

Regulatory Framework

International and National Standards for food and feed safety



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Department of Biotechnology Government of India

ILSI Scientific Workshop On Biotech Safety Assessment

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Today's Topics

- **Introduction to food safety**
- **Principles of risk analysis**
 - **Current established methods for safety assessment of foods derived from GE crops**
 - **In relation to general principles of risk analysis and food toxicology**
 - **Novel Approaches required**
- **National approach-Introduction to Regulatory Framework**
- **Novel approaches required Safety assessment of foods derived from GE crops in the future**



Food Safety Systems—Institutions

- **OECD: Organization for Economic Cooperation and Development**
 - Promotes policies for highest sustainable economic development in member states
 - Establishes guidelines for chemical testing, toxic chemicals, pesticides, and biotechnology
- **Food and Agriculture Organization (FAO) of the United Nations**
 - Leads international efforts to ensure sufficient nutrition for all
- **World Health Organization (WHO) of the United Nations**
 - Provides scientific advice on matters related to food safety through its Food Safety Department
- **International Life Sciences Institute (ILSI)**
 - understanding of scientific issues relating to nutrition, food safety, toxicology, risk assessment, and the environment by bringing together scientists

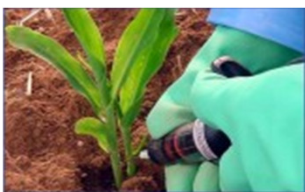
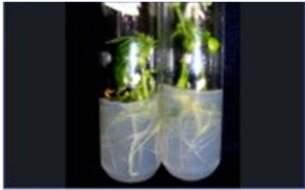
FAO/WHO Codex Alimentarius Commission

Founded in 1963 by a joint initiative of the FAO and the WHO, the Codex Alimentarius Commission

- **Formulates and harmonizes food standards and ensures global implementation**
- **Develops food standards, guidelines, and related texts such as codes of practice under the Joint FAO/WHO Food Standards Programme**
- **Generates guidelines to protect the health of consumers and ensures fair trade practices in food trade, and**
- **Promotes coordination of all food standards work undertaken by international governmental and non-governmental organizations**

The Codex Alimentarius Commission established an Intergovernmental Task Force on Foods Derived from Biotechnology in 1999 to evaluate the health and nutritional implications of such foods.

The task force performs all of the functions listed above in relation to safety assessment of foods derived from genetically engineered organism based on the input of independent scientific expert consultations.



The Evolution of Food Safety Systems

The Codex Alimentarius Commission has issued (since 1963)

237 Food Standards for commodities

41 codes/ Hygiene or technological practice

25 guidelines for Contaminants

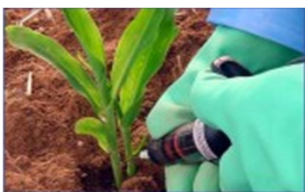
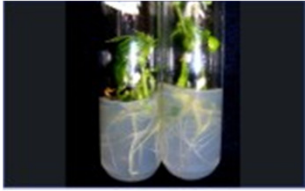
185 evaluations of pesticides

1,005 Evaluations of food additives

54 evaluations of veterinary drugs

3,504 Documents / Limits pesticide residues

So far 5 expert consultation reports regarding safety of foods derived from genetically engineered organisms (including microorganisms, plants and animals) have also been issued.



What Exactly We Ingest When We Eat Food: An example: Common Food X

The Codex Committee had 19 sessions to determine the standards regarding the matter

- **1981 – The standards were adopted**
- **2001 – Draft revision**
- **2003 – Final revised standards**

—Recommended methods of analysis and sampling

—% of total weight of the basic ingredients in the finished product

—Definitions

—Labeling

—Amounts of food additives

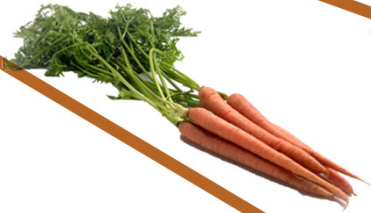
Acidity regulators – 17
Glazing agents – 5
Flavoring agents – 3
Emulsifiers – 8
Antioxidants – 6
Colors – 2
Sweeteners – 11
Bulking agent – 1
Processing aid – 1

Food X: Chocolate



~100 kg/day has
to be consumed
for 2 years to
reproduce
these effects
in humans

Final Standards for Food X



10X more of
Acceptable Daily Intake
of carrots
(~ 1 lb) is more achievable
to consume in a day

Butylate Hydroxyanisole

Chronic exposure – gall bladder, endocrine,
lungs, thorax respiration tumors
Mutagen – DNA inhibition, unscheduled
DNA synthesis, DNA damage
Chronic exposure – reproductive damage
Prolonged repeated exposure can
cause allergies in sensitized individuals
200 mg/kg

Hexane

Flammable
Delayed target organ effect
Peripheral nervous system
Kidney
Testes-tumors
Reproductive effects
Potentially carcinogenic
1 mg/kg



What is there that is not poison?

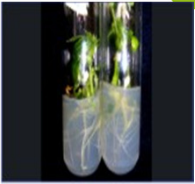
All things are poison and nothing is without poison.

Solely the dose determines that a thing is not a poison.

Paracelcius (1493-1541)



General Principles of Risk Analysis



Risk is associated with hazard & exposure



First Step: Hazard Identification

- Formaldehyde causes cancer
- Cholera toxin causes severe diarrhea



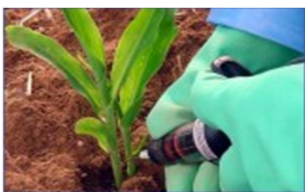
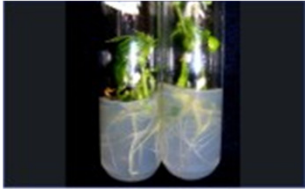
Second Step: Hazard Characterization

- Quantitative and qualitative assessment of the nature of the hazard
- Dose-response relationship
- Usually animals are administered 3 doses: very small to doses that exceed multiple orders of what would be expected to determine NOAEL=(No Observed Adverse Effect Level)
- Margin of safety determination:
 - To account for interspecies and intra-species variation, NOAEL is divided by 100 (uncertainty factor)





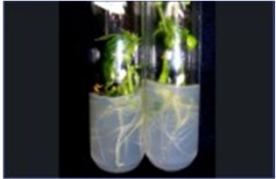
Exposure Assessment



- Determine the amount and distribution of the hazardous substance and routes and locations that the population can come into contact
- In the case of food safety studies, food dietary intake information is needed
- Acceptable daily intake (ADI) is determined – usually with lifetime studies with rodents.



Safety Assessments of Foods



Food toxicology is unique



- Complex—1000s of macromolecules, micronutrients, anti-nutrients
- Ever-changing properties – Environment – Genetic rearrangement occurring in the plant
- For processed foods – Additives and chemicals migrating from the package
- Common food items – Presume their safety based on familiarity and history of use
 - Neurotoxic glycoalkaloids present in potatoes
- Therefore, it is stated that – Safety can not be proved absolutely
- Safety assessment seeks a level of reasonable certainty that harm will not occur (as long as they are free of contaminants)



Concern Level, Tolerance Levels

Are required for the following

- **Pesticide residues**
- **Drugs used in food producing animals**
- **Heavy metals**
- **Food-borne molds and mycotoxins**
- **Bacterial toxins**
- **Substances produced by cooking**

Safety Assessment of Foods Derived from GE Crops

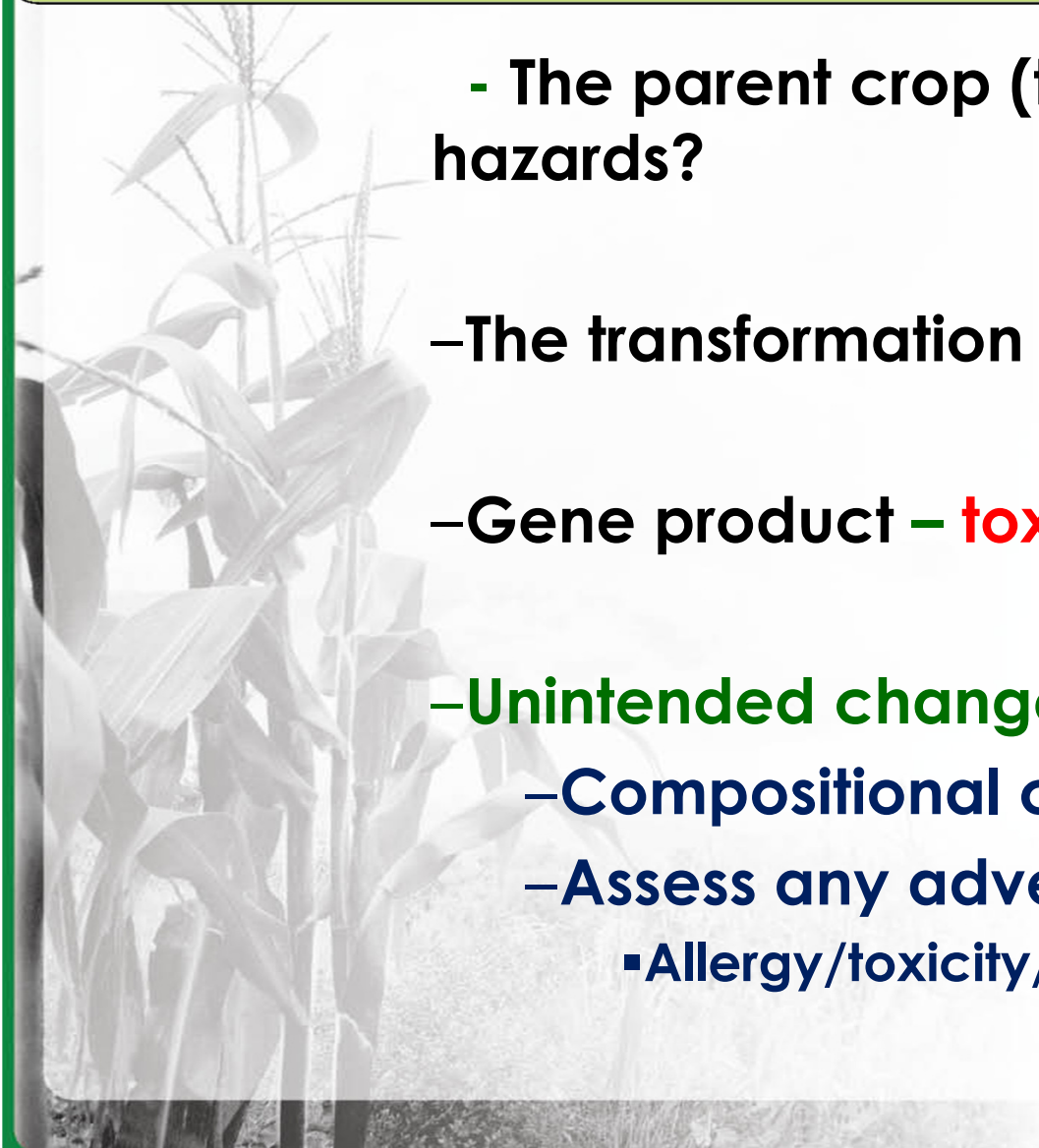
- **Presumption of safety = Comparators Usually the traditionally bred parent crop**
- **Comparative assessment = Substantial Equivalence (FAO/WHO, 1991)**
 - **Agronomical and morphological characteristics**
 - **Chemical composition**
 - **Macro and micronutrients**
 - **Key toxins and anti-nutrients**

