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Executive Summary

BACKGROUND FOR THE STUDY

Genetic engineering and other new technologies are among many advances made to traditional breeding practices in plants, animals, and microbes to enhance food quality and increase productivity. Genetic engineering, the targeted manipulation of genetic material, and non-targeted non-transgenic methods—including chemical mutagenesis and breeding—are components of the entire range of genetic modification methods used to alter the genetic composition of plants, animals, and microorganisms. (For more comprehensive definitions of key terms used throughout this report, please see Appendix A: Glossary.)

In this report, genetic engineering (GE) refers only to recombinant DNA (rDNA) methods that allow the transfer of a gene from any species to be inserted and subsequently expressed in a food crop or product. Although the process involving rDNA technology is not inherently hazardous, the product of this technology has the potential to be hazardous if the inserted gene results in the production of a hazardous substance.

Non-GE methods of genetic modification include embryo rescue, where plant or animal embryos produced from interspecies gene transfer, or crossing, are placed in a tissue culture environment to complete development. Other methods include somatic hybridization, in which the

20 cell walls of a plant are removed and the “naked” cells are forced to hybridize by electrical fu-
21 sion, and induced mutagenesis, in which chemicals or irradiation are used to induce random mu-
22 tations in DNA. The development of these biotechnological approaches has enhanced the array
23 of techniques that can be used to advance food production. However, as with all other technolo-
24 gies for genetic modification, they also carry the potential for introducing unintended composi-
25 tional changes that may have adverse effects on human health.

26 Preventing adverse health effects by maintaining a safe food supply requires the application
27 of appropriate scientific methods to problems of predicting and identifying unintended composi-
28 tional changes that may result from genetic modification of plants, animals, and microbes in-
29 tended for consumption as food. To address this need, the U.S. Department of Health and Human
30 Services Food and Drug Administration, the U.S. Department of Agriculture, and the U.S. Envi-
31 ronmental Protection Agency asked the National Academies to convene a committee of scientific
32 experts to outline science-based approaches for assessing or predicting the unintended health ef-
33 fects of genetically engineered foods and to compare the potential for unintended effects with
34 those of foods derived from other, conventional, genetic modification methods.

35 **COMMITTEE CHARGE AND APPROACH**

36 This report is intended to aid the sponsoring agencies in evaluating the scientific methods to
37 assess the safety of genetically engineered foods before they are sold to the public. The task pre-
38 sented to the committee by the sponsors was to outline science-based approaches to assessing or
39 predicting unintended health effects of genetically engineered foods in order to assist in their
40 evaluation prior to commercialization. The committee was charged to focus on mechanisms by
41 which unintended changes in the biochemical composition of food occur as a result of various
42 conventional and genetic engineering breeding and propagation methods, the extent to which

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43 these mechanisms are likely to lead to significant compositional changes in foods that would not
44 be readily apparent without new or enhanced detection methods, and methods to detect such
45 changes in food in order to determine their potential human health effects. The committee was
46 further charged to identify appropriate scientific questions and methods for determining unin-
47 tended changes in the levels of endogenous nutrients, toxins, toxicants, allergens, or other com-
48 pounds in food from genetically engineered organisms and outline methods to assess the poten-
49 tial short and long-term human consequences of such changes.

50 The committee was charged to compare genetically engineered foods to foods derived from
51 other genetic modification methods, such as cross breeding, with respect to the frequency of
52 compositional changes resulting from the modification process and the frequency and severity of
53 the effects of these changes on consumer health. As part of this comparison, the likelihood that
54 elevated toxin or allergen levels would occur in domesticated animals or plants that are modified
55 by different methods was to be considered. Based on this analysis, the committee was charged to
56 discuss whether certain safety issues are specific to genetically engineered foods, and if so, rec-
57 ommend approaches for addressing these issues. In addition, the committee was to separately
58 evaluate methods to detect potential unintended compositional changes and health effects of
59 foods derived from cloned animals. The evaluation is presented in a short subreport, separate
60 from, but designed to accompany, the committee’s full-length report on foods derived from ge-
61 netic modification methods.

