The Brazilian GMO regulation and transgenic pests: a history of success

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Environmental Release of Engineered Pests
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Summary of this talk

A presentation of the Brazilian regulatory framework

- How it was
- When it changed for better
- How it is now
- Consequences
- Considerations on a science-based regulatory framework
- How it works in real life: GM MOSQUITO risk assessment
- CONCLUSIONS

The Brazilian GM scenario – How it was

1996/2004 Brazilian GMO Regulatory Scenario

Mixed up responsibilities

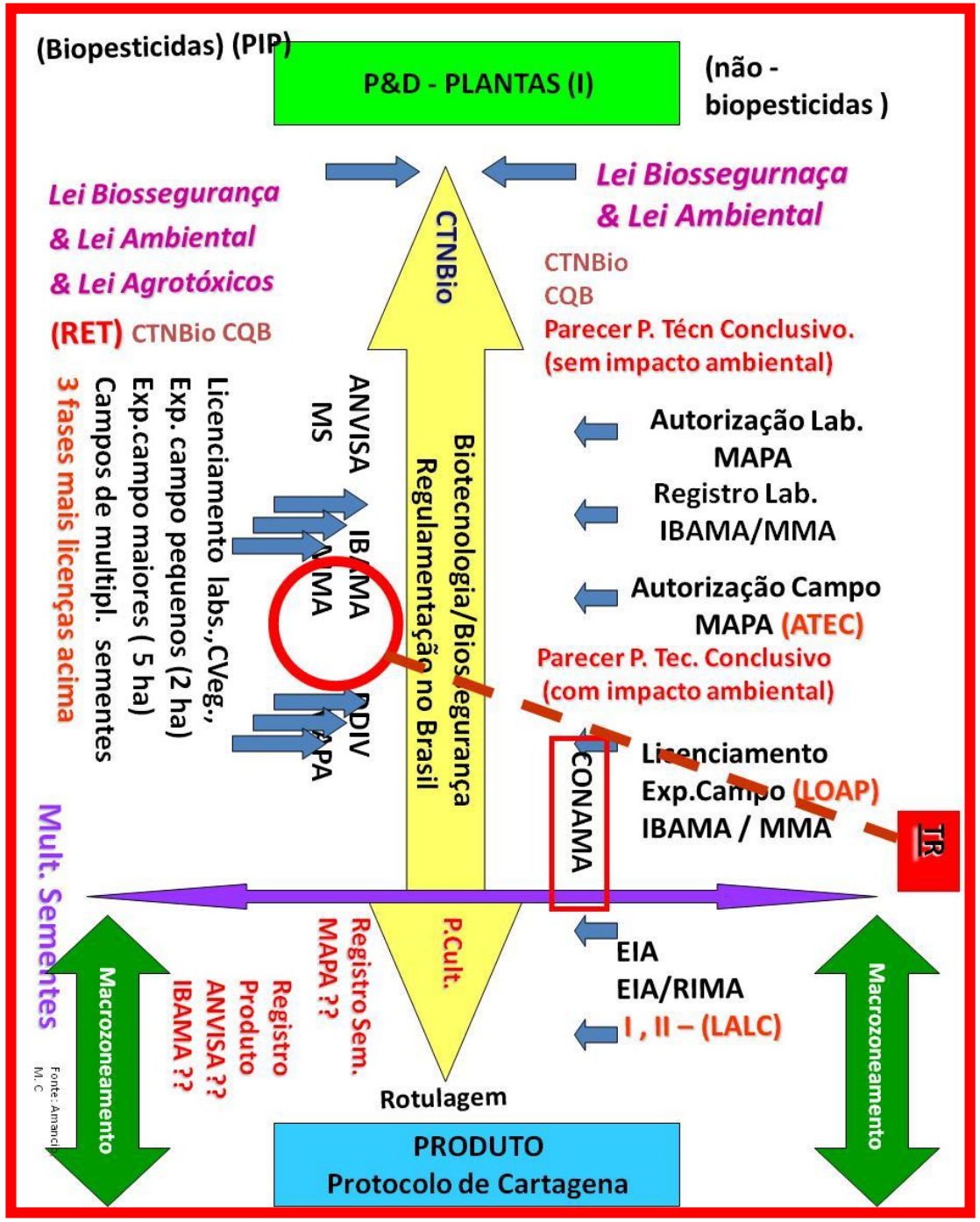
CTNBio (S&T)
IBAMA (Environment)
ANVISA (Health)
CONAMA (Environment)
MAPA (Agriculture)

Why?

