 1996, the need for pesticides and toxins on the average corn hectare has risen from ~4 to over 13, whereas the number increased from 1.8 to ~4 in the 25 years between 1971 and 1996. The increase of about 2 pesticide applications over 25 years (1971-1995), compared to the increase of 9 over the next 25 years, is worrisome. Rising reliance on pesticides and toxins in corn production has diversified the routes and levels of human exposure to both. Despite the absence of the data and knowledge needed for a full accounting, this increase has surely led to new and more serious adverse impacts on human health and the environment. Yet in the U.S., the scope and adequacy of scientific research and regulatory oversight of GE-corn human health impacts has receded in the wake of persistent political pressure for "regulatory relief".[8]

Presence of *Bt* Endotoxins and Herbicide Residues in Corn

For corn events approved in 2002-2007, a paper published by a team of Mexican scientists in 2017 reported the presence of one or more of eight transgenic DNA markers in 82% of 367 corn-based products[9] (tortillas, tostadas, cereal, flour, and snacks). Over 80% of Mexicans incorporate tortillas or tostadas in their daily diet. Out of 209 samples of tortillas, 282 positives were detected for Cry1ab and Cry1Fa2 events, or 1.3 per sample. Substantial differences existed in the presence of markers of *Bt* transgenic events in industrial versus native corn samples. Across 25 samples of industrial corn flour, 32 markers of *Bt* transgenic events were detected. No samples of native corn flour contained *Bt* markers. A *Bt* event was present in 30% of native food samples, compared to 1.4 per sample of industrial food. Accordingly, ***Bt markers were 4.7-fold more common in industrial versus native corn-based foods***. The results would almost certainly be different today if a comparable sample of white-corn-based foods in MX were tested using methods capable of detecting all GE events in contemporary varieties.

[8] For example, the U.S. government has required no testing of stacked varieties, and exempted many CRISPR and related gene silencing technologies from the need for regulation. The EPA dropped requirements for refuge acres not planted to *Bt* corn, a critical component of *Bt* corn resistance- management plans.

[9] The maize-based products were selected between 2013 and 2015 from across several regions in order to encompass the diversity of corn-based food systems and dietary intake in MX. The products were composed of 90% or more corn.

Bt/VIP expression levels in yellow and white corn kernels for contemporary corn varieties are not available because the U.S. government has not required such data, and industry has chosen not to publicly disclose this key information.[10] Hence, it is not possible to produce an accurate estimate of *Bt*/VIP exposure levels across the corn-based products consumed in MX. Furthermore, expression levels vary across hybrids, regions, and growing conditions, creating variability that leads to significant data gaps that must be overcome in carrying out appropriate risk assessments of the potential human health impacts of GE corn cultivars. Available, sometimes dated event-specific data on *Bt*/VIP levels in corn grain is summarized in Table 3.[11] For *Lepidoptera* insect control, the ~79,000 corn plants on a hectare (32,000 seeds per acre) produce between 1.0 and 6.0 ug/g (ppm) of Cry1 and Cry2 proteins in grain kernels, and 9 to 100 ug/gram of Cry3 and VIP toxins targeting corn rootworms. According to the EPA's Vip3Aa20 decision document, "Estimates of mean Vip3Aa20 quantities in transgenic plants were ***highest on a per acre (and per hectare) basis at seed maturity."***

Table 3. *Bt* and VIP Toxins in GE Corn and per Land Area Planted by Major Events and Products Circa 2010 (see notes)

Product Name	Event	Cry/VIP Protein	Cry/VIP per Plant (ug)	Cry/VIP in Grain (ug/g FW)	Cry Protein (kg/ha)	Cry Protein (lb/acre)
Syngenta Agrisure® CB	*BT* 11	Cry1Ab	4,321	5	**0.283**	**0.252**
Monsanto YieldGard® Corn Borer	MON 810	Cry1Ab	2,594	<1	**0.205**	**0.183**
Monsanto YieldGard VT™ Rootworm	MON 88017	Cry3Bb1	7,830	9	**0.619**	**0.551**
DowAgrosciences Pioneer Hi-Bred Herculex® I	TC1507	Cry1F	1,372	2	**0.108**	**0.097**
Dow AgroSciences Pioneer Hi-Bred Herculex® RW	DAS 59122-7	Cry34Ab1	29,023	50	2.294	2.042
		Cr35Ab1	6,392	1	0.505	0.45
		Totals		**51**	**2.799**	**2.492**
Monsanto Genuity™Smart-Stax™, DowAgrosciences SmartStax™	MON 88017	Cry3Bb1	9,551	9	0.755	0.672
	MON 89034	Cry1A.105	3,634	6	0.287	0.256
		Cry2Ab2	5,111	1	0.404	0.36
	TC 1507	Cry1F	1,598	2	0.126	0.112
	DAS 59122-7	Cry34Ab1	27,272	50	2.156	1.918
		Cr35Ab1	5,861	1	0.463	0.412
		Totals		**69**	**4.191**	**3.73**
Syngenta Agrisure Viptera	MIR162	Vip3Aa20	75 ug/g FW	**100**		

