Annex I - Assessment Of Articles Cited In Mexico's Initial Submission Concerning Alleged Adverse Human Health Effects From Consuming Ge Corn[1]

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
130	MEX-118	Bernstein IL, Bernstein JA, Miller M, Tierzieva S, Bernstein DI, Lummus Z, Selgrade MK, DoerflerDL, Seligy VL. "*Immune responsesin farm workers after exposure to Bacillus thuringiensis pesticides. Environ Health Perspect."*	This is a study of applicators of *Bt* sprays, not exposure to transgenic plants.This study is not relevant to *Bt* exposure through transgenic crops or food.	The inclusion of Annex **MEX-118** in Annex I erroneously characterizes the way in which Mexico relied on this test. Mexico did not include Exhibit **MEX-118** as evidence of the risks of GE Corn consumption. Mexico included this study in its Initial Written Submission as proof that "*exposure to Bt spraying could cause allergic skin sensitivity and the induction of antibodies (immunoglobulins), or both*" ¶ 130). The Cry genes present in transgenic constructions resistant to insects, which are obtained from multiple strains of Bt, whose genes are inserted in plants of agricultural importance such as corn or soy, express and maintain the same insecticidal function, precisely because of the Cry genes. The analysis is decontextualized, Mexico refers to this study, taking into account the chronological evolution of negative health consequences. The study "*Immune responses in farm workers after exposure to Bacillus thuringiensis pesticides*" is, precisely, the oldest reference." Therefore, it is confirmed that this research work is an irrefutable reference to maintain that Cry proteins already had a history of their negative effects on human health.
132	MEX-126	Séralini GE, Cellier D, de Vendomois JS. "*New analysis of a rat feeding study with a genetically modified maize reveals*	This is just a statistical re-analysis of data from a biotechnology developer. This pa**rt**icular study is a whole-food animal feeding study, which is known to be difficult to interpret. Because these studies are so difficult to interpret, a comparative	The study explicitly states its objective and the limited variables in the conclusions as follows: "*to study the possible toxicological effects of introducing genetic construction producing an insecticide into the maize; thus it should be*

[1] The extent the United States has not commented on a particular exhibit cited by Mexico in its Initial Submission, such an omission should not be interpretedas endorsement of the exhibit's credibility or relevance.

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		signs of hepatorenal toxicity". Arch Environ Contam Toxicol.	approach to safety assessment is used to specifically avoid having to rely on these kinds of studies[2]. This comparative approach is laid out in the Codex *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants* ("Codex Guidelines").[3] Mexico has effectively taken the least valuable study in the food safety assessment and re-evaluated it. The article does nothing to refute other data and information used in the process that are more routinely relied upon for safety assessment.	*guaranteed that the only variability sources in the results are related to the presence, or not, of this transgene apart from purely random effects*" (**MEX-126**, pp. 600-601). Unlike the biotechnology developer analysis referred to by the U.S., this study separated the analysis first between the GMO groups and control groups, and then between the GMO groups and reference groups to provide a more accurate assessment of the specific effects of GM organisms. (**MEX-126**, p. 601). In fact, U.S. criticism of this methodology as "*difficult to interpret*" lacks rationale and does not address the

[2] In fact, directly responding to Séralini's work, the EU has dedicated three (multi-million euro) special projects to evaluate the need for such studies, and allthree found that such studies were not ordinarily likely to provide useful information and did not meaningfully improve safety assessments for crops with agronomic input traits (*i.e.*, traits that affect yield, quality, and ability to resist biotic and abiotic stressors—the vast majority of GE crops on the market). D.Zeljenková et al., "Ninety-day oral toxicity studies on two genetically modified maize MON810 varieties in Wistar Han RCC rats (EU 7th Framework Programme project GRACE)," 88 ARCHIVES OF TOXICOLOGY 2289 (2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4247492/pdf/204_2014_Article_1374.pdf (total of 17 partners from 13 countries involved) (Exhibit USA-140);

P. Steinberg et al., "Lack of adverse effects in subchronic and chronic toxicity/ carcinogenicity studies on the glyphosate-resistant genetically modified maize NK603 in Wistar Han RCC rats," 93 ARCHIVES OF TOXICOLOGY 1095 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7261740/pdf/204_2019_Article_2400.pdf ("In conclusion, in the European GRACE and G-TwYST projects a series of animal feeding trials were performed (Zeljenková et al. 2014, 2016; this study). This series of studies neither delivered a scientific basis for the 90-day animal feeding trial demanded by the European Commission to be performed for each new GM plant variety nor did it indicate that untargeted, extended feedingstudies with rats fed GM plant material are of value for a final confirmation of safety. Thus, an added value of animal studies relative to the available nonanimal studies for the risk assessment of GM plants (EFSA Scientific Committee et al. 2017) was not substantiated.") (Exhibit USA-141); X. Coumoul et al., "The GMO901 Project: Absence of Evidence for Biologically Meaningful Effects of Genetically Modified Maize-based Diets on Wistar Rats After 6-Months FeedingComparative Trial," 168 TOXICOLOGICAL SCIENCES 315 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6432862/pdf/kfy298.pdf (Exhibit USA-142); *see also* European Food Safety Authority, "Safety and Nutritional Assessment of GM Plants and Derived Food and Feed: The Role of Animal Feeding Trials," 46 FOOD & CHEMICAL TOXICOLOGY S2 (2008), https://www.sciencedirect.com/science/article/abs/pii/S0278691508000884 ("In the situation where molecular, compositional, phenotypic, agronomic and other analyses have demonstrated equivalence between the GM plant derived food and feed and their near isogenic counterpart, except for the inserted trait(s), and do not indicate the occurrence of unintended effects, experiences with GM plants modified for agronomic input traits have demonstrated that the performance of 90-day feeding trials with rodents or feeding trials with target animal species have provided little if anything tothe overall safety assessment (except for added confirmation of safety).") (Exhibit USA-143).

[3] Codex *Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants* ("Codex Guidelines"), sec. 3, paras. 11-12(Exhibit USA-114).

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				study's focus on improving accuracy and limiting variability (**MEX-126**, pp. 600-601).
132	MEX-127	De Vendômois JS, Roullier F, Cellier D, Séralini GE. "*A comparison of the effects of three GM corn varieties on mammalian health"*. Int J Biol Sci. 2009.	This is also a re-analysis of a study conducted by a technology developer. Even if the authors' analysis were to be correct, this would only be one piece of data used in a safety assessment and typically at the exception to other more reliable studies. Moreover, Mexico's COFEPRIS already authorized the three GE corn events referenced here—MON810, MON863, and NK603—as have numerous other regulators around the world,[4] and Mexico has not offered any new analysis from COFEPRIS indicating a need to modify the original assessment, and the associated rationale.	The exhibit constitutes relevant available scientific evidence, and the United States did not refute that capacity, nor did it justify that the study could be disqualified in light of other types of studies that the United States points to as "reliable". In fact, the United States does not even bother to cite these more "reliable" studies. At this time, Mexico does not understand what the United States requires to characterize a study as "reliable" and prefer it over others that meet the scientific requirements set forth in both the USMCA and the SPS Agreement. In addition, when talking about "other regulators around the world" The United States should conduct its analysis on a case-by-case basis, and analyze how risk assessments are carried out in this small group of countries that have approved such transgenic events, which together do not represent even 10% of all the countries in the world. Furthermore, it is relevant to consider that these transgenic events are banned in another group of countries, especially in the European Union, and that these transgenic events are

[4] *See* COFEPRIS Safety Evaluation of MON863 (Sept. 29, 2003) (Exhibit USA-144); COFEPRIS Safety Evaluation of MON810 (Nov. 6, 2002) (Exhibit USA- 145); COFEPRIS Safety Evaluation of NK603 (June 7, 2002) (Exhibit USA-146); Food and Agriculture Organization of the United Nations ("FAO") GeneticallyModified ("GM") Foods Platform, MON810 (listing assessments and authorizations in Australia, Brazil, Canada, China, the EU, Indonesia, Kenya, Malaysia, Mexico, New Zealand, Paraguay, the Philippines, South Korea, Singapore, Thailand, Turkey, the United States, Uruguay, and Vietnam) (Exhibit USA-147); FAO GM Foods Platform, NK603 (listing assessments and authorizations in Australia, Brazil, Canada, Colombia, the EU, Indonesia, Iran, Japan, Malaysia, Mexico, New Zealand, Paraguay, the Philippines, South Korea, Russia, Singapore, Thailand, Turkey, the United States, and Uruguay) (Exhibit USA-148); FAO GM Foods Platform, MON863 (listing assessments and authorizations in Australia, Canada, China, Colombia, the EU, Japan, Malaysia, Mexico, New Zealand, South Korea, Russia, Singapore, Thailand, Turkey, and the United States) (Exhibit USA-149).

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				the ones that have been most studied based on different analyses in experimental animal models, published under strict peer review in scientific journals, warning about the possible harmful effects on human health. This may be reviewed in the National Biosafety Information System (SNIB in Spanish). As if that were not enough, the U.S. criticism does not consider that the approvals issued by COFEPRIS until before 2020 were made exclusively based on the information provided by the company promoting the authorization application, excluding scientific studies, free of conflict of interest, which are fundamental to establish adequate measures and decisions to guarantee biosafety in the face of the potential and proven effects of GMOs. Furthermore, according to the National Registry of GMO Biosafety (RNB in Spanish), the approval issued by COFEPRIS of the MON810 and NK603 events were issued in 2002 and of MON 863 in 2003, all scientific evidence subsequent to those years must be reviewed and considered for the review processes of the health authorizations that is the responsibility of the health authorities. This is relevant because in biomedical, pharmacological, epidemiological and toxicological research, tests with model animals (e.g., mice, rats, pigs) are widely used to determine the probable damage caused by new molecules, drugs, commercial products and even environmental factors. The results of such studies yield data that are extrapolated and interpreted as an indication of potential effects not previously considered, acting to the detriment of human health (**MEX-422**, pp. 4-9; **MEX-423**, pp344-356; **MEX-161**, pp.401-426; **MEX-424** p.10). In this

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				sense, the scientific studies **MEX-127**, **MEX-128**, **MEX-131**, **MEX-132**, cited in Mexico's initial submission, cannot be disregarded: they point to specific evidence regarding effects on organs essential for the life of the animals subjected to the experiments; effects directly due to the feeding of GM corn. The above, in contrast to the confidentiality in which toxicity studies are carried out by the industries promoting GM corn, prior to the authorization of the commercialization of GM corn. In addition, it is essential that the genetic, physiological or metabolic criteria used in research on the toxicology of GM corn to accept or reject a biotechnological development, such as GM corn using animal models for experimentation, be made transparent. Finally, it should be noted that the study that the United States disqualifies, denotes, among others: i) that the three varieties of GM Corn (NK 603, MON 810, MON 863) have relevant effects on the kidneys and liver, organs, the main organs of dietary detoxification, as well as frequent effects on the heart, adrenal glands, spleen and blood cells (page 12); ii) that the three varieties of corn may induce a hepatorenal toxicity state (page 12); iii) that although it is suggested to carry out additional studies, these should be focused on the kidneys and liver, due to the fact that the three varieties of CORN can induce a hepatorenal toxicity state; iii) that while further studies are suggested, they should focus on the kidneys and liver because of the effects that occurred in only 90 days (p. 13). The scientific study **MEX-127**, cited in Mexico's initial submission, is of special relevance, since it presents a re-analysis of measurement data obtained

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				from experiments conducted by an industry promoting of GM corn in laboratory animals (**MEX-374**). These experiments were aimed at demonstrating the safety of three varieties of GM corn used in food. It should be mentioned that, in an inexplicable and non-transparent manner, the original study carried out by the industry promoting GM corn did not present measurements contemplated in the standards and guidelines established by the Organization for Economic Cooperation and Development (OECD). However, through a statistical re-analysis of the data originally presented by the GM corn industry, the **MEX-127** scientific study was able to compensate for the error of origin and determine the effects and damages previously not considered, which are derived from the feeding of experimental model animals with GM corn varieties. The **MEX-127** study showed previously unconsidered effects in the experimental model animals due to the feeding of GM corn varieties, depending on the sex of the animals and the dose of GM corn used: alterations in the renal and hepatic functions (hepatorenal toxicity due to the consumption of GM corn varieties), toxicity, damage to the heart, spleen, blood cells. Study **MEX-127** analyzed the unconsidered health effects on experimental model animals for consuming GM corn varieties: MON810, MON863, and NK603.
132	MEX-128	El-Shamei, Z. S., A.A. Gab-Alla, A. A. Shatta, E. A. Moussa & A. M. Rayan. (2012). "*Histopathological Changes in Some Organs of Male Rats Fed on Genetically Modified*	This is only one part of a safety assessment and even the article acknowledges that point. This is a study done as part of a PhD thesis in Egypt, which approved this variety (MON810) for cultivation (and which Mexico has approved for consumption).	The United States decontextualizes the article in its entirety, since nowhere in the text does it mention that the research conducted "is only one part of a safety assessment", as the United States claims. On the contrary, the text stresses that an assessment is

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		Corn (Ajeeb YG)". Journal of American Science.		based on the concept of "*substantial equivalence*".[5] However, the publication rightly points out that the existence of some studies "*report adverse changes at a cellular level caused by some GM foods*" therefore, the focus or objective of the article is precisely to "*provide new information about the negative effects of genetically modified corn and its effects on the tissues of vital organs of male rats*".[6] In this regard, it is important to note that the United States did not refute the scientific results obtained from the research. That is, the United States failed to comment on the findings derived from the scientific evidence. For example, the scientific studies **MEX-127, MEX-128, MEX-131 and MEX-132**, which point to specific evidence regarding previously unconsidered effects on organs essential for the life of the animals subjected to the experiments; effects directly due to the feeding of GM corn. In particular, the scientific study attached as **MEX-128** is complementary to research **MEX-127**, presented as evidence of organ damage in experimental model animals due to the consumption of GM corn. This scientific research report detected histopathological changes (damage) in the liver and kidney. Additionally, it reports damage to the spleen and small intestine in experimental animals fed GM corn.

[5] **El-Shamei, Z. S., A.A. Gab-Alla, A. A. Shatta, E. A. Moussa & A. M. Rayan. (2012). Histopathological Changes in Some Organs of Male Rats Fed on Genetically Modified Corn (Ajeeb YG). Journal of American Science, p. 684. MEX-128.**

[6] **El-Shamei, Z. S., A.A. Gab-Alla, A. A. Shatta, E. A. Moussa & A. M. Rayan. (2012). Histopathological Changes in Some Organs of Male Rats Fed on Genetically Modified Corn (Ajeeb YG). Journal of American Science, p. 685. MEX-128.**

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				According to ISAAA data, in Egypt, MON 810 was approved in 2008 for cultivation only. Meanwhile, according to the RNB, in Mexico, it was authorized by COFEPRIS for human consumption in 2002. All scientific evidence subsequent to those years should be reviewed and considered for the review processes of health authorizations, which is the responsibility of the health authorities. This transgenic event is banned in several countries and is one of the most studied from different analyses in experimental animal models, published under strict peer review in scientific journals, warning about possible harmful effects on human health. This may be reviewed in the National Biosafety Information System (SNIB in Spanish). In the case of Mexico, all approvals issued by COFEPRIS until before 2020 were made exclusively on the basis of information provided by the company promoting the application for authorization, excluding scientific studies, free of conflict of interest, essential to establish adequate measures and decisions to ensure biosafety in the face of the potential and proven effects of GMOs.
132	MEX-129	Oraby, Hanaa; Kandil, Mahrousa; Shaffie, Nermeen; and Ghaly, Inas (2015) *"Biological impact of feeding rats with a genetically modified-based diet*" Turkish Journal of Biology: Vol. 39: No. 2,	The test article in this study is not defined but rather is just listed as corn and soy without specifying which corn varieties. The study vaguely refers to "a laboratory diet of mainly 60% yellow maize and 34% soybeans," so it is impossible to attribute the effect seen to either corn or soy let alone a specific corn variety (none of which are defined).	The overall subject of the study is highly relevant to Mexico's concerns. The research focuses on the health effects of ingesting GM proteins, including the presence of glyphosate-tolerant enzymes, none of which are contested by the United States.

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
		Article 11.		The study demonstrated the presence of NPTII and P-35S/CTP in transgenic plants by PCR, highlighting that the CaMV35S promoter is present in more than 80% of these plants. A chronic toxicity study was performed in Wistar rats fed a transgenic diet for 30, 60 and 90 days, evaluating biochemical, histopathological and cytogenetic parameters. Alterations were observed in the concentrations of alanine aminotransferase, aspartate aminotransferase, creatinine, uric acid and malondialdehyde, as well as genotoxicity in germ and hepatic cells. Furthermore, contrary to what the United States points out, the conclusions of the study do differentiate the effects for populations fed with GM soybeans (34%) and with GM yellow corn (60%) (**MEX-129**, pp. 271-273). In any case, as Mexico argues, this reference demonstrates that there are significant effects of diets with GM Bt corn. Importantly, the broader perspective of this study helps provide context when analyzing studies that have a narrower focus, e.g., those that isolate a particular corn race. In addition, an experiment that combines different GM crops in a diet is important because it better reflects human diets and fills a research gap identified by academics (**MEX-287**, pp. 6-7). In conclusion, health risks associated with the intake of diets containing genetically modified components were identified.
132	MEX-131/132	M.A.A. Ibrahim, E.F. Okasha, "*Effect of genetically modified corn on the jejunal mucosa of adult malealbino rat"*, Exp Toxicol Pathol.; Zdziarski,	These are additional rat-feeding studies that are considered the least reliable information in assessing food safety of whole foods when compared to the internationally accepted approach that relies on a comparative assessment of thesafety of the new food and its	The United States has not substantiated its assertion that the rat feeding studies are "*the least reliable information in assessing food safety*" nor has it specified which method is internationally accepted. This statement is contrary to the numerous rat studies cited by Mexico that demonstrate health

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
		I.M., Carman, J.A. and Edwards, J.W. (2018) "*Histopathological Investigation of the Stomach of Rats Fed a 60% Genetically Modified Corn Diet"*, Food and Nutrition Sciences.	conventional counterpart.	concerns associated with transgenic proteins. Also, the United States has stated in other sections of its Annex I that mammalian studies are relevant to assessing safety. For example, noting below that "Mammalian laboratory animals, such *as rats*, *mice*, and rabbits, are used given the closer biological similarities to humans" [emphasis added]. The objective of this study was to evaluate the effect of GM corn on the histological structure of the jejunal mucosa of adult male albino rats using different histological, immunohistochemical and morphometric methods. Twenty adult male albino rats were divided into two equal groups; control and transgenic corn fed group administered with 30% transgenic corn for 90 days. Specimens from the GM corn-fed group showed different forms of structural changes. Focal destruction and loss of villi was observed leaving a bare mucosal surface alternating with stratified areas, while some crypts appeared totally altered. Congested blood capillaries and focal infiltration with mononuclear cells were detected. Significant positive up-regulation of PCNA expression, an increase in the number of goblet cells and a significant increase in both villus height and crypt depth were detected. Marked ultrastructural changes of some enterocytes were observed with focal loss of the microvilli border. It was therefore concluded that consumption of GM corn profoundly alters jejunal histological structure. On the other hand, research article **MEX-132** is about research conducted with a triple-stacked GM corn variety containing modifications for insect resistance (through cry1Ab and cry3Bb1 genes) and

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				herbicide tolerance (through an EPSPS gene), which was fed to rats for six months. The study investigated the stomach mucosa. It demonstrated alterations in tight junction apposition, gland dilatations with epithelial elongation and dysplasia in the transgenic-fed rats. These results indicate that transgenic corn may have an effect on the mucosa of the rat stomach, which may have health implications. It is important to note that these studies provide valuable information on possible adverse health effects of GM foods. Studies in rats may detect short-term effects that may not be evident in long-term studies in humans. In addition, rat studies may help identify possible mechanisms of toxicity and guide future research.
132	MEX-133/134	Sagstad A, Sanden M, Haugland O, Hansen AC, Olsvik PA, Hemre GI. "*Evaluation of stress- and immune-response biomarkers in Atlantic salmon, Salmo salar L., fed different levels of genetically modified maize (Bt maize), compared with its near-isogenic parental line and a commercial suprex maize"*. J Fish Dis. 2007; Gu J, Krogdahl Å, Sissener NH, Kortner TM,	It is unclear how a study conducted on salmon, a non-mammalian animal, is relevant to human health in this dispute, nor does Mexico explain the significance of this study to human health.[7]	The statement presented by the United States as an alleged "analysis" seems to denote that the articles in question were not reviewed and implies that it is a study on a fish. The statement appears to be incomplete and lacks scientific, technical, regulatory or legal support. In contrast, this study is on the effect of GM corn on Atlantic salmon and is relevant to human risk assessment for several reasons. *First*, fish are widely used as models in toxicity and food safety studies because of their physiological similarity to humans. *Second*, observed changes in biomarkers of stress and immune response in fish could indicate possible effects on human health, as the biological systems

[7] Studies that are used to evaluate potential genotoxicity in humans are established assays using mammalian systems. Mammalian laboratory animals, such as rats, mice, and rabbits, are used given the closer biological similarities to humans. Assays using non-mammalian species are not established to inform genotoxicrisk in humans.

