Transgenic Aedes aegypti in Brazil

Risk Perception and risk assessment

Uso del *Aedes aegypti* transgénico en Brasil

Percepción de riesgo y evaluación

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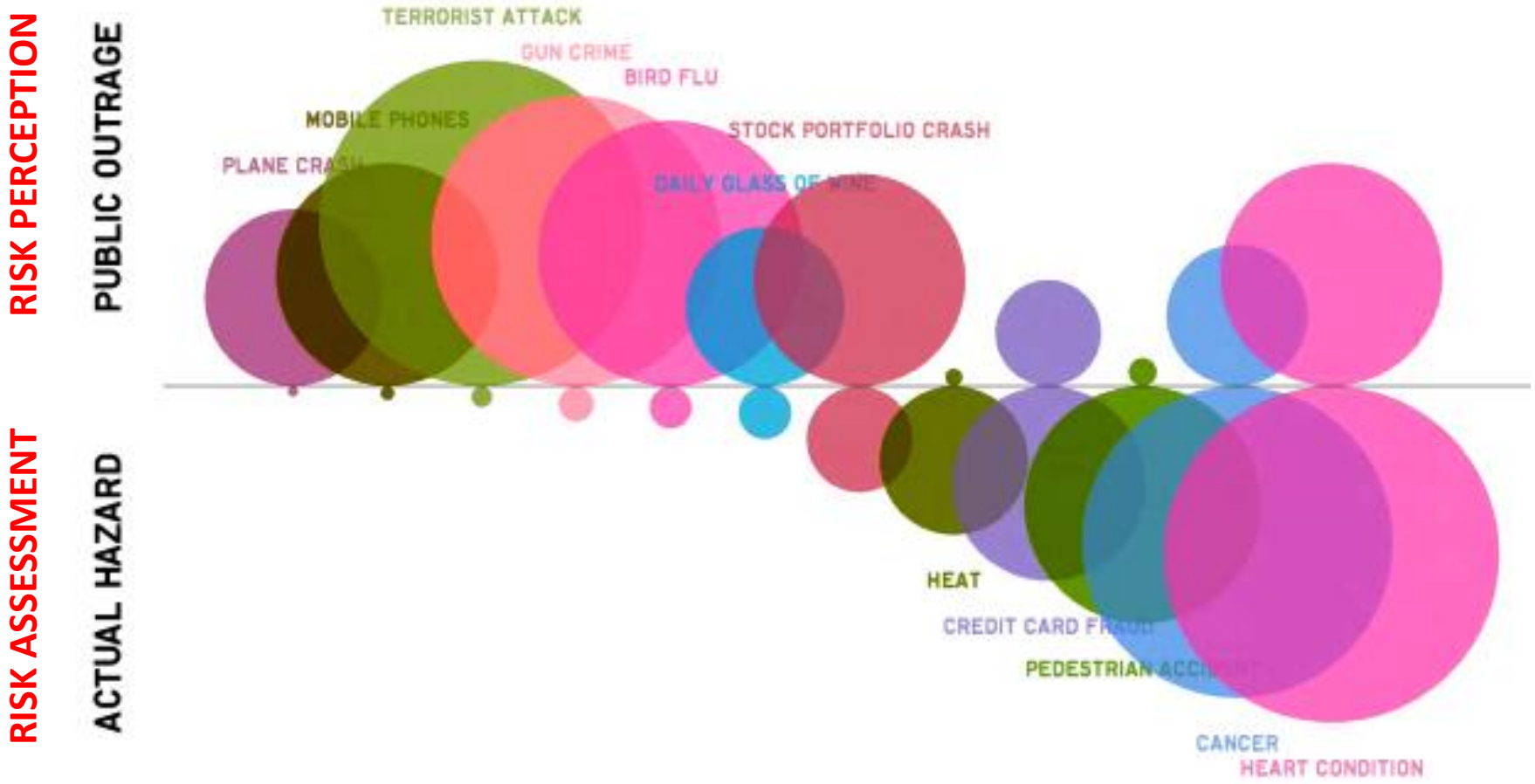
Risk perception X risk assessment

Different values and methodologies



A ***hazard*** is usually derived from someone´s risk perception

Risk perception (and hence, the list of hazards)

- ❑ has no need to be based on a plausible set of hypotheses leading from the hazard to the hypothetical harm (usually no assessment)
- ❑ may be strongly dependent on group opinions
- ❑ may vary a lot under the influence of the media
- ❑ can vary widely
- ❑ may change very fast