Notes and Sources:

1. Expression rates from EPA documents and Table 14.5 in Schnepf, E. (2012). "Chapter 14. *Bacillus thuringiensis* Recombinant Insecticidal Protein Production", In: Sansinenea, E. (eds) Bacillus thuringiensis Biotechnology. Springer, Dordrecht. https://doi.org/10.1007/978-94-007-3021-2_14. FW is Fresh Weight.
2. Corn planting rates used to calculate Cry protein expression quantities per hecatre and acre were 79,040 and 32,000 seeds for all events except *Bt* 11 (65,000 and 26,5000).
3. Amount Cry and VIP protein per plant as reported in EPA documents or estimated from available data.

Residue levels of *Bt*/VIP toxins in corn grain – 2 ppm to 100 ppm -- ***exceed maximum food tolerances for widely used corn insecticides by 40- to 2,000-fold*** (most tolerances governing insecticide residues in corn grain are 0.05 ppm or less). Likewise, several contemporary GE corn varieties express 50- to 100-fold more *Bt*/VIP toxin per hectare compared to typical corn insecticide application rates.

In addition to multiple *Bt*/VIP toxins, GE corn also often contains GLY residues. In 2022 testing by the USDA,[12] residues of GLY were present in 73 of 309 samples of corn grain (24%) at an average level of 0.06 ppm (max value of 0.12 ppm). Monitoring by the FDA in recent years has identified GLY in corn in ~60% of samples, and GLY/AMPA were by far the most common residues detected in animal feed. In testing carried out in 2013-2015 in MX, Gonzalez-Ortega et al. report that 27% of corn-based products tested positive for GLY or AMPA.

[10] Expression level data are routinely generated by seed companies because it plays a direct role in projecting trait performance.

[11] Event-specific data packages submitted to the USDA and EPA typically contain tables of data reporting Cry and VIP expression levels in various tissues. Some but not all such tables include levels in corn grain/kernels. Few independent studies have quantified such levels as the production season progresses; one important exception is Nguygen and Jehle (2009) "Expression of Cry3Bb1 in transgenic corn MON88017" *J Ag Food Chem.*

[12] Corn data is from Appendix C in "Pesticide Data Program Annual Summary: Calendar Year 2022"; mean level calculated by C. Benbrook in the Dietary Risk Index system.

Critical and Emerging GE Corn Human Health Risk Factors

Today, an appropriate GE-corn human health risk assessment must consider the potential for adverse health outcomes triggered or made worse by interactions across and among the *Bt*/VIP toxins and herbicide residues in contemporary GE corn-based foods. Such risks have changed dramatically over time in step with increases in the number and quantity of herbicide residues and *Bt*/VIP toxins present in GE-derived corn grain and corn-based foods. And risks in MX are far greater than in the U.S. because corn-based products in MX are so much more heavily consumed in minimally processed forms.

The question before the tribunal is whether current U.S., MX, and international approvals of GE yellow and white corn are supported by appropriate risk assessments in light of emerging science and given that human-food corn varieties account for 50% of average daily caloric intake in MX. The U.S. position is that the single-event risk assessments done in the 1990s-2000s at expression levels in corn grain kernels generally below 6 ppm were, and remain, adequate today when widely planted GE corn cultivars express 50 to 100 ppm of *Bt*/VIP toxins in grain. Regulators in the U.S. assume that if a trait was judged substantially equivalent and safe in isolation, ***it will remain so in any and all stacked varieties regardless of how many transformation events and traits are packed into a given GE hybrid***. This extremely dubious assumption was endorsed by GE-corn technology developers but challenged as risky and lacking scientific merit by the previously quoted EPA Scientific Advisory Panel that recommended additional safety assessments of stacked-trait corn cultivars.

