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Community Research

SEVENTH FRAMEWORK PROGRAMME

GRACE

Reviews of Human and Animal Health Impacts of GM Plants - Conceptual Models and Review Questions

Draft Document for Stakeholder Consultation

FP7 Collaborative Project
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GMO Risk Assessment and Communication of Evidence


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Table of contents


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1. Introduction

This section features the proposed review questions on the topic of the safety of genetically modified (GM) crops and derived products for human and animal health.

2. Motivation

Within the GRACE project, sources for data on the potential human and health impacts of genetically modified plants (GMPs) and their safety assessments are to be identified, and safety assessment strategies are to be reviewed. In parallel with the reviews of the possible environmental and socio-economic impacts of GM crops, this activity aims at informing various stakeholder groups about the state-of-the-art knowledge of possible impacts of genetic modification of crops on the characteristics of these crops, including any potential effect on the health of humans and animals exposed to them such as through consumption of crop-derived foods and feeds.

3. Background

To assess the food safety of GMPs, current practice follows the internationally harmonized approach based on the comparison between the genetically modified (GM) product and its conventional counterpart with a history of safe use, focusing on the safety of the differences thus identified. The requirements and the data provided in these safety assessments have shown a refinement and expansion over time. The question arises which experience has been garnered with almost two decades of GM crop commercialization and the safety impacts so far identified, as well as possible refinements to the safety assessment methods on various sub-topics such as the comparative assessment, potential toxicity and allergenicity, nutritional values, and exposure assessment.

This document features a number of draft questions for which answers are to be searched through the review activities within GRACE in the field of the safety of GM crops for human and animals. These questions were developed by an internal team of experts from various scientific backgrounds with experience in the safety assessment of GM crops. Besides the questions, the document also provides a cursory introduction into the topic and diagrams showing the “conceptual models.” These diagrams dissect the various issues according to the PICO/PECO approaches in line with the general guidance and protocols developed within a parallel Work Package (WP 8). This way, the issue can be split into a given intervention (I) or exposure (E), the concerns about potential associated hazards, the pathways through which these hazards may eventually develop into potential risks, and the potential harm (outcome, O) thus caused in the population (P) at risk as compared to the comparator/control (C). With these conceptual models, the authors were able to draft relevant review questions in a systematic and focused way. This approach towards questions Stakeholders are invited to provide their feedback on the topics chosen, the conceptual models presented, and the review questions thus formulated.