**Are there any significant changes?
Do they pose a hazard to human health?**

The milestones in the international consensus on the safety assessment of biotechnology-derived foods include the following:

- **ILSI Europe Concise Monograph Series Genetic Modification Technology and Food Consumer Health and Safety (Robinson 2001),**
- **EU-sponsored Research on Safety of Genetically Modified Organisms. “GMO Research in EU 2001 Perspective.” Report of a Workshop held by External Advisory Groups of the “Quality of Life and Management of Living Resources” Program, European Union,**
- **New Zealand Royal Commission on Genetic Modification (NZRC 2001),**
- **FAO/WHO Guidelines for Codex Alimentarius Committee, developed by Task Force for Foods Derived from Biotechnology Codex Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology (FAO/WHO 2002, 2003), and**
- **ILSI Crop composition database (www.cropcomposition.org) (ILSI 2003 to present).**

Hazard Identification & Characterization of GE Crops

- 
- The parent crop (the comparator) – hazards?
 - The transformation and inserted DNA
 - Gene product – **toxic/allergenic?**
 - Unintended changes**
 - Compositional changes
 - Assess any adverse impact
 - Allergy/toxicity/nutritional alterations

Toxicity Testing Methods

Many of the regulatory requirements for chemicals such as food additives and pesticides were first established during the 70s. These led to the development of a battery of tests to assess the safety of chemicals in foods

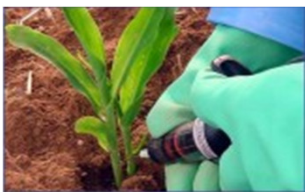
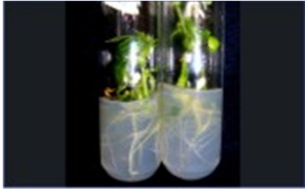
Most often, the results from three approaches are combined

1. Structure/function relationship – toxicity/allergenicity
2. In vitro assays – enzymes, receptors, cell lines
3. In vivo animal studies

In order to monitor the performance of the product and the side effects, post-market surveillance can also be incorporated for certain products.

4. Post-market monitoring

- Early warning
- Facilitates product recall
- Absence of adverse health effects
- Determining consumption patterns – implications and applications relevant to food toxicology to help determine estimated daily intake (EDI)



Up to this point we have briefly examined food safety systems and food safety assessment and have introduced the general principles of risk assessment. We have also looked at basic toxicology testing methods that have applications in the food safety assessment of foods derived from genetically engineered crops.

In the next section of this module, we will introduce the safety assessment of foods derived from GE crops in detail