62 **MECHANISMS BY WHICH UNINTENDED COMPOSITIONAL**
63 **CHANGES IN FOOD OCCUR AS A RESULT OF BREEDING OR**
64 **PROPAGATION METHOD**

65 **Conventional Breeding**

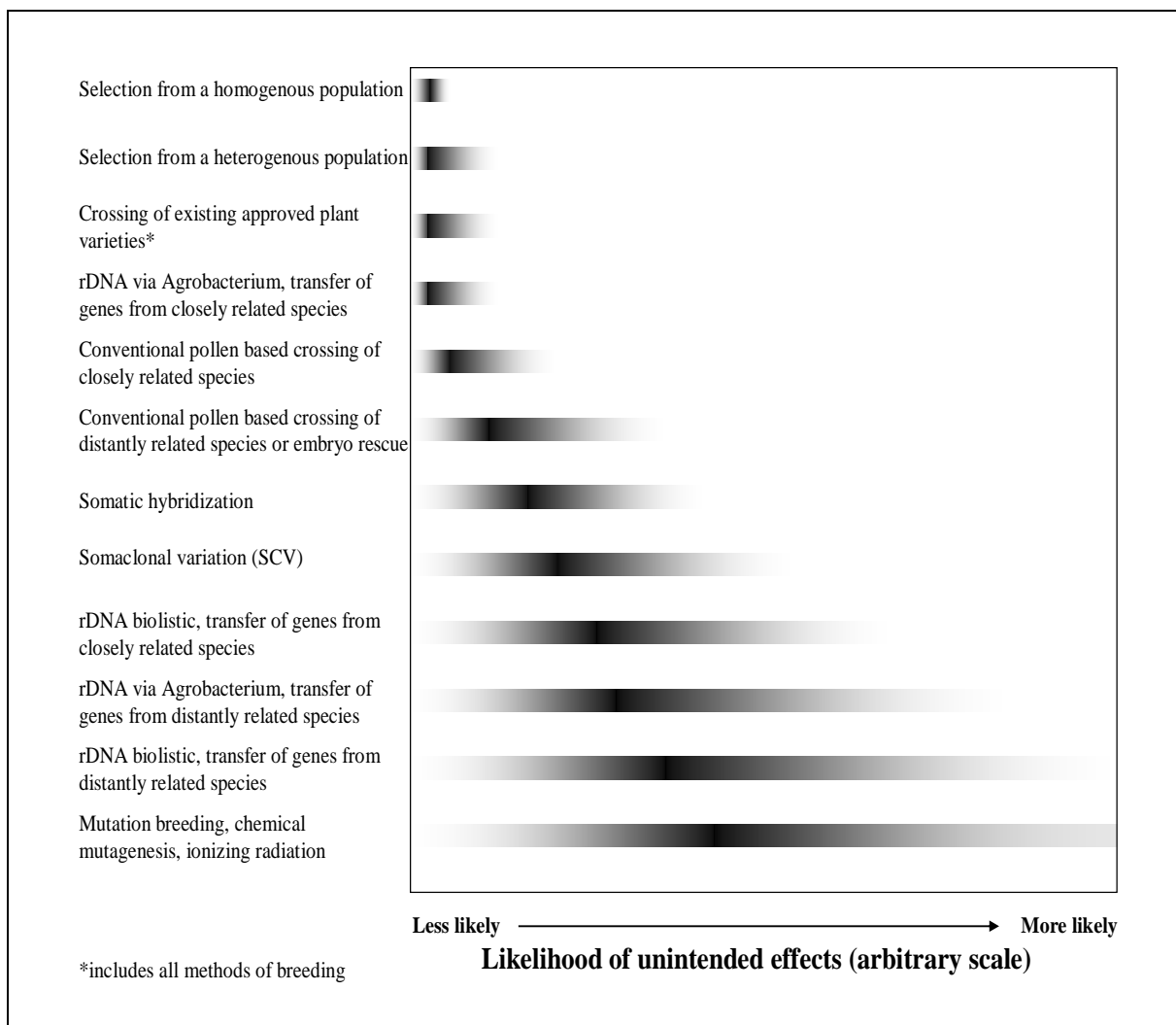
66 The oldest approach to plant genetic modification is simple selection, where plants exhibiting
67 desired characteristics are selected for continued propagation. Modern technology has improved
68 upon simple selection with the use of molecular analysis to detect plants likely to express desired
69 features. Plants that are selected for desired traits, such as reduced levels of chemicals that pro-
70 duce unpalatable taste, may diminish the ability of plants to survive in the wild because they are
71 also more attractive to pests. Selection for other traits, such as chemicals that increase the resis-
72 tance of plants to disease, may also be harmful to humans.