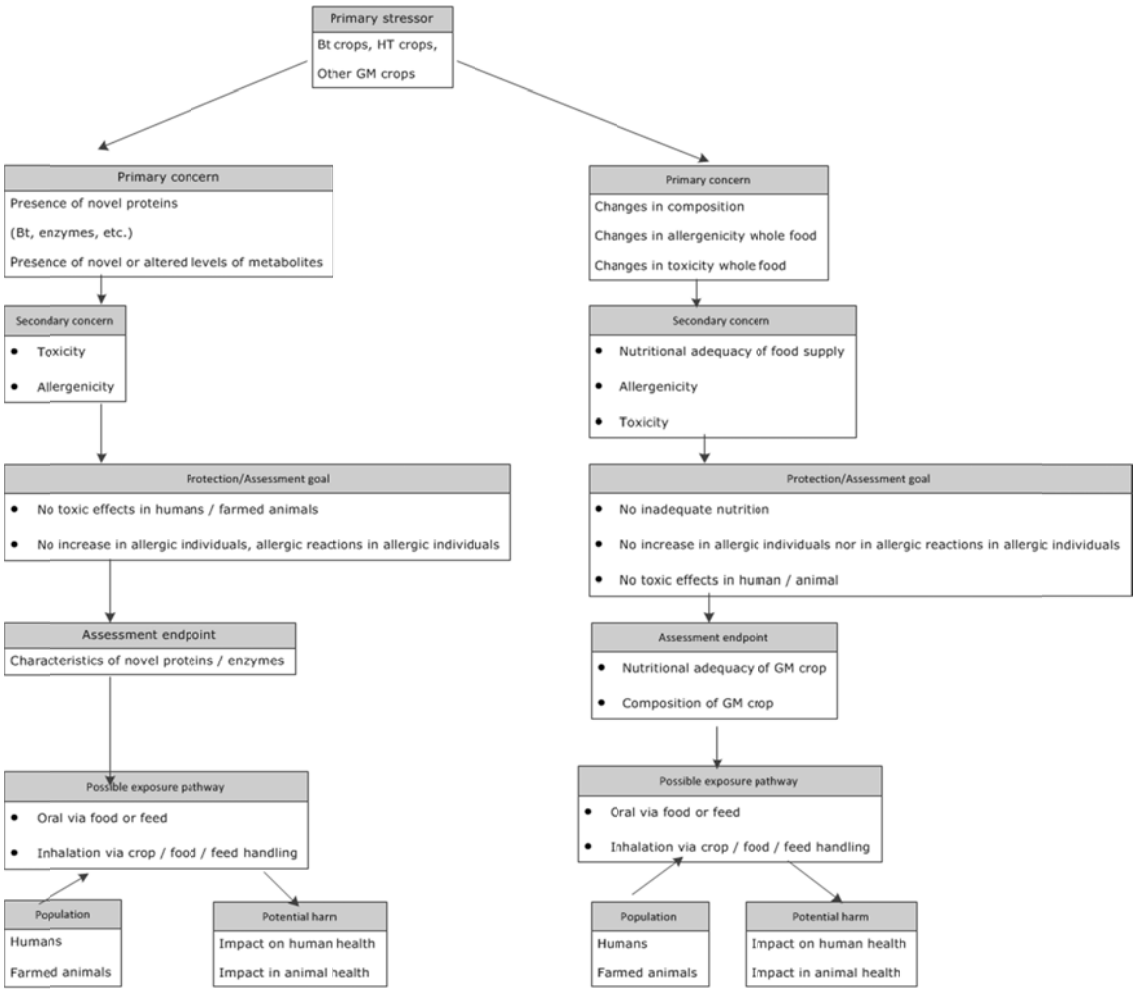
4. Review topics and draft review questions

4.1. Review topic: General considerations (applicable to all topics)

The basic issues addressed in this section straddle the various components of risk assessment, including hazard identification, characterization, exposure assessment, and risk characterization, including:

- Comparative assessment of the GM crop composition;
- Potential risks, such as the toxicological / allergological and nutritional characteristics of the GM variety in comparison with conventional counterparts
- Exposure assessment

4.1.1. Draft review question development: Conceptual model, general safety issues



4.1.2. Basic questions

The basic questions underlying the GRACE project:

- How do current aspects of the food/feed safety assessment address these hazards?
- Is this still the best approach to address these hazards (hazard identification and hazard characterisation) or are there better alternatives (more informative, more cost- time-efficient, use of less laboratory animals etc.)?

This can be assessed for all major aspects of the current approach:

- Phenotypic and agronomic assessment
- Compositional comparison
- Molecular biological characterisation