Test Methods to Assess the Safety of Foods Derived from GE Crops

Hazard Identification/Characterization

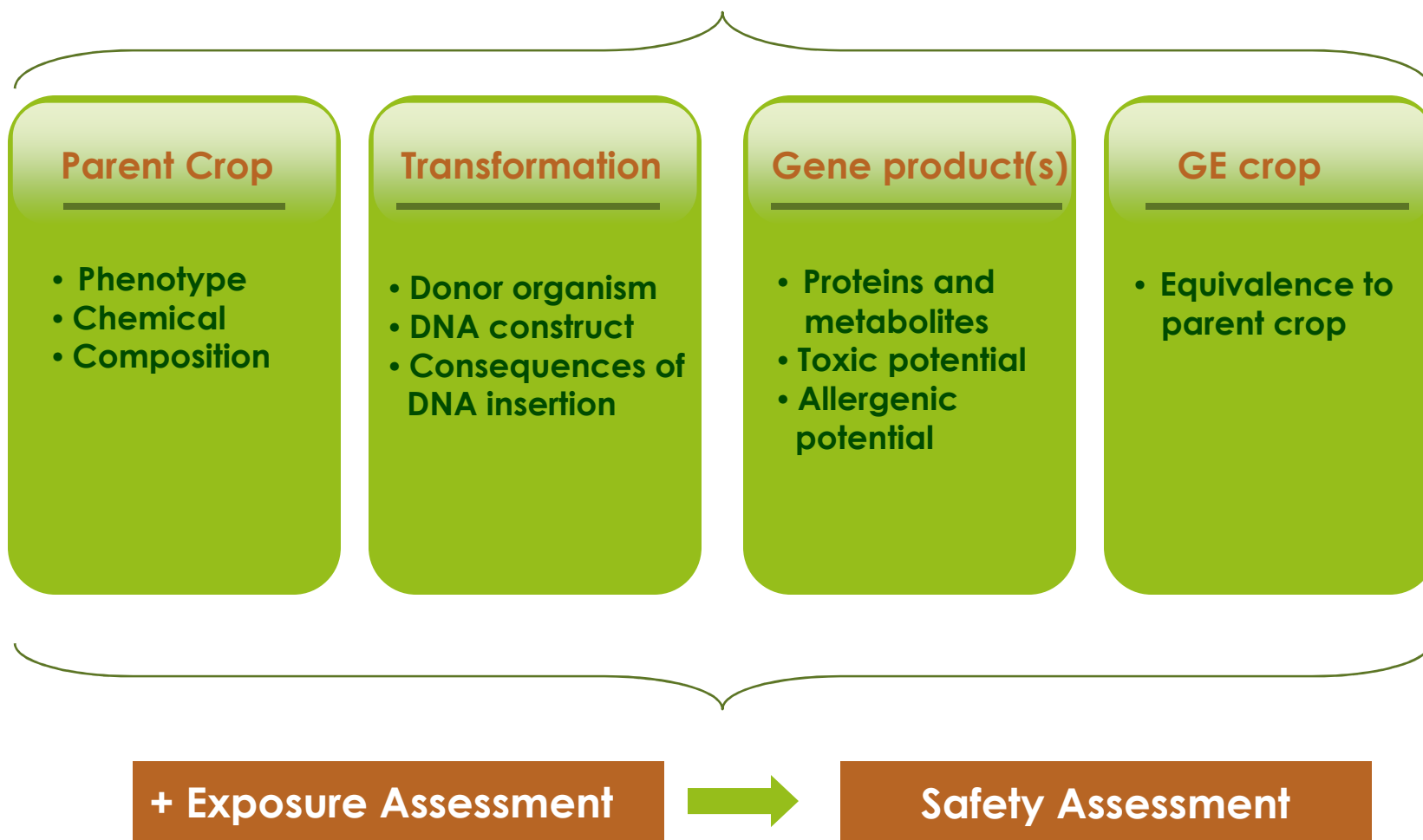


Figure modified from König et al, 2004

Step 1 — Parent Crop

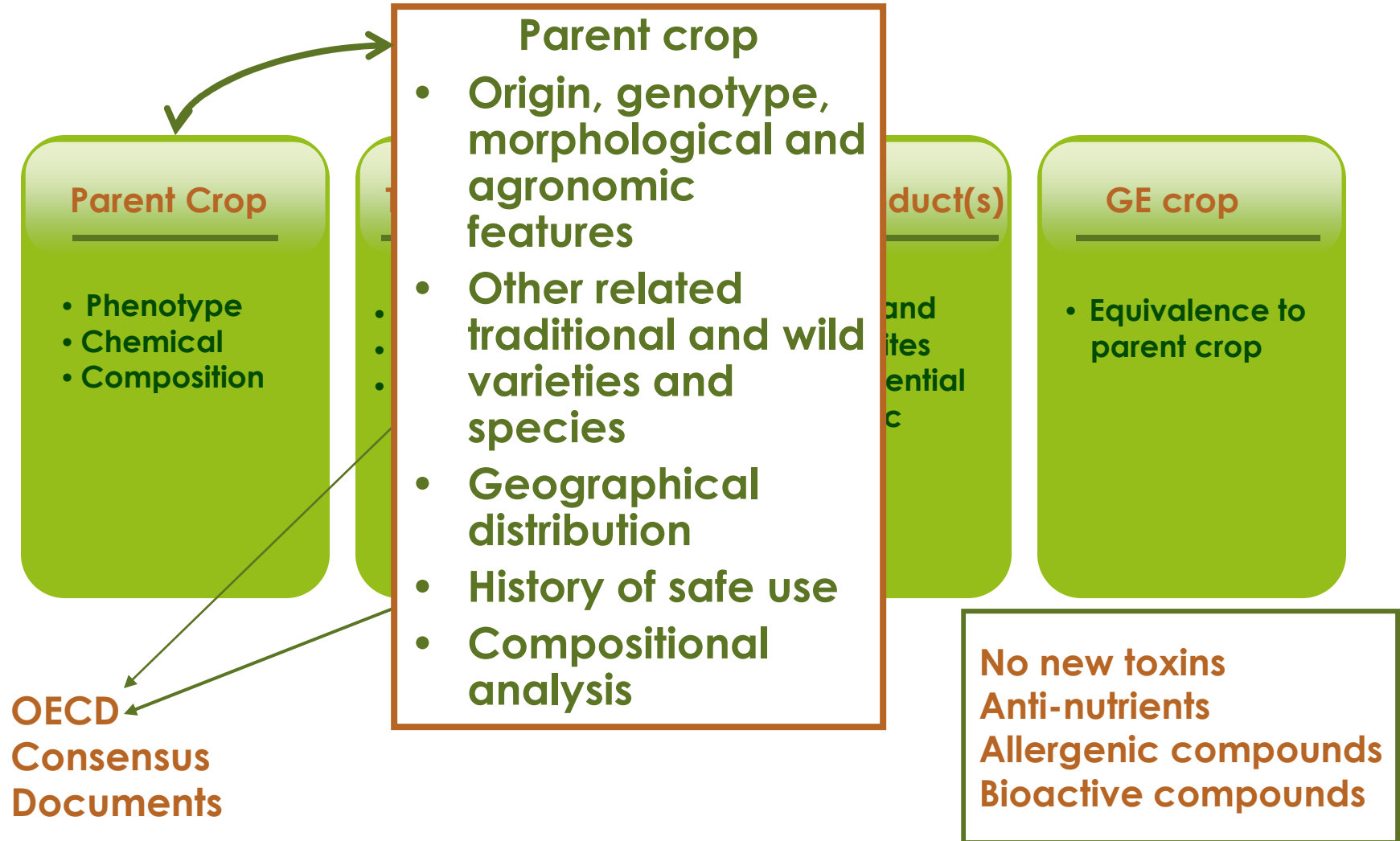


Figure modified from König et al, 2004

Step 2 — Donor Organism and Transformation

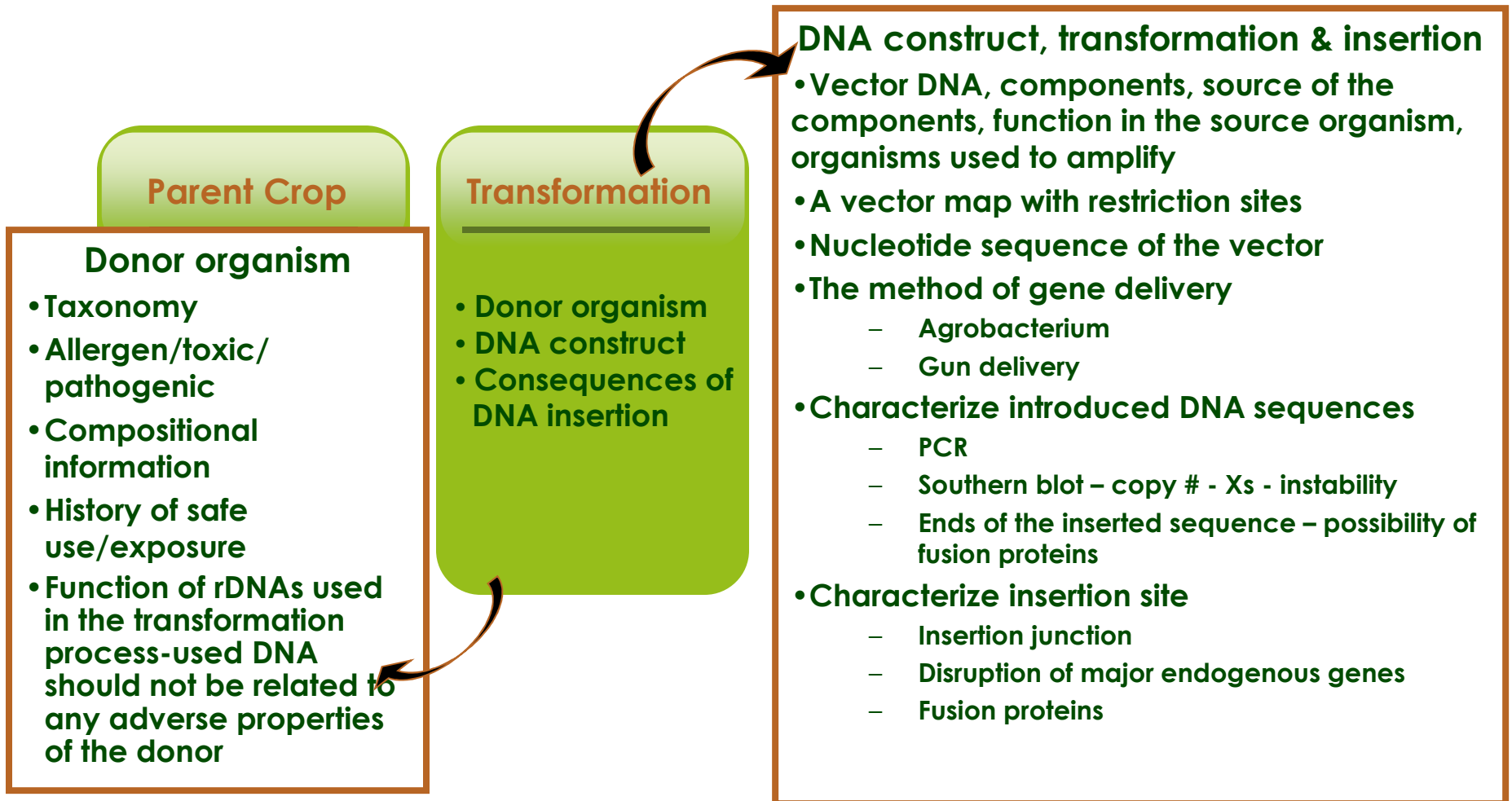


Figure modified from König et al, 2004

Step 3 — Gene Products

Recombinant proteins/metabolites

- Protein-safety concern?
- Previous exposure/novel protein
- Structure, sequence, biochemical properties
 - Equivalent to the version produced in the source
 - MW
 - Aa sequence
 - Post-translational modification
 - Immuno-equivalence
- Mode of action
- Toxicity
- Allergenicity
 - Is the source an allergen/is the protein allergen?
 - Does the recombinant protein induce de novo sensitization?
 - Cross-reactivity with IgE induced by known allergens
 - FAO/WHO(2001), Codex Alimentarius (2003)

Gene product(s)

- Proteins and metabolites
- Toxic potential
- Allergenic potential

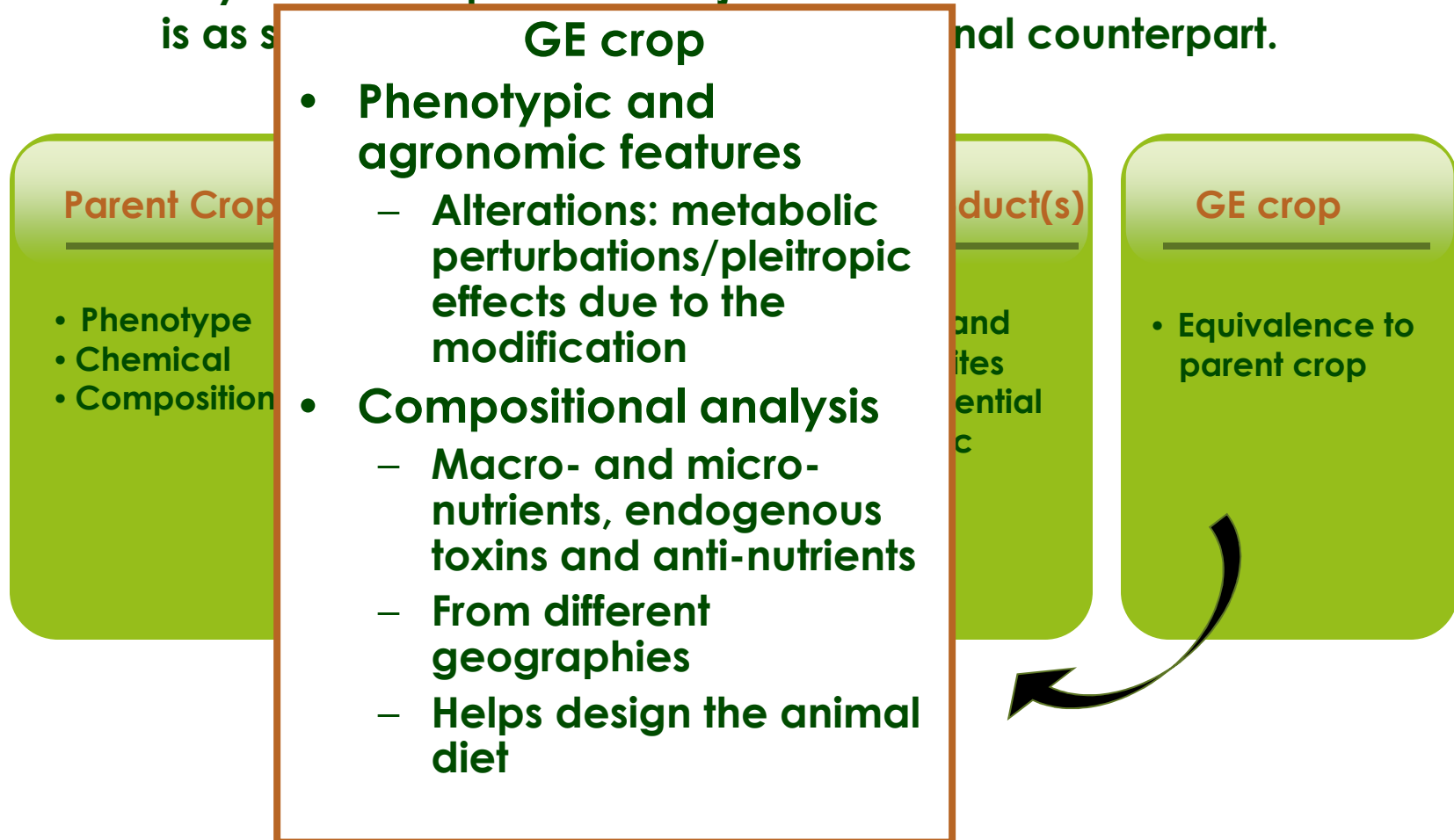
GE crop

- Equivalence to parent crop

Figure modified from König et al, 2004

Step 4 — GM Crop

Finally the GE crop itself is subjected to tests to ensure that it is as safe as its natural counterpart.