73 Another approach, crossing, can occur within a species or between different species. For ex-
74 ample, the generation of triticale, a crop used for both human food and animal feed, arose from
75 the interspecies crossing of wheat and rye. Because most crops can produce allergens, toxins or
76 antinutritional substances, conventional breeding methods have the potential to produce unin-
77 tended compositional changes in a food crop.

78 **Genetic Modification**

79 Hazards associated with genetic modifications, specifically genetic engineering, do not fit
80 into a simple dichotomy of GE vs. non-GE breeding. Not only are many mechanisms common to
81 both genetic engineering as a technique of genetic modification and conventional breeding, but
82 also these techniques slightly overlap each other. Unintentional compositional changes in plants
83 and animals are likely with all conventional and biotechnological breeding methods. The com-

84 mittee assessed the likelihood of a hazard occurring from both GE and non-GE modification
85 techniques and generated a continuum to express the potential for an unintended adverse health
86 effect that resides in the specific products of the modification, regardless of whether the modifi-
87 cation was intentional or not (Figure ES-1).
88



89
90
91 **FIGURE ES-1** Likelihood of unintended genetic effects associated with various methods of plant ge-
92 netic modification. The gray tails indicate the relative degree of the range of potential unintended
93 changes; the dark bars indicate the relative degree of genetic disruption for each method. For example, of

94 the methods shown, a selection from a homogenous population is least likely to express unintended ef-
95 fects, and the range of those that do appear is quite limited. In contrast, induced mutagenesis is the most
96 genetically disruptive and, hence, most likely to display unintended effects from the widest potential
97 range of phenotypic effects.

98 **METHODS TO DETECT UNINTENDED CHANGES IN FOOD**

99 **COMPOSITION**

100 Important advances in analytical methodology for nucleic acids, proteins, and small mole-
101 cules have occurred over the past decade as a result of concurrent advances in technology and
102 instrumentation; however, there is a need for improvement in all of these areas.

103 Currently, there are two basic analytical approaches available to detect compositional
104 changes in food. Targeted quantitative analysis is the traditional approach in which a method is
105 established to quantify a predefined compound or class of compounds. In contrast, profiling
106 methods involve the untargeted analysis of a complex mixture of compounds extracted from a
107 biological sample with the objective of identifying and quantifying all compounds present in a
108 sample. Advanced genetic profiling techniques—using molecular, proteomic (analysis of com-
109 plete complements of proteins), and metabolomic (global analysis of non-peptide small mole-
110 cules) approaches—are rapidly developing to produce technologies with the potential to provide
111 an enormous amount of data for a given organism, tissue, or food product.

112 Despite these technological advances in analytical chemistry, our ability to interpret the con-
113 sequences to human health of changes in food composition is limited. Compositional changes
114 can be readily detected in food and the power of profiling methodologies is rapidly increasing
115 our ability to demonstrate compositional differences among foods. The complexity of food com-

116 position challenges the ability of modern analytical chemistry and bioinformatics to chemically
117 identify and determine the biological relevance of the many compositional changes that occur.

118 **METHODS TO ASSESS THE POTENTIAL HUMAN CONSEQUENCES**
119 **OF UNINTENDED COMPOSITIONAL CHANGES IN FOOD**

120 The major challenges to predicting and assessing unintended adverse consequences to ge-
121 netically modified food—including those that are genetically engineered—are underscored by
122 the severe imbalances between highly advanced analytical technologies and limited abilities to
123 interpret their results and predict health effects that result from the consumption of food that is
124 genetically modified, either by traditional or more modern technologies. The present state of
125 knowledge requires that approaches for assessing the significance of unintended health effects
126 encompass both targeted and profiling approaches, using a range of toxicological, metabolic, and
127 epidemiological sciences. Encompassing both of these approaches exploits what is known and
128 increases the ability to prevent and assess unsuspected consequences.

129 Current safety assessments in the premarket period prior to commercialization focus on com-
130 paring the genetically engineered food with its conventional counterpart to identify uniquely dif-
131 ferent components. Typically, these comparisons are made on the basis of proximate analysis—
132 an analytical determinant of major classes of food components—as well as nutritional compo-
133 nents, toxins, toxicants, antinutrients, and any other characterizing components. The ideal com-
134 parator, in most cases, is a near-isogenic variety of food, genetically identical except for the
135 presence of the novel trait, or a near-isogenic parental variety of food from which the genetically
136 engineered variety was derived.