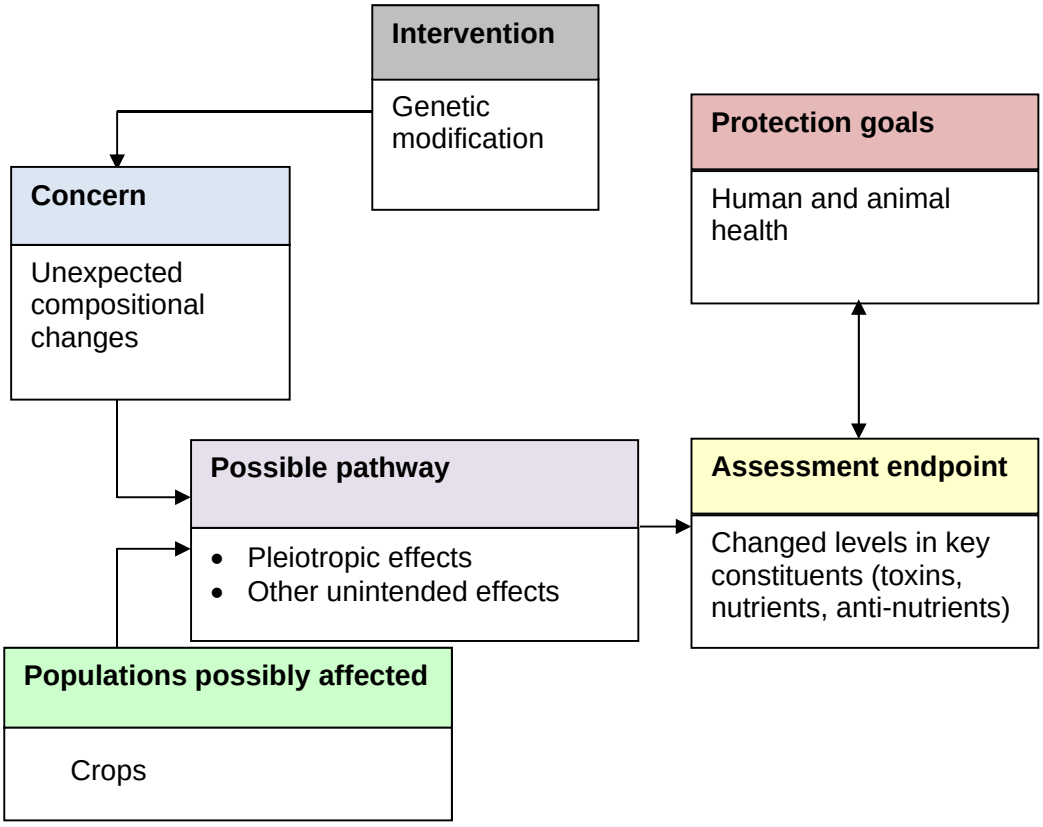
- Overall toxicological assessment, including animal feeding trials
- Overall nutritional assessment, including animal feeding trials

All of these aspects can be further subdivided in different methods of assessment.

4.2. Category: Hazard identification

4.2.1. Review topic: Comparative compositional assessment of GMPs

4.2.1.1. Draft review question development: Conceptual model, unexpected compositional changes



Description:

Approval of any given GMO is subjected to regulation in the EU and elsewhere. This question should initially focus on the targeted compositional analysis that are needed to get approval by the EU, and question to which extent these analyses have entailed identification of unexpected effects of GMOs, always beyond the "normal" variability among conventional commercial varieties, which can be a concern from the risk assessment perspective.