Use of poorly defined <u>existing laws</u> and decrees

Lack of experience (1995)

Intentional mixing up? The influence of anti-GMO stakeholders



Consequences

- *De facto* moratorium from 1998 on

- Smuggling of GM soybean seeds from Argentina and large scale planting in the southern provinces of Brazil (2003)

- Legal insecurity and discouragement to trade

- Legal uncertainty and **discouragement to research** (academic and private)

- Pressure from both private and public sector for a new biotech law

The Brazilian GM scenario – When it changed for better

New Brazilian GMO Regulatory Scenario: 2005 - 2012

Changes due both to private/public pressure *Industries, research institutes, universities, agro-business, politicians, etc.*

Key elements for a successful legal framework:

1) **All stakeholders MUST participate in its design**
2) **It must be science-based (ours was based on the knowledge until 2005)**
3) **It must ERASE all conflicts with previous laws**
4) **The final decision on risks must be collegiate and science-based**
5) **The final commercial approval may be granted on purely safety considerations**
6) **The market CAN EFFECTIVELY decide if the product is suitable for the country**

The Brazilian GM scenario – How is it now

LAW 11.105/ 2005

Creates the National Biosafety Technical Commission – CTNBio - as consultative and deliberative body for all the activities related to genetic engineering techniques in any public or private institution.

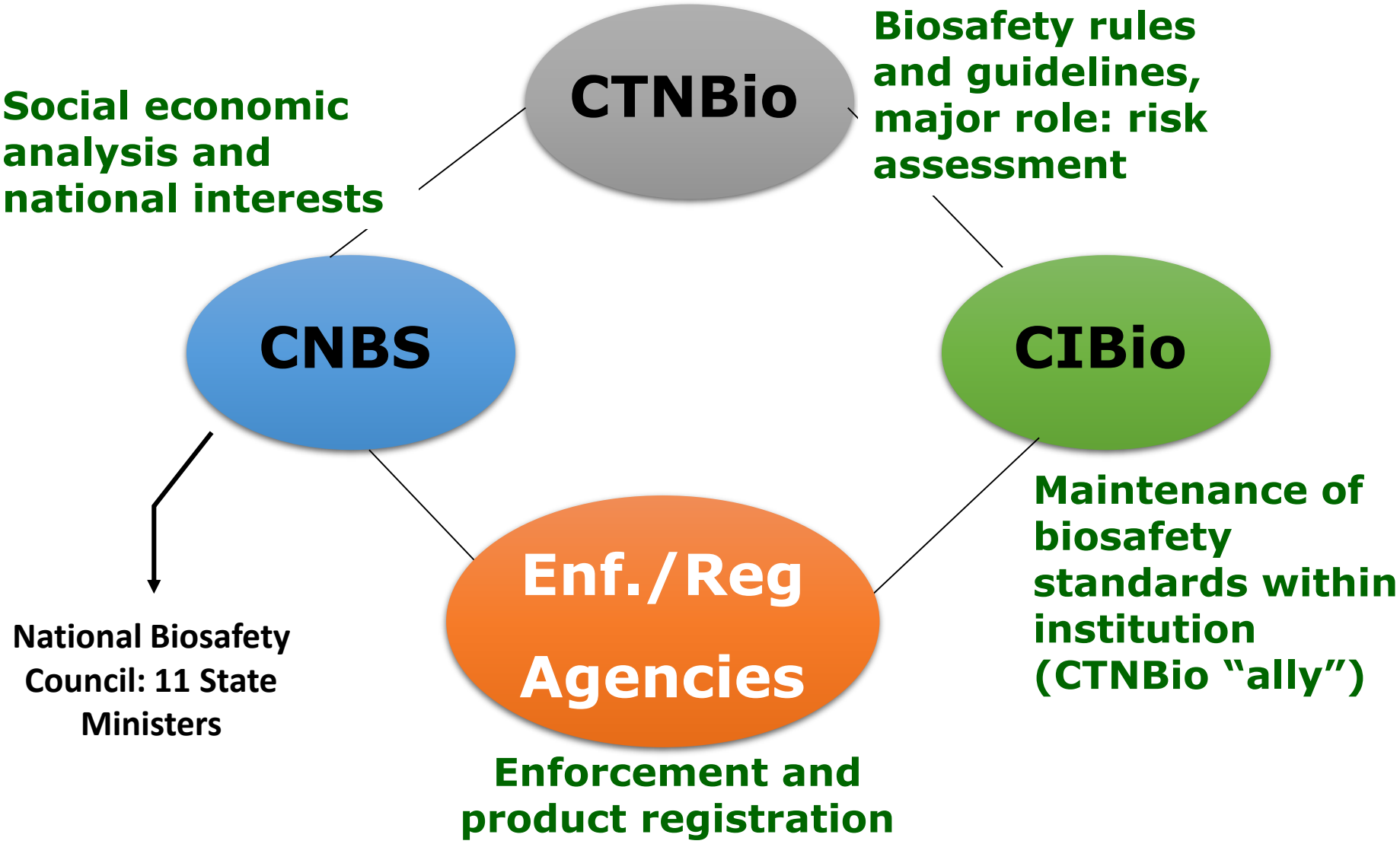
Establishes safety standards and enforcement mechanisms for the activities with GMOs and their derivatives