137 In addition to compositional comparison, agronomic comparisons have been routinely con-
138 ducted as part of the line selection phase in the development of genetically engineered crops.

139 However, these comparisons of phenotypic expression tend to be superficial and could easily
140 miss some varieties containing altered compositions that could impact adversely on human
141 health.

142 Animal feeding trials are also used to compare the nutritional qualities of a genetically engi-
143 neered crop with its conventional counterpart. Any adverse effects on the health of the animals
144 indicate the possible existence of unexpected alterations in the genetically engineered crop that
145 could adversely affect human health, if consumed.

146 Postmarketing surveillance is an approach to verify premarket screening for unanticipated
147 adverse health consequences from the consumption of genetically engineered food. Although
148 postmarketing surveillance has not been used to evaluate any of the genetically engineered crops
149 that are currently on the market and there are challenges to its use, this approach holds promise
150 in monitoring potential effects, anticipated and unanticipated, of genetically engineered foods
151 that are not substantially equivalent to their conventional counterparts or that contain signifi-
152 cantly altered nutritional and compositional profiles.

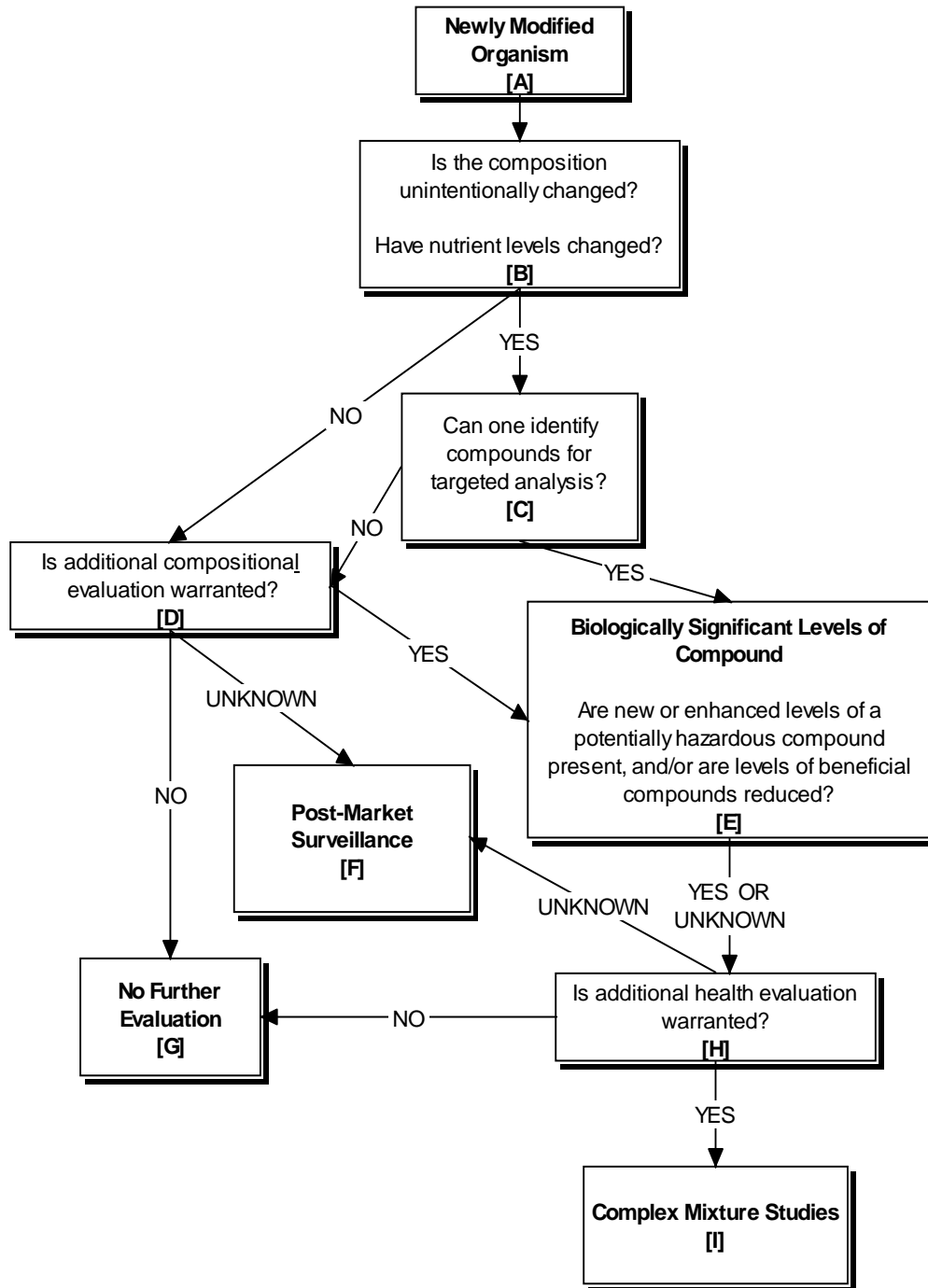
153 **FRAMEWORK FOR IDENTIFYING AND ASSESSING UNINTENDED**
154 **ADVERSE EFFECTS FROM GENETICALLY MODIFIED FOODS**