Other targeted analyses have been published questioning other targets, e.g. lignin composition in maize, and frequently lead to not completely "unexpected" effects. This could be considered only in case they were relevant from the risk assessment perspective.

4.2.1.2. Proposed review questions

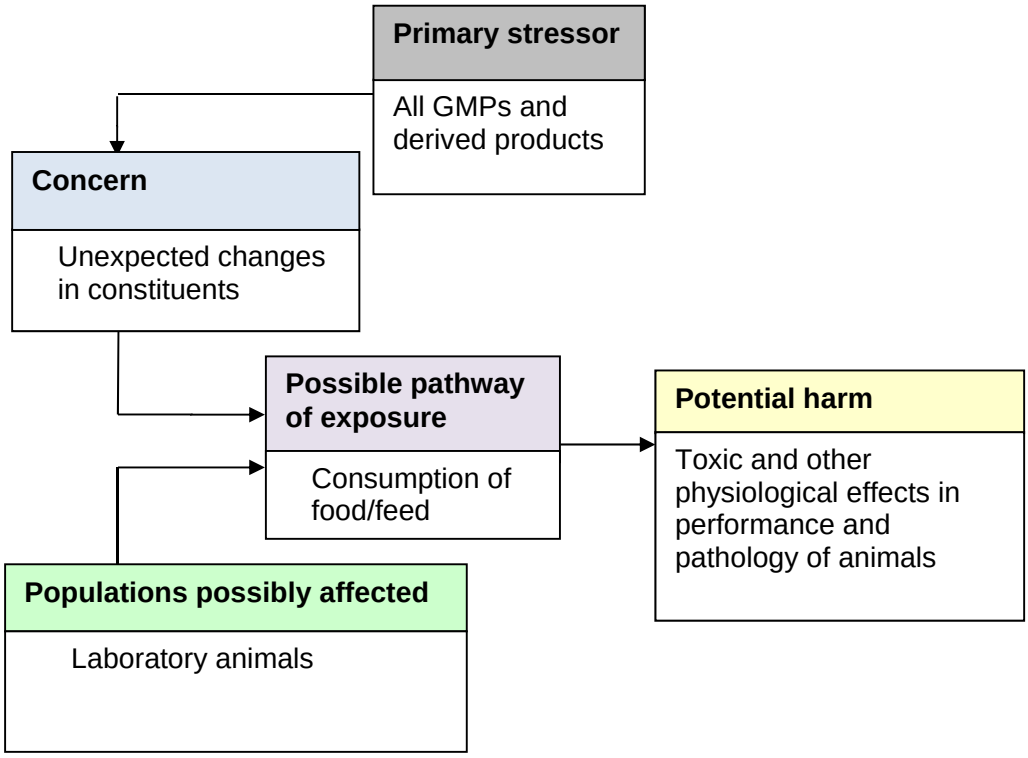
Review questions
Question1: Which relevant unintended changes (O) have been identified in the levels of key constituents (P) in GM crops (I) with agronomic traits commercialized in the EU compared with conventional non-GM food crops (C)?
Question 2: What new evidences for relevant changes in the levels of crop-characteristics nutrients, toxins and antinutrients for the safety (O) of GMPs (P) have the "omics" technologies provided? EM question
Question 3: Is the number of the changes caused in the transcriptomic, proteomic and metabolomic profiles (O) of crops (P) greater if they have been genetically modified (I) as compared to the changes caused by conventional breeding in the same crop (C)? Evidence-Mapping (EM) question