Fosters scientific advances in the area of biosafety and biotechnology

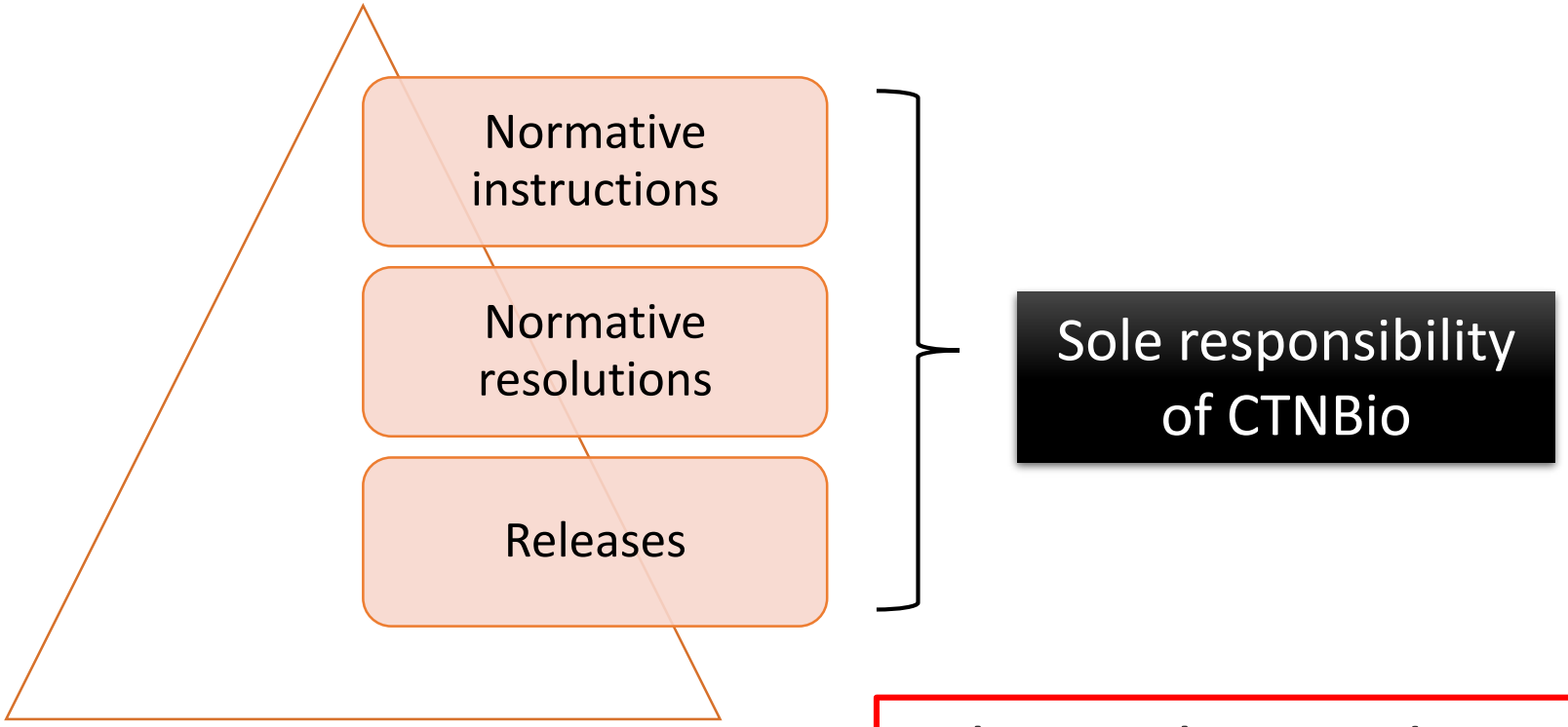
Ensures the protection of life and animal, plant and human health

Is scheduled *for the observance of the precautionary principle* to protect the environment (Brazil is a member of the Cartagena Protocol.