GM Food Safety Evaluation- International Comparisons

Category of Information/Data Requirement	USA	EU	S. Africa	Japan	Philippines	Canada	Australia	Argentina
Host information	X	X	X	X	X	X	X	X
Donor information	X	X	X	X	X	X	X	X
Molecular characterization	X	X	X	X	X	X	X	X
Characterization of expressed protein	X	X	X	X	X	X	X	X
Nutritional composition	X	X	X	X	X	X	X	X
Potential toxicity of novel protein(s)	X	X	X	X	X	X	X	X
Potential allergenicity of novel protein(s)	X	X	X	X	X	X	X	X

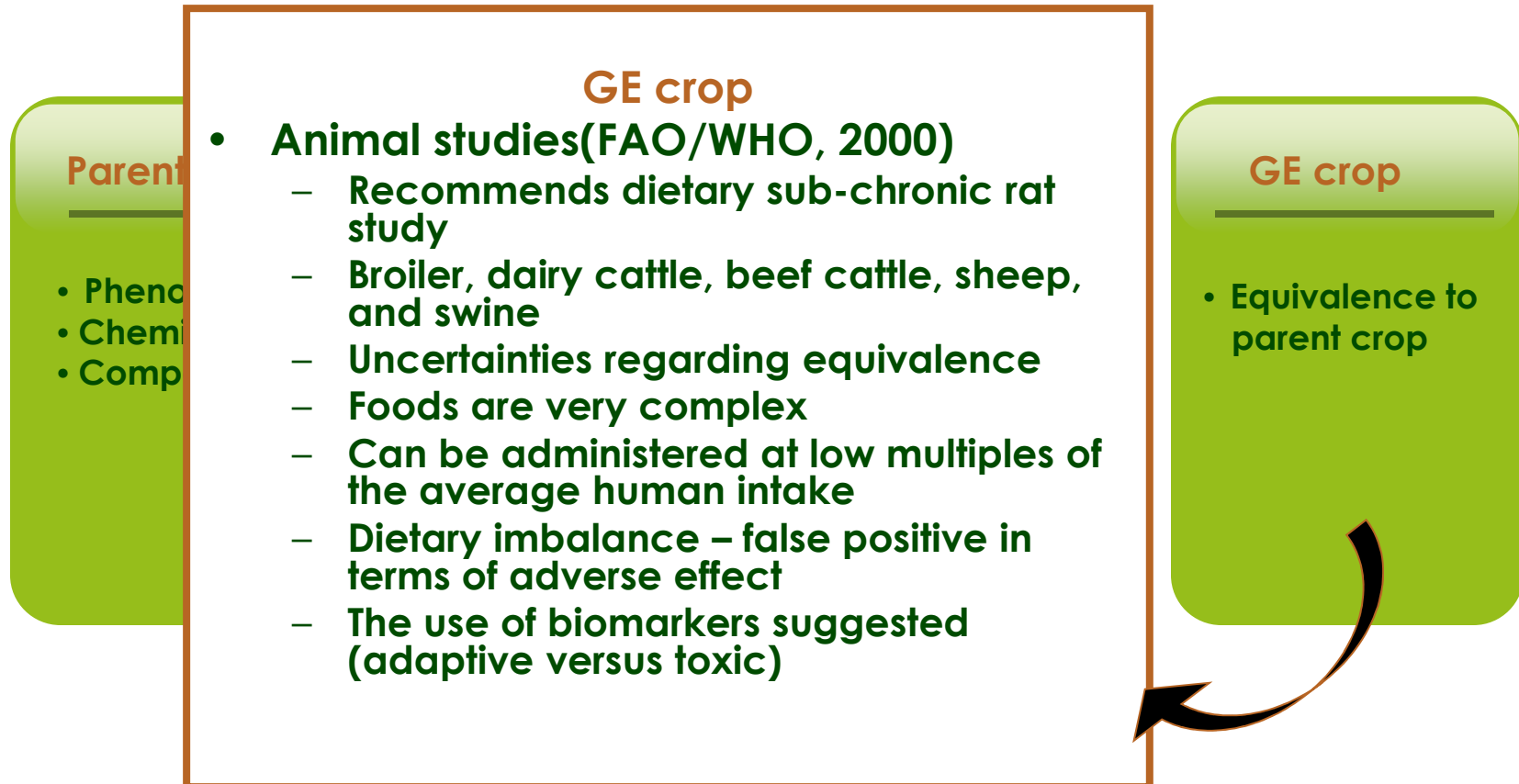
Step 4 — GE Crop

An example:

– Roundup Ready soybeans

- Soybeans naturally contain certain levels of anti-nutrients; trypsin inhibitor, lectins and isoflavones
- Protein, oil, fiber, carbohydrates, moisture content, amino acid and fat composition in seeds and toasted soybean meal compared with conventional counterparts
- Trypsin inhibitor levels were 11-26% higher in GE soybeans in defatted non-toasted soybean meal (not consumed-starting material)
- In defatted, toasted soy meal trypsin inhibitor values were not different than the comparator
- Feeding studies in rats, chickens, catfish, dairy cattle confirmed no nutritional value differences

Step 4 —GE Crop



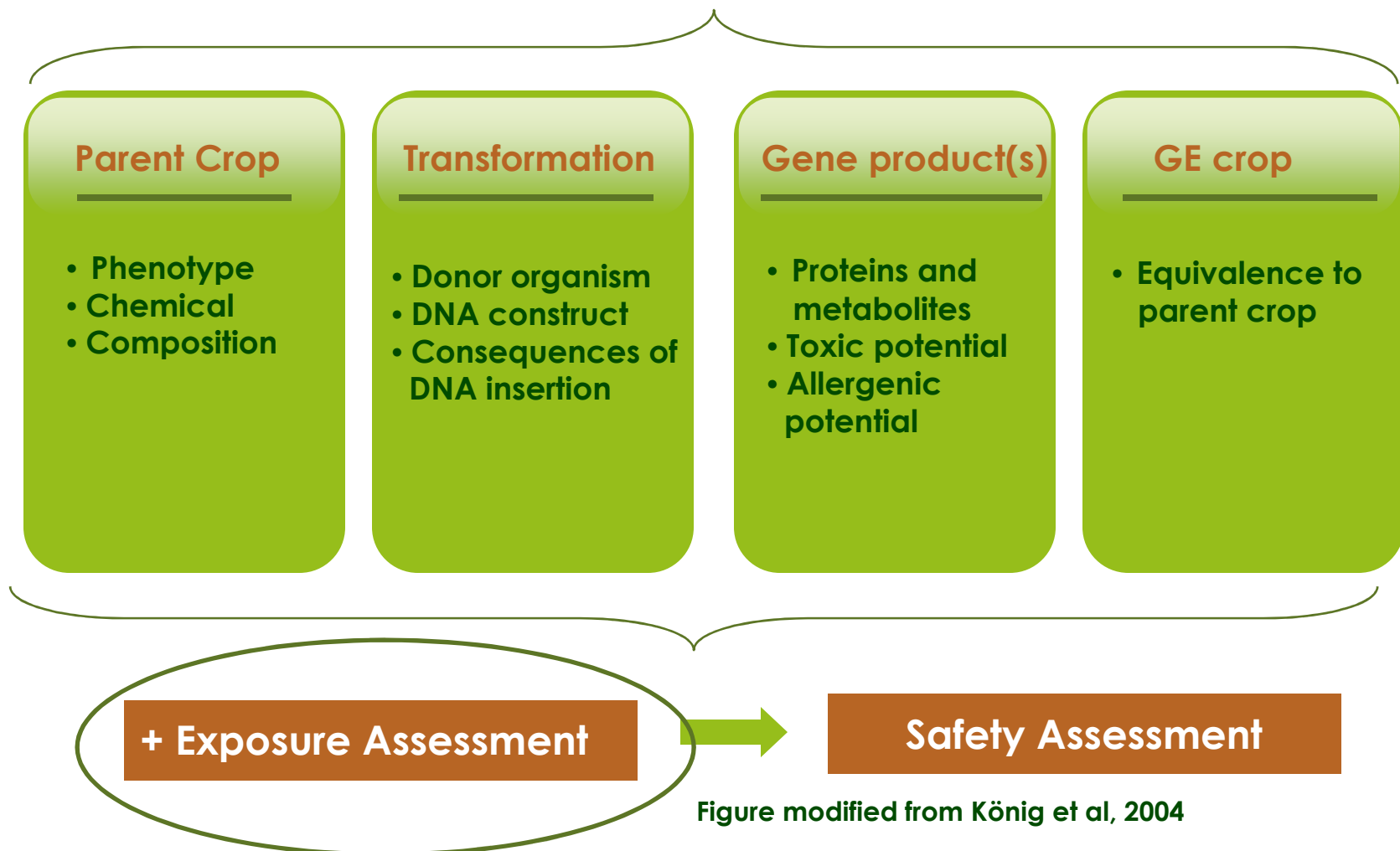
Assessment of the health impact of GM plant diets in long-term and multigenerational animal feeding trials: A literature review.....