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
		Gelencser E, Hemre GI, Bakke AM. "*Effects of oral Btmaize (MON810) exposure on growth and health parameters in normal and sensitised Atlantic salmon, Salmo salar" L*. Br J Nutr.2013.		responsible for these responses are kept between species. For example, superoxide dismutase and catalase activity in the liver and intestine, as well as the proportion of different types of white blood cells in plasma, are indicators of fundamental biological processes that are also present in humans. *Third*, in the aquaculture industry, various corn products are used in fish feed. In the **MEX 133** study, several significant differences in enzyme activity and genic expression related to stress and immune response were found in the liver and distal intestine of fish fed with transgenic corn compared to those fed with non-GM corn and the reference diet group. Catalase (CAT) enzyme activity in the liver was significantly lower in fish fed GM corn compared to fish fed non-GM corn and the reference diet group. In the distal intestine, CAT enzyme activity was significantly higher in fish fed GM corn compared to fish fed the reference diet. Superoxide dismutase (SOD) enzyme activity in the liver and distal intestine was significantly higher in fish fed GM corn compared to fish fed non-GM corn and the reference diet group. In addition, heat shock protein 70 (HSP70) in the liver was significantly higher in fish fed GM corn compared to fish fed the reference diet. In summary, the study found that GM corn affected enzyme activity and gene expression related to stress and immune response in fish, suggesting that it may have potential health effects. On the other hand, the article shown in **MEX 134** is a study that investigated responses to transgenic corn (Bt corn, MON810) expressing the Cry1Ab protein of the soil bacterium Bacillus thuringiensis (Bt) in

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				diets for post-smolt Atlantic salmon. Fish fed Bt corn utilized feed less efficiently, as revealed by lower protein and mineral digestibility and lower lipid and energy retention efficiency. Higher intestinal weights, as well as increased interferon-γ and decreased sodium-glucose cotransporter mRNA expression, and a transient increase in the presence of helper T cells, as measured by cluster of differentiation protein 4 (CD4) in the distal intestine (DI), may partly explain the lower digestibilities and nutrient retentions. Bt corn appeared to enhance oxidative cellular stress in the DI of immunosensitized fish, as indicated by increases in superoxide dismutase mRNA and heat shock protein expression. The data suggest that Cry1Ab protein or other Bt corn antigens have local immunogenic effects in DI salmon. These results are relevant to human risk assessment, as fish are used as models in food toxicity and safety studies due to their physiological similarity to humans. Therefore, this study provides valuable information that may help to better understand the potential effects of transgenic corn on human health, especially in relation to immune response and oxidative stress. In the case of salmon, although it is a non-mammalian organism, it has an immune system with characteristics that make it relevant for comparative immunological studies with more developed organisms such as mammals, due to its reaction against pathogens and the development of adaptive

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				immune responses.[8] Even if the relevance of salmon in comparative immunological studies is ignored, the evidence on the effects caused by GM corn in various organisms stands out. Mexico does not discard the evidence used in organisms other than humans, since, for Mexico, human experimentation is not feasible, especially considering the Mexican diet and its high levels of corn consumption.
132	MEX-135	Mesnage- Robin, Z-Sarah, Tenfen- Agapito, VilperteV-inicius, Renney-George, Ward-Malcolm, Séralini-Gilles Eric, O-Nodari Rubens and N-Antoniou, Michael (2016). "*An integrated multiomics analysis of the NK603 Roundup- tolerant GM maize reveals metabolism disturbances caused by the transformation process*". Nature.	This study looked at the metabolome of NK603 corn and reported: "The most pronounced metabolome differences between NK603 and its isogenic counterpart consisted of an increase in polyamines including N-acetyl- cadaverine (2.9-fold), N-acetylputrescine (1.8-fold), putrescine (2.7-fold) and cadaverine (28-fold), which depending on context can be either protective or a cause of toxicity." (p. 1). The paper also states, "Overall, whether the increased levels of cadaverine and putrescine found in the NK603 maize samples can account for the signs of potential negative health effects upon its consumption by rats, as implied by the blood/urine biochemical analysis, needs to be further analyzed in experiments using more quantitative methods." (p. 10). The author's conclusion that NK603 and its isogenic control	The United States selectively cites the study, omitting a broader context and any conclusions contrary to its position. This study, along with others cited by Mexico, criticizes the concept of substantial equivalence employed by agencies such as the U.S. Food and Drug Administration, noting that "*analysis for residues for such pesticides are neglected in compositional assessment*".[12] While acknowledging that the long-term effects of consumption need further research, the study clearly states that "*the evidence we present clearly shows that NK603 and non-GM isogenic maize are not substantially equivalent and the nutritional quality of GM feed might be hampered by metabolic imbalances related to plant energy and stress metabolism*".[13] It should be noted that the **MEX-135** study used

[8] **Pradipta R. Bauta, Bismita Nayak, Surajit Das, "*Immune system and immune responses in fish and their role in comparative immunity study: A model for higher organisms*", pp. 29-30, MEX-369**

[12] **Mesnage- Robin, Z-Sarah, Tenfen-Agapito, VilperteV-inicius, Renney-George, Ward- Malcolm, Séralini-Gilles Eric, O-Nodari Rubens y N-Antoniou, Michael (2016). "*An integrated multiomics analysis of the NK603 Roundup-tolerant GM maize reveals metabolism disturbances caused by the transformation process*". Nature, p. 2. MEX-135.**

[13] **Mesnage- Robin, Z-Sarah, Tenfen-Agapito, VilperteV-inicius, Renney-George, Ward- Malcolm, Séralini-Gilles Eric, O-Nodari Rubens y N-Antoniou, Michael (2016). "*An integrated multiomics analysis of the NK603 Roundup-tolerant GM maize reveals metabolism disturbances caused by the transformation process*". Nature, p. 10. MEX-135.**

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			are not substantially equivalent does not seem to be based on any objective standard as the analysis of N-acetyl- cadaverine, N-acetylputrescine, putrescine, or cadaverine is not recommended by the Organisation for Economic Co-operation and Development ("OECD") Consensus Document on the compositional analysis of corn, which provides guidance on what analytes should be measured when evaluating the food and feed safety of GE corn.[9] Of the thousands of chemicals present in corn only a few are likely to be meaningful in terms of food safety if their levels were to be changed.[10] Finally, as with other studies of this type, changes in molecular markers such as of oxidative stress, do not necessarily indicate that plant health is negatively affected.[11]	high-precision molecular methods to determine the differences in protein level (proteomics) and metabolite expression (metabolomics) between the GM corn variety NK603 and its conventional non-GM counterpart. These types of techniques allow simultaneous measurement and comparison of the behavior or expression of thousands of components in plants under different treatments or conditions (e.g., comparing conventional non-GM plants with GM plants). Specifically, the use of these techniques for the in-depth characterization and identification of genotypic changes not contemplated by the genetic modification of organisms, including new potentially allergenic substances or toxins. The study found that the GM corn NK603 expresses 117 proteins and 91 metabolites in an altered manner with respect to the conventional non-GM corn variety. Since both the GM corn NK603 and conventional non-GM plants were subjected to the same treatments, the conclusion of this scientific research strongly indicates that the alterations observed in GM corn NK603 are merely due to the technical process of genetic modification, which

[9] OECD, "Consensus Document on Compositional Considerations for New Varieties of Maize (Zea Mays): Key Food and Feed Nutrients, Anti-Nutrients andSecondary Plant Metabolites," Table 14 (Aug. 20, 2002), https://one.oecd.org/document/env/jm/mono(2002)25/en/pdf (Exhibit USA-150).

[10] Moreover, cadavarine is often associated with rotting tissue, meaning that the increase in cadavarine could be a sign that the sample was not in good condition.This is yet another example of Mexico alleging issues but not actually taking subsequent steps to confirm that these are, in fact, food safety issues.

[11] J.E. Chambers et al., "Biomarkers as Predictors in Health and Ecological Risk Assessment," 8 HUMAN AND ECOLOGICAL RISK ASSESSMENT: AN INTERNATIONAL JOURNAL 165 (June 2010) ("[T]he degree of inhibition can be readily influenced by endogenous (*e.g.*, age) and exogenous (*e.g.*, chemical exposures) factors, and [] the degree of inhibition is not readily correlated with toxicological effects. Caution is urged, therefore, in an attempt to utilize biomarkers in the risk assessment process until more complete documentation is available on the specificity, sensitivity, and time course of changes, and on theimpact of multiple exposures or the time of exposures.") (Exhibit USA-151).

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				disprove the concept of substantial equivalence, which has been used to validate the approval and commercialization of genetically modified organisms (e.g., GM corn varieties). In addition, it is important to emphasize that with the advance of biotechnological developments for obtaining genetically modified (GM) seeds and the interest of the producing companies to commercialize them with the least possible restrictions, the Organization for Economic Cooperation and Development (OECD) promoted the adoption of the principle of substantial equivalence as the main basis for the risk assessment of these new biotechnologies.[14] This principle leaves in the background the need to perform relevant analyses capable of detecting metabolic changes that, due to the imprecise nature of the transgenesis technique, may be inherent to the process of genetic transformation.[15]
132	MEX-136	Walsh MC, Buzoianu SG, Gardiner GE, Rea MC, Ross RP, Cassidy JP, Lawlor PG. "*Effects of shortterm feeding of Bt MON810 maize on growth performance, organ morphology and function in pigs"*.Br J Nutr. 2012.	"Higher feed intake" is not necessarily an adverse health outcome. Feed conversion rates are a measure of growth performance and not necessarilysafety.	Although the United States criticizes the study on the basis of higher feed intake, it does not recognize the *"poorer feed conversion efficiency"* associated (**MEX-136**, p. 367), and overlooks other significant findings such as heavier organs e.g. the kidneys, "*indicating possible renal toxicity*" (**MEX-136**, p. 369).
132	MEX-137	Carman, J. A., et al. (2013). "*A long-term toxicology study on pigs fed a*	This study used a mixture of GE corn varieties and GE soy, and thus attributingany effects seen would be very challenging. One would not	The U.S. response to the evidence is unfounded. First, the diet is not poorly defined. For example, the study specifies the corn varieties with which the

[14] **OECD. "*Safety Evaluation of Foods Derived by Modern Biotechnology. Concepts and Principles.*" Organisation for Economic Co-operation and Development, 1993. Disponible en: https://www.oecd.org/science/biotrack/41036698.pdf. MEX-425.**

[15] **Ladics, G. S., et al, " *Genetic basis and detection of unintended effects in genetically modified crop plants*". Transgenic Research, 2015, pp. 587-603, MEX-426**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
		combined genetically modified(GM) soy and GM maize diet. Journal of Organic Systems."	expect a credible food safety study to be performed this way with a diet that is so ill-defined withmultiple variables.	pigs were fed, (**MEX-137**, p. 40). In addition, the study is well supported by a detailed literature review as well as a methodological explanation (**MEX-137**, p. 39). This study is also relevant because the GMO crops it evaluates are those consumed by humans (**MEX-137**, p. 39). These types of studies, which combine different GMO crops in a diet, are important because they more closely resemble human diets and fill a research gap identified by other scholars. (**MEX-287**, pp. 6-7). Likewise, the scientific study **MEX-137**, filed by Mexico in the Initial Written Submission, is in line with the studies previously commented (**MEX-127, MEX-128, MEX-131, MEX-132**) on the damage caused to experimental model animals when subjected to GM feed (e.g., GM corn) and the concern about the presence of GM corn in the food of the Mexican people. The **MEX-137** scientific research designed the study to subject experimental animals (pigs) to GM feeding conditions similar to those existing in the United States for breeding animals for a long period of time. The experimental model animals used in this study are physiologically similar to humans, so the data reported in this research are relevant for evaluating the safety of GM corn feeding. In addition, the research used GM corn varieties also used in the studies of **MEX-128**, **MEX-130**, **MEX-131**, **MEX-132**, particularly GM corn known as NK603, corn genetically modified to tolerate the herbicide glyphosate, so it may be assumed that traces of glyphosate are present in such corn. The study found that the uteri of female animals fed GM corn were 25% heavier compared to organs from animals that were not fed GM corn, which may potentially be related to pathology. Additionally, a

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				statistically significant difference was reported in the inflammation of the stomachs of experimental model animals that were subjected to GM feeding. It should be mentioned that, although in this study GM soybeans were used in addition to GM corn varieties as part of the GM feed to which the experimental model animals were subjected, the treatments designed for experimentation in this study are closer to the reality of animal and human food processing characteristics and conditions, given that the food products employ inputs that include GM products, such as GM soybeans and GM corn, which are a cause for health concern.
132	MEX-138	Glöckner, G. & G-É. Séralini. (2016). "*Pathology reports on the first cows fed with Bt176 maize"* (1997–2002). Scholarly J. Agric. Sci.	This anecdotal paper expressly states that "it was not designed as a scientific experiment." It reports observations that can be useful in forming hypotheses, which can be further tested scientifically, but as observations do not, in and ofthemselves, demonstrate a safety concern.[16]	Although it may be argued that the study was not initially intended as a scientific experiment, this does not imply that the research lacks scientific rigor. In this regard, as pointed out by the United States, the authors of this case study in the livestock field mention in their text that the research does not start from an experimental design; however, the adjective "anecdotal", mentioned by the United States, is inappropriate and could reflect an alarming lack of knowledge of the development of agricultural sciences. In fact, in the next sentence to the portion cited by the U.S. the authors state "It is a detailed observation of a conventionally managed, technologically advanced dairy farm, with access to detailed raw data, which were collected because of unusual pathological problems. These observations were made during the progressive introduction (1997-2002) of the first

[16] Furthermore, contrary to what Mexico states, the referenced paper was not why Bt176 was withdrawn; the reason was the presence of an ampicillin-resistance selection marker, and ampicillin is one of the antibiotic resistance issues the EU wanted to manage. However, studies found no horizontal gene transfer to infectious bacteria from Bt176 corn. *See, e.g.*, E. Badosa et al., "Lack of detection of ampicillin resistance gene transfer from Bt176 transgenic corn to culturable bacteria under field conditions," 48 FEMS MICROBIOLOGY ECOLOGY 169 (May 2004), https://onlinelUSAibrary.wiley.com/doi/epdf/10.1016/j.femsec.2004.01.005 (Exhibit USA-152).

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				genetically modified (GM) maize Bt176 into the European market and in animal feed rations. Thus this the first and longest formal observation of the feeding of cows with an agricultural GMO. [...] *This is the first scientific explanation of these observations*". In other words, the study does not only present the observations, but a scientific explanation of them, as is evident from reading it. Well, although the study was not designed as a scientific experiment, it provides valuable and detailed information that helps to understand the lack of safety of GM crops and highlights the importance of more rigorous and long-term research in this area. The study presents positive aspects that help to understand that this type of corn (Bt176) is not safe and to strengthen the decision to withdraw it from the market: 1. the study provides a detailed observation of a real case in which Bt176 corn was progressively introduced into the diet of cows, allowing a better understanding of the possible long-term effects of this transgenic feed on the animals.; 2. the researchers had access to detailed raw data collected by an experienced farmer and certified veterinarians, which increases the reliability of the findings and allows for a more thorough analysis of the results.; 3. this study is the first and longest to directly observe the effect of feeding Bt176 corn to dairy cows, which makes it of historical value in the context of research on the impacts of transgenic crops on livestock...; 4. although corn Bt176 is no longer in circulation, the results and lessons learned from this study are relevant for

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				understanding the potential risks associated with other transgenic crops and for guiding future research in this field. Concerns about the safety and potential human and animal health impacts of corn Bt176, as well as the need for precautionary measures to protect public health and the environment, influenced the decision to withdraw this GM crop from the market. Furthermore, the research yielded several results that are useful for the analysis of Mexico, among which the following stand out: i. This is the first and most extensive formal observation of the feeding of a GMO to cows. (**MEX-138,** p.1) ii. Biochemical alterations in the kidney and liver, observed in cows fed Bt corn, have already been associated with the consumption of that corn in sub-chronic tests in mammals; similarly, alterations have been observed in the liver. (**MEX-138**, p.7). alterations in embryonic renal cells upon exposure to Bt corn. (**MEX-138**, p.7). **iii.** the increase in the mortality rate of cows when exposed to Bt Corn, and the improvement in health by eliminating exposure to GM Corn. (**MEX-138**, p.7).
133	MEX-139	Mesnage R, Clair E, Gress S, Then C, Székács A, Séralini GE. "*Cytotoxicity on human cells of Cry1Ab and Cry1Ac Bt insecticidaltoxins alone or with a glyphosate- based herbicide".* J Appl	This is an in vitro study in which the Cry1Ab protein was presented to cells in culture. This has limited applicability to human health because one would expect the Cry1Ab protein to be digested and broken down to its component amino acids well before it reached the kidney. This is not the type of study that would be useful to a safety assessment of a *Bt* corn variety. This	*First,* the United States decontextualizes the content of the article, citing that "*The exposure during consumption can appear low enough to avoid side effects, and whether this occurs in vivo remains to be checked"*[17]. This, since the article immediately afterwards clarifies that, in spite of the consumption levels, the following should be taken into consideration "*the bioaccumulation in tissues,*

[17] **Mesnage R, *et al*., "*Cytotoxicity on human cells of Cry1Ab and Cry1Ac Bt insecticidal toxins alone or with a glyphosate-based herbicide*." 2013, p.3, MEX-139.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
		Toxicol.	study admits: "The exposure during consumption can appear low enough to avoid side effects, and whether this occurs in vivo remains to be checked." (p. 3). Cells in real life are never exposed at these concentration levels.	*or bioaccumulative or long-term effects, has to be taken into account since Bt residues were recently claimed to be measured in pregnant women's serum*".[18] *Second,* contrary to unsubstantiated assertions by the United States regarding the methodology used, the article points out that "[i]*n vitro tests are frequently recommended as a first step to replace animal models in toxicity studies. Here, we have tested for the first time the effects of Cry1Ab and Cry1Ac alone and combined with Roundup on human cells*"[19]. *Third,* it should be noted that the United States ignores that the relevance of this scientific evidence is that it deals with exposure to recombinant proteins (from GM corn), as well as exposure to the herbicide glyphosate eventually present in the population's diet, as Mexico has demonstrated in the scientific study **MEX-125**. In addition, the evidence provided shows that traces of GM elements from recombinant proteins present in food have been found in human fluids (e.g., fetal umbilical cord blood and serum),[20] so that, contrary to what might be supposed regarding the degradation of GM proteins in the stomach or intestines, this does not occur, according to the evidence shown. It was even determined that GM proteins cross the placental barrier to the fetus.
134	MEX-	Monica Andreassen, Elena	This study states the opposite of what Mexico	As in the case of the study **MEX-118**, this work

[18] **Mesnage R, *et al*., "*Cytotoxicity on human cells of Cry1Ab and Cry1Ac Bt insecticidal toxins alone or with a glyphosate-based herbicide*." 2013, p.3, MEX-139.**
[19] **Mesnage R, *et al*., "*Cytotoxicity on human cells of Cry1Ab and Cry1Ac Bt insecticidal toxins alone or with a glyphosate-based herbicide*." 2013, p.1, MEX-139.**
[20] **Aris A, y Leblanc, S. "*Maternal and fetal exposure to pesticides associated to genetically modified foods in Eastern Townships of Quebec, Canada*", 2011. MEX-427.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
	140	Rocca, Thomas Bøhn, Odd-Gunnar Wikmark, Johnnie van den Berg, Martinus Løvik, Terje Traavik & Unni Cecilie Nygaard (2015) "*Humoral and cellular immune responses in mice after airway administration of Bacillus thuringiensis Cry1Ab and MON810 cry1Ab-transgenic maize"*, Food and Agricultural Immunology.	asserts.[121] In any event, the factthat pollen, plant debris, or even Cry1Ab protein may be an inhalant allergen does not mean that it is unsafe when present in food. Mexico's measures focus on food, not aeroallergens. This is not the type of test typically considered in theinternationally accepted Codex Guidelines.	serves to demonstrate that there was already a history that Bt aerosols may cause negative effects to human health, due to the action of Cry proteins. Mexico did not rely on this exhibit to make a claim about the health risks associated with the consumption of GE corn. Mexico specifically cited this article to demonstrate that "*detrimental effects of GM Bt corn producing Cry1Ab have occurred without the need for ingestion*" (Mexico's Initial Written Submission, ¶ 134). The study suggests that aerial exposure to *Bacillus thuringiensis* Cry1Ab and the transgenic corn MON810 cry1Ab may trigger humoral and cellular immune responses in mice. Given the widespread use of transgenic Bt corn in food and feed, these findings underscore the need to carefully evaluate the safety of GM crops for possible effects on the immune system. Special attention is recommended for animal models, humans, vulnerable age groups and hypersensitive individuals. Furthermore, in footnote 10 of the exhibit, the United States selectively quotes the abstract of the article, ignoring the main text of the study, which states the following, "*[a]lthough no Cry protein immunogenicity could be observed at the present dose of MON810 pollen or leaf extract, the specific antibody response against the purified Cry1Ab protoxin and toxin preparations demonstrates the principle that these proteins may affect the immune system.*" (**MEX-140**, p. 534).
135	MEX-141	Shen, C., Yin, XC., Jiao, BY. et al."*Evaluation of adverse effects/events of*	This is a literature review of published studies. The only human data reported was from one crossover study that is not relevant to corn	As Mexico indicated in its Initial Written Submission, this is a "systematic review of studies conducted in animals and humans on the

[21] Mexico's Initial Submission alleges "[i]mmunogenicity and allergenicity from inhalation of pollen and plant debris from GM Bt corn (MON810), as well as exposure to purified Cry1Ab proteins." Mexico's Initial Submission, para. 134 (citing MEX-140). MEX-140 states: "No anti-Cry1Ab antibodies were detectedfollowing exposure to the plant materials." (p. 521).