Brazilian regulatory system of GMO Biosafety

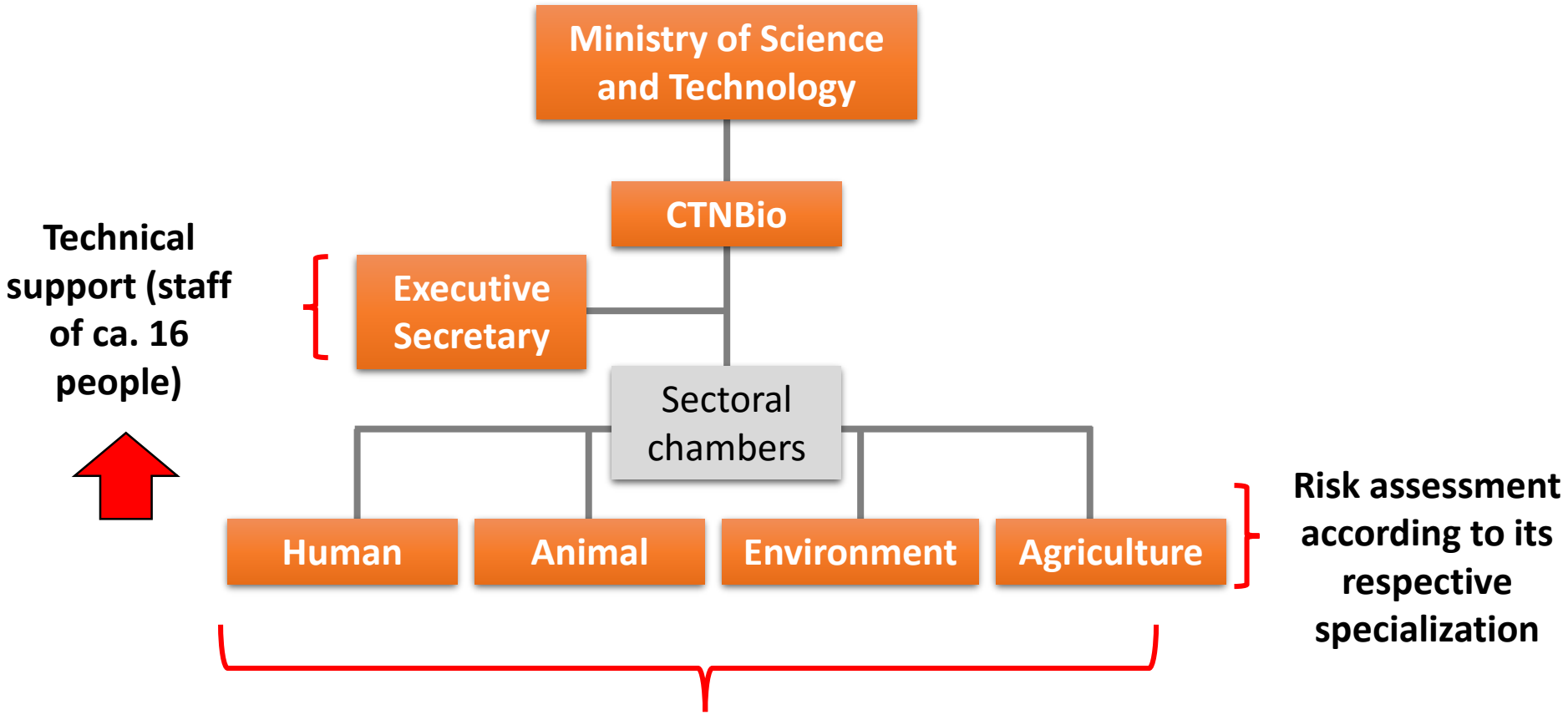


Regulatory levels established by Law 11,105 and its decree



Policy makers and regulators have to provide adaptive regulations **that can adjust to new products**!

CTNBio ORGANIZATION CHART



GMO risks for commercial releases are assessed by all four sectoral chambers

Risks involving controlled (field) releases may be assessed by just two sectoral chambers

CTNBio composition (Ministry of S&T)

12 specialists of recognized scientific and technical knowledge in the areas of human and animal health, plant and environmental sciences

9 ministerial representatives:
MCT (Science and Technology)
MAPA (Agriculture and Livestock)
MS (Health)
MMA (Environment)
MDA (Agricultural development)
MDIC (Industry and Commerce)
MD (Defense)
MAP (Fisheries)
MRE (Foreign Affairs)

6 specialists: Consumer Protection (Ministry of Justice), health (MS), environment (MMA), biotechnology (MAP) family farms (MDA) and worker health (Ministry of Labor)

Total: 27 members and **27** substitutes – all of them must hold a Ph.D. degree on an area relevant to risk assessment (not risk analysis!). In all cases, they are nominated by the Ministry of Science and Technology

Monthly meetings

Far too large (54 members + 16 permanent technicians), heterogeneous and expensive…
Advantages X disadvantages