- 12 long-term studies (of more than 90 days, up to 2 years in duration) and 12 multigenerational studies (from 2 to 5 generations)
- 90-day studies on GM feed for which long-term or multigenerational study data are 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.
- **Seven with Bt Maize on chicken, cattle , goats sheep and one Rice on monkey**

Test Methods to Assess the Safety of Foods Derived from GE Crops

As risk is correlated with levels and frequency of exposure to a certain hazard, safety assessment of food derived from GE crops can be completed with exposure assessment

Hazard Identification/Characterization



Exposure Assessment

- Food supply information
- Household expenditure
- Food consumption surveys
- Import statistics
- Recombinant proteins in transgenic plants: 0.01-0.1% of total protein content (Betz et al, 2000)
- Estimated daily intake (EDI) for humans: 0.017 0.07mg/kg/day (König et al, 2004)
- NOAEL with acute toxicity tests >100 mg/kg/day (Chassy et al, 2002)

Even if people consumed ~1,400X that of the EDI, there would not be a safety concern.

Some facts of Gene products

Protein studied	NOEL	Stable to digestion	Stable to processing?
Cry1Ab	>4000	No (30s)	No
Cry1Ac	>5000	No(30s)	No
Cry 2Aa	>4011	No(30s)	No
Cry 3A	>1450	No(30s)	No
Cry 3Bb	>3780	No(30s)	No
Cry 9C	>3760	+/- No(30s)	Partial
NPTII	>5000	No	No
CP4EPSPS	>572	No	N.A
GUS	>100	No	N.A

Exposure Assessment

- GE seeds may be commingled with conventional ones
- Food ingredients derived from commodity crops are in many different products
- Food processing might alter ratios, may cause degradation

Therefore, current exposure assessment approach does not take these degradation and overestimation into account to achieve the highest level of safety

Toxicity Testing Methods

As described so far toxicity testing methods are used with slight modifications to assess safety of food derived from GE crops

1. Structure/function relationship – toxicity/allergenicity

- Common structural features, databases
- Allergenicity (FAO/WHO 2001, Codex Alimentarius Commission 2003)

2. In vitro assays – enzymes, receptors, cell lines

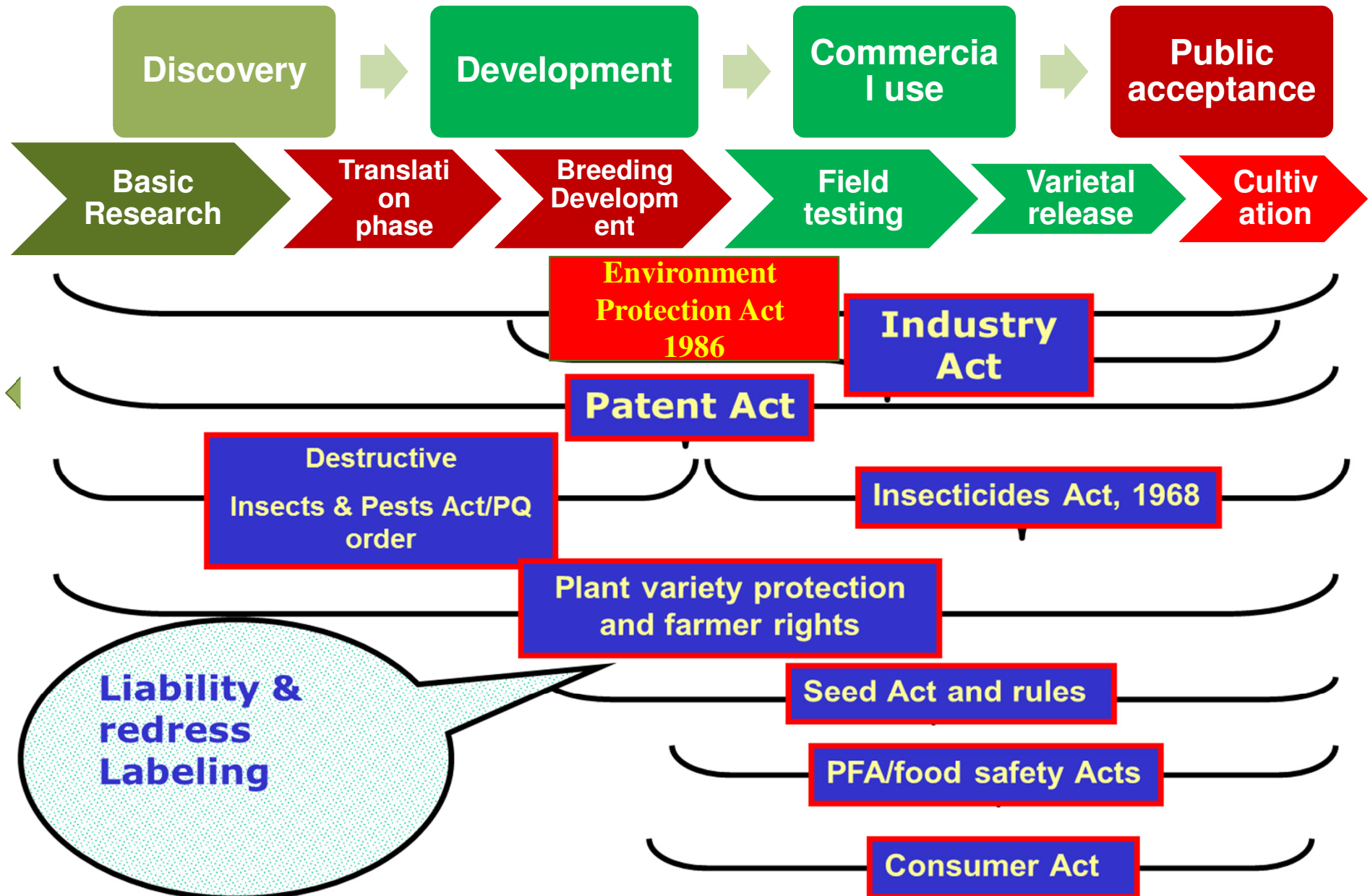
- Simulated gastric digestion

3. In vivo animal studies

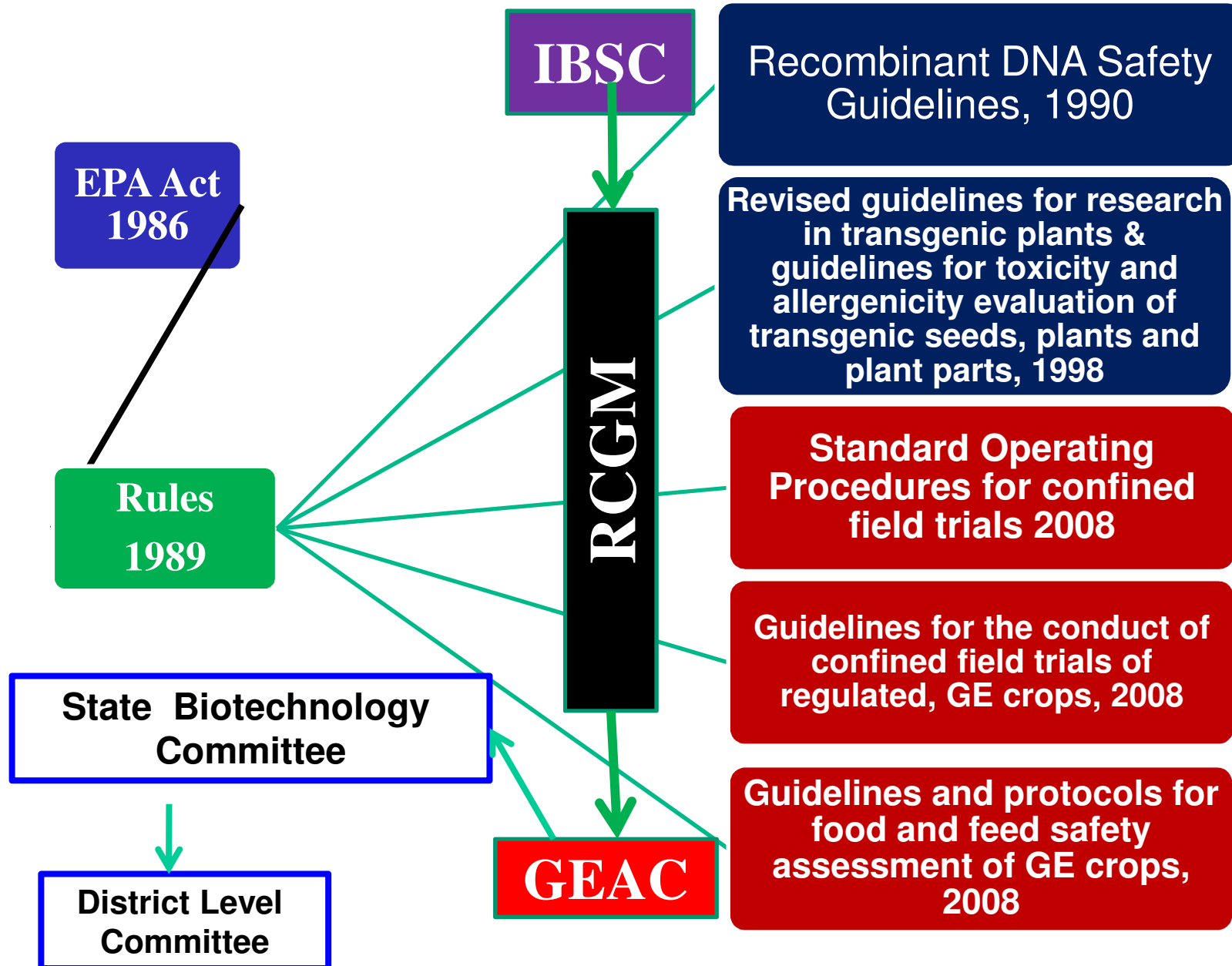
4. Post-market monitoring

- Several companies for certain products
 - Early warning
 - Facilitates product recall
 - Absence of adverse health effects
 - Determining consumption patterns – implications and applications relevant to food toxicology as it might help to determine estimated daily intake (EDI) of a given