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
		genetically modified food consumption: a systematic review of animal and human studies". Environ Sci Eur 34, 8 (2022).	because the test articlewas camelina.	consumption of GM foods" (¶ 135), i.e. a detailed and predefined protocol was followed to establish the inclusion and exclusion criteria for studies, search methods, data extraction and analysis, to identify, critically evaluate and synthesize all available relevant evidence on the adverse effects/events of GM food consumption. The fact that the U.S. qualifies such publication as a literature review is of concern, since it is based on a lack of knowledge of the relevance of the scientific production of knowledge and dissemination of knowledge generated from such production, in this case through review publications, which are relevant because, based on a protocol and the systematic review of the scientific literature on a topic, broader and more comprehensive conclusions may be drawn on that topic from the approaches of the various research studies included in the *review*. Included in this *review* were studies conducted on 7 specific events related to adverse effects on human consumption of GM foods, including 5 GM corn (NK603 × MON810, NK603, MON863, MON810, MON863 × MON810 × NK603), 1 GM soybean (GTS 40-3-2), and 1 GM rice. Several adverse events related to the consumption of GM corn were identified as tumors or cancer, decreased number of offspring delivery, decreased learning and reaction abilities, and abnormalities in organs such as stomach, intestine, mammary glands, pituitary, liver and kidney. The fact that only one study included a human crossover test is totally irrelevant, as it is explained by the absence of human experiments. Furthermore, the United States ignores the very fact that it states in

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				Annex I itself, "[s]tudies that are used to evaluate potential genotoxicity in humans are established assays using mammalian systems", since more than 90% of the animal studies that were analyzed were conducted in mammals (**MEX-141**, p. 6). This research is likely to help the Panel because it includes recent studies on the safety of GM foods, pointing to several cases where adverse effects have been reported. (**MEX-141**, p. 7). However, the United States has not addressed these significant findings. Moreover, of the 160 plant-related studies evaluated, 52 are of corn, i.e., almost one-third of the studies focus on corn.
137	MEX-142	Futuyma, D. J. (2013). "*Evolution"*.Third edition. Sunderland, Massachusetts U.S.A, Sinauer Associates, Inc. Publishers.	Mexico states: "There are mechanisms that can modify the evolutionary structure of individuals within a population, such as gene flow, which is the transfer of genes from one population to another." The United States does notdispute this statement. This is true and it is a natural phenomenon that occurs absent of genetic engineering.	It is important to note that Mexico agrees with the United States that transgenesis may occur naturally. However, the United States decontextualizes Mexico's comment, and to this effect, Mexico takes the opportunity to clarify in its written submission, that it is concerned about what has been called "genetic contamination", which is that in which, in the case of GMOs, the structure is artificially modified, in several occasions causing phenomena such as gene stacking and causing potentially irreversible damage with undesirable effects to the organisms exposed to it. Mexico explained this using a variety of evidence (**MEX-143, MEX-144, MEX-145, MEX-135, and MEX-146.)** In essence, the discussion is not that gene flow is a natural phenomenon, but rather that gene flow is the means by which a GMO and its conventional or wild counterparts exchange genetic material, which could

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				have unfavorable repercussions for the species and the ecological niche in which it coexists.[22]
138	MEX-143/144	Herrero, M., E. Ibañez, P. J. Martín- Álvarez and A. Cifuentes (2007). "A*nalysis of Chiral Amino Acids in Conventional and Transgenic Maize*" Anal. Chem; Levandi, T., C. Leon, M. Kaljurand, V. García- Cañas and A. Cifuentes (2008). "*Capillary Electrophoresis Time-of- Flight Mass Spectrometry for Comparative Metabolomics of Transgenic versus Conventional Maize*". Anal. Chem.	These phenomena—disparities in the content and chirality of amino acids and differences in the production of metabolites—typically are not themselves safetyconcerns.	Contrary to what the United States argues, the article in question explicitly describes the importance of the study in issues of "safety concern". Specifically, the article highlights that the methodology used in the research is relevant, since it may "*assess food adulteration, food quality, or digestibility and nutritional value of foods*".[23] Additionally, it states that "*the present work […] can be used as an additional indicator for assessing the existence (or not) of unexpected modifications in other metabolic pathways linked to the amino acids profile within GMO*".[24] Second, the U.S. commentary overlooks Mexico's concern,[25] regarding evidence of unwanted epigenetic alterations. In particular, the study **MEX-143** demonstrated significant differences in % D-aa (D-amino acids) levels between GM corn varieties and their corresponding non-GM lines. D-amino acids are not common in proteins of living organisms and may have adverse biological effects. The elevated presence of these amino acids in GM corn indicates metabolic alterations that could adversely affect digestibility and metabolism in both human and animal consumers. On the other hand, the chiral-MEKC-LIF method

[22] **Warwick, S. I., Beckie, H. J., & Hall, L. M. "*Gene flow, invasiveness, and ecological impact of genetically modified crops*". Annals of the New York Academy of Sciences, 2009 1168(1), 72-99, MEX-428**

[23] **Herrero, M., E. Ibañez, P. J. Martín-Álvarez y A. Cifuentes (2007). "*Analysis of Chiral Amino Acids in Conventional and Transgenic Maize*" *Anal. Chem* 79, pp. 5072. MEX-143.**

[24] **Herrero, M., E. Ibañez, P. J. Martín-Álvarez y A. Cifuentes (2007). "*Analysis of Chiral Amino Acids in Conventional and Transgenic Maize*" *Anal. Chem* 79, pp. 5077. MEX-143.**

[25] **Escrito Inicial de los Estados Unidos Mexicanos, 15 de enero de 2024, ¶ 138.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				was used, with which "different d-amino acids were detected in all the corn samples investigated, providing reproducible quantification of the d-enantiomeric excess." The production of secondary metabolites may have important implications for food safety. Alterations in these metabolites may result in the production of toxic or harmful compounds that are not identified in standard substantial equivalence evaluations. The chiral-MEKC-LIF method revealed differences in metabolite production that suggest changes in the metabolic pathways of the GM plant. Taking into account that the principle of substantial equivalence, adopted by the OECD and FAO/WHO, does not constitute a safety assessment in itself. It is based on limited comparisons and may not detect significant metabolic changes. This study showed that enantioselective techniques, such as chiral-MEKC-LIF, may identify differences that are not detected by conventional analysis, calling into question the reliability of substantial equivalence as the sole assessment criterion. In addition, the study demonstrates that: "The transgenic corn induced significant changes in white blood cell populations that are associated with an immune response."[26] Therefore, although differences in amino acids and metabolites may not present immediate risks, their

[26] **Herrero, M., E. Ibañez, P. J. Martín-Álvarez y A. Cifuentes (2007). "Analysis of Chiral Amino Acids in Conventional and Transgenic Maize"** ***Anal. Chem*** **79. MEX-143**.

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				long-term cumulative effects are not well understood. Prolonged ingestion of transgenic corn with altered amino acid and metabolite profiles may have negative health impacts that require thorough evaluation. The differences in amino acid chirality and metabolite production observed in the study raise serious concerns about the safety and substantial equivalence of GM crops. With respect to Annex **MEX-144**, the U.S. argument that differences in amino acid content and chirality and differences in metabolite production do not generally constitute safety concerns by themselves, fails to take into account the broader scientific and biological implications that these factors may have. Regarding significant metabolic differences, the study demonstrated significant and systematic differences in the amounts of certain metabolites between the transgenic corn varieties and their corresponding non-transgenic lines. These metabolic differences indicate alterations in the biochemical pathways of transgenic plants, which may have important implications for long-term food safety and health. Data from the study, "using this approach, significant differences were systematically observed between the detected amounts of some metabolites in conventional varieties compared with their corresponding transgenic lines."[27]

[27] **Levandi, T., C. Leon, M. Kaljurand, V. García-Cañas y A. Cifuentes (2008). "Capillary Electrophoresis Time-of-Flight Mass Spectrometry for Comparative Metabolomics of Transgenic versus Conventional Maize". Anal. Chem. p.6329. MEX-144.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				The identification of certain metabolites as potential biomarkers of transgenic Bt corn suggests that there are specific changes in metabolism that are unique to transgenic plants. These biomarkers may serve as indicators of other possible biological and toxicological effects that are not detected in conventional studies. The principle of substantial equivalence, which is used to assess the safety of GM crops, is not sufficient to detect significant metabolic changes that could have health implications. This study shows that metabolomics procedures based on CE-TOF-MS can provide a more detailed and accurate assessment of the differences between GM organisms and their conventional counterparts. The study concluded that "metabolomics procedures based on CE-TOF-MS can open new perspectives in the study of transgenic organisms in order to corroborate (or not) their substantial equivalence with their conventional counterparts."[28] Prolonged ingestion of GM corn with altered metabolite profiles may have negative health impacts that require thorough evaluation. Alterations in the metabolic profile of GM plants could affect nutrition and digestibility, as well as potentially induce unanticipated adverse effects.

[28] **Levandi, T., C. Leon, M. Kaljurand, V. García-Cañas y A. Cifuentes (2008). "Capillary Electrophoresis Time-of-Flight Mass Spectrometry for Comparative Metabolomics of Transgenic versus Conventional Maize". Anal. Chem. p.6329. MEX-144.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				Significant differences in metabolites observed in the study indicate metabolic alterations that may have important biological and health implications. These differences call into question the reliability of the principle of substantial equivalence as the sole evaluation criterion and justify the need for strict regulation.
138	MEX-145	Agapito-Tenfen, S.Z., M.P. Guerra, R.O. Nodari & O. Wikmark. (2020). *"Untargeted Proteomics-Based Approach to Investigate Unintended Changes in Genetically*	This paper identifies a potential allergenic protein in its sample set, and does not determine that the protein is an allergenic protein, contrary to what Mexico states in paragraph 138 of its Initial Submission.	The authors of this article found that "*data shows that the GM variety [of maize] is not substantially equivalent to its non-transgenic near-isogenic variety"* because *"proteomic data showed that energy metabolism and redox homeostasis were unequally modulated in GM Bt and non-GM maize variety samples.*" and also observed a protein with allergenic potential. (**MEX-145**, pp. 1, 10, 11). The authors explain that "*it is possible that the allergenic potential of GMOs may be increased due to the introduction of potential foreign allergens, to potentially upregulated expression of allergenic components caused by the modification of the wild type organism or to different means of exposure*" (**MEX-145**, p. 10). According to FAO/WHO, cross-reactivity between a query protein and a known allergen should be considered when there is more than a 35% identity match in the amino acid sequence of the expressed protein. The result of the above-mentioned research showed an allergenicity match of 42.4%. (**MEX-145**, p. 10) In addition, the allergenic potential of the protein studied is related to common allergens, including its potential isoforms. In this sense, a study revealed that 96% of patients presented outbreak pollinosis and

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				oral allergy syndrome to the potential allergen isoform. (**MEX-145**, p. 10)
138	MEX-146	Benevenuto, R. F., H. J. Venter, C. B. Zanatta, R. O. Nodari & S. Z. Agapito-Tenfen. (2022). "*Alterations in genetically modifiedcrops assessed by omics studies: Systematic review and meta-analysis"*. Trends in Food Science & Technology.	This article does not present any adverse effects on plant health or food safety but rather just proposes that omics could be incorporated into a risk assessmentprocess.	The United States provides no references to support its assertion and ignores a key section of this study that Mexico cites in its Initial Written Submission. This section explicitly addresses metabolic changes in GM plants, which corroborates Mexico's concerns. In other words, it details alterations in carbohydrate and energy metabolism and abnormal growth, crucial elements of Mexico's argument. (**MEX-146**, Sección 4.1, pp. 332-334). In addition, the **MEX-146** study employed molecular profiling techniques that allow precise and simultaneous measurements of the expression of thousands of components (proteins, metabolites) in organisms (e.g., GM plants) subjected to different treatments or conditions (e.g., molecular, biochemical, physiological and metabolic comparison between GM and conventional non-GM plants). The results of the study showed the identification by comparison of previously known allergens of a protein with allergenic potential. This protein was detected only in the GM corn variety MON-810, genetically modified to insert, by microparticle bombardment, a genetically modified version of the cry1Ab gene, which confers to the modified corn plants the trait of resistance to lepidopteran insects. Additionally, in **MEX-146,** 16 different proteins were identified to be positively or negatively regulated (in short, altered expression) between GM corn and conventional non-GM plants. Eleven of the 16 differentially expressed proteins were detected only in the GM corn. It cannot be ruled out

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				that the proteins identified in GM corn have allergenic potential, since the identification and classification of allergenic or toxic molecules is done on the basis of specific toxicological studies. It should be mentioned that currently no regulatory authority requires molecular profiling studies of GM corn varieties during the application process for authorization of transgenic corn varieties. Finally, omics technologies assess differences at the molecular level, as opposed to substantial equivalence studies that are limited to looking at differences in nutrient composition. These technologies are relevant because they identify alterations or changes in protein levels relevant to biological processes (i.e., it is a tool that could be used to detect increased hazards of GMOs).
139	MEX-147	Giraldo, P. A., Shinozuka, H., Spangenberg, G. C., Smith, K. F., &Cogan, N. O. I. (2021). "*Rapid and Detailed Characterization of Transgene Insertion Sites in Genetically Modified Plants via Nanopore Sequencing"*. Frontiers in plant science.	Mexico's claim that "any modification of the genetic material of any species, have an enormous and possibly irreversible effect on the way it evolves" alsoapplies to corn bred through traditional breeding, including native Mexican varieties. This phenomenon is not unique to GE corn.	The United States has provided no references to support its claims that the undesirable effects of genetic modifications affect naturally-crossbred corn. Regardless of the above, the U.S. claims do not contradict the research findings regarding the potential health risks associated with GM plants. (**MEX-147**, pp. 7-8) The U.S. confusion is useful for Mexico to clarify its position, which is essential to understanding the dispute. Mexico is concerned about "genetic contamination" from the use of GMOs. In the case of GMOs, genetic transfer includes the transfer of genes from one species to another, this insertion results in the fictitious acquisition of dominant risks, which leads to the loss of specific traits of the species, due to the GMO generation methods themselves, this brings with it undesirable effects, such as the stacking of genes or those

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				mentioned in the response to the claims of the Exhibit **MEX-142**. The statement made by the United States is again of concern because it denotes a lack of understanding of the principles of the theory of evolution, whose processes explain what is happening with the artificial selection carried out by farmers for thousands of years. In addition, it also seems to denote a confusion between a process called hybridization between different varieties of corn and their wild relatives, and another that is the introgression of transgenic sequences in the populations of native, conventional corn and its wild relatives, referred to as "genetic contamination. The first, in fact occurs naturally between corn varieties and their wild relatives, has allowed the great genetic diversity to exist in corn varieties around the world and is used as a basis for conventional genetic improvement of a complete process. Actually, the effects of transgenic sequence introgression on conventional, native or wild relatives corn populations do have indeterminate effects and do not depart from a natural process as these transgenes come from species of taxa far from the species of interest. Now, this article **MEX-147** reports the results of a study that shows that the method developed offers a greater degree of resolution to identify and characterize transgenic events in the host genome. This is crucial because it allows specific genetic modifications to be detected with greater precision and detail than traditional methods, which was

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				previously not possible with Illumina's standard short-range sequencing strategies. The method identifies moderate-sized secondary inserts that would previously have been overlooked. These inserts may have significant biological effects that may not be detected by less precise methods. The proposed workflow takes only about a week from DNA extraction to the analyzed result. The new workflow is fast, simple and cost-effective, providing accurate results in a few days. This is a significant advantage for risk assessment and traceability, as it allows rapid identification and characterization of transgenic events prior to marketing. Detailed molecular characterization of GM plants is crucial to develop detection and identification methods that meet traceability and labelling requirements. This is essential to ensure food safety and consumer confidence in transgenic products. The method complements existing approaches, making the molecular characterization process more complete and robust. This ensures that any unwanted or unexpected transgenic event is detected, mitigating potential risks to health and the environment. The article states that "The method will complement existing approaches to molecular characterization of transgenic plants, as it makes the process faster, simpler and more cost-effective." In conclusion, an advanced and detailed methodology is provided for the molecular characterization of transgenic plants that surpasses traditional techniques in precision and efficiency.
139	MEX-148	Bushey DF, Bannon GA, Delaney BF, Graser G, Hefford M, Jiang X, Lee TC, Madduri KM, Pariza M, Privalle LS, Ranjan R,	This paper shows the exact opposite of what Mexico is arguing. Mexico alleges that "the expression of new proteins can trigger allergic reactions whose effects are not estimated in comparative analysis." The paper shows the	The United States chooses not to mention that this study questions the efficacy of traditional safety assessments that are based on the concept of "*substantial equivalence*", highlighting in particular the difficulties presented by the new

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
		Saab-Rincon G, Schafer BW, Thelen JJ, Zhang JX, Harper MS. "*Characteristics and safety assessment of intractable proteins in genetically modified crops"*. Regul Toxicol Pharmacol,2014.	diligence that scientists are taking to consider how to assess the potential allergenicity of proteins that may have physical characteristics that make them hard to assess by the typical processes. There is an entire annex to the Codex Guidelines that explains how to perform an allergenicity assessment.[29]	generations of transgenic crops.[30] In addition, the study reinforces Mexico's concern that "*the thresholds of exposure for most food protein allergens have not yet been determined*",[31] refuting the U.S. assertion that there are diligent efforts to address the scientific risk assessment of these concerns about the safety of genetically modified crops. On the other hand, the United States ignores that the scientific article already evidences the existence of backgrounds in which Bt aerosols could cause negative effects to human health. This background is fundamental in the scientific work because it gives rise to the arguments that the Cry proteins constitutively expressed by Bt are the cause of the negative health effects related to allergic skin sensitivity and the induction of antibodies (immunoglobulins), or both. The Cry genes present in the transgenic constructs, which are obtained from multiple Bt strains, inserted in agriculturally important plants such as corn or soybean, express and maintain the same insecticidal function. Therefore, it is confirmed that the present research work is an irrefutable reference to sustain that Cry proteins already had a history of negative effects on human health. Thus, the reason

[29] *See* Codex Guidelines, Annex 1 ("Assessment of Possible Allergenicity") (Exhibit USA-153).