Corn varieties expressing multiple *Bt*/VIP and multiple herbicide-tolerant traits pose novel food safety risks, unintended pleiotropic effects,[13] and nutritional aberrations. Over decades, corn breeding has reduced protein levels, a trend that has continued in the GE corn era. The nutritional superiority of non-engineered white and colored corn has been demonstrated in phenolic compounds, total antioxidant activity, and fiber (Colin-Chaves et al., 2020). In a section entitled "GM Crops: An Imperfect technology," Raman (2017) writes that problems with GE foods "…could be caused by inserted gene products and their potential pleiotropic effects,[14] the GMO's natural gene disruption or a combination of both factors." Unintended genetic effects can arise from expression of foreign DNA in multiple or wrong places, disruption of signal pathways that undermine normal plant responses to biotic or abiotic stresses,[15] and altering non-target gene expression in ways that undermine plant health and/or food safety.

A 2000 FAO/World Health Organization reports states that: "In the future, genetic modifications of plants are likely to be more complex perhaps involving ***multiple between-species transfers*** and this may lead to an increased chance of unintended effects … the possible implications of the differences with respect to health need to be considered." The U.S. National Academy of Sciences has also noted the need for more rigorous food safety assessments of stacked varieties and has called for making compositional and expression data on

[13] Pleiotropic impacts arise when a change in a gene brings about changes in gene expression and fitness beyond the primary, intended impact of the genetic change. GE crops are known to trigger a long list of pleiotropic impacts.
[14] Most GE corn events have been created with Agrobacterium tumefaciens, an erratic transformation vehicle (see Jupe el al).
[15] These changes can alter the nutrient composition of harvested seeds, impair a crop's ability to respond to unfavorable growing conditions, and increase yield variability caused by drought, cold, excess water, pest pressure, and nutrient imbalances.

all GE cultivars public.[16] Unfortunately, the testing and food safety assessments called for in the 2000s by the FAO/WHO, NAS, and the EPA's Scientific Advisory Panel have not been acted upon in the case of ***any high-expression level, stacked corn variety***. Nearly all existing GE corn animal feeding studies have been short-term and incapable of detecting subtle, chronic effects. Future animal studies assessing exposures to the multiple toxins and pesticides associated with modern-day GE corn cultivars must go beyond traditional endpoints via an integrated experimental design (e.g. see the Global Glyphosate Study).

The GI tract is vulnerable to a range of adverse health impacts following exposures to GLY and/or Cry or VIP toxins. The antimicrobial activity of GLY disrupts the bacterial microbiome in humans and other mammals, while *Bt* endotoxins can damage the lining and functionality of the stomach and intestines.[17] A study in mice found that the Cry1Ac protoxin binds to the mucosal surface (brush border membrane vesicles) of the small intestines, thereby possibly affecting its electrophysiological properties and permeability. Another team working on Cry1Ab reported significant changes in the lower intestines of rats and concluded that "consumption of GM-corn profoundly alters the jejunal histological structure." These findings are important since Cry1A toxins kill lepidopteran insects by binding to the same brush border membrane vesicles in the gut of insects, increasing membrane permeability. A study published in 2021 noted that some Cry proteins can stimulate the immune system and the response "can be as potent as that elicited by cholera toxin." Some Cry proteins are, in fact, being developed as adjuvants in human and animal vaccines. Finally, a 2017 study found that increased exposure to *Bt* crops (primarily maize) led to increased prevalence of antibodies against Cry toxins***. About 8% of Americans in this study had IgG antibodies against Cry1Ac***, clear evidence this *Bt* toxin was mostly intact after passing through the human GI tract.

Such impacts would likely be more pronounced in MX where maize accounts for such a large share of daily caloric intake. Plus, ***almost all of the short-term in vivo animal feeding studies to date have been done with Cry1 and Cry2 toxins expressed between 1 ppm and 6 ppm in corn kernels (see Table 3), as opposed to most of today's GE corn cultivars in which 50-100 ppm of one or more Bt/VIP toxins are present in corn grain at harvest***. One paper calls for "additional long-term (up to two years) animal feeding studies…in at least three distinct species" and routine monitoring of expression levels "in distinct GMO cultures."

