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Review

# Assessment of the health impact of GM plant diets in long-term and multigenerational animal feeding trials: A literature review

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ABSTRACT

The aim of this systematic review was to collect data concerning the effects of diets containing GM maize, potato, soybean, rice, or triticale on animal health. We examined 12 long-term studies (of more than 90 days, up to 2 years in duration) and 12 multigenerational studies (from 2 to 5 generations). We referenced the 90-day studies on GM feed for which long-term or multigenerational study data were available. Many parameters have been examined using biochemical analyses, histological examination of specific organs, hematology and the detection of transgenic DNA. The statistical findings and methods have been considered from each study. Results from all the 24 studies do not suggest any health hazards and, in general, there were no statistically significant differences within parameters observed. However, some small differences were observed, though these fell within the normal variation range of the considered parameter and thus had no biological or toxicological significance. If required, a 90-day feeding study performed in rodents, according to the OECD Test Guideline, is generally considered sufficient in order to evaluate the health effects of GM feed. The studies reviewed present evidence to show that GM plants are nutritionally equivalent to their non-GM counterparts and can be safely used in food and feed.

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## 1. Introduction

In Europe, GM food and feed safety is assessed by the European Food Safety Authority (EFSA), which recommended that "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" (EFSA, 2008). With different methods, key elements of the assessment procedure such as molecular, compositional, phenotypic, and agronomic traits are analyzed in both the GM line and its near isogenic counterpart (EFSA, 2008). When "molecular, compositional, phenotypic, agronomic and other analyses have demonstrated equivalence of the GM food/feed, animal feeding trials do not add to the safety assessment" (EFSA, 2009; updated in EFSA, 2011). However, animal feeding studies may provide additional and useful information to complement safety and nutritional value assessments of whole GM food and feed, especially when unintended effects are suspected. The EFSA experts panel recommend that "the use of 90-days studies in rodents should be considered for the detection of possible unintended effects in food and feed derived from GM plants which have been more extensively modified in order to cope with environmental stress conditions like drought or high salt conditions, or GM plants with quality or output traits with the purpose to improve human or animal nutrition and/or health" (EFSA, 2008).

The protocols for *in vivo* toxicological studies are adapted from the 90-day rodent study as described in OECD Test Guideline No. 408 (Organisation for Economic Co-operation and Development, 1998), which defines the experimental material to test and the practical conditions used to test it (target animal species, housing, number of doses administered, gender and number of animals, etc.). The appropriate methods used to measure phenotypic responses (body weight, food consumption, clinical biochemistry, etc.) in test animals throughout the test are also provided. Over the last few decades, these parameters have been refined for an improved toxicological assessment of low molecular weight xenobiotics such as drugs, pesticides or additives, and serve as a foundation for the evaluation of GM-based food or feed. While feeds are identical between animal groups (treated or control) in the normal 90-day rodent study, adaptation of this test to food safety studies raises many specific questions on the strengths and weaknesses of such tests. For example, to assess the potential health effects of GM-based food or feed, 33% GM animal feed is usually incorporated (see recommendations of Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, ANSES, 2011). Feeding experiments using rodent models allow whole GM material to be tested, this assessment being motivated by either a modification in the GM plant composition, or by indications of potential unintended effects (EFSA, 2006, 2008). More precisely, 90-day animal feeding studies do not search for one particular effect of a given molecule, but are supposedly designed to detect most of the changes that may occur, including those potentially generated by the genetic modification as well as those resulting from a compositional change which is directly or not linked to the transgene. Thus, these studies might appear too wide and insufficient to detect weak effects, as EFSA (2008) has already stated "*It is unlikely that substances present in small amounts and/or with a low toxic potential will result in any observable unintended effects*". The key point is that in the case of a chemically defined molecule for which human exposure is very low, one can increase its dose in the classical 90-day feeding studies, whereas one cannot do so with a food or with a quantitatively important constituent in the diet.

Moreover EFSA (2008) states that "the subchronic, 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. Thus, in some cases, testing of the whole food and feed beyond a 90-day rodent feeding study may be needed. In cases where structural alerts, indications from the subchronic study or other information on the whole GM plant derived food and feed are available that suggest the potential for reproductive, developmental or chronic toxicity, the performance of such testing should be considered".

Possibly, some 90-day rodent feeding studies may be insufficient to reveal the presence of late effects in animals. Therefore, long-term studies, namely those performed for longer than 90 days, as well as multigenerational studies, will evaluate whether unintended effects are only detected by such studies and whether long-term studies have different findings than 90-day studies. In this paper we address the following question: Do recently published studies on long-term effects of GM plants, i.e. studies significantly longer than the 90-day sub-chronic tests, as well as multigenerational studies, present new evidence indicative of some adverse effects? The goal of this review is to compile and discuss the results of recently published studies on long-term effects as well as multigenerational studies for GM plants on which 90-day studies are also available. Twelve long-term and twelve multigenerational studies are examined. This review highlights the knowledge generated by these recently published studies to evaluate the possible existence of long-term health effects. The necessity to renew the current regulatory designs will also be discussed.

## 2. Material and methods

For this systematic review, 55 peer-reviewed references were identified from our database ('BergeRicrochGMLibrary'; Ricroch et al., 2010), which includes 32,000 references on transgenic plants, collected since 1996, using the keywords "*GM plant*", "*health*", "*long term*" and "*multigenerational*". Studies that were neither multigenerational nor longer than 96 days (OECD protocols + 10%), nor concerning animal feeding trials were discarded.

The duration and number of generations in every study concerned were identified. The one-generation long-term studies were manually sorted from the multigenerational ones. All 90-day rodent studies using the same GM line are referenced in Table 1. Twelve studies using a one-generation design, and longer

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