RISK ASSESSMENT AND SCIENCE-BASED DECISION MAKING

For every product risks must be classified according to the intended use

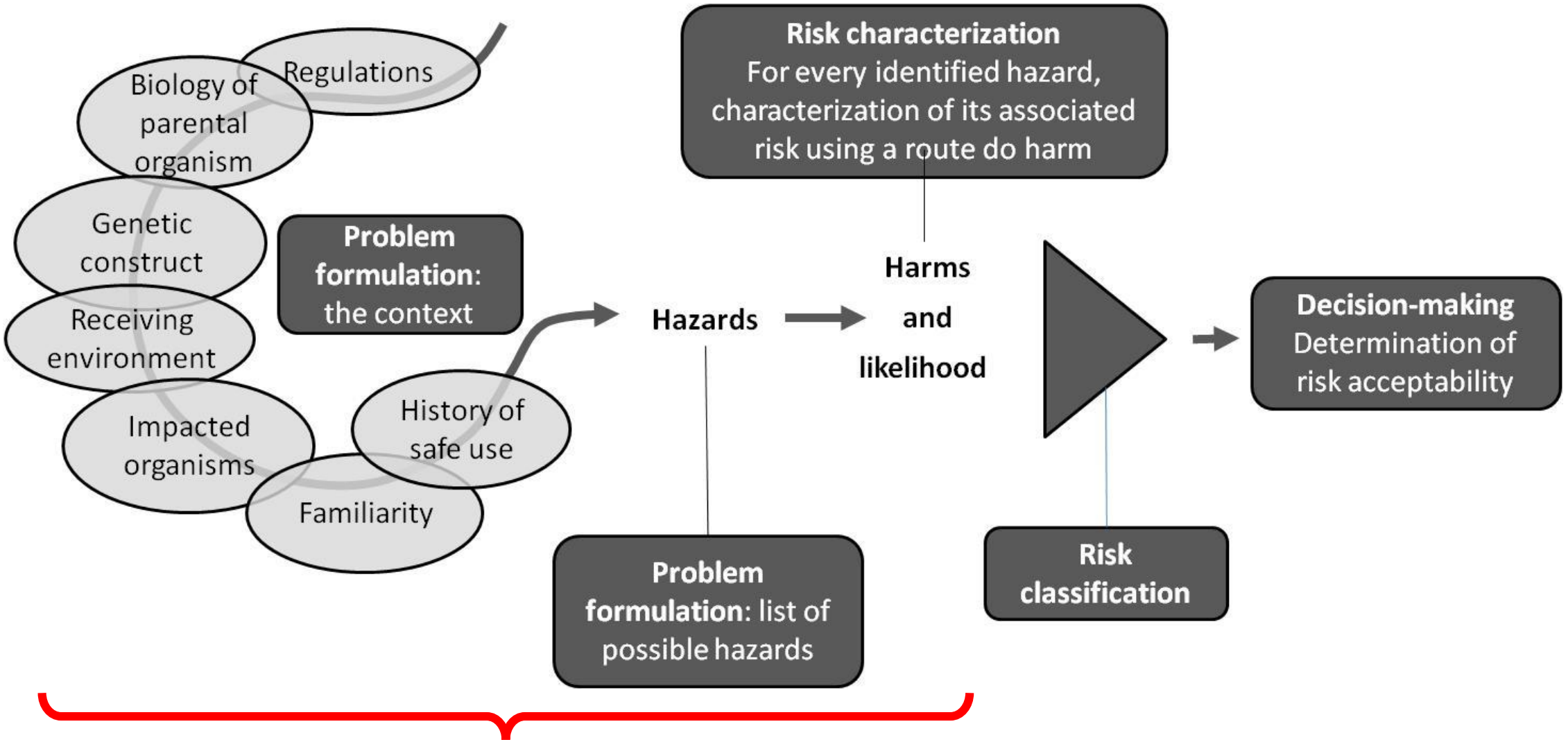
Although a formal pipeline doesn´t exist in CTNBio (only forms and lists of questions embedded in the resolutions), members and technical assistants follow an ***"internationally agreed" pipeline***, which was built on technical and scientific data and on 20 years of GMO assessment

The pipeline can be applied to any GMO (including gene drives) and leads from perceived hazards to plausible risks, allowing a science-based decision

Nice to know X need to know: regulators require " enough" to make a decision, but not everything.

(language matters: assessment/analysis, , hazards, harm, pathway to harm, risk classification, etc.)

The five steps in risk assessment



An adequate Problem Formulation (and Risk characterization) warrants a successful R.A.

WHO Bulletin Volume 94, Number 10, October 2016, 709-784

Use of transgenic *Aedes aegypti* in Brazil: risk perception and assessment

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Abstract The OX513A strain of *Aedes aegypti*, which was developed by the British company Oxitec, expresses a self-limiting transgene that prevents larvae from developing to adulthood. In April 2014, the Brazilian National Technical Commission on Biosafety completed a risk assessment of OX513A and concluded that the strain did not present new biological risks to humans or the environment and could be released in Brazil. At that point, Brazil became the first country to approve the unconstrained release of a genetically modified mosquito. During the assessment, the commission produced a comprehensive list of – and systematically analysed – the perceived hazards. Such hazards included the potential survival to adulthood of immature stages carrying the transgene – should the transgene fail to be expressed or be turned off by exposure to sufficient environmental tetracycline. Other perceived hazards included the potential allergenicity and/or toxicity of the proteins expressed by the gene, the potential for gene flow or increased transmission of human pathogens and the occupation of vacant breeding sites by other vector species. The Zika epidemic both elevated the perceived importance of *Ae. aegypti* as a vector – among policy-makers and regulators as well as the general public – and increased concerns over the release of males of the OX513A strain. We have therefore reassessed the potential hazards. We found that release of the transgenic mosquitoes would still be both safe and of great potential value in the control of diseases spread by *Ae. aegypti*, such as chikungunya, dengue and Zika.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

health workers and other municipal workers supported by a heterogeneous and broad set of collaborators, remains the

GM Aedes risk assessment

Problem Formulation: What are the protection goals in the case of a commercial release of the genetically modified OX513A *A. aegypti* in Brazil? *(Based on the other elements of the context)*

1. *A. aegypti* is highly anthropophilic and transmit s diseases only to humans and a few non human primates *(Biology)*
2. it is found only in urban areas, within or near human dwellings (at least in Brazil) *(Biology)*
3. Non-human large primates *could* be relevant, but they do not exist in Brazilian urban areas. *(Biology)*
4. *A. aegypti* does not mate wit other native mosquito species (and essentially with no other mosquito) *(Biology)*
5. No animal feeds exclusively on *A. aegypti* (or **on any single mosquito species!!**). Those feeding on them ARE NOT VALUED SPECIES and, therefore, are not protection goals, per se. *(Biology)*