[30] **Bushey DF, Bannon GA, Delaney BF, Graser G, Hefford M, Jiang X, Lee TC, Madduri KM, Pariza M, Privalle LS, Ranjan R, Saab-Rincon G, Schafer BW, Thelen JJ, Zhang JX, Harper MS. *Characteristics and safety assessment of intractable proteins in genetically modified crops*. Regul Toxicol Pharmacol, 2014, p. 155. MEX-148.**

[31] **Bushey DF, Bannon GA, Delaney BF, Graser G, Hefford M, Jiang X, Lee TC, Madduri KM, Pariza M, Privalle LS, Ranjan R, Saab-Rincon G, Schafer BW, Thelen JJ, Zhang JX, Harper MS. *Characteristics and safety assessment of intractable proteins in genetically modified crops*. Regul Toxicol Pharmacol, 2014, p. 163. MEX-148.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				for including this research work in Mexico's Initial Written Submission is explained**.**
144	MEX-155	Oraby HA, Kandil MH, Hassan AAM, Al-Sharawi HA. 2014. "*Addressing the issue of horizontal gene transfer from a diet containing genetically modified components into rats tissues"*. Afr J Biotechnol.	This is a poorly performed study that lacked controls investigating whether components in common between the test and control diet would each appear in these tissues. The researchers sampled tissues of liver and brain, but did not show that the DNA was in the cells (as opposed to blood or fluid) such that whennew cells were produced the new cells also had the DNA. Presence of antibiotic resistance genes in blood and fluid is not a hazard. What could possibly start to be a hazard were if it were incorporated into certain cells of the body, but the study did not show that. Further, this article vaguely refers to "laboratory chow impossible to attribute the effect seen to either corn or soy let alone a specificcorn variety.	The U.S. response lacks citations to support its scientific claims, especially given the technical nature of its criticisms. Nor is there any such support to demonstrate that the study lacks scientific method and should therefore be dismissed. In addition, it is completely contrary to scientific ethics to request human experimentation and even more so when the purpose of the study is to observe health effects over a prolonged period of time. The study investigates the potential threats of GM foods by analyzing the effects of GM cauliflower on rat tissues using a controlled experimental design with control and treatment groups. A detailed evaluation of various tissues, such as liver and brain, was performed using molecular biology techniques, such as PCR, to detect GM food DNA in tissues. The findings of GM DNA in blood and fluids raise several concerns: the possibility of horizontal gene transfer, how this genetic material might interact with the consumer's genome and its impact on genetic integrity, and food safety issues that require further evaluation of the potential long-term effects of ingesting these foods. In addition, as in the case of Mexico's response to Exhibit **MEX-129**, the broader perspective of this study helps to provide context when analyzing studies that have a more restricted approach, which could isolate particular breeds of corn. Also, an experiment that combines different GM crops in a diet is important because it more closely resembles

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				human diets and contributes to a line of research followed by academics in the field (**MEX-287**, pp. 6-7).
144	MEX-156	Oraby, H.AS., Aboul-Maaty, N.AF., Al-Sharawi, H.A. et al. 2022. "*Horizontal transfer of antibiotic resistance genes into microflora and blood cells in ratsfed on GM-diet"*. Bull Natl Res Cent.	This study states that "[n]one of these animal diets were labeled as genetically modified" (p. 2) but purports to show that the diets contain genetic elements often used in genetic engineering. The article states: "Animal feed samples were obtained from different animal feed suppliers in Cairo." As a result, it is not clear (i) what the test article was; (ii) whether it was, in fact, genetically engineered or how much of it was genetically engineered; (iii) where the researchers actually purchased the food; or (iv) how someone could repeat the study. A scientific study should be well-documented so that others can perform the same study and confirm the results. Given that the test material was not generally well characterized, it is very difficult to interpret this study. The studyalso should have had a control group that received diet without the genetic elements to show that what the authors were measuring was not an artifact of something other than the diet. The paper also does not say how the researchers chose which bacterial colonies to study after culturing 24-48 hours, or what kinds of bacteria were present. For example, it is possible that some of the bacteria could have naturally contained the antibiotic resistance markers, as some bacteria naturally contain the genes that the researchers looked for. It would have been important to rule out that the bacteria the researchers found didnot naturally have the genes they were intending to detect.	Criticisms of the reliability of the study are unfounded. The aim of this study was to investigate whether after a 90-day transgenic diet containing the ARM genes *nptII* and *aadA*, the DNA from the *nptII* and *aadA* genes would be transferred to the blood and bacterial cells present in the gastrointestinal tract and blood cells of two groups of rats (**MEX-156**, p. 1). The United States ignores that this study explains, (in the same paragraph cited by them), how the GM content of animal feed samples was verified by the conventional polymerase chain reaction ("PCR") test which confirmed the presence of the target genetically modified ingredients (P35S, *nptII* and *aadA*) (**MEX-156**, p. 2). On this basis, the researchers were subsequently able to demonstrate the transfer of DNA from the genetically modified diets to the enteric microflora and blood cells of the animals after 90 days on the diets. (**MEX-156**, p. 10). The study is also published in the "Bulletin of the National Research Centre", a renowned journal indexed in various academic databases and search engines of scientific journals, which adheres to high standards of quality and academic rigor. This is a solid indicator that the study has undergone a thorough and rigorous review and selection before its publication, and has also met the criteria of originality, relevance and scientific validity required by the journal. The process of peer review and critical evaluation of the methodology, results and conclusions of the study, to which the article

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				was submitted, guarantees its quality and reliability. In addition, the study provides solid evidence of horizontal transfer of antibiotic resistance genes in rats fed transgenic diets, based on detailed experimental methods and results confirmed by sequencing and analysis of genetic information, which we explain below: 1. the absence of labeling does not rule out the possibility that the food contained genetically modified components, since PCR and sequencing tests confirmed the presence of genetic elements commonly used in genetic engineering, such as the antibiotic resistance genes *nptII* and *aadA*.; 2. the lack of detailed information on the origin of the diets does not invalidate the reproducibility of the study, as the methods used for DNA extraction, detection of antibiotic resistance genes and analysis of the results are clearly described; 3. the study establishes a group of control rats that were not exposed to the transgenic diet; 4. the selection of bacterial colonies for analysis was based on specific criteria and accepted protocols, which supports the validity of the results obtained.
145	MEX-157	ISAAA. (s/f). "*GM Events with Antibiotic resistance. International Service for the Acquisition of Agribiotech Applications.*	As Mexico notes: "At the international level, there is a record of 161 approved GM events with antibiotic resistance, several of which are edible plants, including corn with 34 events." Rather than supporting Mexico's position, these data just reinforce how inconsistent Mexico's	The United States seeks to decontextualize the source used by Mexico. Contrary to what the United States claims, the list demonstrates that the cases of GMO events with antibiotic resistance are well documented.

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
			views are compared to other regulators around the world. By Mexico's own language, regulators chose to approve events with antibiotic resistance markers more than 34 times based on scientific evidence of safety. The Codex Guidelines address how to assess the safety of antibiotic resistance markers.[32] Moreover, these antibiotic resistance markers are just "selection markers," which are tools developers use in the process of developing the transgenic crop, and not intended to confer resistance to antibiotics in the field.	The horizontal transfer of antibiotic resistance genes through GM foods has not been a minor concern for Mexico, as there is no scientific evidence that foods with these genes are safe; they are not just selection markers as the US intends to show, they are an element of the transgenic corn processing technology, which as evidenced in Mexico's initial written submission, may potentially contribute to the spread of this resistance in non-target intestine bacteria, and this could have serious implications for public health and the efficacy of medical treatments. This document was used by Mexico to interpret evidence from other sources regarding the unintended consequences of transgenic crops, such as horizontal gene transfer, allergenicity and decreased efficacy of antibiotics in humans. (See **MEX-150**, **MEX-151**, **MEX-152**, **MEX-153**, **MEX-154**, **MEX-155**, **MEX-156**; **MEX-158**).
146	No citation	N/A	Mexico claims, citing nothing, that "[s]ince 2013, robust scientific evidence (over 1000 human samples from four independent studies) have shown that DNA fragments large enough to carry genes from food can avoid degradation and enter the human circulatory system." This statement appears to refer to MEX-158 (below). This study does not mention that the DNA obtained from food was stably integrated into the human DNA, let alone expressing any proteins. The presence of food-origin DNA in the blood stream is not harmful, and MEX-158 does not distinguish transgene DNA from any other DNA that was	Within the analysis made by the United States, there is an assertion of form and another that would seem to be relevant in substance. The first is worth mentioning and lies in the assertion of the United States that Mexico did not include a scientific source to support its argument contained in paragraph 146 of the Initial Written Submission. However, Mexico points out that the two ideas contained in the paragraph in question are supported by the source **MEX-158**.[33] Regarding said scientific evidence, it is important to mention that at no time, both in Exhibit **MEX-159** as well as in Mexico's Initial Written Submission, does

[32] Codex Guidelines, sec. 5, paras. 55-58 (Exhibit USA-114).

[33] **Spisák S, Solymosi N, Ittzés P, Bodor A, Kondor D, Vattay G, Barták BK, Sipos F, Galamb O, Tulassay Z, Szállási Z, Rasmussen S, Sicheritz-Ponten T, Brunak S, Molnár B, Csabai I.** ***Complete genes may pass from food to human blood.*** **PLoS One. 2013. MEX-158.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
			present in the plant.	it state (as indicated by the United States) that DNA obtained from food, when passing through the bloodstream, will be stably integrated into human DNA. Nor is it mentioned that this DNA has the capacity to express itself in the form of proteins. On the other hand, the U.S. response mentions, without giving a clear reference, that "*the presence of food-origin DNA in the blood stream is not harmful, and MEX-158 does not distinguish transgene DNA from any other DNA that was present in the plant."* There are still no reports where it has been investigated that the presence of transgenic sequences may not be harmful or may otherwise be harmful in the bloodstream, however, in three works cited in the Exhibit **MEX-158**,[34] the possibility of distinguishing transgenic DNA from any other DNA present in the plant is mentioned, contrary to what the United States claims.
146	MEX-158	Spisák S, Solymosi N, Ittzés P, Bodor A, Kondor D, Vattay G, Barták BK, Sipos F, Galamb O, Tulassay Z, Szállási Z, Rasmussen S, Sicheritz-Ponten T, Brunak S, Molnár B, Csabai I. *"Complete genes may pass from food to human blood".* PLoS One. 2013.	Mexico claims that "[S]tudies in animals (trout, goats, pigs and mice) fed GMOdiets support this idea [that DNA fragments from food can enter the human circulatory system], which means that these fragments have been found in the digestive tract and leukocytes." The studies cited in this article do not appear toaddress consumption of GE corn (and non-mammalian trout are irrelevant as it relates to adverse effects in humans in this case). This article also did not reportor evaluate stable integration into the DNA of the organism consuming it.	This study, published in a high-impact scientific journal, is based on the analysis of more than 1,000 human samples from four independent studies. (**MEX-158**, pp. 1, 9). The authors point out that, depending on the degree of food processing, various fractions of DNA molecules may remain in consumed products, including products such as corn chips and chocolate. (**MEX-158**, p. 1). This study is relevant because it demonstrates that some "*DNA fragments large enough to carry complete genes can pass from the digestive tract to blood*", supporting Mexico's argument on the transfer of GM traits to non-GM

[34] **Chainark P, et al, "*Availability of genetically modified feed ingredient: investigations of ingested foreign dna in rainbow trout oncorhynchus mykiss*"; Fisheries Science, 74: 380–390. MEX-429; Mazza R, Soave M, Morlacchini M, Piva G, Marocco A "*Assessing the transfer of genetically modified DNA from feed to animal tissues*". Transgenic Res, 2005, 14: 775–784. MEX-430 y, Sharma R, et al "*Detection of transgenic and endogenous plant DNA in digesta and tissues of sheep and pigs fed Roundup Ready canola meal*". J Agric Food Chem, 2006, 54: 1699– 1709. MEX-431**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				organisms, including access to the circulatory system (**MEX-158**, p. 3). Contrary to U.S. claims, the samples analyzed were taken directly from human subjects, which reinforces the validity of these results. This is reinforced by similar research in various animal species, including non-mammals, to which the United States refers, which only confirms the conclusions of the human study. Although trout are not mammals, studies in goats, pigs and mice, which are mammals, support the idea that DNA fragments from food may enter the circulatory system. These studies provide additional and relevant evidence that reinforces the possibility that DNA fragments from GM foods may enter the human circulatory system. The fact that plant DNA was found in human plasma, while control samples were free of plant DNA, suggests that this phenomenon is neither isolated nor anecdotal. In addition, the precise logarithmic distribution of plant DNA concentration in plasma samples suggests a systematic and reproducible process of entry of exogenous DNA into the bloodstream, which is a significant finding that cannot be ignored. This discovery highlights the need for a more rigorous and detailed evaluation of the effects of transgenic foods on human health. Mexico states that "any modification of the genetic material of any species has an enormous and possibly irreversible effect on the way it evolves".[35] The potential integration of transgenic DNA fragments

[35] **Escrito Inicial de México, para. 139.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				into the organism that consumes it, even if it has not been evaluated in this specific article, is a legitimate and justified concern. The possibility of transgenic DNA entering the circulatory system and being able to interact with human DNA requires a thorough and careful evaluation, given that the long-term effects of such interaction are unknown and could be harmful.
147-148	MEX-044	Chávez, C., Virgen-Ortiz, J. J., Serrano-Rubio, L. E., Martínez- Téllez, M. A., & Astier, M., "*Comparison of nutritional properties and bioactive compounds between industrial and artisan fresh tortillas from corn landraces*", 2020, Current Research in Food Science.	Mexico claims that "GM corn has reduced levels of protein, fiber and antioxidants compared to native corn varieties." The cited article does not even address GE corn. The article discusses blue tortillas, white tortillas, and industry-made tortillas. The "BT" referred to in this article refers to blue tortillas. Similarly, Mexico claims: "GM corn has demonstrated marked disparities in its levels of macronutrients, micronutrients and essential minerals compared to native corn," citing this article. Again, this article does not investigate GE corn, but rather it focuses on nutritional value of tortillas made from blue corn, white corn, or industrial corn. The article provides no evidence to indicate where the corn is sourced from or whether any of the corn is GE.	The answer provided immediately above for Exhibit **MEX-158** is relevant here as well, affirming the scientific integrity of the study. This research does not specifically focus on the effects of GM corn, but on the poor nutritional quality of industrial tortillas made predominantly with GM corn ingredients. This again shows that the United States may have deliberately misinterpreted or misrepresented Mexico's arguments regarding the connection between ultra-processed foods and GM corn. The United States has not yet effectively refuted these points. Besides, this study was designed to evaluate the difference in the content of nutrients and bioactive compounds between tortillas made from native corn grown without agrotoxics and tortillas made from hybrid corn flour. All tortillas were analyzed in terms of chemical composition, dietary fiber, calcium and phytochemical content, antioxidant capacity and phenolic acid profile. The chemical and nutritional variation of tortillas was estimated by analysis of main components. The data showed that artisanal tortillas made with local varieties of blue and white corn (native corn) had a significantly higher content ($p < 0.05$) of nutritional and bioactive compounds compared to those of the supermarket (hybrid corn). HBMT tortillas had a high content of free phenolics and the highest

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				antioxidant capacity which was about 1.7 to 2.1 times that of CWMT tortillas. Total dietary fiber was higher in HBMT (15.7 ± 1.06 g/100 g) than in CWMT (11.6 ± 0.96 g/100 g). CWMT had the lowest calcium content (42.1 ± 0.9 mg/100 g) compared to handmade tortillas (155.5 ± 4.5 mg/100 g). The results of HPLC indicated the presence of ferulic, p- cumaric, caffeic, syrinic and 4-hydroxybenzoic acids. Interestingly, handmade blue corn tortillas had a ferulic acid content 4.5 times higher compared to commercially produced white corn tortillas, so they can be a good source of phenolic antioxidants, particularly ferulic acid. This study showed that fresh homemade corn tortillas had superior nutritional-nutraceutical properties compared to CWMT.
148	MEX-049	De la Parra, C., Serna Saldivar, S. O., & Liu, R. H. "*Effect of processing on the phytochemical profiles and antioxidant activity of corn for production of masa, tortillas, and tortilla chips*, 2007, Journal of Agricultural and Food Chemistry.	Mexico alleges that "[s]ince [GE corn] come[s] mostly from commercial hybrid lines of corn, they have a lower amount of phenolic compounds and anthocyanins and, therefore, a lower antioxidant capacity," citing this article. This article is about the processing of corn in general and is not specific to GEcorn. Whether GE or not, most commercialized corn varieties are hybrid varieties.	The comments made for Exhibits **MEX-158** and **MEX-044** are applicable. The publication mentioned does not correspond to the paragraph analyzed by the U.S. government. The article cited for paragraph 148 is **MEX-144**. In this work a comparison was made between tortillas with processed flours and tortillas made from native colored corn, finding significant nutritional differences between these two groups. Indeed, in this other work it was not determined whether the commercial masas with which tortillas are made in Mexico come from transgenic corn. However, in the **MEX-125**., when analyzing different industrialized products based on corn, including the masa with which commercial tortillas are made, transgenic sequences were detected in 82% of all foods, also 30% of samples with GMO events containing glyphosate residues.
149	MEX-068	Steven A. Abrams, Jaclyn Lewis Albin,	Mexico cites this article as support for the contention that GE foods are used to produce	This clinical report, conducted by the American Academy of Pediatrics, provides sources that

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
		Philip J. Landrigan. Committee on nutrition, council on environmental health and climate change. (2023). "*Use of Genetically Modified Organism (GMO)-Containing Food Products in Children. Pediatrics."*	large quantities of nutritionally-deficient "ultra-processed foods." This article suffers from numerous deficiencies. Although the article claims "widespread use of GMO ingredients in food, including nearly all ultra- processed foods in the United States," there is not a clear equivalency to the use of GE-derived ingredients and "ultra-processed" foods, and the article does not cite any scientific studies to support such equivalency. In addition, this paper places undue emphasis on the International Agency for Research on Cancer ("IARC") classification of glyphosate as "probably carcinogenic to humans" in 2015 (*see also* analysis of this IARC classification in MEX-301, below). The article does not acknowledge that IARC did not assess the risks of glyphosate residues on or in food but simply identified the hazards potentially associated with glyphosate in general, without consideration of exposure levels. Nor does the article acknowledge that subsequent to the IARC classification, the joint Food & Agriculture Organization of the United Nations ("FAO")/World Health Organization ("WHO") Meeting on Pesticide Residues ("JMPR") considered the body of evidence for cancer outcomes for glyphosate, including the studies reviewed by the IARC and additional relevant studies, and still concluded that glyphosate "is unlikely to pose a carcinogenic risk to humans	support the claim that ultra-processed or multicomponent foods are more likely to contain transgenic ingredients,[37] against U.S. criticism. This study is significant for its analysis of the risks associated with GM foods, especially those consumed by children, in various jurisdictions. For example, the study highlights a notable case involving genetically modified salmon in the United States, where its approval by the Food and Drug Administration was challenged in federal court, leading to a ban on their use pending further safety assessments.[38] On the subject of ultra-processed foods, it is important to note that, one of the first causes of death in industrialized and other developing countries such as Mexico, are chronic and non-communicable diseases such as diabetes, cardiovascular diseases, overweight and obesity. The cause of the increase in these diseases is closely related to eating habits. Recent research has documented that the western diet which consists mainly of ultraprocessed foods of low nutritional quality, especially for the high amount of calories produced by sugars and refined flours are the direct causes of this global crisis. Sweeteners become more relevant because sugar cane, beet and of course corn are used for the production of sucrose in the case of sugar cane and high fructose from beet and corn.

