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Safety and nutritional assessment of GM plants and derived food and feed: the role of animal feeding trials.

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Abstract

In this report the various elements of the safety and nutritional assessment procedure for genetically modified (GM) plant derived food and feed are discussed, in particular the potential and limitations of animal feeding trials for the safety and nutritional testing of whole GM food and feed. The general principles for the risk assessment of GM plants and derived food and feed are followed, as described in the EFSA guidance document of the EFSA Scientific Panel on Genetically Modified Organisms. In Section 1 the mandate, scope and general principles for risk assessment of GM plant derived food and feed are discussed. Products under consideration are food and feed derived from GM plants, such as maize, soybeans, oilseed rape and cotton, modified through the introduction of one or more genes coding for agronomic input traits like herbicide tolerance and/or insect resistance. Furthermore GM plant derived food and feed, which have been obtained through extensive genetic modifications targeted at specific alterations of metabolic pathways leading to improved nutritional and/or health characteristics, such as rice containing beta-carotene, soybeans with enhanced oleic acid content, or tomato with increased concentration of flavonoids, are considered. The safety assessment of GM plants and derived food and feed follows a comparative approach, i.e. the food and feed are compared with their non-GM counterparts in order to identify intended and unintended (unexpected) differences which subsequently are assessed with respect to their potential impact on the environment, safety for humans and animals, and nutritional quality. Key elements of the assessment procedure are the molecular, compositional, phenotypic and agronomic analysis in order to identify similarities and differences between the GM plant and its near isogenic counterpart. The safety assessment is focussed on (i) the presence and characteristics of newly expressed proteins and other new constituents and possible changes in the level of natural constituents beyond normal variation, and on the characteristics of the GM food and feed, and (ii) the possible occurrence of unintended (unexpected) effects in GM plants due to genetic modification. In order to identify these effects a comparative phenotypic and molecular analysis of the GM plant and its near isogenic counterpart is carried out, in parallel with a targeted analysis of single specific compounds, which represent important metabolic pathways in the plant like macro and micro nutrients, known anti-nutrients and toxins. Significant differences may be indicative of the occurrence of unintended effects, which require further investigation. Section 2 provides an overview of studies performed for the safety and nutritional assessment of whole food and feed. Extensive experience has been built up in recent decades from the safety and nutritional testing in animals of irradiated foods, novel foods and fruit and vegetables. These approaches are also relevant for the safety and nutritional testing of whole GM food and feed. Many feeding trials have been reported in which GM foods like maize, potatoes, rice, soybeans and tomatoes have been fed to rats or mice for prolonged periods, and parameters such as body weight, feed consumption, blood chemistry, organ weights, histopathology etc have been measured. The food and feed under investigation were derived from GM plants with improved agronomic characteristics like herbicide tolerance and/or insect resistance. The

majority of these experiments did not indicate clinical effects or histopathological abnormalities in organs or tissues of exposed animals. In some cases adverse effects were noted, which were difficult to interpret due to shortcomings in the studies. Many studies have also been carried out with feed derived from GM plants with agronomic input traits in target animal species to assess the nutritive value of the feed and their performance potential. Studies in sheep, pigs, broilers, lactating dairy cows, and fish, comparing the in vivo bioavailability of nutrients from a range of GM plants with their near isogenic counterpart and commercial varieties, showed that they were comparable with those for near isogenic non-GM lines and commercial varieties. In Section 3 toxicological in vivo, in silico, and in vitro test methods are discussed which may be applied for the safety and nutritional assessment of specific compounds present in food and feed or of whole food and feed derived from GM plants. Moreover the purpose, potential and limitations of the 90-day rodent feeding trial for the safety and nutritional testing of whole food and feed have been examined. Methods for single and repeated dose toxicity testing, reproductive and developmental toxicity testing and immunotoxicity testing, as described in OECD guideline tests for single well-defined chemicals are discussed and considered to be adequate for the safety testing of single substances including new products in GM food and feed. Various in silico and in vitro methods may contribute to the safety assessment of GM plant derived food and feed and components thereof, like (i) in silico searches for sequence homology and/or structural similarity of novel proteins or their degradation products to known toxic or allergenic proteins, (ii) simulated gastric and intestinal fluids in order to study the digestive stability of newly expressed proteins and in vitro systems for analysis of the stability of the novel protein under heat or other processing conditions, and (iii) in vitro genotoxicity test methods that screen for point mutations, chromosomal aberrations and DNA damage/repair. The current performance of the safety assessment of whole foods is mainly based on the protocols for low-molecular-weight chemicals such as pharmaceuticals, industrial chemicals, pesticides, food additives and contaminants. However without adaptation, these protocols have limitations for testing of whole food and feed. This primarily results from the fact that defined single substances can be dosed to laboratory animals at very large multiples of the expected human exposure, thus giving a large margin of safety. In contrast foodstuffs are bulky, lead to satiation and can only be included in the diet at much lower multiples of expected human intakes. When testing whole foods, the possible highest concentration of the GM food and feed in the laboratory animal diet may be limited because of nutritional imbalance of the diet, or by the presence of compounds with a known toxicological profile. The aim of the 90-days rodent feeding study with the whole GM food and feed is to assess potential unintended effects of toxicological and/or nutritional relevance and to establish whether the GM food and feed is as safe and nutritious as its traditional comparator rather than determining qualitative and quantitative intrinsic toxicity of defined food constituents. The design of the study should be adapted from the OECD 90-day rodent toxicity study. The precise study design has to take into account the nature of the food and feed and the characteristics of the new trait(s) and their intended role in the GM food and feed. A 90-day animal feeding trial has a large capacity (sensitivity and specificity) to detect potential toxicological effects of single well defined compounds. This can be concluded from data reported on the toxicology of a wide range of industrial chemicals, pharmaceuticals, food substances, environmental, and agricultural chemicals. It is possible to model the sensitivity of the rat subchronic feeding study for the detection of hypothetically increased amount of compounds such as anti-nutrients, toxicants or secondary metabolites. With respect to the detection of potential unintended effects in whole GM food and feed, it is unlikely that substances present in small amounts and with a low toxic potential will result in any observable (unintended) effects in a 90-day rodent feeding study, as they would be below the no-observed-effect-level and thus of unlikely impact to human health at normal intake levels. Laboratory animal feeding studies of 90-days duration appear to be sufficient to pick up adverse effects of diverse compounds that would also give adverse effects after chronic exposure. This conclusion is based on literature data from studies investigating whether toxicological effects are adequately identified in 3-month subchronic studies in rodents, by comparing findings at 3 and 24 months

for a range of different chemicals. The 90-day rodent feeding study is not designed to detect effects on reproduction or development other than effects on adult reproductive organ weights and histopathology. Analyses of available data indicate that, for a wide range of substances, reproductive and developmental effects are not potentially more sensitive endpoints than those examined in subchronic toxicity there be structural alerts for reproductive/developmental effects or other indications from data available on a GM food and feed, then these tests should be considered. By relating the estimated daily intake, or theoretical maximum daily intake per capita for a given whole food (or the sum of its individual commercial constituents) to that consumed on average per rat per day in the subchronic 90-day feeding study, it is possible to establish the margin of exposure (safety margin) for consumers. Results obtained from testing GM food and feed in rodents indicate that large (at least 100-fold) 'safety' margins exist between animal exposure levels without observed adverse effects and estimated human daily intake. Results of feeding studies with feed derived from GM plants with improved agronomic properties, carried out in a wide range of livestock species, are discussed. The studies did not show any biologically relevant differences in the parameters tested between control and test animals. (ABSTRACT TRUNCATED)

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