As a consequence, there are **no plausible assessment endpoints** except the **human being** *(Familiarity and history of safe use)*

List of hazards (second step of Problem formulation)

Hazards derive from risk perception

- Different stakeholders have vey different risk perceptions
- It usually sounds unfair to discard *a priori* some hazards based on previous knowledge

Therefore

Every hazard should be submitted to the risk assessment pipeline (through the use of plausible pathways to harm)

I – Examples of some concerns related to the direct impact of the GM mosquito on some target (presumably, a protection goal)

a) Allergic or toxic reactions to the transgenic proteins in the OX513A mosquito saliva

b) Oral toxicity to insectivorous animals

c) Inter-specific crossing and transmission of the lethal trait to other insects

d) Failure of the lethal gene expression by mutation or other genetic cause and consequent spread of the GM population

e) Induction of tetR among GM *A. aegypti* gut bacteria and spread of this trait among other environmental bacteria, eventually reaching human pathogens

II – Examples of some concerns related to the impact of the technology on human health (disease control)

e) Maintenance of a sizable population of transgenic mosquitoes in dengue transmission areas due to the presence of tetracycline in breeding places (harm?...)

f) A small but significant percentage of females among males during the release could contribute to dengue transmission(harm?...)

g) The niche left vacant could allow the establishment of another vector species, for example, *A. albopictus* *(not a direct impact of the GM mosquito, however)*

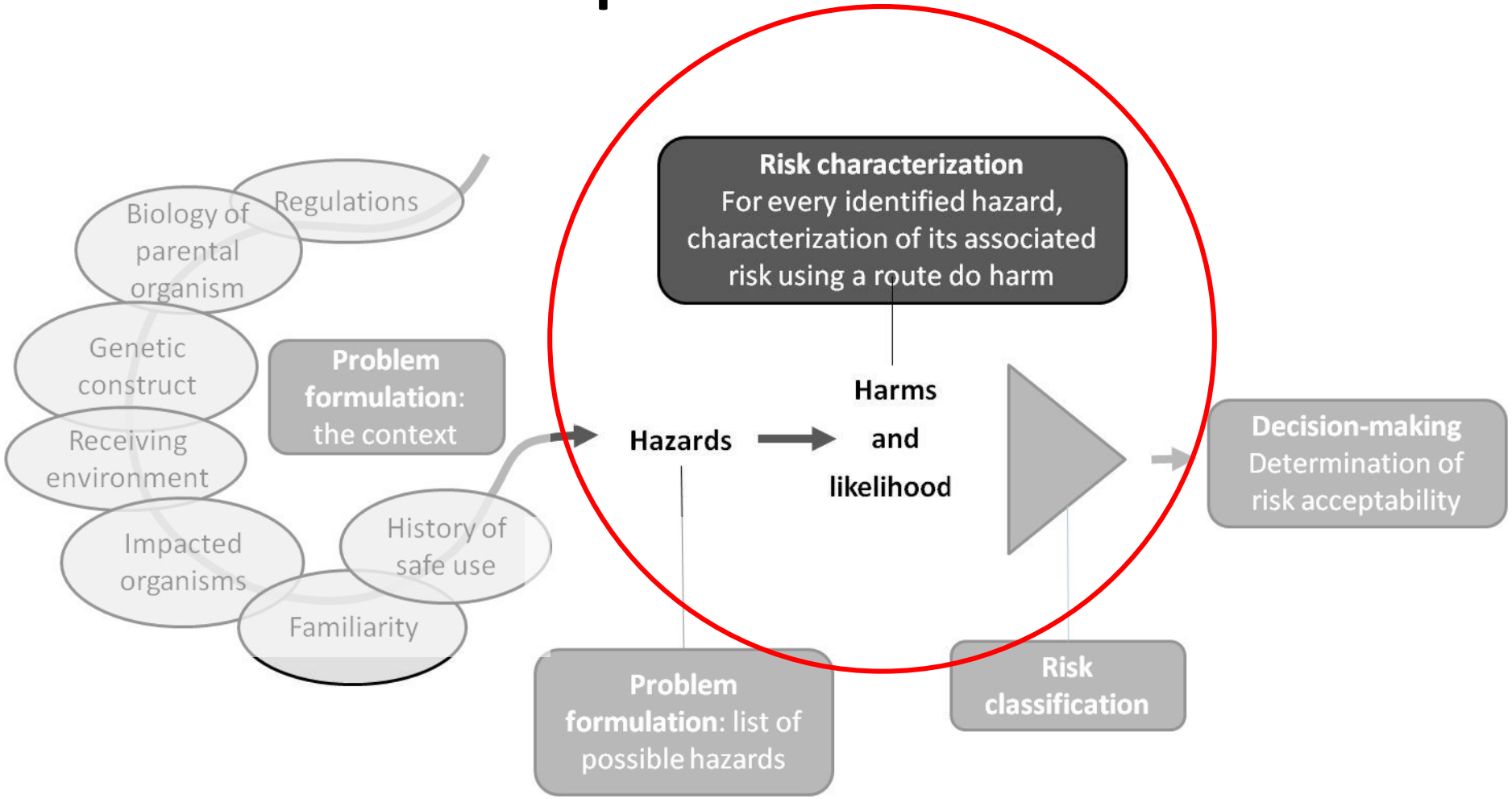
III – Concerns related to economical and operational aspects (not a concern for risk assessors, but for risk analysts)

h) Cost-effectiveness with that of other measures already in place

i) Other operational concerns such as the effective reduction of *A. aegypti* populations, frequency of releases, sample size, etc.