[37] **Steven A. Abrams, Jaclyn Lewis Albin, Philip J. Landrigan. Committee on nutrition, council on environmental health and climate change. (2023).** ***Use of Genetically Modified Organism (GMO)-Containing Food Products in Children. Pediatrics*****, p. 3. MEX-068.**

[38] **Oraby, H.AS., Aboul-Maaty, N.AF., Al-Sharawi, H.A. et al. 2022.** ***Horizontal transfer of antibiotic resistance genes into microflora and blood cells in rats fed on GM-diet*****. Bull Natl Res Cent 46, p. 3. MEX-156.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
			via exposure from the diet."[36] This article also does not acknowledge the conclusions of multiple global regulatory authorities and experts that glyphosate is not likely to be carcinogenic to humans (*see* analysis of MEX-301, below). Finally, the article implies that consumption of GE products is inherently associated with increased pesticide exposures and that exposure to pesticide residues inherently means there is increased risk. These implications relate to a misunderstanding, or lack of awareness, of pesticide tolerances and the rigorousassessments that support those determinations. The article also ignores that pesticides may be used on both GE and non-GE crops (*see* Annex II, concerning agrochemical usage and GE crops). The risk of an exposure depends on the toxicity of the compound and the type and amount of exposure. It is not accurate to imply that any exposure to glyphosate residues in one's diet necessarily results in an increase in risk of adverse health effects, as the United States furtherexplains in Section IV.A of its Rebuttal.	As mentioned above, there is no need for an equivalence between the production of high-fructose corn that is entirely destined for the production of ultra-processed foods with respect to the amount of transgenic corn used for the production of this syrup on the understanding that 90% of the corn produced in the United States is of transgenic origin. In addition, the largest GM corn sweetener industries belong to the United States. On the other hand, other ingredients that are most used in ultraprocessed foods are corn oil, canola soybean cotton and palm. Coincidentally, the first four species at least in the USA, their agrosystems are supported by genetically modified plants. The United States also criticizes the important research carried out by the International Cancer Research Centre (IARC), the World Health Organization's cancer-fighting body, in relation to the carcinogenicity of glyphosate and other herbicides used in the production of genetically modified food.[39] This research appears to have provided the basis for the American Academy of Pediatrics to thoroughly examine glyphosate-containing compounds in genetically modified foods. It found glyphosate residues in commonly

[36] Joint FAO/WHO Meeting on Pesticide Residues ("JMPR"), "Pesticide Residues in Food – 2016: Toxicological Evaluations," at 257 (May 2016) (Exhibit USA-154). When glyphosate was last evaluated by JMPR in 2019, the Meeting concluded that acute and long-term dietary exposures to residues of glyphosateare unlikely to present a public health concern for the uses considered by JMPR. Extra Joint FAO/WHO Meeting on Pesticide Residues, "2019 Report – Pesticide Residues in Food," at 81 (2019) (Exhibit USA-155).

[39] **Oraby, H.AS., Aboul-Maaty, N.AF., Al-Sharawi, H.A. et al. 2022. *Horizontal transfer of antibiotic resistance genes into microflora and blood cells in rats fed on GM-diet*. Bull Natl Res Cent 46, p. 5. MEX-156.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				consumed children foods, which are identified for toxic and carcinogenic risks.[40] Notably, the United States vigorously attempts to undermine these findings, despite having previously stated in its submissions that this concern is irrelevant to the current dispute. In this regard, the US government maintains that from a Joint Meeting to evaluate evidence by the FAO/WHO on Pesticide Residues ("JMPR"), "Pesticide Residues in Food - 2016: Toxicological Evaluations," (May 2016) concluded that glyphosate is unlikely to pose a carcinogenic risk to humans from dietary exposure, however, at such a meeting the exact conclusion was "*unlikely*". Improbable and unlikely are not synonymous and even more, the term, unlikely also has no scientific validity in the fact that you have to give numerical values that support the degree of damage of this herbicide. As the United States has repeated countless times, this kind of research needs more research on the equivalences between glyphosate doses in food and what they cause. In the meantime, it is imperative to take measures to prevent probable irreversible damage to human health.
150	MEX-160	Matos, R.A., Adams, M., Sabaté J. (2021). "*Review: The consumption of ultra-processed foods and noncommunicable diseases in Latin America"*. Frontiers in	Mexico asserts that "[t]he impact of these ultra-processed foods on the Mexican diet is alarming." Genetic engineering has nothing to do with ultra-processed foods, to the extent the latter is even a health issue. Foods well beyond corn canbe used as ingredients in ultra-processed products, such as wheat, canola, cottonseed, and	The United States has omitted, both here and in its written submissions, arguments and references to the link between ultra-processed foods and GM corn, ignoring Mexico's position that intensive agriculture involving the use of pesticides predominantly serves to produce these foods (Mexico's Initial Submission, paras. 149-151,

[40] **Oraby, H.AS., Aboul-Maaty, N.AF., Al-Sharawi, H.A. et al. 2022. *Horizontal transfer of antibiotic resistance genes into microflora and blood cells in rats fed on GM-diet*. Bull Natl Res Cent 46, p. 4. MEX-156.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
		Nutrition.	even sugar, and is not something unique or specific to genetic engineering. This article does not discuss information about corn, let alone GE corn.	**MEX-068, 069, 159, 160**). Surprisingly, it even questions that ultra-processed foods constitute a health problem, despite evidence pointing to a strong association between consumption and health damage such as obesity, hypertension, cardiovascular diseases, type 2 diabetes, cancer and all-cause mortality risk. (**MEX-160**, p. 1). It is absurd to think that genetic engineering does not influence ultra-processed foods. The NIH (National Institute of Health) describes genetic engineering as the alteration of an organism's DNA, which includes modifications to yeast, bacteria, animals and plants, such as corn, to produce ultra-processed products.[41] **MEX-160** mentions that 90% of canola, cotton and sugarcane crops in the U.S. are GM, demonstrating the relevance of genetic engineering in the production of ultra-processed foods. In addition, using multiple transgenic species can cause cumulative damage to health. In addition, the U.S. focuses on the claim that other ingredients in ultraprocessed foods could have the same health effects as GM corn. However, assuming that this is true, this does not diminish the results of the study, which highlight the risks and health problems associated with ultraprocessed foods containing GM corn ingredients. Although the analysis does not directly address GM corn, it is important to consider all references to understand the impact of related research.
181	MEX-217	Krimsky, S. (2015). "*An Illusory Consensus behind GMO Health Assessment."* Science, Technology & Human Values.	Mexico, in claiming that "[t]he safety of GMOs is completely illusory," is simply reiterating the title of the paper, which is emotive. The author provides a review of the literature, much of which has shown no negative health impacts of GE foods and feed, and uses a methodology that	The U.S. criticism that this study is simply the result of keyword searches is speculative and unfounded. In addition, Mexico is aware that there are studies that support the safety of GM foods, some of which are cited in this article. However, contrary to what the United States asserts in this dispute, Mexico

[41] NIH, "*Ingeniería Genética"*, p.2., **MEX-437**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
			is ill-defined but appears to be the result of keyword searches.	emphasizes that the supposed consensus on the safety of genetically modified products is fictitious. That is why it exhibited this Annex. This article also confirms the conflict of interest in the publication of papers related to GMOs as a result of pressure from biotechnology developers. Mexico requires an explanation and indication of what that ill-defined methodology is and the scientific reasons for this disqualification.
181	MEX-218	Hilbeck, A., Binimelis, R., Defarge, N. et al. "*No scientific consensus on GMO safety*". Environ Sci Eur 27, 4 (2015).	This is a statement purportedly signed by 300 researchers (who are not listed inthis paper); it is not a research article. The main point of this paper is that a blanket statement of food and environmental safety for all GMOs cannot be made and thus the Cartagena Protocol on Biosafety and Codex advocate for reviews on a case-by-case basis. If Mexico agrees with this statement, then Mexico should conduct a case-by-case risk assessment, as the United States argued in its Initial Submission and this Rebuttal. The statement relies on multiple Séralini studies (*see* Section II.A of U.S. Rebuttal) and also cites blog posts, some of which no longer exist, as well as Wikipedia.	This article is consistent with relevant WTO jurisprudence for provisions related to the obligation to base a risk analysis on available scientific evidence. This article exemplifies the above, as it gives voice to a large and independent community of scientists who question the supposed consensus on the safety of genetically modified foods, directly contradicting U.S. claims that there is an established agreement on the safety of GM crops. (**MEX-218**, p. 1). There is no response to these points from the United States. Furthermore, in relation to the reference to the endorsement by 300 researchers of the lack of consensus on the safety of GM foods, the article makes explicit reference to the European Network of Scientists for Social and Environmental Responsibility, backing up their claims with a public statement available online, as indicated in footnote 7 (**MEX-225**, p. 2). The European Network of Scientists for Social and Environmental Responsibility - ENSSER questions the notion of a consensus on the safety of GMOs, and highlights the debate on the issue and contradictory

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				evidence in the scientific community. The widely recognized ENSEER network advocates the benign and peaceful use of new technologies to protect the environment, biological diversity and human health against their adverse impacts; it also promotes critical, independent and transparent analyses to foster sustainable and humane technological development, as well as the creation of more democratic and participatory processes, and therefore includes diverse sources of scientific knowledge. The authors of the article emphasize the need for more independent research and informed public discussion on the safety of GM products.
185	MEX-225	Séralini GE, Clair E, Mesnage R, Gress S, Defarge N, Malatesta M, Hennequin D, de Vendômois JS. Republished study: "*long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified corn"*. Environ Sci Eur. 2014.	This is a republication of Séralini's retracted 2012 study (*see* Section II.A of U.S. Rebuttal). The study concludes: "Our findings imply that long-term (2 year) feeding trials need to be conducted to thoroughly evaluate the safety of GM foods and pesticides in their full commercial formulations." The EU hasthoroughly evaluated the need for such feeding trials and has uniformly concluded across three comprehensive studies that they are not routinely warranted.[42] The value of long-term studies has also been refuted by Codex since 2003.[43] Moreover, the journal provides a disclaimer that it is republishing the study fortransparency but disclaims its contents: "ESEU aims to enable	The United States selectively omitted text from the journal's introductory note that emphasizes the purpose of republishing an article to highlight methodological controversies. This omission circumvents the journal's assertion that "*science needs controversial debates aiming at the best methods as basis for objective, reliable and valid results*".[44] This approach undermines U.S. attempts to discredit Séralini's research as unreliable, illustrating the need for the scientific process to include diverse, sometimes contradictory, research results. In particular, the authors themselves acknowledge the different results of research on the safety of genetically modified foods, from

[42] *See supra* Analysis of **MEX-128.**

[43] Codex Guidelines, sec. 3, para. 11-12 (reflecting consensus that animal studies, including long-term animal studies, are not widely accepted to assess the safetyof whole foods and are extremely difficult to interpret) (Exhibit USA-114). As of March 2024, the United States has completed more than 200 evaluations of food from genetically engineered or genome edited plants and has not yet seen a need to request such a study.

[44] **Séralini GE, Clair E, Mesnage R, Gress S, Defarge N, Malatesta M, Hennequin D, de Vendômois JS. Republished study: *long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize*. Environ Sci Eur. 2014, pp. 2. MEX-225.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
			rational discussions dealing with the article from G.-E. Séralini et al. (Food Chem. Toxicol. 2012, 50:4221–4231) by re-publishing it. By doing so, any kind ofappraisal of the paper's content should not be connoted. The only aim is to enable scientific transparency and, based on this, a discussion which does not hide but aims to focus methodological controversies." (p. 2).	confirmations of safety to findings of metabolic alterations.[45] Also, the United States conveniently failed to mention the study's critical findings linking long-term consumption of NK603 transgenic corn to serious organ damage in various dietary trials, as noted in the same paragraph that cites.[46] In addition, the United States omits to comment on other findings mentioned in the article in question, i.e., the detection of significant chronic renal impairment in rats and results related to a high degree of carcinogenicity.[47] On the other hand, in the Codex Compendium, Section 3, paragraphs 11 and 12 on *Guidelines for the Conduct of the Safety Assessment of Foods Derived from Recombinant DNA Plants*, there is a mention that prolonged studies (2 years) are not conclusive to analyze chronic diseases in laboratory animals resulting from long-term intake of processed food based on GMOs. Codex paragraph 11 only talks about the low amounts of feed to which laboratory animals should be subjected, the nutritional value and balance to which the animals should be subjected and whether it is necessary to subject the animals to such an experiment as it would be unlikely to find

[45] **Séralini GE, Clair E, Mesnage R, Gress S, Defarge N, Malatesta M, Hennequin D, de Vendômois JS. Republished study: *long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize*. Environ Sci Eur. 2014, p. 2. MEX-225.**

[46] **Séralini GE, Clair E, Mesnage R, Gress S, Defarge N, Malatesta M, Hennequin D, de Vendômois JS. Republished study: *long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize*. Environ Sci Eur. 2014, p. 3. MEX-225.**

[47] **Séralini GE, Clair E, Mesnage R, Gress S, Defarge N, Malatesta M, Hennequin D, de Vendômois JS. Republished study: *long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize*. Environ Sci Eur. 2014, pp. 9-13. MEX-225.**

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				significant information. The article by Séralini et al., 2014 complies with the specifications of paragraph 11 of the Codex. Paragraph 12 only talks about compliance with the standards associated with substantial equivalence. Again, if you read the research work, this is a variable that is perfectly controlled in Séralini's study.
193	MEX-085 (citing MEX-125)	CONAHCYT, "*Scientific Record on Glyphosate and GM Crops*", 2020 (in turn citing González-Ortega, E., Piñeyro-Nelson, A., Gómez-Hernández, E., Monterrubio-Vázquez, E., Arleo, M., Dávila-Velderrain, J., Martínez- Debat C. y Álvarez-Buylla E. R., "*Pervasive presence of transgenes and glyphosate in corn-derived food in Mexico*", 2017).	MEX-125 is not a risk assessment of glyphosate (or of dietary exposure to glyphosate) but rather focuses on identifying transgenes and glyphosate in Mexico. This paper is a snapshot in time at a specific location of a limited number of processed maize-based food samples (as opposed to raw agricultural commodity samples) pulled from a marketplace and tested for the presence of transgenes and glyphosate residues. Due to the methods used, the presence of glyphosate cannot be conclusively connected to the application of glyphosate to glyphosate-tolerant corn. Glyphosate is used extensively, and there are many potential sources along the value chain. The glyphosate residues detected are well below the trade standard maximum residue limits ("MRLs"). The majority of the transgene-containing samples contained no detectable glyphosate residuesat all, according to the analytical methods in the study. Risk is a function of exposure and toxicity, and the presence of residues alone does not equate to risks.	The US comments refer to Exhibit **MEX-125**, unlike Exhibit **MEX-085**. The evidence provided in Exhibit **MEX-125** is relevant and valuable to the Panel because it analyzes the food landscape in the most populated area of Mexico (**MEX-125**, p. 6). Noting also that the United States did not provide any support to demonstrate the absence of a scientific method and that, therefore, this study should be dismissed. Only products whose main ingredient was corn were included in the sampling. (**MEX-125**, p. 7). Using a molecular analysis based on a PCR and liquid chromatography assays with tandem mass spectrometry (LC MS/MS) after acid extraction and derivatization of the samples, the researchers observed a "*high frequency of samples positive for transgenes*" *and that* "*glyphosate and AMPA residues were found in 50% of the samples assayed for herbicide presence… but neither glyphosate, AMPA or ammonium glufosinate could be detected in any of the 9 Artisan Tortilla samples assayed*"(**MEX-125**, pp. 7, 10, 15-16). The MEX-125 study found that up to 90.4% of tortilla samples and 83.3% of corn flour samples contained GM corn varieties. In addition, in 43% of the samples, the GM corn content was higher than 5%. The herbicide glyphosate was also detected in approximately 27% of the samples. The glyphosate

Paragraph	Exhibit	Source Title	USA's Analysis	Mexico's Reply
				tolerant corn variety GM NK603 was the most frequently identified. This study provides an important frame of reference for public health in Mexico regarding the consumption of GM corn. The United States claims that glyphosate is used along the value chain. However, it does not provide any evidence or explanation that glyphosate is used at any point beyond agriculture. Given that this study refers to corn-based foods, it is not clear how such glyphosate proportions might otherwise be found in products. Finally, the United States acknowledges the presence of glyphosate residues. This, together with the potential genotoxicity of glyphosate, exposed by Mexico in its initial written submission, (**Mexico's Initial Written Submissions**, paragraph 134) are consistent with Mexico's position regarding the risk of glyphosate in the Mexican diet.

ANNEX II - ASSESSMENT OF STATEMENTS IN MEXICO'S INITIAL SUBMISSION CONCERNING AGROCHEMICAL USAGE AND GE CROPS[48]

Paragraph	Mexico's arguments	United States' Allegations	Mexico's Response
92	"A systemic herbicide (and the contaminants or toxins into which it canbe broken down within the plant) cannot be 'washed out' because it accumulates within the plant itself."	This is not accurate. Glyphosate is rapidly metabolized in plants and does notpersist in the organism.[49]	The US claim is not true. The same Exhibit **USA-156** argues that "[…] a comprehensive taxonomic survey of higher plant metabolism of glyphosate has not been conducted […]". Also, in order for plants to metabolize, glyphosate is necessary to produce aminomethyl-phosphonic acid (AMPA) and glyoxylate. However, as the same Exhibit submitted by the United States establishes "[t]he enzyme(s) that produce(s) AMPA in plants has/have been unknown". This in addition to the fact that AMPA also presents toxicity.
93	"GMO do not reduce the amount ofagrochemicals."	This is a highly nuanced space, and context is key. Studies have actually found that herbicide use has risen more quickly with non-GE crops than GE crops.[50] However, usage alone is not a good measure, because the toxicity of each pesticide is not directly related to the amount (weight) applied and there is no consideration of how the active	As the United States points out, context is key. The first of the studies mentioned by the United States (**USA-157**) indicates as "plausible" that glyphosate resistant organisms (GMOs), and glyphosate resistant herbs, have caused an increase in the use of herbicides in the case of corn, soy and cotton (**USA-157**, p.6) Moreover, in the context of the United States, where Mexico claims to have increased the use of herbicides and GMOs, the study shows as an "obvious" result that farmers in the United States will increase the use of glyphosate. On the other hand, the United States boasts

[48] To the extent the United States has not commented on a particular statement by Mexico in its Initial Submission, such an omission does not imply anendorsement of the statement's credibility or accuracy.

[49] *See, e.g.*, S. Duke, "Enhanced Metabolic Degradation: The Last Evolved Glyphosate Resistance Mechanism of Weeds?," 181 PLANT PHYSIOLOGY 1401 (2019)(Exhibit USA-156).

[50] *See, e.g.*, A. Kniss, "Long-term Trends in the Intensity and Relative Toxicity of Herbicide Use," NATURE COMMUNICATIONS (Apr. 2017) (Exhibit USA-157).

