Issue	Complaint	Answer from the Commission	Comment	Conclusion
Substantial equivalence and compositional analysis	Many significant differences in the compositional analysis were found in the comparison with its conventional counterparts, but these were not investigated further. Instead, references were made to unspecific and questionable 'historical' data from industry unrelated to the actual field trials.	It should be highlighted that the EFSA GMO Panel considered the nature and magnitude of the observed compositional differences between maize MON89034 x MON88017 and its conventional counterpart in the light of the field trial design, biological variation and level of the studied compounds in commercial non-GM maize varieties, and provided a scientific rationale for concluding that maize MON89034 x MON88017 is compositionally equivalent to its conventional counterpart and commercial non-GM maize varieties except for the introduced traits. (page 9)	In the data provided by Monsanto many significant findings are listed in comparison with the conventional counterparts of MON80934 x MON88017. However, in order to avoid meaningful discussion of substantial equivalence, the applicant has developed a biased rationale to interpret these data (which is also adopted by EFSA). According to this biased rationale, any significant findings can be mixed up and 'diluted' with other data to prevent any evidence emerging from field trials: *"The statistical analyses showed that all of the 366 comparisons made between the test substances, MON 89034 × MON 88017, and the conventional control corn substance, LH198 × LH172, were either: a) not significantly different, b) were significantly different ($p<0.05$) but the composition values for the test substances were within the calculated 99% tolerance interval for the population of conventional reference substances and not considered biologically relevant, or c) were significantly different ($p<0.05$) but the composition values for the test substances were within the range of values obtained from the ILSI Crop Composition Database and not considered biologically relevant. Thus, the forage and grain from MON 89034 × MON 88017 are compositionally equivalent to conventional corn forage and grain."* (Reynolds. T., Drury, M., Nemeth, M., Trujillo, W., Sorbet, R. (2006) Amended Report for MSL-20098: Compositional	Data used in risk assessment should only be derived from field trials under defined conditions involving the genetically engineered plants and their comparators. Significant differences should be investigated further regarding possible interaction with the environment, changes in the activity of plant genes and detailed analysis of metabolic data. References made to historical data cannot be accepted as sufficient to establish compositional equivalence.

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			Analyses of Corn Forage and Grain Collected from MON 89034 x MON 88017 Grown in 2004 U.S. Field Trials, Monsanto Company, Product Safety Center, MSL # 20404) While this document was accepted by EFSA, the Vice-Chair of EFSA's GMO Panel has stated publicly in March 2011: *"I think we're in a situation where we would be unwise at the present time (maybe in the future this will be different), but at the present time we can't trust the ILSI database. There is not sufficient environmental information from where these trials were done and that's why we insist that the commercial reference variety should be planted simultaneously with the GM and the non-GM. Otherwise I think we are in an unsafe situation and I would worry that the limits would be too wide."* (Observations of Mr. Joseph Perry, Vice-Chair, at EFSA's consultative workshop on its draft guidance for the selection of Genetically Modified (GM) plant comparators, held in Brussels on 31 March 2011, http://www.efsa.europa.eu/en/events/event/gmo110331.htm).	
Phenotypic evaluations and ecological observations	Attention must be paid to effects that might occur under certain environmental conditions , in particular,	The trials were located within the major maize-growing regions of the USA and provided a variety of environmental conditions. (page 5)	As stated by Monsanto, the data presented regarding phenotype and ecological reactions of the plants do not meet GLP standards. This is a violation of EU Regulation 1829/2003 which states (Recital 9):	Data from the applicant should meet necessary scientific standards.