155 The committee developed a framework for a model system based on methods to identify ap-
156 propriate comparators; increase the knowledge of the determinants of compositional variability;
157 increase the understanding of the biological effects of secondary metabolites in foods; develop
158 more sensitive tools for assessing potential unintended effects from complex mixtures; and, im-
159 prove methods for tracing exposure to genetically modified foods.

160 The framework, illustrated in a flowchart (Figure ES-2), was used to examine, identify, and
161 evaluate systematically the unintended compositional changes and health effects of genetically

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162 modified and, specifically, genetically engineered foods. By raising the appropriate questions in
163 this systematic flowchart, the committee has provided a guide for overall decision-making, pro-
164 viding alternative routes that can and should be taken according to the specific genetically modi-
165 fied target. Further, the flow chart illustrates the need for appropriate tools to assess and utilize
166 both pre- and post-market approaches in the process of identifying unintended compositional
167 changes and potential unintended adverse health effects. This model system for selecting and
168 validating methods to detect and assess compositional changes in food serves as the basis for the
169 committee's recommendations to overcome limitations to current methods used to identify com-
170 positional differences and evaluate the significance of new or altered compounds in genetically
171 modified foods.



172

173 **FIGURE ES-2** Flowchart for determining potential unintended effects from genetically modi-

174 fied foods.

175 **Overall Findings and Recommendation**

176 *Findings*

177 All new crop varieties, animal breeds (cloning report), and microbial strains carry modified
178 DNA that differs from parental strains. Methods to genetically modify plants, animals, and mi-
179 crobes are mechanistically diverse and include both natural and human-mediated activities.

180 Health outcomes could be associated with the presence or absence of specific substances added
181 or deleted using genetic modification techniques, including genetic engineering, and with unin-
182 tended compositional changes.

183 The likelihood that an unintended change will occur can be placed on a continuum that is
184 based on the method of genetic modification used (see Figure 3-1). The genetic modification
185 method used, however, should not be the sole criterion for suspecting and subsequently evaluat-
186 ing possible health effects associated with unintended compositional changes.

187 All evidence evaluated to date indicates that unexpected and unintended compositional
188 changes arise with all forms of genetic modification, including genetic engineering. Whether
189 such compositional changes result in unintended health effects is dependent upon the nature of
190 the substances altered and the biological consequences of the compounds. To date, no adverse
191 health effects attributed to genetic engineering have been documented in the human population.

192 *Recommendation 1*

193 The committee recommends that compositional changes that result from all genetic modifica-
194 tion in food, including genetic engineering, undergo some safety assessment. Modified foods
195 should be assessed prior to commercialization only when warranted, based on the presence of
196 novel compounds or substantial changes in the levels of naturally occurring substances, such as

197 nutrients that are above or below the normal range for that species (see Chapter 3), taking into
198 account the organism modified and the nature of the introduced trait.

199

200 **Safety Assessment of Tools for Assessing Unintended Effects Prior to**
201 **Commercialization**

202 *Findings*

203 Current voluntary and mandated safety assessment approaches focus primarily on intended
204 and predictable effects of novel components of genetically engineered foods. Introduction of
205 novel components into food through genetic engineering can pose unique problems in the selec-
206 tion of suitable comparators for the analytical procedures that are crucial to the identification of
207 unintended compositional changes. Other jurisdictions, particularly the European Union, evalu-
208 ate all genetically engineered food products prior to commercialization, but exempt from similar
209 evaluation all other genetically modified foods. As previously discussed in Chapter 3, the policy
210 to assess products based exclusively on their method of breeding is scientifically unjustified.