Complexity with Research Development and Commercialization of Transgenics



Current Indian Regulatory System



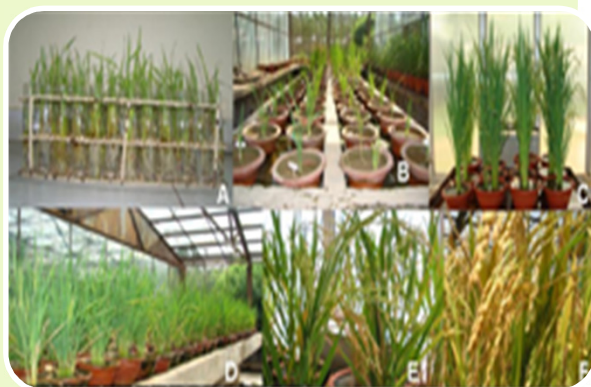
COVERAGE OF 1989 RULES

The 1989 Rules cover the entire spectrum of activities relating to research, development and use of Genetically Modified Organisms (GMOs) and their products.

- Manufacture, import and storage of microorganisms and gene technological products
- Genetically engineered organisms/microorganisms and cells and correspondingly to any substance and products and food stuffs, etc., of which such cells, organisms or tissues form part
- New gene technologies in addition to cell hybridization and genetic engineering

PUBLIC PERCEPTION AND RESPONSE

**Task force on
Agricultural
Biotechnology
M/o Agriculture**



2003-2005

**Need for New
Authority
Priorities
Do 's do
not's**

**Task force on
biopharma
M/o Environment
& Forests**



2004-2006

**Need for New
Authority
Simplification of
biopharma
regulations**

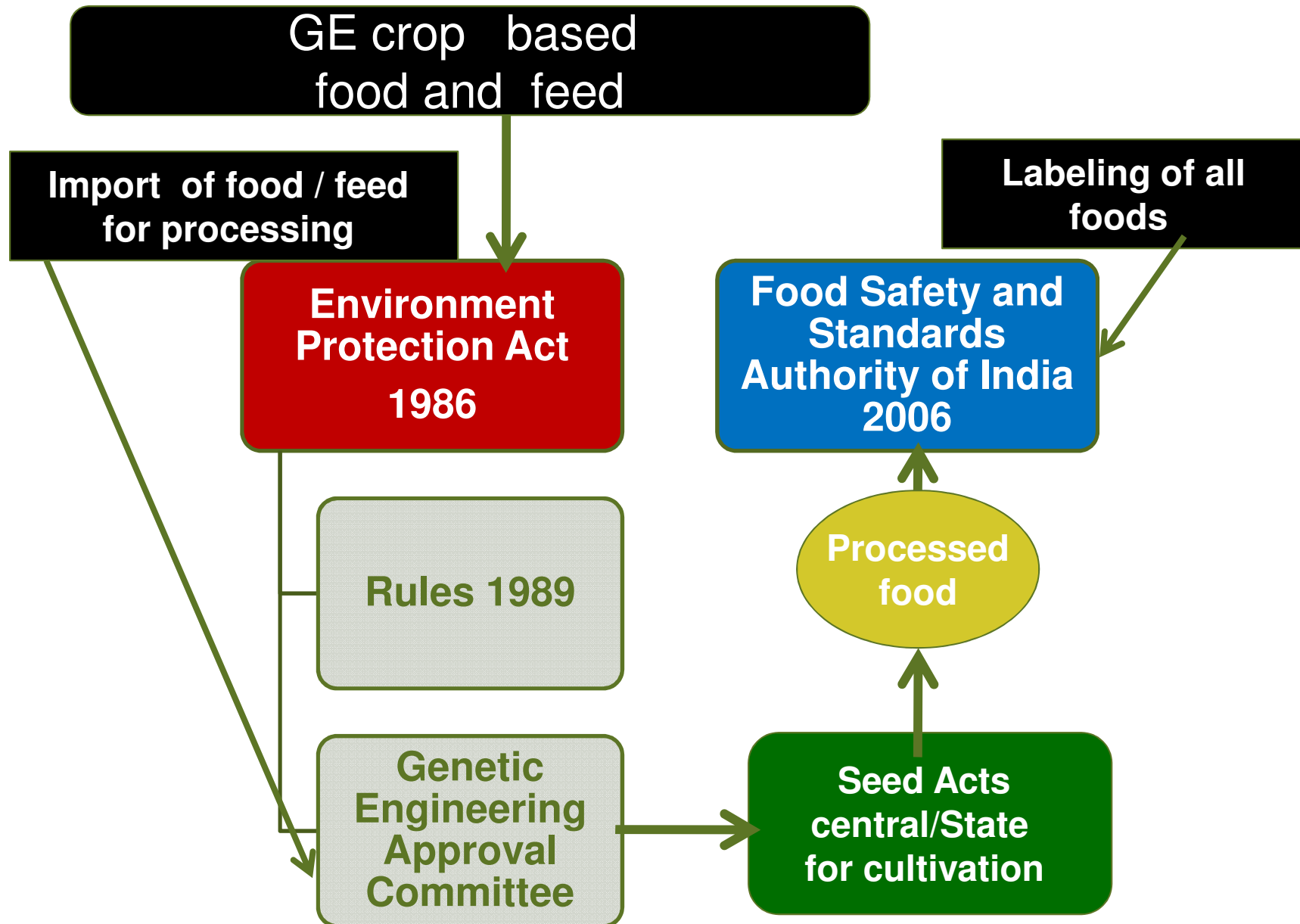
**Expert
Committee On
Genetically
Modified on food
safety**



2005-2006

**Harmonize food
safety
assessment with
international
systems**

GE Food Safety In India.



THE BIOTECHNOLOGY REGULATORY AUTHORITY OF INDIA BILL, 2013

ARRANGEMENT OF CLAUSES

CHAPTER I

Preliminary

CLAUSES

1. Short title, extent and commencement.
2. Declaration as to expediency of control by Union.
3. Definitions.

CHAPTER II

Biotechnology Regulatory Authority of India

4. Establishment of Biotechnology Regulatory Authority of India.
5. Composition of Authority.
6. Qualifications for appointment of Chairperson and Members.
7. Selection Committee for selection of Chairperson and Members.
8. Functions of Chairperson.
9. Term of office and other conditions of service of Chairperson and Members.
10. Restriction on Chairperson or Members on employment after cessation of office.
11. Removal of Chairperson and Members.
12. Meetings of Authority.
13. Vacancies, etc., not to invalidate proceedings of Authority.
14. Chief Regulatory Officers and other employees of Authority.

CHAPTER III

Inter-Ministerial Governing Board and Biotechnology Advisory Council

15. Constitution of Inter-Ministerial Governing Board.
16. Constitution of Biotechnology Advisory Council.
17. Meetings of Inter-Ministerial Governing Board and Biotechnology Advisory Council.

CHAPTER IV

Functions and powers of Authority

18. Functions and powers of Authority.
19. Powers of Authority to call for information, conduct investigations, etc.
20. Power of Authority to issue directions.