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	climate (drought, heat, moist conditions). Technical failures and genetic instabilities might give rise to undesirable components in the plants or diminish valuable components.		*„Thus, genetically modified food and feed should only be authorised for placing on the Community market after a scientific evaluation of the highest possible standard, to be undertaken under the responsibility of the European Food Safety Authority (Authority), of any risks which they present for human and animal health and, as the case may be, for the environment.“* The variety of environmental conditions was not sufficiently documented in the application, and the data stemming from the field trials are not correlated to specific environmental conditions. Thus, particular factors that might cause unexpected plant reactions and unintended changes in plant compositions cannot be identified. All the following steps in risk assessment are affected by these major uncertainties. The way in which the data are interpreted, shows that it is mainly concerned with weediness. This is the wrong endpoint when it comes to safety in food and feed. The correct endpoint would be to correlate environmental conditions to potential changes in plant reactions that can lead to a change in composition.	EFSA should require data that are correlated to a variety of defined environmental conditions. Compositional analysis and reaction to environmental conditions both have to be correlated to these defined external conditions.
Expression data	It is necessary to define the protocol for measuring the toxins, since different methods	There is no legal obligation for EFSA to fully publish protocols used for conducting the measurements of the Bt toxins.	The Commission does not address the relevant point. The complaint demands the applicant provide protocols for measurement of the relevant Bt toxins that are sufficiently evaluated and can be	EFSA should require sufficiently reliable protocols for measurements of Bt proteins from the applicant.

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	for measuring can result in highly varying results. The technical protocols should be fully published and evaluated by independent laboratories to allow other institutions to conduct further measurements to control the exact level of toxins.	(page 11)	used by independent laboratories to verify or falsify the data. Without such protocols, EFSA does not have a reliable basis for risk assessment and the risk manager cannot monitor the most essential characteristics of the plants after commercialization. The need for evaluated and fully published protocols to conduct risk assessment is also shown by recent research (Székács A., Weiss, G., Quist D., Takács E., Darvas B., Meier M., Swain T., Hilbeck A., (2011): Inter-laboratory comparison of Cry1Ab toxin quantification in MON 810 maize by enzyme-immunoassay, Food and Agricultural Immunology, http://dx.doi.org/10.1080/09540105.2011.604773) In this context, reliable data on expression rate are not only necessary to assess actual exposure in food and feed, but also to determine the rate of degradation by processing, and the stability of the toxin in soil and manure. As the data from Monsanto show there was no method available at the time of risk assessment to determine stability of Cry2Ab2 and CrylA 105 in soil.	Data from the applicant should meet necessary scientific standards.
Toxicity	As comments made by experts from several Member States show,	Specific toxicity studies were performed on the proteins Cry1A.105, Cry2Ab2 and	The statement of the Commission is misleading. The risk assessment of the Bt proteins as performed by EFSA is in fact, based on a	A much more comprehensive assessment on the toxicity of the Bt proteins has to be performed.

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	this maize needs to be tested much more carefully for potential health risks. The market application of MON89034 x MON88017 is based on a series of insufficient studies that were never subjected to the scrutiny of independent quality controls. Relevant studies that raise new questions concerning the mode of action and the selectivity of Bt toxins were not taken into account by EFSA.	Cry3Bb1 and the evaluations were therefore not made by comparison with the ones from native Bt toxins. Neither proteins showed toxicity in acute oral toxicity studies in mice, nor did they show relevant similarities to known toxic or allergenic proteins in bioinformatics-supported comparisons of their amino acid sequences.	comparison with native toxins (see also issue of synergies below). The toxicity studies mentioned were performed with purified toxins and not with the ones produced by the plants. As Saeglitz et al., 2006, show the toxicity of Bt proteins can vary substantially between different batches (Saeglitz, C., Bartsch D., Eber, A., Gathmann, K., Priesnitz, U., Schuphan, I. (2006) Monitoring the Cry1Ab Susceptibility of European Corn Borer in Germany, J. Econ. Entomol. 99(5): 1768-1773). The basic questions concerning mode of action of the Bt toxins are neither addressed by EFSA nor the Commission. All things considered, substantial uncertainties remain regarding the real toxicity of the Bt proteins produced in the plants.	This should be based on data showing that not only structure but also toxicity of proteins used for experiments are identical to those produced by the plants. Different modes of actions have to be assessed case by case when it comes to different Bt toxins as well as their potential synergies (see below).
Synergies	Studies on potential synergies were only conducted with target organisms. No specific tests related to risks for food and feed e.g. on mammalian cell systems were performed. Therefore, risk assessment of the impact on food and feed cannot	In the framework of the assessment of maize MON 89034 x MON88017, the EFSA GMO Panel concluded that, based on the known function and mode of action of the newly expressed proteins Cry1A.105, Cry2Ab2, Cry3Bb1 and CP4 EPSPS, the occurrence of interactions among these proteins are unlikely.	The opinion of EFSA that synergies are not likely is in contradiction to cited literature that shows a broad range of possible interactivities between the toxins and synergies with other compounds within the food and feed chain. This answer from the Commission contradicts their own statement (above) that evaluations concerning the toxicity of the Bt toxins were “not made by comparison with the ones from native Bt toxins”.	A much more comprehensive assessment should be performed on the possible synergies between the Bt proteins and with other compounds in the food and feed chain. The points raised above (“toxicity”) and below (“accumulated effects”) have to be taken into account.