211 The most appropriate time for safety assessment of all new food is in the premarket period
212 prior to commercialization, although verification of safety assessment may continue in the
213 postmarket period, generally in cases when a potential problem has been identified or if there is
214 elevated cause for concern. Examples of specific premarket assessments of newly introduced
215 proteins from selected genetically engineered food are:

- 216 • protein, fat, carbohydrate, fiber, ash, and water in a proximate analysis;
- 217 • essential macro- and micronutrients in a nutritional analysis;
- 218 • known endogenous toxicants and antinutrients in specific species;

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- 219 • endogenous allergens;
- 220 • other naturally occurring, species specific constituents of potential interest, such as
- 221 isoflavones and phytoestrogens in soybean or alkaloids in tomato or potato;
- 222 • gross agronomic characteristics;
- 223 • data derived from domestic animal feeding trials to assess the nutritional quality of
- 224 new crops; and,
- 225 • data derived from toxicological studies in animals.

226 *Recommendation 2*

227 The committee recommends that appropriate federal agencies determine if evaluation of new
228 genetically modified foods for potential adverse health effects from both intended and unin-
229 tended compositional changes is warranted by elevated concern, such as identification of a novel
230 substance or levels of a naturally-occurring substance that exceeds the range of recommended
231 intake.

232 *Recommendation 3*

233 For those foods warranting further evaluation, the committee recommends that a safety as-
234 sessment should be conducted prior to commercialization and continued evaluation postmarket
235 where safety concerns are elevated. Specifically, the committee recommends the following
236 safety assessment actions.

- 237 • Develop a paradigm for identifying appropriate comparators for genetically engi-
238 neered food.
- 239 • Collect and make publicly available key compositional information on essential nutrients,
240 known toxicants, antinutrients, and allergens of commonly consumed varieties of food

241 (see the “Research Needs” section, later in this chapter). These should include mean val-
242 ues and ranges that typically occur as a function of genetic makeup and environmental
243 variables and include a detailed description of the environmental and growth conditions
244 of the crop under consideration. These should include mean values and ranges that typi-
245 cally occur as a function of genetic makeup, differences in physiological state, and envi-
246 ronmental variables,

- 247 • remove compositional information on genetically engineered foods from proprietary do-
248 mains to improve public accessibility and,
- 249 • continue some safety assessments after commercialization to verify premarket evalua-
250 tions, particularly if the novelty of the introduced substance or the level of a naturally
251 occurring substance leads to increased safety concerns.

252 **Analytical Methodologies**

253 *Findings*

254 During the past decade, analytical methodologies for separating and quantifying messenger
255 ribonucleic acids (mRNA), proteins, and metabolites have improved markedly. Applying these
256 methodologies to the targeted analysis of known nutrients and toxicants will improve the
257 knowledge base for these food constituents. The broad application of targeted methods and
258 continuing development of profiling methods will provide extensive information about food
259 composition and further improve the knowledge base of defined chemical food constituents. The
260 knowledge and understanding needed to relate such compositional information to potential
261 unintended health effects is far from complete, however. Furthermore, currently available

262 bioinformatics and predictive tools are inadequate for correlating compositional analyses with
263 biological effects.

264 Analytical profiling techniques are appropriate for establishing compositional differences
265 among genotypes, but they must also take into account modification of the profile obtained due
266 to genotype-by-environmental interactions (the influence of the environment on expression of a
267 particular genotype). The knowledge base required to interpret results of profiling methods,
268 however, is insufficiently developed to predict or directly assess potential health effects
269 associated with unintended compositional changes of genetically modified food, as is the
270 necessary associative information (e.g., proteomics, metabolomics, and signaling networks).
271 Additionally, predictive tools to identify the expected behavior of complex and compound
272 structures are limited and require *a priori* knowledge of their chemical structure, their biological
273 relevance, and their potential interactive targets.

274 *Recommendation 4*

275 The committee recommends the development and employment of standardized sampling
276 methodology, validation procedures, and performance-based techniques for targeted analyses
277 and profiling of genetically modified food performed in the manner outlined in the flow chart
278 shown in Figure 7-1. Sampling methodology should include suitable comparisons to the near
279 isogenic parental variety of a species, grown under a variety of environmental conditions, as well
280 as ongoing assessment of commonly consumed commercial varieties of food. These include:

- 281 • Reevaluation of current methodologies used to detect and assess the biological conse-
282 quences of unintended changes in genetically modified food, including better tools for
283 toxicity assessment and a more robust knowledge base for determining which novel in-
284 creased naturally-occurring components of food have a health impact.