Once the list is considered to be representative of the mostly probable causes of concern, the second step of Problem formulation is fulfilled (*Only for hazards derived from the direct impact of the GM mosquito*).

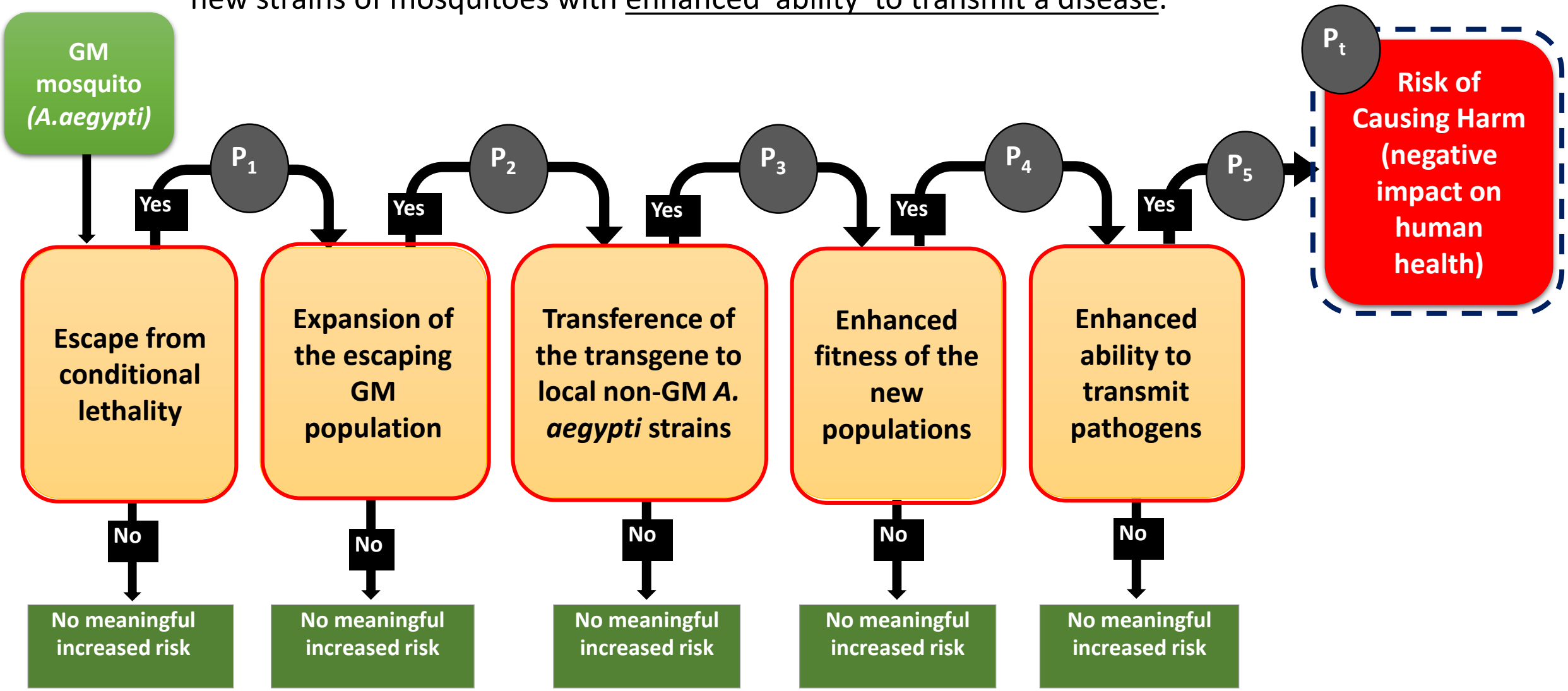
3rd step: Risk characterization



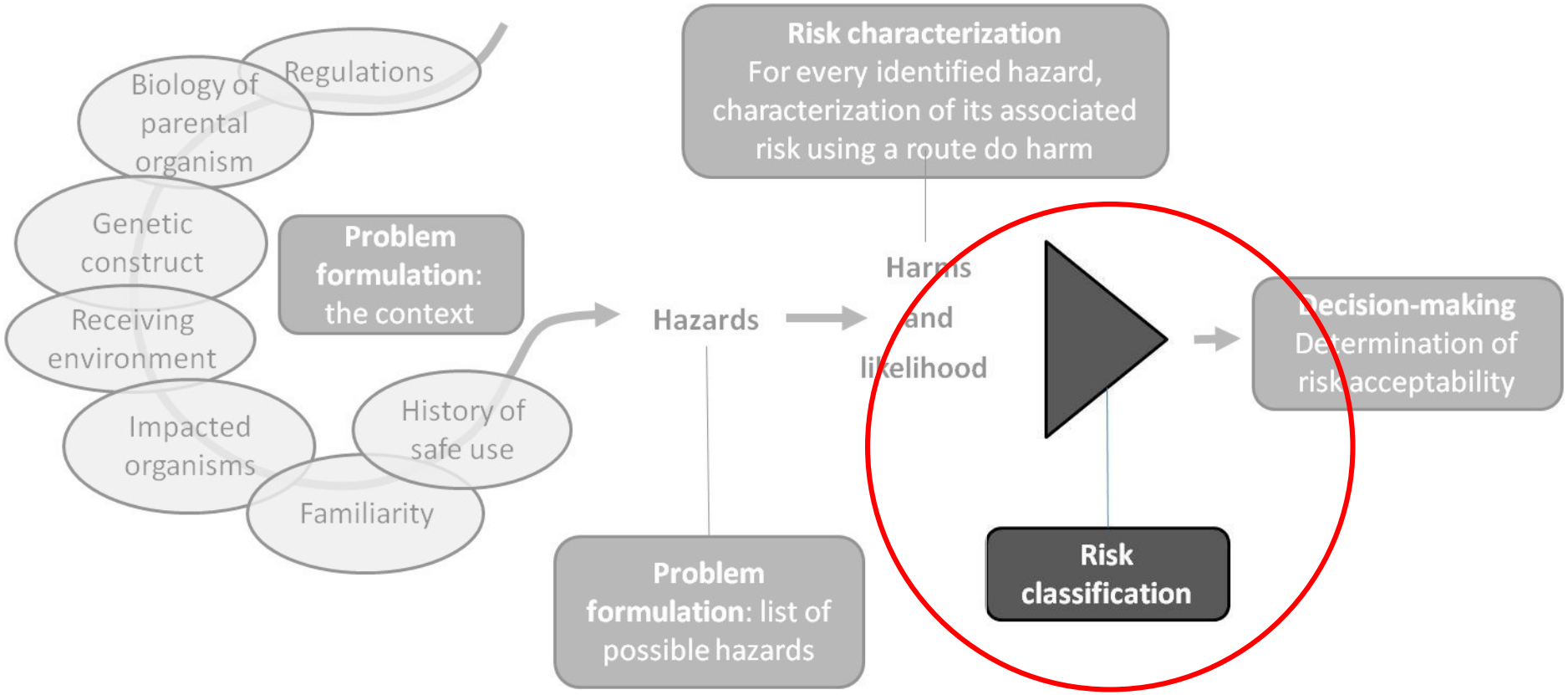
Risks have to be "calculated", "estimated" or classified for every hazard; to that purpose pathways to harm ("Routes do damage") have to be constructed for every perceived hazard in order to classify its risk

Example of a multi-step pathway to harm

General hypothesis: the transgene does not work properly (there may be different reasons for that) and may be transferred to the local *A. aegypti* population, leading to new strains of mosquitoes with enhanced ability to transmit a disease.



4th step: Risk classification



Risk classification (or risk estimation)

Once the likelihood and the extension of harm (also called consequences) are estimated, it is possible to classify the risk for the first proposed hazard (the proteins in the saliva). The same exercise must be done for all other hazards.

RISK ESTIMATE				
PROBABILITY				
Very high	Low	Moderate	High	High
High	Low	Low	Moderate	High
Low	Negligible	Low	Moderate	Moderate
Very low	Negligible	Negligible	Low	Moderate
	Marginal	Minor	Great	Major
	Amount of Harm			

5th step: decision making in the Brazilian GMO regulatory framework

If only negligible risks have been identified, the use of the new product will depend exclusively on its registration by the competent authority (if a plant, livestock or a plant or livestock pest , the Ministry of Agriculture; otherwise, another federal authority has to register the product)

It never happened, but if a product has small risks associated to its intended uses, it may still be registered and sold, depending on the adoptions of risk management actions.

Decisions based on science-based risk assessment can only be reverted by the majority decision of the eleven-ministers board (the National Concil of Biosafety), but the arguments must nor involve GMO risks.

Final considerations: other regulatory scenarios

A difficult identification of the agency responsible for the risk assessment derives from the use of an old regulatory framework to assess a new technology… and may lead to some startling “adaptations”.

US regulations creating confusion for regulation of GMO mosquitos

Henry Miller | September 12, 2016 | Forbes

FDA regulates the genetic material introduced into the Oxitec mosquito as a “new animal drug”…The rationale is that introducing DNA into the genome of the mosquitoes is analogous to dosing them with a drug.
That presents a bizarre…regulatory conundrum, because…[r]egulators would somehow have to conclude that the genetic material that causes a male mosquito to self-destruct after producing defective offspring is*safe and effective for the mosquito*.

Final considerations (ctn)

Product developer, regulators, consumers and scientists may have to pave together the road to the adoption of a new product (as it is the case of Oxitec´s OX513A)

A formal risk assessment process gives transparency and may serve as a ***risk communication element*** to explain what has been assessed and why, and how the decision has been made

Thanks for your attention

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