Paragraph	Mexico's arguments	United States' Allegations	Mexico's Response
		ingredients disperse into the environment.[51] When the environmental impact quotients ("EIQ") are calculated—a measure incorporating the amounts applied and their relative toxicity to particular environmental indicators such as fish or pollinators—there is a net decrease in the EIQ with GE crops.[52] The chronic toxicity for herbicides used in maize remained unchanged between 1990 and 2015 (even while acre treatments increased), and acute toxicity for herbicides used in maize fell 88% over this same time period, largely because glyphosate replaced older and more toxic herbicides previously used more widely.[53]	that glyphosate, although toxic, is less toxic than herbicides of yesteryear; however, according to Mexico's zero-risk NADP, a lower degree of toxicity does not imply a non-compliance by Mexico. In the light of the above, Mexico may be more precise and point out that GMOs do not reduce the amount of agrochemicals, but rather encourage them, and this is a plausible result in accordance with the evidence provided by the parties to the dispute, as well as additional evidence, in which the following is noted: The adoption of herbicide-resistant crops, such as those that tolerate glyphosate, has led to an increase in the use of these chemicals. Benbrook, **MEX-432** reported that herbicide use in the United States increased by 239 million kilograms (527 million pounds) between 1996 and 2011 due to herbicide-resistant transgenic crops. This increase is largely a result of the evolution of glyphosate resistant weeds.[54] Contrary to frequently repeated claims that current GM crops have reduced and are reducing the use of pesticides, the spread of glyphosate-resistant weeds in herbicide-resistant weed management systems has led to substantial increases in the number and volume of herbicides applied. If new

[51] *e* G. Brookes, "Genetically Modified (GM) Crop Use 1996–2020: Environmental Impacts Associated with Pesticide Use Change," 13 GM CROPS & FOOD – BIOTECHNOLOGY IN AGRICULTURE AND THE FOOD CHAIN 262, 264 (2022) https://www.tandfonline.com/doi/epdf/10.1080/21645698.2022.2118497?needAccess=true&role=button (Exhibit USA-46)

[52] *Id.* at 277 (finding that, between 1996 and 2020, the widespread use of insect-resistant and herbicide-tolerant seed technology reduced pesticide application by 748.6 million kilograms (-7.2 percent) and, as a result, decreased the environmental impact associated with insecticide and herbicide use on these crops by 17.3percent) (Exhibit USA-46)

[53] **A. Kniss, "Long-term Trends in the Intensity and Relative Toxicity of Herbicide Use," NATURE COMMUNICATIONS, at 3 (Apr. 2017) (Exhibit USA-157).**

[54] **Benbrook, C. M. "*Impacts of genetically engineered crops on pesticide use in the U.S. -- the first sixteen years*". Environmental Sciences Europe, 2012, 24, 24. MEX-432. Landrigan, P. J., & Benbrook, C."*GMOs, herbicides, and public health.*" The New England Journal of Medicine, 2015. 373(8), 693-695. MEX-433.**

Paragraph	Mexico's arguments	United States' Allegations	Mexico's Response
			genetically modified forms of 2,4-D tolerant corn and soya are approved, the volume of 2,4-D sprayed could increase herbicide use by about another 50% Weed resistance to glyphosate has increased the use of additional herbicides, contradicting the premise that transgenic crops would reduce the need for agrochemicals. The emergence of glyphosate-resistant weeds has forced farmers to use herbicide mixtures and to apply larger quantities to control these weeds. **(MEX-179)** Although the use of glyphosate may have replaced more toxic herbicides, glyphosate itself and its metabolite AMPA have significant adverse effects on the environment and health. Myers et al. (2016) highlighted that glyphosate has negative impacts on soil biodiversity, affects the health of aquatic ecosystems and can have endocrine disrupting effects in humans and animals. (**MEX-320)** Measures such as the Environmental Impact Quotient (EIQ) may be insufficient to capture the complexity of herbicide impacts. EIQs do not always reflect the long-term and cumulative effects of herbicides on the environment and human health. In addition, studies have suggested that, despite a possible reduction in acute toxicity, chronic exposure to glyphosate may have significant long-term effects that are not fully captured in EIQ. On the other hand, the second study cited by the United States (**USA-46**) reinforces Mexico's arguments that dependence on herbicides, including glyphosate, has fostered resistance to these agrochemicals and has required the mixing of these, and an increase in its use. (**USA-47**, p. 17)

Paragraph	Mexico's arguments	United States' Allegations	Mexico's Response
94	"*Bt* technology has also failed to reducethe use of insecticides."	Mexico cites nothing to support this statement, and it is simply not true.[55]	The United States conveniently ignores the evidence supporting the claim. Exhibit **MEX-078**, evidence that the "*The massive and constant use of glyphosate in […]transgenic crops has led to the emergence of super weeds*",[56] reason why it is now being proposed "*introduction of transgenic crops that are resistant to much stronger and more harmful herbicides*",[57] that for the specific case of *Bt* crops "*problems arise with the emergence of super pests, as insects become resistant to transgenic toxins and become a difficult problem to control*".[58] Derived from the above, we reach the inevitable conclusion that Mexico supports with evidence its claim, that is, that with the *Bt* technology, the reduction of insecticides in GMOs has not been achieved, which makes it unsustainable environmentally and agronomically. It also argues that one of the most significant problems with *Bt* crops is the development of resistance in pest insect populations. Studies have shown that several insects have developed resistance to *Bt* toxins, which has led to an increase in the use of insecticides. For example, Tabashnik et al. (2013) found that insects such as cotton worm (Helicoverpa zea) have developed

[55] *See, e.g.*, E. D. Perry et al., "Genetically Engineered Crops and Pesticide Use in U.S. Maize and Soybeans," 2 SCIENCE ADVANCES 1 (Aug. 2016), https://www.science.org/doi/pdf/10.1126/sciadv.1600850 (finding that adopters of GE insect-resistant (Bt) maize used 11.2 percent (0.013 kilogram per hectare)less insecticide than nonadopters) (Exhibit USA-47).

[56] **Bravo Velásquez, E., "*Los cultivos GM y los paradigmas científicos de los que emergen a la luz de los derechos de la naturaleza*", 2014, Letras Verdes. *Revista Latinoamericana de Estudios Socioambientales*, p.66. MEX-078.**

[57] **Bravo Velásquez, E., "*Los cultivos GM y los paradigmas científicos de los que emergen a la luz de los derechos de la naturaleza*", 2014, Letras Verdes. *Revista Latinoamericana de Estudios Socioambientales*, p.66. MEX-078.**

[58] **Bravo Velásquez, E., "*Los cultivos GM y los paradigmas científicos de los que emergen a la luz de los derechos de la naturaleza*", 2014, Letras Verdes. *Revista Latinoamericana de Estudios Socioambientales*, p.66. MEX-078.**

Paragraph	Mexico's arguments	United States' Allegations	Mexico's Response
			resistance to *Bt* toxins, forcing farmers to use traditional insecticides to control these pests.[59] Some studies indicate that, in certain areas, insecticide use has increased due to insect resistance to *Bt* toxins. An analysis by Benbrook, **MEX-432** shows that although *Bt* crops initially reduced the use of insecticides, this trend has been reversed in some cases due to the emerging resistance of pest insects.[60] In addition, there is evidence that Bt crops may have unintended effects on non-target insects and biodiversity in general. A study by Andow and Zwahlen (2006) highlights that Bt toxins can affect beneficial and non-target insects, which can also lead to an increase in the use of insecticides to control other emerging pests.[61] A more recent study by Perry et al. (2016) shows that the use of insecticides in some Bt crops has increased due to the appearance of secondary pests and resistance to Bt toxins, which counteracts the initial expected benefits of insecticide reduction[4]. These studies provide evidence that Bt crops have not always achieved a sustained reduction in insecticide use, and in some cases, have led to an increase in their use due to insect resistance and other unwanted factors.
94	"[T]he insecticidal toxins produced by GM plants have led to the development of resistance in pest insects, which wouldindicate that Bt	The scientific community has always known that *Bt* resistance was going to occur. Resistance to *Bt* powders in diamondback moth was first reported in	The US response confirms that the amount and types of pesticides to be applied on agricultural land will not only increase but will eventually become more toxic.

[59] **Tabashnik, B. E., Brevault, T., & Carriere, Y."*Insect resistance to Bt crops: lessons from the first billion acres*." Nature Biotechnology, 2013, 31, 510-521. MEX-434.**

[60] **Benbrook, C. M. "*Impacts of genetically engineered crops on pesticide use in the U.S. -- the first sixteen years*". Environmental Sciences Europe, 2012, 24, 24. MEX-432.**

[61] **Andow, D & Zwahlen, C, "*Assessing environmental risks of transgenic plants*". 2006, MEX-435.**

Paragraph	Mexico's arguments	United States' Allegations	Mexico's Response
	technology is environmentally and agronomically unsustainable."	1990, and resistance management has always been part of GE corn and cotton production.[62]	Confirming that *Bt* technology is environmentally and agronomically unsustainable. In that sense, the use of Bt technology is unsustainable both environmentally and agronomically due to the development of resistance in pest insects. Although USA. recognizes the inevitability of this resistance and argues that its management has been an integral part of the production of transgenic crops, numerous studies support Mexico's position on the unsustainability of Bt technology. Research has documented that corn root worm has developed resistance to Bt toxins, which has increased the use of traditional insecticides.[63] It has also been noted that emerging resistance has reversed the initial reduction in insecticide use in Bt crops.[64] Also, resistance has led to an increase in secondary pest populations and raises questions about the long-term sustainability of Bt crops due to the lack of adequate resistance management strategies. These studies support Mexico's claim that Bt technology is unsustainable.
158	"[G]lyphosate is a highly dangerouspesticide and this is irrefutable."	Mexico cites the U.S. Environmental Protection Agency's ("EPA") "Draft National Level Listed Species Biological Evaluation for Glyphosate," which does not lead to the conclusion that Mexico alleges. EPA submitted a "Final National Level Listed Species Biological Evaluation for Glyphosate" to the U.S. Fish and Wildlife Service and National Marine Fisheries Service to initiate formal consultation under section 7 of the Endangered Species Act. This document is not relevant for a human	As Mexico has stated in various responses to the US claims in Annex I, the United States has established that mammal studies are relevant to assessing safety. In this sense, the "Draft National Level Listed Species Biological Evaluation for Glyphosate" (**MEX-174**) established that, of 99 mammals studied, glyphosate can adversely affect 75 species of mammals. Moreover, of 949 plant species analyzed, glyphosate could negatively affect 940. That is, 99.15% of the plants analyzed. Based on these data, Mexico maintains that glyphosate is a highly dangerous pesticide and that is irrefutable.

62 *See, e.g.*, B. Tabashnik, "Evolution of Resistance to *Bacillus Thuringiensis*," 39 ANNUAL REVIEW OF ENTOMOLOGY 47 (1994) (Exhibit USA-158).

63 **Gassmann, et al, "*Field-evolved resistance to Bt maize by western corn rootworm*". PLoS ONE, 2011, 6(7), pp. 1 y 4, MEX-436**

64 **Benbrook, C. M. "*Impacts of genetically engineered crops on pesticide use in the U.S. -- the first sixteen years*". Environmental Sciences Europe, 2012, 24, pp. 1 y 10. MEX-432.**

Paragraph	Mexico's arguments	United States' Allegations	Mexico's Response
		health risk assessment and is limited in scope to potential impacts on endangered and threatened animal and plant species and their critical habitats from the application of glyphosate and subsequent exposure to non-target wildlife and plants within the United States. The purpose of this document was not to determine if glyphosate is "dangerous" for purposes of a human health risk assessment.[65]	
161	"[T]he main function of GM corn is to tolerate greater amounts of herbicides, specifically glyphosate. This means that direct consumption of GM corn results in consuming a product that has been exposed to a greater amount of an herbicide[.]"	It is incorrect to assume that plants that are tolerant to glyphosate automatically will have higher residues of glyphosate in the edible plant parts. The amount of pesticide applied, and the timing of application both impact residue levels. Anexample of this can be seen in the glyphosate residue data that the JMPR 2011 (glyphosate-tolerant maize only). In 2005, the recommended MRL of 5.0 ppm was based on the conventional maize data. The 2011 meeting reconfirmed the previous MRL recommendation of 5.0 ppm because the dataset of conventional maize actually gave rise to a higher maximum residue level.[66]	United States criticizes Mexico's assertion, ignoring evidence used by Mexico regarding use of glyphosate as an herbicide and end consumer intake. In this regard, Mexico invites the United States and the Panel to review the Exhibits: **MEX-180, MEX-181, and MEX-182.** Furthermore, the same evidence shared by the United States (**USA-46**, p.7) cites studies, for example, by the IARC, which support the claim that glyphosate is inside food, air and water. The U.S. premise that there are no risks from consuming GM plants containing glyphosate residues is incorrect.

[65] For additional context, EPA's Biological Evaluations are by design very conservative in nature and rely on the worst-case exposure scenarios (maximum application rates, shortest application intervals, maximum number of applications per year). The objective of a Biological Evaluation is to make the determination as to whether use of glyphosate is Not Likely to Adversely Affect or Likely to Adversely Affect each of the 1,795 threatened and endangered species in the United States. EPA's threshold for this determination is effects to a single individual of a given population of threatened or endangered species.Separate analyses are then carried out to determine if there are likely to be population-level effects. The exposure assumptions are very high, because the evaluation uses extremely conservative model inputs, and the bar for effects to threatened and endangered species is extremely low. This document does not have anything to do with glyphosate exposure from human dietary consumption (or any other form of human exposure), let alone human health risk from consuming GE corn.

[66] MPR, "Pesticide Residues in Food 2005," at 129-130, 144 (2005) (Exhibit USA-159); JMPR, "Pesticide Residues in Food 2011," at 155, 159 (2011) (ExhibitUSA-160).

Paragraph	Mexico's arguments	United States' Allegations	Mexico's Response
		Residue levels are primarily a function of how glyphosate is used and not whether the crop is glyphosate-tolerant. From a dietary exposure and risk perspective, what matters is the potential residue level at the consumption point, not how much was applied in the field, and both GE and conventional corn can be treated with glyphosate.	As field studies do not monitor good pesticide application practices. An analysis of the composition reports of glyphosate tolerant crops found that, of the 15 studies conducted by the industry, none applied glyphosate to the plant material produced, Consequently, none of the studies indicated the presence of glyphosate in glyphosate tolerant plants. This was done, systematically ignoring issues and evidence of importance for regulatory evaluation.[67] Another independent study of those conducted by the industry showed high accumulation of glyphosate residues in soybean crops in Iowa, USA. In the case of GMOs, which is totally different from conventional, non-GM crops, where there is no residue or minimal. (**MEX-319**). This shows that glyphosate residues are present in GM plants, and strengthens the argument that, by consuming these GM plants, the population exposes its health to traces of glyphosate, surfactants and other metabolites (AMPA), which accumulate in organisms. This could lead to a long-term impact. [68]
182	"GBHs of commercial brands such as *Roundup* contain toxic agents such as petroleum derivatives and heavy metals."	The cited studies (MEX-219 & MEX-220) do not demonstrate actual risk upon consumption of the food products at biologically relevant levels.	The United States erroneously mentions that Exhibits **MEX-219** and **MEX-220** do not cover human risks arising from GBHs, as the same text of those Articles mentions that *"GBH formulants are more toxic on*

[67] **Cuhra, M. "*Review of GMO safety assessment studies: glyphosate residues in Roundup Ready crops is an ignored issue*". Environmental Sciences Europe, 2015, 27, 1-14. MEX-438.**

[68] **Meftaul, I., et al. "*Controversies over human health and ecological impacts of glyphosate: Is it to be banned in modern agriculture?*" Environmental Pollution, 2020263, 114372. MEX-439. Solomon, K. R..."*Glyphosate in the general population and in applicators: a critical review of studies on exposures*". Critical Reviews in Toxicology, 2016, 21-27. MEX-440. Bøhn, T., M. Cuhra, T. Traavik, M. Sanden, J. Fagan & P. Primicerio. "*Compositional differences in soybeans on the market: Glyphosate accumulates in Roundup Ready GM soybeans*." 2014. 153:207–15. MEX-319.**

Paragraph	Mexico's arguments	United States' Allegations	Mexico's Response
			plants than G in a short term. This is even more obvious in human cells, as we previously demonstrated".[69] On the other hand, the articles in question rightly highlight the toxicological effects on human cells, derived from pesticides with the presence of petroleum, a substance which "*has been known to be toxic and carcinogenic for a long time*",[70] same which can generate "*possible epigenetic consequences, thus affecting several generations at the human and all biosphere levels*".[71] If that were not enough, the evidence provided also indicates that "*among the diseases linked to pesticides in which petroleum is involved are in particular autism, psychiatric diseases, reproductive pathologies, and a decline in fertility*".[72] In particular, it should be noted that Exhibit **MEX-219** clarifies the importance of considering complete pesticide formulations, rather than just the declared active ingredient; the real risk after consumption of foodstuffs containing residues of glyphosate-based herbicides (GBH) lies in the possible exposure to toxic compounds such as polycyclic aromatic hydrocarbons (PAHs), which can increase the risk of developing diseases such as cancer, endocrine disorders, neurological disorders, congenital malformations and reproductive problems.

[69] **Defarge N., J. Spiroux de Vendômois & G-E. Séralini. (2018).** ***Toxicity of formulants and heavy metals in glyphosate-based herbicides and other pesticides*****. Toxicology Reports, p. 161. MEX-220.**

[70] **Jungers G., F. Portet-Koltalo, J. Cosme & G-E. Seralini. (2022).** ***Petroleum in Pesticides: A Need to Change Regulatory Toxicology*****. Toxics, p. 14. MEX-219.**

[71] **Jungers G., F. Portet-Koltalo, J. Cosme & G-E. Seralini. (2022).** ***Petroleum in Pesticides: A Need to Change Regulatory Toxicology*****. Toxics, p. 13. MEX-219.**

[72] **Jungers G., F. Portet-Koltalo, J. Cosme & G-E. Seralini. (2022).** ***Petroleum in Pesticides: A Need to Change Regulatory Toxicology*****. Toxics, p. 14. MEX-219.**

Paragraph	Mexico's arguments	United States' Allegations	Mexico's Response
			Exhibit **MEX-220**, for its part, is a detailed study on the comparative toxicological effects of glyphosate and its formulations, clarifying the debate on its safety; also recommends that calculations of the Acceptable Daily Intake and other regulatory experiments should be performed with the complete formulations and all their components, since the toxic effects can be synergistic and other active ingredients could be present in the formulants. Formulants present in pesticides such as glyphosate can act as endocrine disruptors and have toxic effects even at concentrations below those considered cytotoxic. Therefore, according to this study, the real risk after consumption of food products treated with pesticides, including glyphosate, lies in exposure to substances that may interfere with the endocrine system and have long-term adverse health effects.
191	"[A]pplication of glyphosate causes native corn to become even more exposed to insect pests."	The cited study (MEX-234) merely postulated this and did not present data.	The study focuses specifically on the impacts of glyphosate on the plant, exposing postulates such as "*Plant-induced IAA production can induce JA signaling, and a rapid production of defense compounds against necrotrophic pathogens. IAA is mutually antagonistic to SA and, in turn, SA is mutually antagonistic to JA. Thus, while suppressing SA biosynthesis, IAA indirectly promotes JA signaling, and consequently increases resistance to necrotrophicpathogens. Several biotrophic pathogens have* been shown to *synthesize IAA in an attempt to decrease SA-mediated plant defense responses, and to enhance plant vulnerability to their attack. Low glyphosate-mediated IAA concentrations may decrease JA-induced defense responses, while also increasing SA-mediated defense responses*." In summary, **MEX-234** documents the effects of glyphosate residues on plant physiology and their interactions with other species, affecting plant defense

Paragraph	Mexico's arguments	United States' Allegations	Mexico's Response
			and the attraction of beneficial insects. The application of glyphosate in crops can increase the vulnerability of native corn to pest insects by inhibiting the shikimate pathway, essential for producing aromatic amino acids, phytoalexins, and other defense substances. Besides, inhibition of this pathway affects the production of hormones such as jasmonic acid and volatile compounds of green leaves, crucial for defense against herbivores and the attraction of beneficial insects.