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	be conducted on the basis of these existing studies. Further, the tests were not performed in independent research facilities under the supervision of independent experts and institutions. No independent institution was involved in quality control. The results were not published in peer-reviewed articles.	(page 4)	As stated by Monsanto, the data presented do not meet GLP standards. This is a violation of EU Regulation 1829/2003 which states (Recital 9): *„Thus, genetically modified food and feed should only be authorised for placing on the Community market after a scientific evaluation of the highest possible standard, to be undertaken under the responsibility of the European Food Safety Authority (Authority), of any risks which they present for human and animal health and, as the case may be, for the environment.“*	Data from the applicant should meet necessary scientific standards.
Accumulated effects	Potential synergies with residues from herbicide spraying were left aside. Further, other relevant compounds that can trigger synergistic effects such as components from food or feed (such as proteinase inhibitors) or other stressors were completely ignored.	The EFSA Panel concluded that the product in question is as safe as its conventional counterpart, and did not consider it necessary to request additional experimental data related to combinatorial effects. (page 10)	The answer from the Commission misses the relevant problems. Combinatorial effects between Bt toxins and several compounds are described in scientific publications. Thus, this issue has nothing to do with the general concept of substantial equivalence, but is a specific risk being described for the active ingredients of Bt plants.	Accumulated and combinatorial effects have to be investigated comprehensively especially in the case of Bt plants which can lead to the chain of food and feed production being permanently exposed to insecticidal proteins.
Immune system	Some of them are known to show immunological activity: the toxin	An adjuvant effect of Cry proteins has indeed been demonstrated in animals;	Besides the studies with Cry toxins demonstrating an adjuvant effect, there are several feeding studies with Bt-plants also showing immune reactions in	Bt plants in particular should not be placed on the market without testing their impact on

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	Cry1Ac that is one of the Bt proteins used for the production of the synthetic toxin Cry1A.105, is known to be a potent immune stimulator.	however, the studies were performed using relatively high doses and routes of administration that are different from those occurring during intake of maize containing Cry proteins by human consumers. In addition, the adjuvant effect observed enhanced the immune response to the co-administered proteins but was not shown to induce an allergic reaction or an IgE response. Therefore, the GMO panel does not consider that there is a safety concern.	animals. Further, immune reactions in humans are also under discussion, as mentioned by the experts from the member states in their comments to EFSA. There is no reason why immune reactions to proteins should be regarded in general as posing no risks to human health just because they do not seem to trigger allergic reactions. As Valenta & Spök (2008) show, the opposite is true. (Valenta, R. &Spök, A. (2008) Immunogenicity of GM peas, BfN Skripten 239, Bundesamt für Naturschutz, Bonn, http://www.bfn.de/0301_veroe.html) Several studies expose immune reactions in feeding studies with Bt plants.	the immune system.
Residues from Spraying	The residues of the herbicide glyphosate and its additives may have a negative impact on health at very low dosages (e.g. hormone disruption). Because of potential health risks, farmers in Germany are advised not to use certain mixtures of glyphosate for the production of food and feed. A significant level of residues from these herbicides can be	The risk assessment with the purpose of setting maximum residue levels in imported commodities falls within the scope of Regulation (EC) No 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and is independent of the risk assessment conducted under the provisions and requirement of Regulation (EC) No 1829/2003 and Directive 2001/18/EC of the European Parliament and of the Council. However, before authorising a	The answer of the Commission underlines the problems raised by the complaint. By emphasizing that the risk assessment of herbicide tolerant plants and the risk assessment of the herbicides are independent issues that are kept separate from each other, supports the need for a strong interplay between regulations. The Commission has already taken first steps to establish such an interplay for the environmental risk assessment of herbicide tolerant plants. A strong interplay is also needed for food and feed.	Without a strong interplay in the risk assessment of herbicides, the health risks of herbicide tolerant plants cannot be assessed sufficiently. Residues from complementary herbicides are an inevitable element of the plants constituents causing a long term exposure of food and feed chain. Data on the actual load of residues in the plants resulting under varying agricultural practises have to be made