Existing GE corn trait approvals rest upon FDA acceptance of industry claims that the events are "substantially equivalent" to non-engineered crops. Independent analyses of industry-submitted data suggest otherwise. In recent years, genomic sequencing has allowed more sensitive studies of the impacts of GE transformation events. Papers have reported multiple, meaningful differences in a variety of proteins and enzymes driving plant development and metabolism (e.g., see Colin-Chavez et al., 2020 and Mesnage et al). Such new science drives home that the notion of "substantial equivalence" upon which all GE crop and corn approvals rest is empirically untrue and essentially meaningless.

[16] This recommendation, plus a call for post-approval monitoring, appears on page 181 of the 2004 NAS report "Safety of Genetically Engineered Foods: Approaches to Assessing Unintended Health Effects." This report can be downloaded free of charge.

[17] One study in rats used sensitive analytical methods to detect ultrastructural alterations in the rat GI tract, and concluded that corn expressing two *Bt* endotoxins and the glyphosate-resistance gene could be causing subtle changes in the permeability and reactivity of the rat stomach and intestinal lining.

In the U.S. and MX, the use of GBHs and exposures to GLY and AMPA is an unavoidable consequence of planting today's GE corn varieties. Such exposures in MX will inevitably impact public and environmental health. The evidence is now strong that exposures to GLY/GBHs increase the risks of blood cancers including non-Hodgkin lymphoma, and leukemia based on human and animal studies. While several mechanisms can lead to such cancers, genetic damage to hematopoietic stem cells in bone marrow is likely one of the most common. In addition, a long-term U.C. Berkeley birth-cohort study of Hispanic farmworker families in central California has reported troubling evidence of GLY/AMPA-induced liver damage, along with increased risk of metabolic syndrome, among more heavily exposed children ***as young as 4-years old***. Based on their findings for GLY/AMPA levels in urine, the authors conclude that "Childhood exposure to glyphosate and AMPA may increase risk of liver and cardiometabolic disorders in early adulthood, which could lead to more serious diseases later in life." A study drawing on the U.S. National Health and Nutrition Examination Survey reported that the odds of metabolic syndrome were three-times higher among those individuals most heavily exposed to GLY compared to those least exposed. Multiple studies have linked exposures to GLY/AMPA to kidney and liver disease, preterm birth, and neurodevelopmental problems. A 2023 study in pigs reported that even very low levels of GLY in the porcine colon can be toxic to enteric neurons. This study identified changes that "reduce motor and secretory activity of the GI tract or cause changes in the blood flow as a result of a relaxing effect on the muscular layer of blood vessels."

Conclusions

Since the commercial introduction of GE corn in 1996 and event-specific approvals in the 1990s and 2000s, dramatic changes have occurred in corn production systems. There has been an approximate four-fold increase in the number of toxins and pesticides applied on the average hectare of contemporary GE industrial corn compared to the early 1990s. Unfortunately, this upward trend is bound to continue, and may accelerate.

White corn is likely to remain the most important single food ingredient in the Mexican diet. The number of *Bt*/VIP toxins expressed in GE yellow and some white corn varieties will surely rise, as will levels of toxins remaining in grain at harvest. In the U.S. case statement, a number of assurances are offered regarding the total absence of risk stemming from the presence of *Bt*/VIP toxins and herbicide residues in GE-corn based human foodstuffs. These assurances are not based on data and science, nor does the U.S. submission even give lip service to the profound differences in risks arising from the toxins and herbicide residues, and their exposure levels, that could become common in corn-based foods in MX. ***The U.S. is, in effect, asking Mexico to trust the completeness and accuracy of the initial GE corn safety assessments carried out 15 to 30 years ago by the companies working to bring GE corn events to market***. The Mexican government is both wise and on solid ground in refusing to allow its people to participate in the experiment that the U.S. government is seeking to impose on Mexico.

The absence of any systematic monitoring of human exposure levels to *Bt*/VIP toxins and herbicides from consumption of corn-based foods is regrettable. It is also unfortunate that the U.S. government rejected the Mexican proposal to jointly design and carry out a modern battery of studies able to overcome gaps in knowledge regarding GE corn impacts in MX. Such gaps perpetuate significant uncertainties in contemporary GE-corn human health risk assessments, thereby undermining efforts to detect and prevent avoidable risks.