CHAPTER V

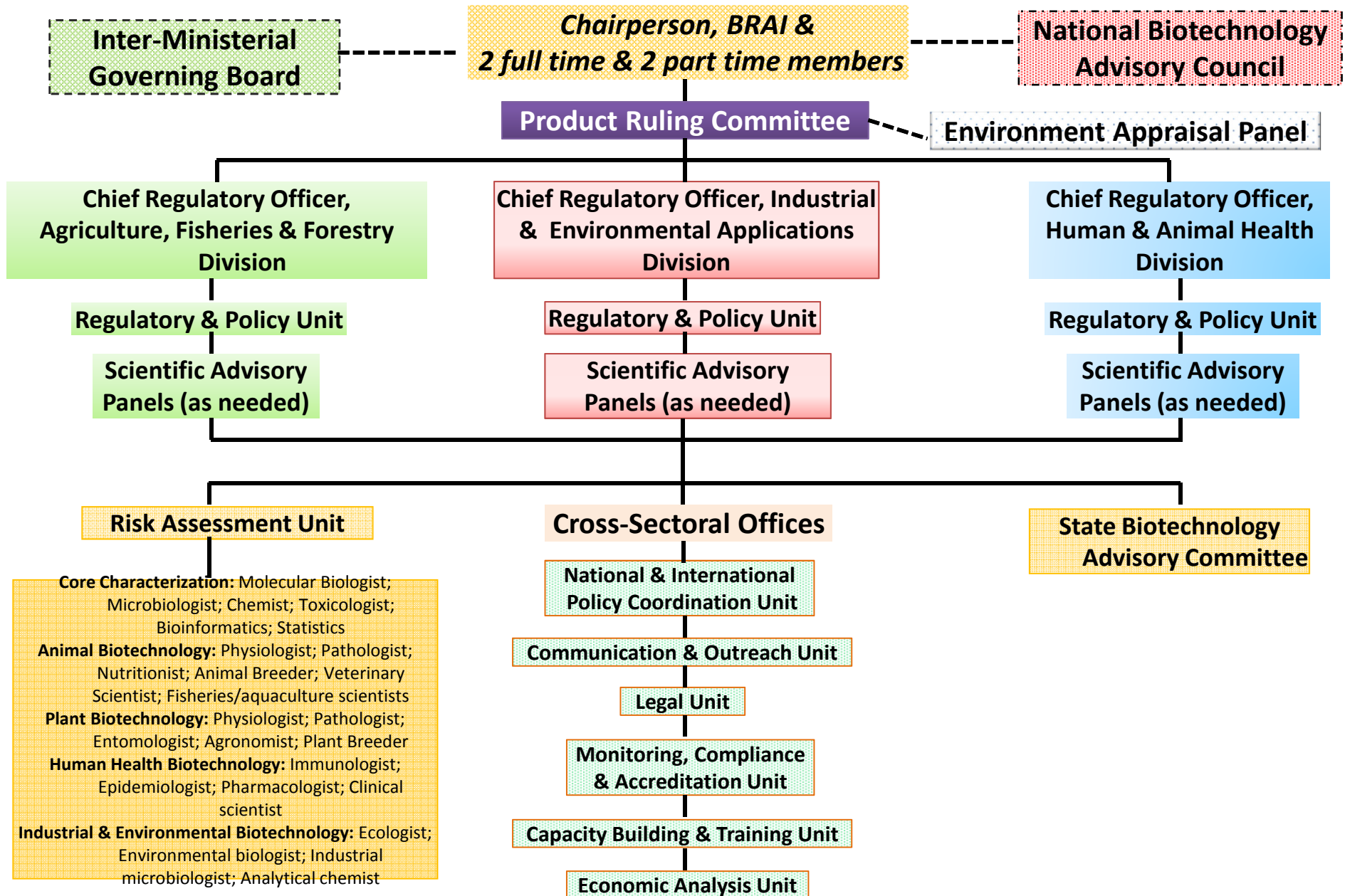
Divisions, Units and Product Release Committee of Authority

21. Regulatory Divisions of Authority.
22. Risk Assessment Unit.
23. Other Units.
24. Procedure by Risk Assessment Unit for research, transport or import of organisms or products.

BIOTECHNOLOGY REGULATORY AUTHORITY OF INDIA (BRAI) BILL, 2013

Introduced in Lok Sabha on
22.4.2013 referred to
joint Parliament
standing committee
which invited comments
again from stakeholders
with 60 days deadline
and more than 125
comments received as
on 25th August 2013

ORGANIZATION STRUCTURE OF BRAI



KEY FEATURES OF BRAI BILL, 2013

- The proposed statutory independent regulator nodal agency of the Government of India to ensure comprehensive safety assessment of organisms and products of modern biotechnology.**
- Commercialization of biotechnology products in agriculture and healthcare would be subject to all other laws whether Central or State, for the time being in force and rules and regulations made there under.**
- The organizational plan of the Authority also provides collaborative arrangements, co-ordination and mechanisms with other existing regulatory agencies.**



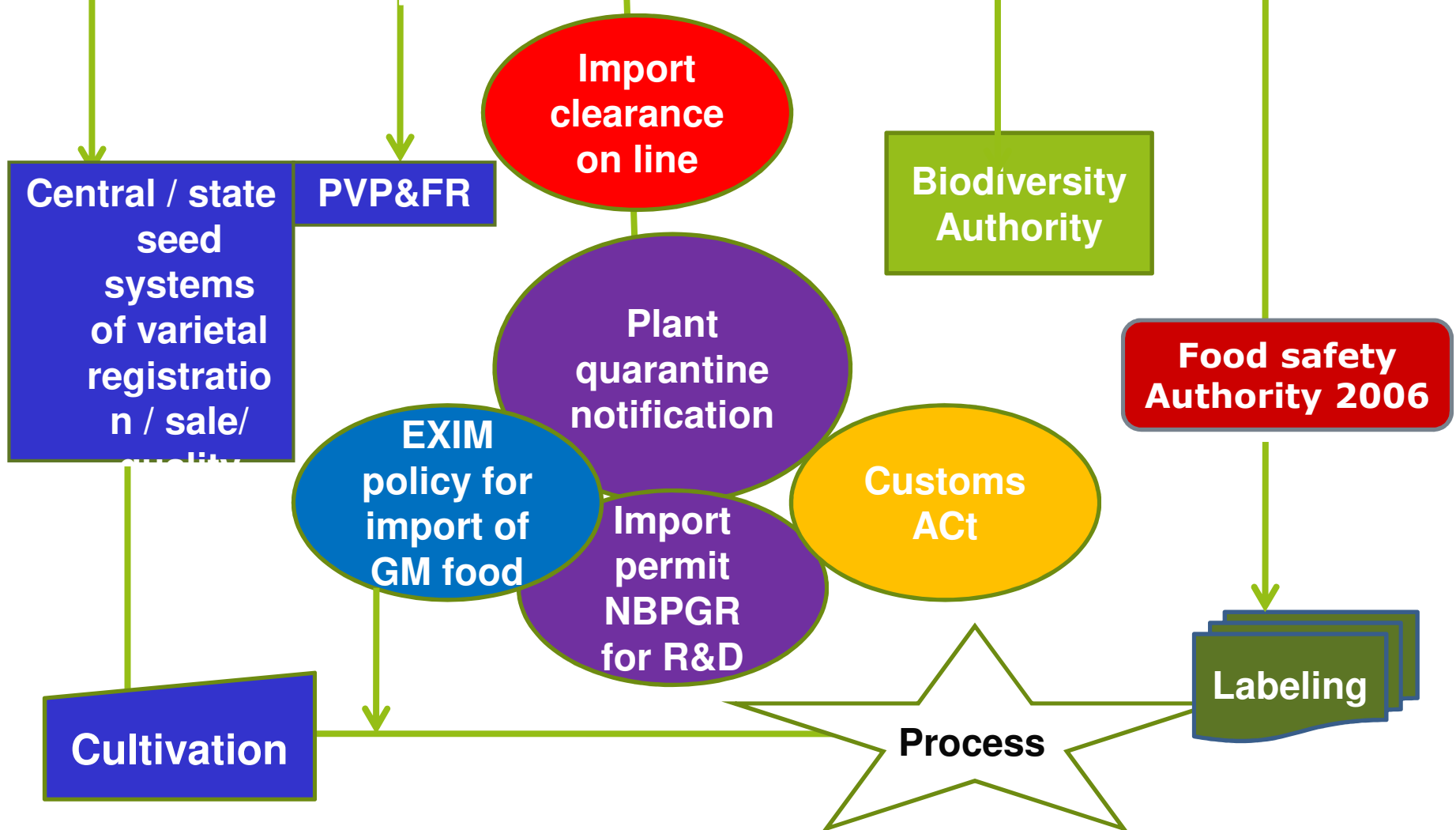
Responsibilities of governmental authorities as regards the regulation of GMOs in India (excluding pharmaceutical applications).

Activity	Responsible Authority	AFTER ENACTMENT OF BRAI
Contained research (laboratory and greenhouse)	RCGM (DBT)	BRAI
Event selection trials/BRL 1 trials	RCGM and GEAC (MoEF)	
Food safety assessment of GM foods (viable and processed)	FSSAI	
Environmental risk assessment of GM organisms	GEAC	
Approval for commercial release of GM foods (processed)	FSSAI	
Approval for commercial release of GM foods (viable <i>i.e.</i> LMOs)	GEAC	
Approval for environmental (commercial) release of GM organisms	GEAC	FSSAI
Labeling	FSSAI	