- 285 • Use of data collection programs, such as the Continuing Survey of Food Intakes by
286 Individuals and the National Health and Nutrition Examination Survey (NHANES), to
287 collect information, prior to commercial release of a new genetically modified food, on
288 current food and nutrient intake and exposure to known toxins or toxicants through food
289 consumption. The information collected should be used to identify food consumption
290 patterns in the general population and susceptible population subgroups that indicate a
291 potential for adverse reactions to novel substances or increased levels of naturally
292 occurring compounds in genetically modified food.

293 **Additional Tools for Postcommercialization: Identification and Assessment**
294 **of Unintended Effects**

295 *Findings*

296 Postcommercialization or postmarket evaluation tools for verifying and validating premarket
297 assessment of novel substances in food or detectable changes in diet composition, including
298 tracking and epidemiological studies, are important components of the overall assessment of
299 food safety. These tools provide a way to check the efficacy of premarket compositional and
300 safety evaluations through a feedback process. In addition, information databases that result from
301 postmarket studies can be valuable assets in the development of future premarket safety
302 assessment tools.

303 Postmarket surveillance is a commonly accepted procedure, for example, with new
304 pharmaceuticals and has been beneficial in identification of harmful and unexpected side effects.
305 As a result, pharmacologists, accept postmarket surveillance as a part of the process to identify
306 unexpected adverse outcomes from their products. This example is especially pertinent to

307 genetically engineered foods because of the unique ability of this process to introduce gene
308 sequences to generate novel products into organisms intended for use as food and especially in
309 situations where the novel products are introduced at levels that have the potential to alter dietary
310 intake patterns, e.g. elevated levels of key nutrients.

311 Given the possibility that food with unintended changes may enter the marketplace despite
312 premarket safety mechanisms, postmarket surveillance of exposures and effects is needed to
313 validate premarket evaluations. On the other hand, there are many instances in which postmarket
314 surveillance may not be warranted. For example, when compositional comparison of a new ge-
315 netically modified crop or food (e.g. Roundup Ready soybeans) with its conventional counterpart
316 indicates they are compositionally very similar; exposure to novel components remains very low.
317 Thus the process of identifying unintended compositional changes in food is best served by com-
318 bining premarket testing with postmarket surveillance, when compositional changes indicate that
319 it is warranted, in a feedback loop that follows a new genetically modified food or food product
320 long term, from development through utilization. (See Figure 7-1).

321 *Recommendation 5*

322 The committee recommends the following, when warranted by changes such as altered levels
323 of naturally-occurring components above those found in the product's unmodified counterpart, or
324 by population-specific vulnerabilities or by unexplained clusters of adverse health effects to im-
325 prove the tracking of potential health consequences from commercially available foods that are
326 genetically modified, including those that are genetically engineered:

- 327 • Improve the ability to identify populations that are susceptible to food allergens and
328 develop databases relevant to tracking the prevalence of food allergies and intoleran-
329 ces in the general population, as well as susceptible population subgroups;

- 330
- Improve and include other postmarket resources for identifying and tracking unpre-
331 dicted and unintended health effects from genetically modified foods:
 - Improve the sensitivity of surveys and other analytical methodologies cur-
332 rently used to detect consumer trends in purchase and use of genetically modi-
333 fied foods after release into the marketplace,
334
 - Standardize methods for monitoring reports of allergenicity to new foods in-
335 troduced into the marketplace and apply them to new genetically modified
336 foods,
337
 - Assure that current food labeling includes relevant nutritional attributes so that
338 consumers can receive more complete information about the nutritional com-
339 ponents in genetically modified foods introduced into the marketplace, and
340
 - Improve utilization of potential traceability technology, such as bar coding of
341 animal carcasses and other relevant foods.
342
 - Develop a database of unique genetic sequences (DNA, PCR sequences) from geneti-
343 cally engineered foods entering the marketplace to enable their identification in post-
344 market surveillance activities.
345
 - Utilize existing nationwide food intake and health assessment surveys, including
346 NHANES, to:
347
 - collect comparative information on diet and consumption patterns of the gen-
348 eral population and ethnic subgroups in order to account for anthropological
349 differences among population groups and geographic areas where genetically
350 modified foods may be consumed in skewed quantities, recognizing that this
351 will be possible only under selected circumstances where intakes are not
352

353 evenly distributed across population subgroups of interest and the relevant
354 outcome data are available.