ANNEX III - ASSESSMENT OF EXHIBITS IN MEXICO'S INITIAL SUBMISSIONALLEGING GLYPHOSATE EXPOSURE[73]

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
165	MEX-183/184	Krüger. M. et. al. (2014). "*Detection of Glyphosate Residues in Animals and Humans".* Environ Anal Toxicol 2014/ Krüger. M. et. al. (2013). "*Field Investigations of*	The presence of glyphosate in excreta does not mean there is an adverse health effect; elimination is expected.[74] To the extent residues appear in animal tissue,Codex and the United States (as well as other countries) have set MRLs for residues of glyphosate in meat byproducts (including liver and kidney). Neither MEX-183 nor MEX-184	The United States presents a misrepresented analysis of Exhibits **MEX-183** and **MEX-184**. Mexico uses these Exhibits to demonstrate that "[E]xposure in humans [of glyphosate] is not the only issue to consider. This is because there is

[73] To the extent the United States has not commented on a particular exhibit cited by Mexico in its Initial Submission, such an omission does not imply an endorsement of the exhibit's credibility or accuracy. As noted in the U.S. Rebuttal Submission, Mexico cited a large volume of studies that have nothing to dowith glyphosate exposure through dietary consumption, let alone through consumption of GE corn. *See, e.g.*, Sections V.D.1.c, V.D.2.a, V.D.2.b.1, V.D.2.c. Nevertheless, in the interest of reinforcing the lack of relevance of Mexico's cited support, the United States will address certain exhibits that Mexico cited in relation to its Article 9.6.8(a) arguments, concerning its "risk assessment." *See* Mexico's Initial Submission, Section VII.E.4.

[74] A common, but erroneous, conclusion from biomonitoring data is that low levels of a chemical in a biological sample (*e.g.*, urine, blood) will be harmful to humans; however, detection is not equivalent to risk. Biomonitoring data requires conversion to estimated external dose levels in order to evaluate whether potential risks may exist. For instance, urinary glyphosate levels have been reported by several organizations and research groups, including the U.S. Centers forDisease Control and Prevention. Detection is expected given how glyphosate enters, distributes, breaks down, and exits the body. When converted to external doses, the estimated doses associated with these urinary levels are orders of magnitude lower than the current dietary reference dose (*i.e.*, the maximum acceptable oral dose of a substance, below which no adverse health effects should result from a lifetime of exposure).

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
		Glyphosate in Urine of Danish Dairy Cows". Environ Anal Toxicol 2013.	analyzed samples of food or feed forresidues of glyphosate or provided information how much (or the types) of food/feed was consumed by the livestock. Additionally, there are other limitations to the utility of these studies including that not all of the data were shown and the data were presented graphically. MEX-183 provided limited information (a graph) about residues observed in several livestock tissue samples. The highest levels were in lung tissue and were well below the Mexican and U.S. tolerance levels for residues of glyphosate in meat byproducts (1 ng/g = 0.001 ppm) and therefore would not be considered a risk of concern.	evidence of glyphosate in the urine of dairy cows and fattening rabbits fed with GMO and also in organs and tissues of cows fed with GMO. Similarly, Exhibit **MEX-183** itself concludes that "[p]resence of glyphosate in urine and its accumulation in animal tissues is alarming even at low concentrations." This is related to the appropriate level of protection that Mexico established and demonstrate the risk derived from glyphosate exposure. For greater description, the aim of these studies was to investigate whether glyphosate residues in different biological samples from humans and animals could be used to obtain information on exposure to this compound (**MEX-183**) and investigate the excretion of glyphosate in the urine of Danish dairy cows and evaluate its impact on blood parameters and animal health (**MEX-184**), which is why they do not show food or forage data. The first study (**MEX-183**) analyzed urine samples from German dairy cows, Danish cows, hares, fattening rabbits and humans, in order to evaluate the presence of glyphosate residues and compare concentrations between different

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
				groups of animals and humans. Glyphosate residues were detected in the urine of German dairy cows, lower than in Danish, and lower levels in GMO-free areas; residues were also found in organs of slaughtered cows and in fattening rabbits, in addition to higher levels in humans with a conventional (non-organic) diet and in chronic patients compared to healthy individuals. The second study (**MEX-184**) found that all the cows investigated excreted glyphosate in their urine, although in different amounts; elevated levels of enzymes were observed in blood serum indicative of cytotoxicity (GLDH, GOT, CK) as well as high levels of cholesterol, creatinine and urea, suggesting possible effects of glyphosate on liver, muscle and kidney cells in cows; Correlations were also found between glyphosate levels in the urine and creatinine and urea levels in blood serum, suggesting a possible relationship between glyphosate exposure and changes in blood parameters in cows. Contrary to the idea that the levels found "would not be considered a worrying risk", the presence of glyphosate in the urine and tissues suggests that the individual has been exposed to the herbicide, either

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
				through contaminated food, water, inhalation of aerosols, or direct contact with treated surfaces and this is worrying given that exposure may be more common than thought and there are multiple independent studies that have associated glyphosate exposure with kidney, liver, hormone disorders, negative effects on the gut microbiota, among others. Although glyphosate does not bioaccumulate to the same extent as other contaminants, continuous detection in the urine indicates persistent exposure, which is of great concern In addition, it is alarming that the United States claims that the presence of glyphosate in urine is not associated with diseases, especially by studies that have been conducted in its population that show correlation of the presence of glyphosate in human urine, for example, with molecular markers of oxidative stress[75] (associated with carcinogenicity and other diseases).
406	MEX-301	IARC, "*Monograph on Glyphosate*",	The IARC report is not a risk assessment. The IARC is a cancer agency withinthe WHO whose purpose is to "identif[y] and classif[y] hazards," *i.e.*, to assesses whether a chemical product is	The carefully chosen evidence about IARC by the United States is not the only study conducted by this institution to determine that

[75] **Chang VC et Al. "*Glyphosate exposure and urinary oxidative stress biomarkers in the Agricultural Health Study*". J Natl Cancer Inst. 2023. 115(4): 394–404. MEX-371.**

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
		2015.	capable of producing harm and what harm it may produce.[76] The IARC's work constitutes "hazard identification"— the first step in a "risk assessment."[77] A "risk assessment" would go on to evaluate exposure and characterize the overall level of risk.[78] The FAO/WHO JMPR is responsible for these subsequent steps and assesses the risk of pesticide residues in and on food.[79] The IARC did not assess the exposure and risks associated with glyphosate residues in or on food; instead, it identified and characterized the hazards potentially associated with glyphosate exposure, without consideration of exposure levels. The IARC report simply found that, at some level of exposure, glyphosate probably had the potential to increase therisk of a particular type of cancer (non-Hodgkin's lymphoma) in humans. The release of the IARC report expressly indicated that the IARC findings were neither a risk assessment nor a modification of the technical instructions for glyphosate.[80] Subsequently, the JMPR (the FAO/WHO pesticide risk assessment body) considered the body of evidence for cancer outcomes for glyphosate, including the studies reviewed by the	glyphosate is "likely carcinogenic to humans" (**USA-46**, p.7). The study cited above is part of the conglomerate of relevant scientific evidence that is taken into consideration by Mexico for effects of the damage inherent to glyphosate. However, it is pertinent to give context to the evidence criticized by the United States. However, the objective of the IARC program on the assessment of carcinogenic risks to humans is to prepare, with the assistance of international expert Working Groups, and to publish in the form of monographs, critical reviews and assessments of evidence on carcinogenicity of a wide range of human exposures. Indeed, these Monographs represent the first step in assessing the risk of carcinogens, which involves examining all relevant information to

[76] *See* Pan American Health Organization ("PAHO"), "Questions and Answers on the Use Diazinon, Malathion and Glyphosate" (Sept. 2015), https://www.paho.org/en/documents/questions-and-answers-use-diazinon-malathion-and-glyphosate-2015 (Exhibit USA-161).

[77] *See id.* at 3 (Exhibit USA-161); *see also* Panel Report, *European Communities – Measures Concerning Meat and Meat Products (Hormones), Complaint bythe United States*, WT/DS26/R/USA, para. 8.103 (adopted Feb. 13, 1998) (Exhibit USA-162).

[78] (Exhibits USA-161 & USA-162).

[79] AHO, "Questions and Answers on the Use Diazinon, Malathion and Glyphosate," at 1 (Sept. 2015), https://www.paho.org/en/documents/questions-and- answers-use-diazinon-malathion-and-glyphosate-2015 ("JMPR is an international scientific group of experts administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and WHO, tasked with evaluating the risk associated with pesticide residues in food and elsewhere. It is also known asthe Joint FAO/WHO Meeting.") (Exhibit USA-161).

[80] *Id.* (Exhibit USA-161).

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
			IARC and additional relevant studies, and concluded that glyphosate "is unlikely to pose a carcinogenic risk to humans via exposure from the diet."[81] International expert panels and regulatory authorities—including the U.S. EPA[82], Australian Pesticide and Veterinary Medicines Authority[83], Canadian Pest Management Regulatory Agency[84], European Food Safety Authority[85], European Chemicals Agency[86],	evaluate the strength of available evidence that an agent could alter the incidence of cancer in humans. In this case glyphosate was evaluated by the IARC Working Group, study evaluations were carried out in experimental systems and only data that were in the public domain and available for independent scientific review were considered. Moreover,

81 JMPR, "Pesticide Residues in Food – 2016: Toxicological Evaluations," at 257 (May 2016) (Exhibit USA-154).

82 U.S. Environmental Protection Agency ("EPA"), "Human Health Risk Assessment in Support of Registration Review" (Dec. 12, 2017) (Exhibit USA-164); EPA Office of Pesticide Programs, "Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential" (Dec. 12, 2017) (Exhibit USA-173). In the UnitedStates, existing pesticides must be re-evaluated periodically to ensure that they continue to meet the appropriate safety standard, a process known as registrationreview. In December 2017, as part of glyphosate's ongoing registration review, EPA conducted a comprehensive human health risk assessment of glyphosate that considered hazard and exposure data, including an in-depth review of all relevant animal carcinogenicity and genotoxicity studies for the active ingredient glyphosate, as well as epidemiological studies that investigated potential cancer outcomes from using pesticide products containing glyphosate. EPA's risk assessment process combines hazard, dose-response, and exposure assessments to describe the overall risk from glyphosate. EPA's independent evaluation of the available scientific data for glyphosate found no risks of concern to human health when used in accordance with the current label instructions; found no indication that children are more sensitive to glyphosate; concluded that glyphosate is "not likely to be carcinogenic" to humans; and concluded that glyphosate does not interact with the thyroid, estrogen, or androgen signaling pathways based on a weight-of-evidence review. EPA anticipates issuing its final registrationreview decision on glyphosate in 2026. As part of registration review, EPA intends to revisit and further explain its evaluation of the carcinogenic potential of glyphosate, but the underlying scientific findings regarding glyphosate, including its finding that glyphosate is not likely to be carcinogenic to humans, currentlyremain the same. *See* EPA, "Glyphosate" (Sept. 2023), https://www.epa.gov/ingredients-used-pesticide-products/glyphosate (Exhibit USA-174).

83 Australian Pesticides & Veterinary Medicines Authority, "Final Regulatory Position: Consideration of the Evidence for a Formal Reconsideration of Glyphosate" (Mar. 2017), https://www.apvma.gov.au/sites/default/files/publication/26561-glyphosate-final-regulatory-position-report-final_0.pdf (Exhibit USA-175); *see also* Australian Pesticides & Veterinary Medicines Authority, "Glyphosate" (last updated Oct. 2023), https://www.apvma.gov.au/resources/chemicals- news/glyphosate ("Glyphosate has also been assessed by other government regulators and independent scientists around the world. These assessments consistently found that glyphosate has low toxicity for humans, animals, fish, insects (including bees) and other invertebrates.") (Exhibit USA-176).

84 Canada Pest Management Regulatory Agency, "Glyphosate – Re-evaluation Decision" (Apr. 2017), https://publications.gc.ca/collections/collection_2017/sc-hc/H113-28/H113-28-2017-1-eng.pdf (Exhibit USA-177).

85 European Food Safety Authority ("EFSA"), "EFSA Explains the Scientific Assessment of Glyphosate" (July 2023), https://www.efsa.europa.eu/sites/default/files/2023-07/glyphosate_factsheet.pdf (Exhibit USA-178).

86 European Chemicals Agency, "EU Glyphosate Renewal - Risk Assessment Committee opinion" (May 30, 2023), https://www.glyphosate.eu/grg/whatsnew/eu-glyphosate-renewal-risk-assessment-committee-opinion/ (Exhibit USA-179).

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
			German Federal Institute for Risk Assessment[87], New Zealand Environmental Protection Authority[88], and the Food Safety Commission of Japan[89]—have all found the available data on glyphosate sufficiently robust for deciding that there is no basis for human hazard concern with respect to this herbicide. TheIARC Monograph's conclusion is not consistent with any other international organization or regulatory authority that has evaluated the carcinogenic potential of glyphosate.	exposure data were examined, including agent identification, production and use, as well as occupational and para-occupational exposure to glyphosate in different industries and countries. In 2015, the Working Group reviewed nearly 1000 studies (**MEX-302**) assigning glyphosate the category of probable human carcinogen (Group 2A), which can act through genotoxicity (DNA damage) and oxidative stress. In 2023, researchers from the University of Berkeley resumed the IARC study and conducted a bibliographic search based on ten key cancer hazard characteristics. They found strong evidence that glyphosate can cause genotoxicity, epigenetic alterations, oxidative stress, chronic inflammation, endocrine alteration and damage to the intestinal microbiota, all pathways related to lymphoma development.[90]
406	MEX-305	Martin, E., "*Glyphosate Toxicological*	This is simply an annotated bibliography based on keyword searches of severaldatabases of scientific journals. This is not a risk assessment nor do any of	Contrary to what the United States argues, the bibliography provided is

[87] German Federal Institute for Risk Assessment, "WHO/FAO committee (JMPR) re-assesses glyphosate and confirms the BfR and EFSA conclusion that a carcinogenic risk is not to be expected" (May 2016), https://www.bfr.bund.de/cm/349/who-fao-committee-jmpr-re-assesses-glyphosate-and-confirms-the-bfr-and-efsa-conclusion-that-a-carcinogenic-risk-is-not-to-be-expected.pdf (Exhibit USA-180).

[88] New Zealand Environmental Protection Authority, "Review of the Evidence Relating to Glyphosate and Carcinogenicity" (Aug. 2016), https://www.epa.govt.nz/assets/Uploads/Documents/Everyday-Environment/Publications/EPA-glyphosate-review.pdf (Exhibit USA-181).

[89] Food Safety Commission of Japan, "Glyphosate – Summary" (Sept. 2016), https://www.jstage.jst.go.jp/article/foodsafetyfscj/4/3/4_2016014s/_pdf/-char/en ("Glyphosate had no neurotoxicity, carcinogenicity, reproductive toxicity, teratogenicity, and genotoxicity.") (Exhibit USA-182).

[90] **Rana, I., et al "*Mapping the key characteristics of carcinogens for glyphosate and its formulations: a systematic review*". Chemosphere, 2023. MEX-441**

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
		Anthology", 2020.	the listed titles present an appropriate assessment of risk from consuming GE corn that may have glyphosate residues.	an anthology that compiles 1,108 studies of high scientific rigor, which demonstrate the negative effects of glyphosate on health and the environment. Each of these studies assesses the genotoxic potential of glyphosate and details the diseases or health problems that result from it,[91] for example: non-Hodgkin lymphoma, a condition that has led affected people to file lawsuits against companies marketing formulations containing the herbicide glyphosate as an active substance. The compilation document also includes links to eco-toxicological scientific studies that determine the effects and damage of glyphosate or commercial formulations of this herbicide on selected species of biological diversity.
406	MEX-304	ATSDR U.S. Department of Health and Human Services. "*Agency for Toxic Substances and Disease Registry. Toxicological Profile for Glyphosate*", 2020.	Mexico incorrectly states that the ATSDR toxicological profile makes findings that are consistent with the IARC Monograph (*see* analysis of MEX-301 above). Although the glyphosate ATSDR toxicological profile summarizes current studies and conclusions from other organizations and regulatory authorities related to carcinogenic potential, ATSDR did not conduct an independent cancer evaluation and merely referenced the IARC classificationalongside summarizing other studies.	Among the arguments of the United States is the absence of scientific evidence to support Mexico's arguments about the health effects related to glyphosate. Precisely this publication evaluates the evidence of different studies with valuable information on the mechanisms of toxicity of glyphosate in mammals, based on toxicological,

[91] **Escrito Inicial de los Estados Unidos Mexicanos, 15 de enero de 2024, ¶ 406-407.**

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
			Mexico similarly alleges that the ATSDR shows a "strong correlation between exposure" and certain adverse effects (Mexico's Initial Submission, para. 406) without any consideration ofthe doses where the effects were observed.	epidemiological and toxicokinetic evaluations. Among the proposed mechanisms are endocrine disruption in human cell lines, which may affect hormonal homeostasis; neuro-toxicity in the immature hippocampus of rats; and alterations in reproductive and uterine development by exposure to glyphosate formulations, affecting testosterone levels and testicular morphology in male mice, as well as uterus development in rats. These exposure conditions are particularly worrisome for humans living near areas where glyphosate is widely used. It is important to note that these studies come from different contexts and countries, but all agree on: i) their scientific rigor and ii) the verification of toxicology and health effects of glyphosate. Both issues endorsed by the United States Department of Health and as regards cancer, the 2017 IARC monograph is used at least 9 times to confirm the relationship between cancer and glyphosate. (**MEX-304** pp. 6, 15, 81-82, 127, 138, 142-143, 210)
408	MEX-306	Vandenberg, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs,Jr., D.R., Lee, D.H., Shioda, T., Soto,	This study does not have anything to do with GE corn. Mexico claims: "Dataand information from animal studies and human cell studies suggest that exposure to low doses of glyphosate effects hormone levels and reproductive systems,	This Exhibit is cited by Mexico in a section where it argues about the risks of glyphosate exposure, even in small doses.

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
		A.M., vom Saal, F.S., Welshons, W.V., Zoeller, R.T. y Peterson Myers, J. "*Hormones andEndocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses*"2012.	leading to endocrine disruption." The cited study does not describe glyphosate in depth, and only mentions it among others in Table 6 (where it is erroneously referred to as "glyphosphate"). It is unclear what methods or levels of exposure are being addressed, or the details of the alleged findings.	Exhibit **MEX-306** precisely establishes the glyphosate exposure, even in low doses, has negative impact in human health. The methodology of the study is clear, through a Weight of Evidence (WoE) approach the authors analyze the non-linear dose-effect curve (non-monotonic responses), through which they demonstrate the fallacy of "the dose makes the poison" and, consequently, emphasis must be placed and attention paid to the constant exposure of small doses of herbicides such as glyphosate.
408	MEX-307	Ingaramo, P., "*Are glyphosate and glyphosate-based herbicides endocrine disruptors that alter female fertility*?".	This study does not have anything to do with GE corn. This is a review article,with no new data presented. The overall conclusions of this article are unclear.[92]	The article is relevant even to the extent that it speaks of one of the most used herbicides and with a greater impact on the increase in the use of herbicides in the case of corn planting (**USA-157**). The methodology of the study is clear, through a Weight of Evidence (WoE) approach the authors analyze the non-linear dose-effect curve (non-monotonic responses), through which they demonstrate the fallacy of "the dose makes the poison" and, consequently, emphasis must be placed and attention paid to the

[92] In addition to the lack of relevance, this study discusses reproductive effects observed in a study by Almeida et al. (2017) where rodents were exposed to 500mg/kg of a glyphosate-containing product, which is considered relatively high for mammalian toxicological studies and would not typically be considered relevant for a human health risk assessment. This study does not report effects at doses that would be considered "low levels," contrary to what Mexico asserts.*See* Mexico's Initial Submission, para. 408.

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
				constant exposure of small doses of herbicides such as glyphosate. Mexico considers that the conclusions are clear, and among others they highlight that, based on the results of the review of glyphosate and glyphosate-based herbicides, these could have the properties to be considered as endocrine disruptors, which cause adverse effects on the ovary and the female reproductive tract, affecting implantation and/or embryonic development, even when animals are exposed to low doses. This and other characteristics allow us to postulate that there is a relationship between the endocrine activities of glyphosate/GBHs and the adverse effects on female reproduction. Furthermore, since the development of GM crops with herbicide tolerance trait, the use of glyphosate-based herbicides has increased over the past two decades. Glyphosate is currently the most widely used herbicide in the world.[93] Additionally, traces of this and other herbicides have been determined in harvested grains and even in food (**MEX-319**).