4.3. Category: Potential risks

4.3.1. Review topic: Potential toxicity of GMPs

There are certain types of studies for assessment of the possible health effects of GMPs and derived products which outcomes concern the manifestation of toxicity of the tested sample (purified substance or whole plant/plant organ). Unintended toxic effects of GMPs may be due to genetic rearrangements triggered by the genetic modification, followed by changed, induced or knocked expression of key molecules that are present in the plant cell. In the frame of this topic we are focused on data obtained from animal feeding trials performed with whole or part of the transgenic plant investigating for possible toxic effects of commercialized GM plants that are not related to the trait, i.e. unintended toxic effects.
The use of animals for assessing the toxicity of whole foods/feeds inevitably raises ethical concerns and should be avoided, or only be used if there is no other alternative. It would therefore be useful to explore causal relationships, *i.e.* whether toxic effects observed in laboratory animal feeding studies could be linked to dietary constituents that were either new or whose levels or availability had been altered in the GM crop-derived diets as compared to the diets derived from conventional counterparts. Vice versa the question can be raised as to whether advanced analytical techniques may pick up unintended effects in GMPs more sensitively than feeding trials with laboratory animals.

4.3.1.1. Review question development



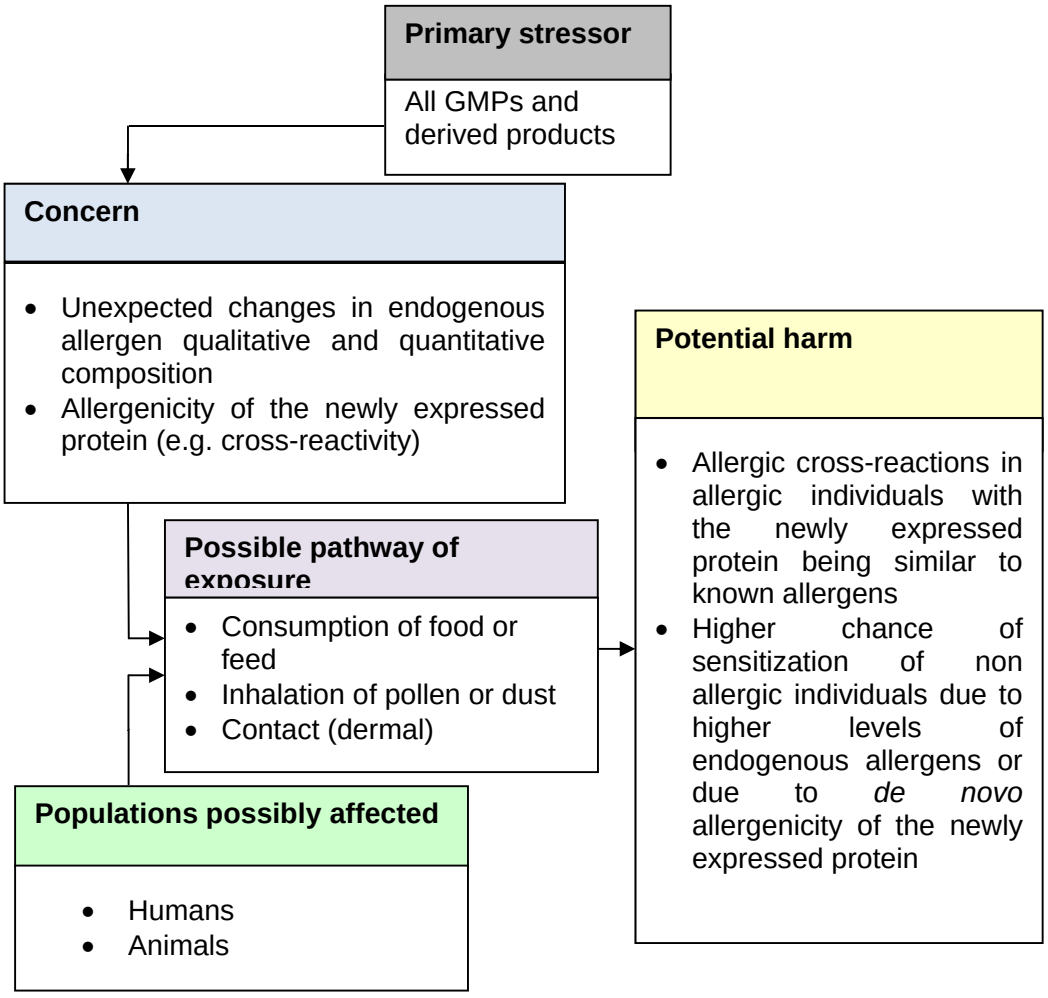
4.3.1.2. Proposed review questions

Review questions
Question 1: Is there evidence for toxic effects (O) to laboratory animals (P) fed diets containing whole foods or feeds derived from commercial GM plants (I) for at least three months compared to animals fed diets derived from their non-GM counterparts (C)?
Question 2: Could these toxic effects (O) in laboratory animals (P) be linked to changes in the presence or levels of specific diet constituents (I) of the diets containing GM crops as compared to their levels in diets derived from non-GM counterparts (C)?
Question 3: Is there evidence that laboratory animal (P) feeding experiments with GMPs (I) can identify hazards (O) more effectively compared to advanced analytical studies (C)?

4.3.2. Review topic: Potential allergenicity of GMPs

Various crops are known to have allergenic properties, namely to cause allergic reactions in patients allergic to these plants, either via ingested food or inhaled pollen from these crops, for example. The regulatory pre-market safety assessment of GMPs also addresses the potential allergenicity of these plants. This assessment follows the "weight-of-evidence" approach as recommended by internationally harmonized guidelines for the safety assessment of GMPs as developed by Codex alimentarius. This approach involves the use of various different tests applied to the GMP so as to be able to conclude with reasonable certainty as to whether the GM crop is capable of causing allergic reactions and is different from non-GM forms of the same crop species in its capacity to elicit allergies. This is because, at present, there is no single predictive test for allergenicity available. Using the Codex alimentarius guidance as a basis, EFSA's guidance has elaborated the methodology for the various tests recommended by Codex into greater detail (as accommodated by the recently adopted guidelines in Annex to Regulation (EC) No. 1829/2003).

4.3.2.1. Review question development



Description:

1) Intended/expected: Newly expressed protein
- Bioinformatics
- Structure-Activity relationship
- Digestibility
- Immunological studies
- IgE binding capacity (ELISA)
- Cell based tests
- Animal models and in vivo experiments > metabolomics