- 355 ○ provide better representation of the long term nutritional and other health
356 status information on a full range of children and ethnic groups whose intakes
357 may differ significantly from those of the general population to determine
358 whether changes in health status have occurred as a consequence of consum-
359 ing novel substances or increased levels of naturally-occurring compounds in
360 genetically modified foods released into the marketplace, recognizing again
361 that this will be possible only under selected circumstances that allow one to
362 assess associations between skewed eating patterns and specified health out-
363 comes. Such associations would have to be followed up by other more con-
364 trolled assessments.

365 **Research Needs**

366 *Findings*

367 There is a need, in the committee’s judgment, for a broad research and technology
368 development agenda to improve methods for predicting, identifying, and assessing unintended
369 health effects from the genetic modification of food. An additional benefit is that the tools and
370 techniques developed can also be applied to safety assessment and monitoring of foods produced
371 by all methods of genetic modification.

372 The tools and techniques already developed can be applied to safety assessment and
373 monitoring of foods produced by all methods of genetic modification. However, although current

374 analytical methods can provide a detailed assessment of food composition, limitations exist in
375 identifying specific differences in composition and interpreting their biological significance.

376 *Recommendation 6*

377

378 A significant effort should be made in research to support analytical methods technology,
379 bioinformatics, and epidemiology and dietary survey tools to detect health changes in the popula-
380 tion that could result from genetic modification and, specifically, genetic engineering of food.

381 Specific recommendations to achieve this goal include:

- 382 • Focusing research efforts on improving analytical methodology in the study of food
383 composition to increase understanding of nutrient content, relationships between
384 chemical components in foods, and safety of the food
- 385 • Conducting research to provide new information on chemical identification and
386 metabolic profiles of new genetically modified foods, and proteomic profiles on indi-
387 vidual compounds and complex mixtures in major food crops and use that informa-
388 tion to develop and maintain publicly accessible databases,
- 389 • Developing or expanding profiling databases for plants, animals, and microorganisms
390 that that are organized by genotype, maturity, growth history, and other relevant envi-
391 ronmental variables to improve identification and enhance traceability of genetically
392 modified organisms,

393 Developing improved bioinformatics tools to aid in the interpretation of food composition data
394 derived from targeting and profiling methods.

395 *Recommendation 7*

396 Research is also needed to determine the relevance to human health of dietary constituents
397 that arise from or are altered by genetic modification. This effort should include:

- 398 • Focusing research efforts on developing new tools that can be used to assess the po-
399 tential unintended adverse health effects that result from genetic modification of
400 foods, e.g., profiling techniques that relate metabolic components in food with altered
401 gene expression in relevant animal models to specific adverse outcomes identified in
402 genetically modified animal models (animals genetically modified by contemporary
403 biotechnology methods that are proposed to enter the food system).
- 404 • Developing improved DNA-based immunological and biochemical tags for selected
405 genetically modified foods entering the marketplace that could be used as surrogate
406 markers to identify rapidly the presence and relative level of specific foods for post-
407 market surveillance activities.
- 408 • Developing improved techniques that enable toxicological evaluation of whole food
409 and complex mixtures, including:
 - 410 ○ microarray analysis,
 - 411 ○ proteomics, and
 - 412 ○ metabolomics.

413 **CONCLUSION**

414 In response to its charge, the committee has developed a framework to identify appropriate
415 scientific questions and methods for determining unintended changes in the levels of nutrients,
416 toxicants, allergens, or other compounds in foods from genetically modified organisms, in order

417 to assess potential short- and long-term human health consequences of such changes. Although
418 the array of analytical and epidemiological techniques available has increased, there remain size-
419 able gaps in our ability to identify compositional changes that result from genetic modification of
420 organisms intended for food; determine the biological relevance of such changes to human
421 health; and, devise appropriate scientific methods to predict and assess unintended adverse ef-
422 fects on human health. The committee has identified and recommended pre- and postmarket ap-
423 proaches to guide assessment of unintended compositional changes that could result from genetic
424 modification of foods, and research avenues to fill the knowledge gaps.

425 The recommendations presented in this report reflect the committee’s application of its
426 framework to questions of identification and assessment of unintended adverse health effects
427 from foods produced by all forms of genetic modification, including genetic engineering, and
428 can serve as a guide for evaluation of future technologies.