[93] **Benbrook, C.M, "*Trends in glyphosate herbicide use in the United States and globally*". Environ. Sci. Eur, 2016, 28 (1), 3. MEX-442.**

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
				Evidence accumulated in a growing number of scientific studies on the effects of the herbicide glyphosate has determined that both glyphosate and commercial formulations that have glyphosate as an active substance are endocrine and hormonal disruptors.[94] Document **MEX-307** is a bibliographic review that gathers the historical scientific information that confirms the characteristic as endocrine and hormonal disruptor of glyphosate, the herbicide deeply related to GM corn**.**
408	MEX-308	Davico, C. E, Pereira, A.G., Nezzi,L., Jaramillo, M.L., de Melo, M.S., Müller, Y.M.R., y Nazari, E.M., "*Reproductive toxicity of Roundup WG® herbicide: impairments in ovarian follicles of model organismDanio rerio*".	This study used a formulated product (Roundup WG® (RWG)), and dose concentrations appear to be based on the formulated product, as opposed to glyphosate. As such, potential effects cannot be attributed to glyphosate exposure.	The United States mistakenly considers that the results of scientific evidence cannot be attributed to glyphosate. Mexico maintains that the results of the scientific evidence are also applicable to glyphosate exposure, that is, reproductive and epigenetic effects that affect egg maturation, generating reproductions with toxicity and compromising the dynamics of exposed populations, are attributable to glyphosate.[95] This scientific study is also relevant because it complements the **MEX-**

[94] **Daruich J, et al. "*Effect of the herbicide glyphosate on enzymatic activity in pregnant rats and their fetuses*". Environ Res, 2001, Mar;85(3):226-31. MEX-443.**

[95] ***Ver* Escrito Inicial de los Estados Unidos Mexicanos, 15 de enero de 2024, ¶ 408.**

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
				306 and **MEX-307** studies, which prove that the herbicide glyphosate has characteristics of endocrine and hormonal disruptor. On the other hand, historically, glyphosate commercial assessment and approval processes have evaluated the characteristics, analyzed the potential health and environmental risks of glyphosate as an isolated molecule and not as the complex formulation offered commercially. Studies have determined that commercial herbicide formulations containing glyphosate as an active ingredient also contain substances declared as inert, surfactants, heavy metals, petroleum derivatives (Defarge N, 2017).[96] Additionally, commercial herbicide formulations based on glyphosate have been presented as confidential by the manufacturing companies. Complex mixtures that make up commercial herbicide formulations based on glyphosate have also been identified as cytotoxic (Mesnage R,

[96] **Defarge N., J. Spiroux de Vendômois & G-E. Séralini. (2018).** ***Toxicity of formulants and heavy metals in glyphosate-based herbicides and other pesticides*****. Toxicology Reports. 5:156-163. MEX-220**

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
				et al, 2012,[97] Vanlaeys A, et al 2018,[98] Simasotchi C, et al 2022,[99] Hao Y, et al 2019, Howe CM, et al. 2004,[100] Mesnage R, et al. 2022,[101] Defarge N, et al. 2016.[102] Crucially, commercial glyphosate-based herbicide formulations have been found to be cytotoxic even below legally permitted levels (Defarge N, et al. 2016.)
408	MEX-309	Masood, M.I, Mahrukh Naseem, S., Warda, A., Tapia-Laliena, M.A., ur Rehman, H., Nasim, M.J. and Schäfer, K.H., "*Environment permissible concentrations of glyphosate in drinking water caninfluence the fate of neural stem cells from the subventricular zone of the postnatal mouse*".	The study examined isolated stem cells from animals not exposed to the compound. The cells were exposed in vitro in a petri dish. The test compound was the technical grade material, and not the formulated product. This is not a risk assessment of dietary exposure to glyphosate, nor does this study haveanything to do with GE corn.	This study was cited with the purpose of exemplifying cases of risks from exposure to glyphosate in small doses. Specifically demonstrating that even with the level of glyphosate allowed by environmental authorities in drinking water, it can induce environmental neurotoxicities in the nervous system. (**MEX-309** pp. 6 y 12) Consequently, this study is related to the risks to human health associated with glyphosate exposure in GM corn even in small doses.

[97] **Mesnage, R., B. Bernay y Séralini, G. E. *Ethoxylated Adjuvants of Glyphosate-based Herbicides Are Active Principles of Human Cell Toxicity.* Toxicology, 2013 Nov 16;313(2-3):122-8., MEX-207.**

[98] **Vanlaeys A, Dubuisson F, Seralini GE, Travert C. Formulants of glyphosate-based herbicides have more deleterious impact than glyphosate on TM4 Sertoli cells. Toxicol In Vitro, 2018, MEX-444.**

[99] **Simasotchi C, et al, "*A Glyphosate-Based Formulation but Not Glyphosate Alone Alters Human Placental Integrity*." Toxics. 2021, 9(9):220, MEX-445.**
Hao Y, et al, "*Evaluation of the cytotoxic effects of glyphosate herbicides in human liver, lung, and nerve*". J Environ Sci Health B, 2019;54(9):737-744, MEX-446.

[100] **Howe CM, et al, "*Toxicity of glyphosate-based pesticides to four North American frog species*". Environ Toxicol Chem. 2004 ;23(8):1928-38, MEX-447**

[101] **Mesnage R, et al, "*The surfactant co-formulant POEA in the glyphosate-based herbicide RangerPro but not glyphosate alone causes necrosis in Caco-2 and HepG2 human cell lines and ER stress in the ToxTracker assay*". Food Chem Toxicol, 2022, MEX-448.**

[102] **Defarge N, et al, "*Co-Formulants in Glyphosate-Based Herbicides Disrupt Aromatase Activity in Human Cells below Toxic Levels*". Int J Environ Res Public Health. 2016 Feb 26;13(3):264, MEX-449**

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
408	MEX-310	Kubsad, D., Nilsson, E.E., King, S.E., Sadler-Riggleman, I., Beck, D. and Skinner, M.K., "*Assessmentof Glyphosate Induced Epigenetic Transgenerational Inheritance of Pathologies and Sperm Epimutations: Generational Toxicology*," in "*Scientific Reports."*	This study found no effects in the parental or first generation following intraperitoneal (gut) injections to gestating rats, but effects on the second and third generations in terms of ≥1 disease at one year of age—however, there wasno clear pattern when looking at any one disease. This is not a risk assessment of dietary exposure to glyphosate through dietary consumption of GE corn.	Like Exhibit **MEX-306**, this Exhibit is cited by Mexico in a section where it argues about the risks to human health arising from glyphosate exposure even in small doses. As the United States points out, the study did find harmful effects caused by glyphosate in "non-observable-effect-level" to the 3rd generation of rats. It is therefore clear that the use of this evidence is appropriate to demonstrate the existence of risks associated with glyphosate exposure.
408	MEX-311	Wilson, VS, Bobseine, K, Lambright, CR, Gray, LE Jr., "*A novel cell line, MDA-kb2, that stably expresses an androgen- and glucocorticoid-responsive reporterfor the detection of hormone receptor agonists and antagonists."*	Mexico falsely alleges that "[t]he endocrine involvement of exposure to low doses of glyphosate in humans was demonstrated by assays in MDA-kb2 cell lines that allow the detection of hormone receptor antagonists, and in placental JEG3 cell lines." The cited study (MEX-311) does not even mention glyphosate. This study also does not reference GE corn.	The foregoing is merely an error in Mexico's final document, which should not be severely singled out as a "false claim".
408	MEX-312/207/193	Richard S., Moslemi S., Sipahutar H., Benachour N., Séralini G-E., "*Differential effects of glyphosate and roundup on human placental cells and aromatase*", 2005/Mesnage, R., Bernay, B., Séralini, G.E. (2013). "*Ethoxylated adjuvants of glyphosate-*	These studies expose isolated cells to technical grade glyphosate and formulated RoundUp. There is no discussion if the concentrations tested are likely to be relevant to circulating levels of glyphosate within an organism. Ingested or absorbed pesticides do not circulate within the organism at the concentration they are exposed to; rather, the concentration is usually significantly less. These studies are not a dietary risk assessment, nor do theyhave anything to do with consumption of GE corn.	In the aforementioned article, an experimental trial was conducted in which in vitro placental cells were administered glyphosate and the commercial formula Roundup, 100 times lower than the recommended use in agriculture. Even so, from such low concentrations the study concluded that in these cells the expression of aromatase is affected and therefore Roundup can be

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
		based herbicides are active principles of human cell toxicity". Toxicology/ Benachour, N. y Séralini, G.E. "*Glyphosate Formulations Induce Apoptosis and Necrosis in Human Umbilical, Embyonic, and Placental Cells"*.	In fact, none of the articles Mexico has cited has had a comparison of the concentrations causing effects on cells in a petri dish to what concentrations arecirculating in the body following exposure. Without that information, one cannot say if the tested concentrations have any relevance to real-worldexposures or not.[103]	considered as an endocrine disruptor. The argument put forward to dismiss this research work is the concentration of glyphosate and Roundup to which the placental cells were subjected. It is argued that the accumulation concentrations in the human body when consuming products contaminated with these substances are much lower; however, the United States does not at any time clarify that said amount may vary several orders of magnitude because that concentration depends on the time of exposure, as well as the concentration and intensity of food products containing it. In addition, those doses to which the cells were subjected are two orders of magnitude lower than what is normally sprinkled in the field. The conditions of farmers who at the same time spray these herbicides directly and also consume large amounts of glyphosate through food

[103] These studies have several limitations that have been previously identified that would limit their ability to be used in a risk assessment context. *See* EPA, "Glyphosate - Systematic Review of Open Literature" (2017), https://www.regulations.gov/document/EPA-HQ-OPP-2009-0361-0067 (Exhibit USA-163). For MEX-312, major limitations include not characterizing the test substance properly, and experiments focused more on the formulation as opposed to the active ingredient. *Id.* at 27, 149-150 (Exhibit USA-163). For MEX-207, major limitations include a focus on adjuvants, as opposed to the active ingredient, and deficiencies in reporting of study data. *Id.* at 26, 141-142 (Exhibit USA-163). For MEX-193, major limitations include incomplete characterization of the testsubstances and unknown relevance of in vitro effects to in vivo effects. *Id.* at 21, 100-102 (Exhibit USA-163).

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
				are additive factors that lead to large quantities of glyphosate being stored and that undoubtedly, may exceed the concentrations tested in this study. The allowable amount for Europe is 22 micrograms per kilo. However, when you accumulate this amount by feeding with various products contaminated with these herbicides, as well as that which may be acquired by direct spraying, there would be a large accumulated amount of various sources circulating in our tissues. Thus under the same argumentative precedents that the United States handles, it can be said that the concentrations tested have some relevance with the exposures in the real world.
410	MEX-139	Mesnage R, *et al*., "*Cytotoxicity on human cells of Cry1Ab and Cry1Ac Bt insecticidal toxins alone or with a glyphosate-based herbicide."*	This section of Mexico's Initial Submission refers to "the presence of GMOsand glyphosate residues," but this study does not even study the amount of glyphosate residues on plants, much less GE corn.	Precisely the study reported that "*pesticides residues co-occur in the plant, synthesized by the plant itself, by the expression of the inserted transgene … or through external pesticide treatment.... In turn, such residues exert their effects upon consumption or release into the environment*". (**MEX-139** p. 1)
410	MEX-208	Xu, J., Smith, S., Smith, G., Wang, W. y Li, Y. "*Glyphosate contamination in grains*	This is a review of glyphosate generally, and corn grain is not listed in the table of glyphosate	Indeed, it is a review of glyphosate, that is why it is called "*Glyphosate contamination in grains and foods: An overview*", but it is a general

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
		and foods:An overview".	residues.[104]	review of GM plant grain contamination including corn. The virtue of having scientific review works is that they make a synthesis of the state of the art of a certain area of scientific knowledge. In this particular case there are a lot of accumulated works that have investigated this particular topic and it is when the same researchers can make a review with several or large amount of independent scientific works that support a general conclusion. Science has a number of virtues embedded in the experimental scientific method, for example, that from particular cases can issue general conclusions that can serve to interpret other cases that are investigated. Unfortunately for the United States, by not carefully reviewing the multiple evidence presented they leave aside the following references that appear in this review article and that talk about glyphosate contamination in GM

[104] This study, and other studies cited by Mexico, also reference the glyphosate degradate, aminomethylphosphonic acid ("AMPA"). AMPA has a lower toxicityprofile than that of glyphosate, with any observed effects associated with AMPA exposure occurring at doses much higher than glyphosate, even well above maximum dose levels set for guideline studies known as limit doses that are typically too large to be considered relevant for human health risk assessment. *See,e.g.*, EPA, "Human Health Risk Assessment in Support of Registration Review," at 30 (Dec. 12, 2017) (reflecting 90-day rodent study of AMPA (MRID 00241351) where effects seen at 1200 mg/kg/day, which is above the limit dose of 1000 mg/kg/day, and 90-day non-rodent study (MRID 43334702), with no effects up to the highest dose tested (~300 mg/kg/day)) (Exhibit USA-164). Residues of AMPA in both wild-type and GE crops are consistently less than residues of glyphosate. As both toxicity and magnitude of residues of AMPA are less than those for glyphosate, any risk assessment for glyphosate is protectiveof AMPA exposures.

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
				corn grains, this is the transcription including the quote that may be analyzed: • In addition, it is expected that genetically-modified (GM) crops such as soybean and corn may contain higher amount of glyphosate residues. (**MEX-208** p.4) • The Food and Drug Administration (FDA) is then responsible for ensuring at the imported and domestic foods available at retail do not exceed the limits set by the EPA. The EPA published the tolerances for glyphosate residues in the CFR §180.364, which set the maximum residue limit (MRL) of 30 mg/kg for all group 15 cereals, except for corn (5 mg/kg) and rice (0.1 mg/kg), and 40 mg/kg for all group 20 oilseeds, except for canola (20 mg/kg). (**MEX-208** p.10) • A survey of corn and soy products collected from Philadelphia and U.S. metropolitan area showed that ten out of twenty-eight (36%) soy sauce samples

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				contained glyphosate at a concentration above the method LOQ (0.075 mg/L) with a range between 0.088-0.564 mg/L, while glyphosate concentrations in all organic soy sauce 13 264 samples, soy milk and tofu, and corn syrups tested were below the method LOQ. (**MEX-208** p.12) In addition, figures 2 and 3 should be reviewed in greater detail, they information related to glyphosate residue concentration and its main metabolite in cereals and related foods and detection methods and their limits of work in the analysis of glyphosate.
410	MEX-313	LEISA. *"Glyphosate in wheat, oatsand beans."*	This short web article is highly emotive and displays significant bias. For example, this article uses words such as "food soaked in poison," "silent genocide," "accomplices" such as Argentine government agencies "turn[ing] ablind eye," and use of glyphosate "for greed and to sell more and faster." Thisarticle does not follow any standard journal practices and does not include proper citations to other research.	Although the article is not a scientific article, it is a general audience article based on a scientific article. There is no rule, either in the USMCA or in the WTO, that using general audience or opinion articles automatically dismisses them, especially when using sources based on a scientific method, as in this case. The scientific article by Dr. Benbrooke on which this general audience article is based was published in 2016 and to date has more than 1000 citations, which

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
				overwhelmingly support and reproduce the findings of this research. Among the conclusions of this article is the verification of the discussed topic on reduction or increase of herbicides by the appearance in agrosystems of genetically modified plants. Using data from the same U.S. government, it is concluded that since 1996 the amount of glyphosate has increased considerably without having a higher yield per hectare in both soybeans and corn.[105]
410	MEX-314	Rubio, F., Guo, E., & Kamp, L., "*Survey of glyphosate residues in honey, corn and soy products."*	This study expressly says that glyphosate residues were not detected on the corn (syrup) samples. (p. 7). No other type of corn sample was tested.	The United States ignores the general conclusions of this article, in which discusses, amongst other things, that "food consumption is an important pathway of human exposure to pesticides and other chemical contaminants. […] Contaminants can enter the dos supply in carious ways including direct pesticide application to food crops, indirect application through the air (from drift from aerial spraying of adjacent fields), through the soil (from direct application during previous growing seasons), through the water supply (from run-off from treated areas), or through food processing (from cross-contamination from shared processing equipment)" and that

[105] **Benbrook, C.M., 2016. "*Trends in glyphosate herbicide use in the United States and globally*". Environ. Sci. Eur., 2016, 28, 3, MEX-442**

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				"this herbicide may be a key contributor to the obesity and autism epidemics in the United States, as well as a factor in several diseases and conditions including celiac disease, Alzheimer's, Parkinson's, infertility, depression, and cancer".[106] It is important to note that samples of honey, corn syrup, soy sauce and other products were analyzed to determine glyphosate traces. First, glyphosate concentrations above the 75 ppb LOQ of the method were found, in 10 of the 28 soy sauce samples evaluated with a concentration between 88 and 564 ppb. In the case of honey from the 69 samples analyzed, 41 had glyphosate concentrations above LOQ, 15 ppb, with a mean of 64 ppb. In the case of corn syrup no concentrations higher than LOQ were found; however, it was not demonstrated that the syrup came from GM corn.
N/A	MEX-085, at 15-16 (citing Swanson	Swanson, NL, A. Leu, J. Abrahamson & B. Wallet. (2014). "Genetically Engineered Crops, Glyphosate and the	Mexico's "risk assessment" (MEX-085) presents an adaptation and modification of the information presented in Swanson et al. (2014) and purports to show a correlation between an increased incidence of certain diseases as	The scientific dossier (**MEX-085**) replicates the graphs presented by Swanson et al. in their study. None of these tables were adapted or modified.[107]

[106] **Rubio, F., Guo, E., & Kamp, L., "*Survey of glyphosate residues inhoney, corn and soy products*", p.1. MEX-314.**

[107] **Swanson, NL, et al, "*Genetically Engineered Crops, Glyphosate and the Deterioration of Health in the United States of America,*" Journal of Organic Systems, 2014, 9(2): 6-37), pp. 16-29. MEX-450**

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
	et al. (2014))	Deterioration ofHealth in the United States of America," *Journal of Organic Systems*. 9(2): 6-37).	reported in data from the U.S. Centers for Disease Control and Prevention against survey data on the planting of GE crops. However, the Swanson et al. report lacks any data that demonstrate that the people that reported these diseases also were exposed to glyphosate (*e.g.*, in proximity to areas during glyphosate applications, from exposure to food, et cetera).	As the study specifies from the information collected, "data show very strong and highly significant correlations between the increasing use of glyphosate, GE crop growth and the increase in a multitude of diseases. Many of the graphs show sudden increases in the rates of diseases in the mid-1990s that coincide with the commercial production of GE crops. The large increase in glyphosate use in the US is mostly due to the increase in glyphosate-resistant GE crops".[108] The study itself explains that "The probabilities in the graphs and tables show that it is highly unlikely that the correlations are a coincidence. The strength of the correlations shows that there is a very strong probability that they are linked somehow" and that "we do not imply that all of these diseases have a single cause as there are many toxic substances and pathogens that can contribute to chronic disease. However, no toxic substance has increased in ubiquity in the last 20 years as glyphosate has. The disruption by glyphosate

[108] **Swanson, NL, et al, "*Genetically Engineered Crops, Glyphosate and the Deterioration of Health in the United States of America,*" Journal of Organic Systems, 2014, 9(2): 6-37), pp. 16-29, 32, MEX-450.**

Paragraph	Exhibit	Source	U.S. Analysis	Mexico's Response and Person in Charge
				of the detoxification pathways in the human body can intensify the effect of other toxic chemicals".[109]

[109] **Swanson, NL, et al, "*Genetically Engineered Crops, Glyphosate and the Deterioration of Health in the United States of America,*" Journal of Organic Systems, 2014, 9(2): 6-37), pp. 16-29. MEX-450**