2) Unintended/unexpected: whole plant

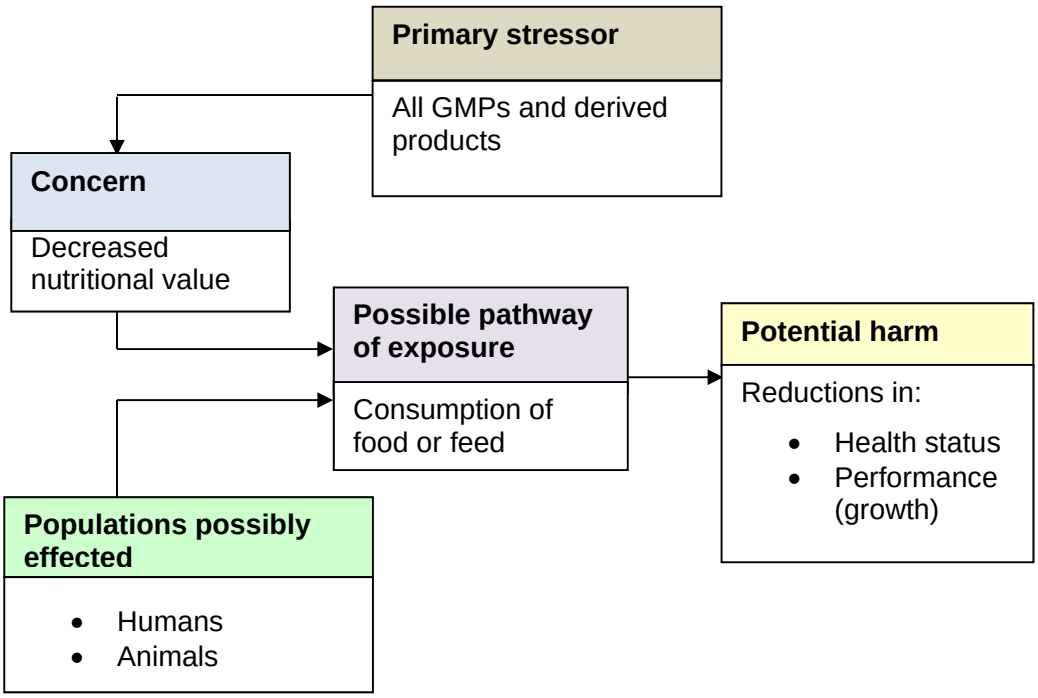
4.3.2.2. Proposed review questions

Review questions
Question 1.1: Are there changes in the qualitative and quantitative composition of endogenous allergens (O) in commercial GM (I) plants (P) compared to non-GM counterparts (C)? **Question 1.2:** Do changes in endogenous allergen levels (I) in GMPs compared to those (C) in conventional varieties affect the risk of allergy (O) for human / animal consumers (P)?
Question 2.1: What impact does the presence of the food matrix (I) have, as compared to its absence (C), on digestibility (O) of food proteins (P)? **Question 2.2:** How can this influence be accounted for when using in-vitro models (Index test) for digestibility (Test outcome) of newly expressed proteins (P) encoded by genes introduced into crops through genetic modification?

4.3.3. Review topic: Nutritional assessment of GMPs

The nutritional assessment of GMPs which are intended to be used as food or feed include compositional analysis of a GM crop compared to its near isogenic counterpart as a comparator and also may include non-transgenic commercially available varieties as reference probes. As the incorporation of a novel DNA sequence in the plant genome may affect its nutritional value, such assessments give essential information concerning mainly the emergence of unintended effects (for example, changes in the quality or quantity of one or more of the compounds) in the plant tissue.

4.3.3.1. Review question development



Description:
The assessment of anticipated alterations in the composition of the GM plant contributes to the completion of the whole biosafety assessment insight. The general outcome that is to be subjected to evaluation is the reveal of possible negative impact (direct or indirect) of the GM crops upon human health based on the altered diet composition. The nutritional analysis include evaluation of the macro- and micro- nutrients, proximates, vitamins, etc., and also may include animal feeding studies.