**Harmonization of BRAI with other acts/ policies
/ systems/ authorities**

Inter-ministerial Governing Board

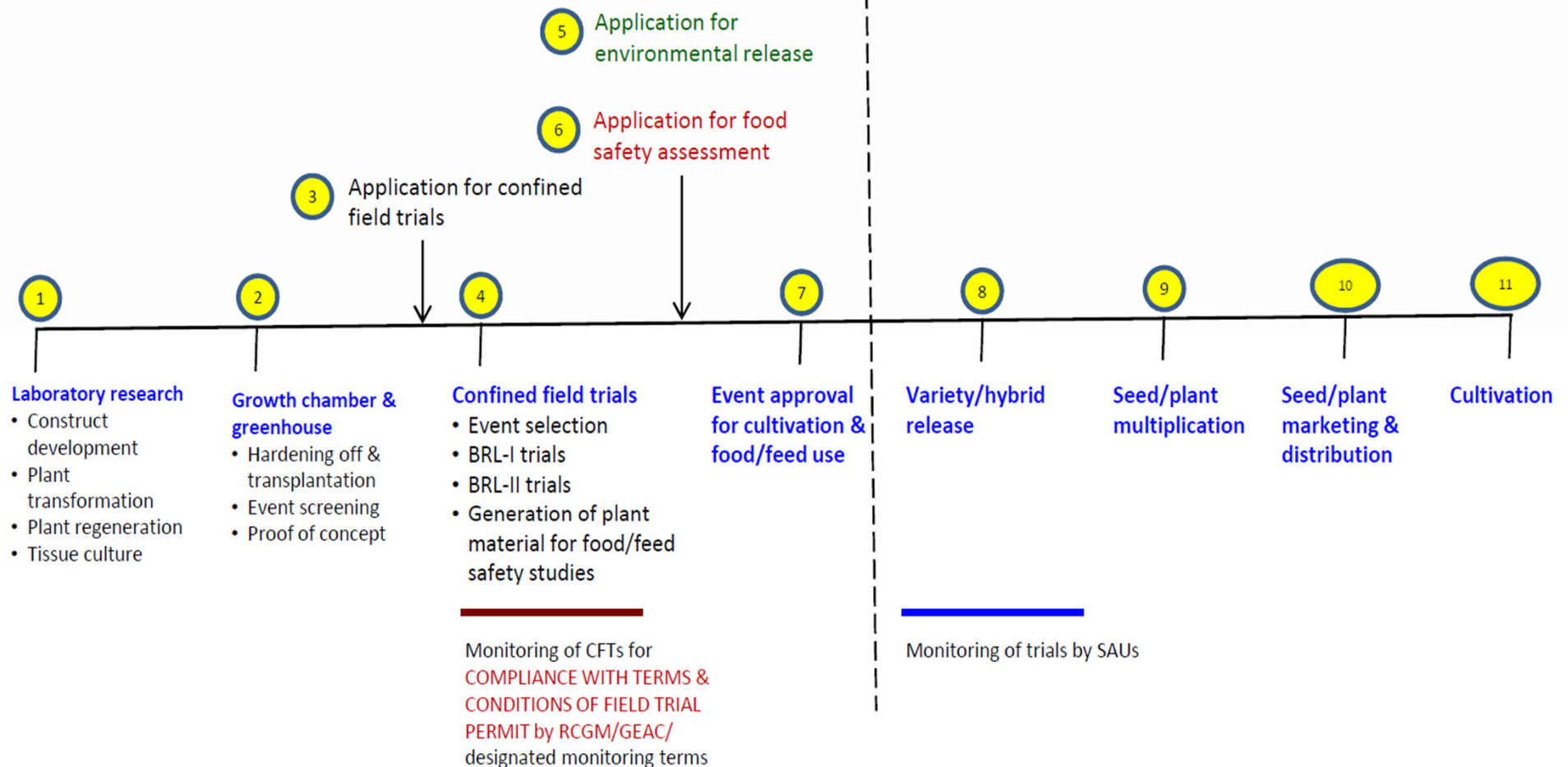
Safety and efficacy certification



CURRENT ROADMAP DEVELOPMENT PROCESS OF A GM CROP

GE PLANT MATERIAL REGULATED UNDER RULES, 1989 & RELEVANT GUIDANCE IS IN PLACE

- Guidelines for Research in Transgenic Plants, 1998
- Guidelines and Standard Operating Procedures (SOPs) for Confined Field Trials of Regulated Genetically Engineered (GE) Plants
- Guidelines for the Monitoring of Confined Field Trials of Regulated, GE Plants
- Guidelines for the Safety Assessment of Foods Derived from Genetically Engineered Plants
- Protocols for Food and Feed Safety Assessment of GE crops



Guidelines for Food and environmental Risk assessment

EARLY

**Recombinant DNA
Safety Guidelines,
1990**

**Revised guidelines for
research in transgenic
plants & guidelines for
toxicity and allergenicity
evaluation of transgenic
seeds, plants and plant
parts, 1998**

NEW

**Standard Operating Procedures
for confined field trials 2008**

**Guidelines for the conduct of
confined field trials of regulated,
GE crops, 2008**

**Guidelines and protocols for food
and feed safety assessment of GE
crops,, 2008**

Risk assessment – data generation

STUDIES TO BE COMPLETED	Food & Feed Safety Assessment			Environmental Risk Assessment		
	Before first field trial	Field studies	Non-field studies*	Before first field trial	Field studies	Non-field studies*
Description of the genetically engineered plant						
Biology of the non-transgenic host plant						
Donor organism information						
Bioinformatic analysis: potential toxicity and allergenicity						

**run concurrently with field trials*

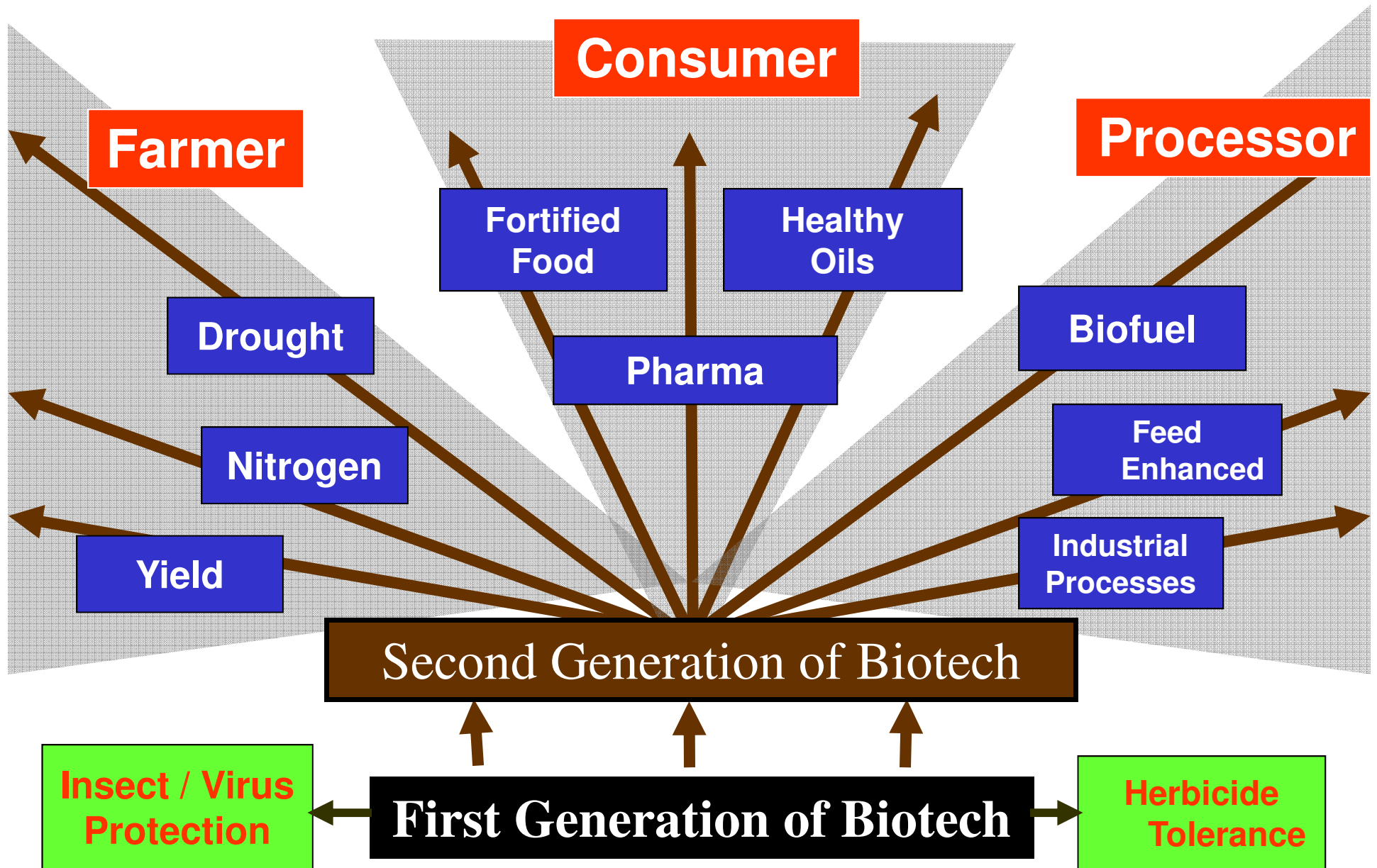
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Recommendations for staged completion of specific information and data requirements for the safety assessment of GE plants

STUDIES TO BE COMPLETED	Food & Feed Safety Assessment		Environmental Risk Assessment	
	Field studies	Non-field studies*	Field studies	Non-field studies*
Acute oral safety limit study				
Pepsin digestibility assay				
Protein thermal stability				
Subchronic feeding study in rodents (if required)				
Livestock feeding study (if required)				
Molecular characterization				
Inheritance of introduced trait				
Stability of introduced trait				
Expression of introduced protein(s)				
Compositional analysis				
Reproductive and survival biology				
Impact on non-target organisms: Tier I testing				
Impact on non-target organisms: Tier 2 testing				

**run concurrently with field trials*

Second Generation of Biotech Crops



In the future?

- Existing methodologies are considered sufficient for safety assessment of GE crops
- First generation of GE crops; herbicide tolerant or insect resistant
- Next generation of GE crops; more complex – nutritionally enhanced or resistant to abiotic stress
- New methodologies for safety assessment?
- Most likely

Now and In The Future

- **FAO/WHO, 1991, 1996, 2000, 2001**
- **Codex Alimentarius Commission, 2003**
- **NAS, 1987**
- **NRC, 1989, OECD, 1993, 1996, 1998, 2002**

Conclusions

Potential risks that foods derived from GE crops are not different than those of new varieties produced with conventional breeding

- **Substantial equivalence**
- **Case-by-case analysis tailored for the GE crop under question**
- **No adverse effects so far**
- **Future? – Advances in molecular biology, biochemistry, allergy science, nutrition, and toxicology**

Resources

<http://www.who.int/foodsafety/biotech/en/>

http://www.fao.org/UNFAO/about/index_en.html

<http://www.cfsan.fda.gov/list.html>

<http://www.foodsafety.gov/~fsg/biotech.html>

**BIGMAP (Biosafety Institute for Genetically Modified
Agricultural Products) Iowa State University**

Thanks