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	expected in the plants because they were created to be tolerant to these chemicals and the plants will be sprayed as part of agricultural practice for herbicide-tolerant genetically engineered plants. Recent studies show the need for a comprehensive reassessment of health risks posed by the pesticide glyphosate and its additives such as POEA. It is a matter of deep concern that the current process to reassess glyphosate under pesticide regulation is severely delayed, but meanwhile further market authorisations are still being granted for genetically engineered crops that might contain high levels of residues from spraying with glyphosate and its	new GM food and feed under Regulation (EC) 1829/2003, the Commission always ensures that an MRL has been fixed for the herbicide residue in question and its metabolites on the concerned products.		available by the applicant. The data about residues are also relevant for assessment of combinatorial effects.

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	additives.			
Feeding trials	Feeding studies involving the plant material to investigate effects on health are necessary before any usage in the food chain and feed could be considered. In the case of MON89034 x MON88017, the parental lines used to produce the stacked event were tested in animal feeding studies and showed some signs of toxicity that need further investigation. Nutritional studies have almost no relevance to possible health risk assessment. In the case of MON89034 x MON88017, only one nutritional feeding study was performed by industry, there was no feeding study to investigate the effects on human and animal health.	A 90-day feeding study on MON89034 x MON88017 was not requested by EFSA since the GMO Panel considered the outcomes of the 90-day rat feeding studies with grains of the single events and other relevant factors. No adverse effects were observed in these studies.	EFSA and the Commission do not require feeding trials with the stacked events. They assume that in this case single 90-day studies with the parental events are sufficient to judge the safety of the plants with this unique combination of Bt toxins and further residues from spraying. But it is known from science literature that combinatorial effects are very difficult to predict without empirical investigations. No such tests have been performed in non- target organisms or with organisms all along the food and feed chain. It is evident that under these circumstances feeding trials with the stacked events are essential.	Especially in the case of Bt plants, risk assessment of stacked events has to be based on a comprehensive examination of the final product. In general, since these plants produce active insecticidal proteins, the standards of the required feeding trials should at least meet the standards as required under pesticide legislation. This is relevant for single events as well as for stacked events.

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Monitoring (1)	No plan for surveillance as required by European regulation was made available that would allow identification of particular health impacts that might be related to the use of these genetically engineered plants in food and feed.	Article 5 (3) k of the Regulation (EC) No 1829/2003 on GM Food and Feed explicitly states that an applicant shall provide a proposal for post-market monitoring regarding use of the food for human consumption only when appropriate.	General surveillance of health effects is requested for all genetically engineered plants to be authorised for food and feed. This general surveillance should allow identification of negative health effects after market authorisation. The authorisation is not in compliance with this requirement.	General surveillance of health effects has to be reorganised completely.
Monitoring (2)	Monitoring of health effects should include the risks associated with the spraying of glyhosate formulations and their residues in the plants.	As already mentioned, the risk assessment with the purpose of setting maximum residue levels (or import tolerances) in imported commodities falls within the scope of Regulation (EC) No 396/2005 and is not linked to the assessment of the genetic modification as such.	There is a need for strong interplay between these EU regulations, just as there is for risk assessment and the surveillance/ monitoring of health effects.	Monitoring of health effects should include the risks associated with the spraying of complementary pesticides since they are an inevitable element of the plants constituents causing a long term exposure of food and feed chain.