4.3.3.2. Proposed review questions

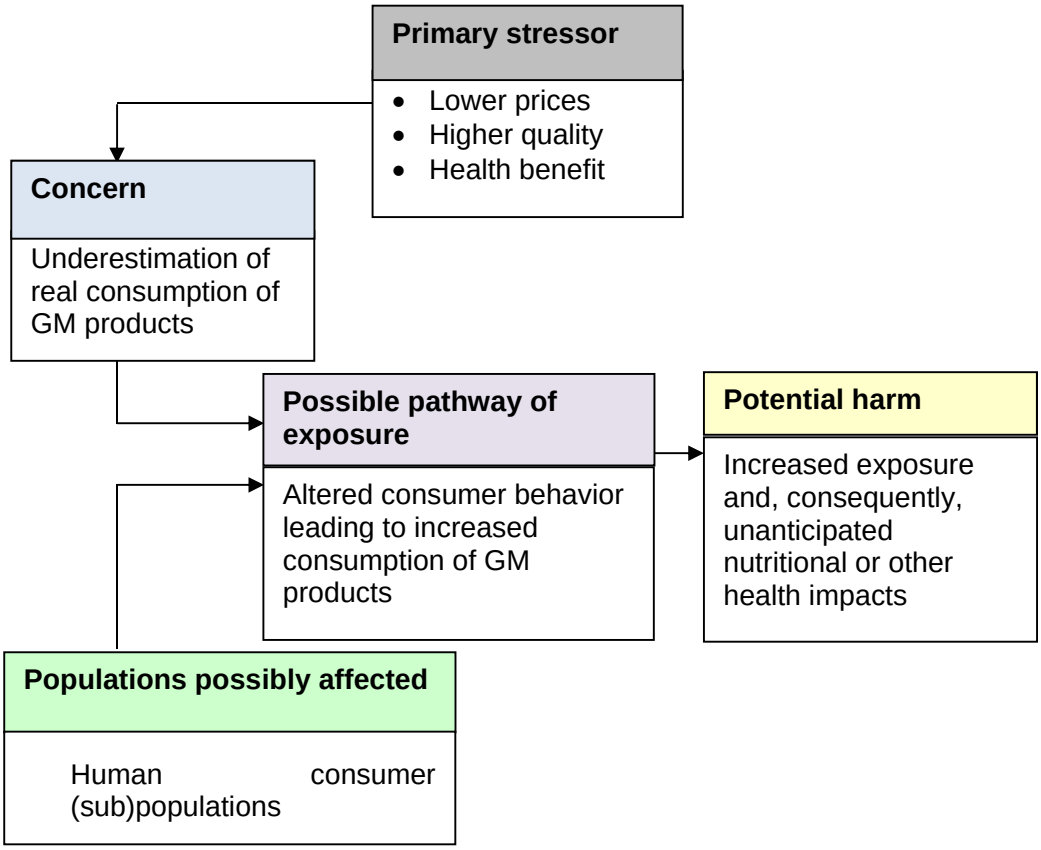
Review questions
Question1: Are there changes in the performance and health (O) of livestock animals fed (P) with GM crops with agronomic traits (I) compared to livestock animals fed with their conventional counterparts (C)?

4.4. Category: Exposure assessment

4.4.1. Review topic: Estimated exposure

Exposure assessment, besides hazard characterization, is an essential element of the risk characterization, allowing for the safety thresholds found in the hazard characterization to be compared with the actual or anticipated exposure to the substance implicated. Based on this comparison, advice can be established as to whether the marketing of a product will lead to safe consumption levels or if measures are needed to protect public health (for example, prohibition, limited marketing, labelling).

4.4.1.1. Review question development



Description:

During the exposure assessment stage of current safety assessments, the whole or partial replacement of a conventional non-GM product by its GM version is usually considered as a marketing scenario. Yet certain attributes of the GM product may actually increase the consumption of it, for example if its price is lowers than for the substituted non-GM ingredient, if its quality is better, or if the modification imparts

benefits to the consumer (e.g. nutrition). As far as no safety thresholds apply to the product and the levels of new or altered components do not raise issues, this may not be of safety concern, while for a number of nutritionally improved crops, there may be an issue of nutritional status changes. This issue touches also upon socio-economic issues, which may therefore have to be explored jointly. This may also touch upon the issue of the need for post-market monitoring (and consequently, GM product traceability) to verify estimates of consumption by different consumer subgroups that were made during the pre-market assessment

Other exposure issues may relate to increased exposure through other than oral routes, such as the inhalation of pollen from crops.

4.4.1.2. Proposed review questions

Review question
Question1: Which impact can changed product attributes, including price, quality, and perceived health benefits (I), of GM-crop-derived products as compared to those of non-GM products (C) have on consumers' (P) exposure (O)?