As a consequence, risk perception can be vey much dependent on communication strategies, stakeholders, power and interest

The lack of an efficient risk communication strategy can be much deleterious to the adoption of any biotech product, incl. GM mosquitoes

Risks must be derived from the scientific assessment of hazards

Opposite from risk perception, GMO risk assessment

- ❑ is a widely used, ***essentially similar*** methodology
- ❑ Is based on science
- ❑ Uses hard data
- ❑ Does not balance benefits against risks
- ❑ Can not change its final result over time except if new data is available

As a consequence, risk assessment should be independent of communication strategies, stakeholders, power and interest

However… as ***risk analysis*** is sometimes intermingled with ***risk assessment***, the final results can be fuzzy and dependent on political decisions alien to science

The transgenic Aedes aegypti OX513A
Some hazards derived from public perception and their risk classes

(according either to the public or to risk assessors)

Risk perception (hazard)	Associated harm	Public outrage	Real risk level
GM mosquitoes may bite people	Disease transmission	Big	Negligible
Unexpected survival of GM mosquitoes	Ecological damage	Low	
Allergenicity and/or toxicity of two new proteins expressed	Allergy and intoxication	Low	
Horizontal flow of the transgene	Ill defined (to Zika virus?)	Moderate	
Enhanced viral transmission	Epidemics	Moderate	
Tetracycline resistant bacteria	Diseases outbreaks	Low	
Vacant niche occupation	New vectors, new diseases	Big	

How should the regulator produce relevant questions for the risk assessment of a GMO?

What is the answer to the Ultimate Question of Life, The Universe, and Everything?

From the Hitchhiker's Guide to the Galaxy

A ***relevant answer*** must comes from a ***relevant question***!

How relevant questions concerning the environmental release of the GM *Aedes aegypti* have been produced in Brazil?

Most regulatory frameworks have:

- List of questions
- Case-by-case risk assessment

Useless mandatory questions frequently imply new experiments/field releases and imply costs. Setting too high standards, disproportionate to risks, and disregarding previous experience also increase costs

High regulatory costs will preclude the release of GM animals

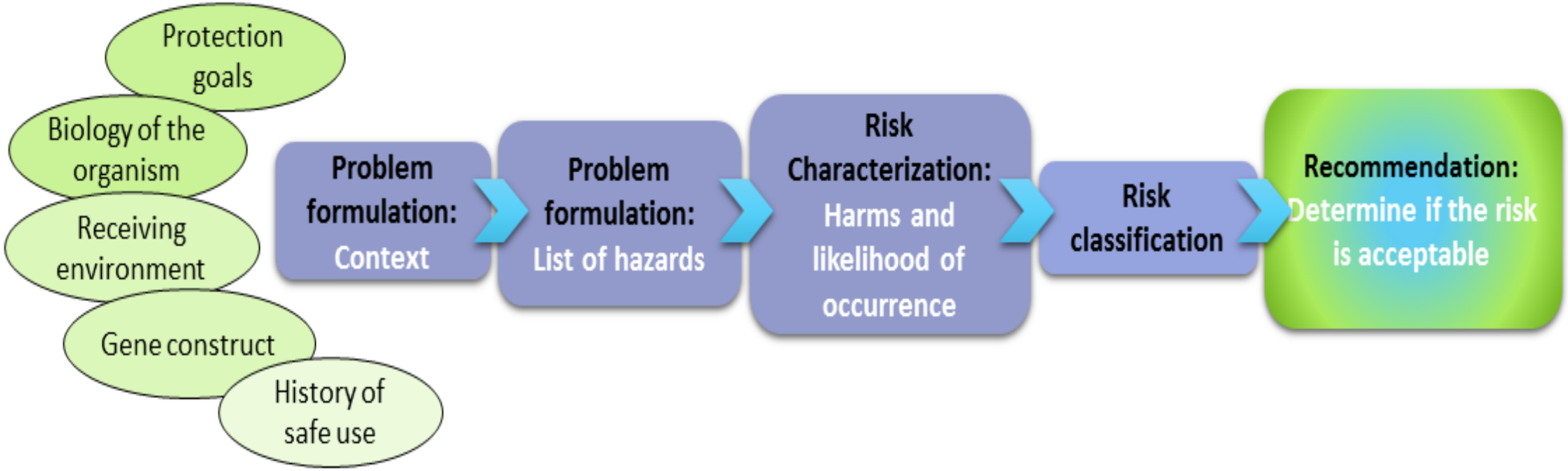
The logical approach would be:

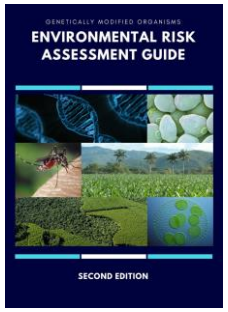
- Case-by-case risk assessment

Only relevant questions will trigger new experiments

Lower regulatory costs will allow the release of GM animals

The bulk of ***relevant*** questions will be derived from the environmental risk assessment (ERA) step by step procedure as accepted today – it can be applied to many, possibly all, GMOs inclusive GM mosquitoes





Environmental risk assessment of GMOs (Draft - June 2017)

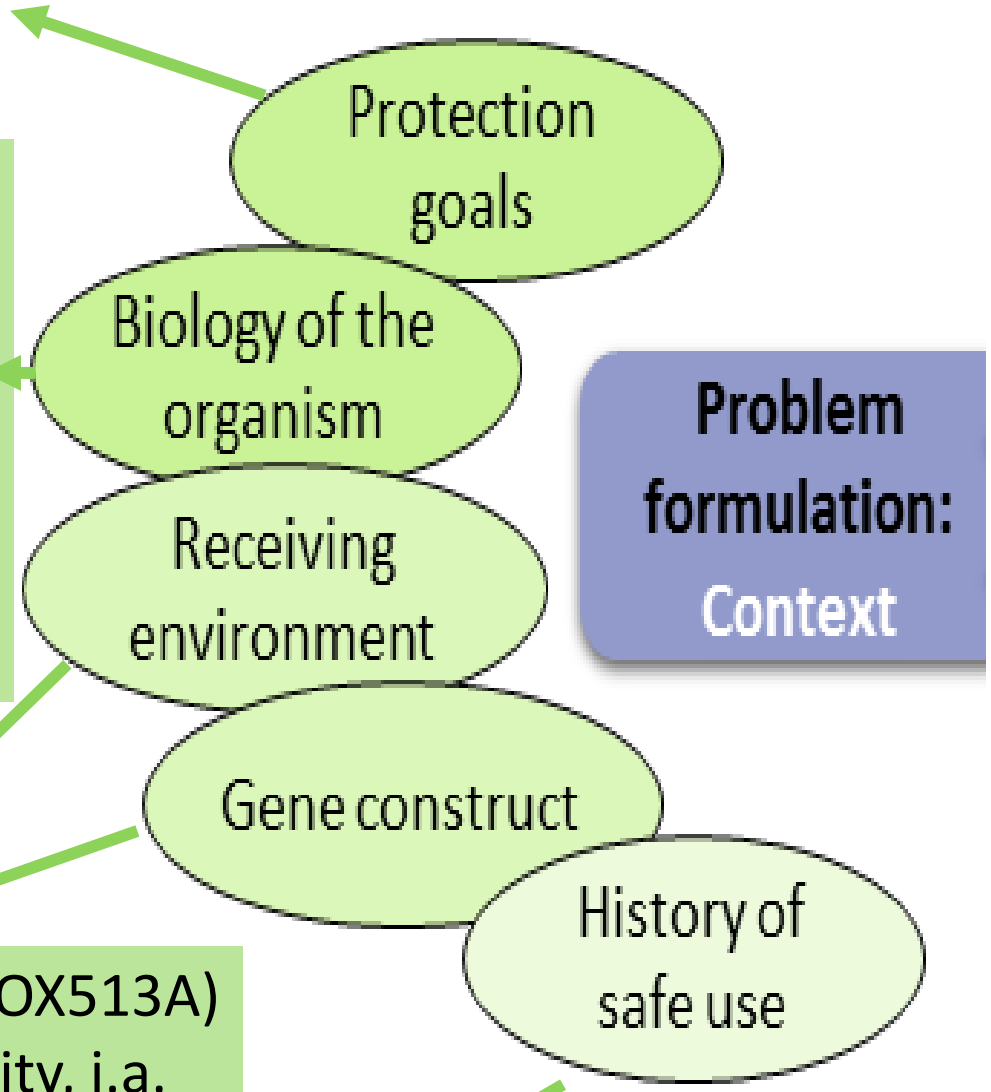
https://goo.gl/T4Uxnl

How to derive relevant questions for OX513A Aedes aegypti?

Main issue to keep in mind: what are the <u>protection goals</u> that I can derive from my assessment?

Biodiversity: **none**

Problem formulation: the context



Non native
No sexually compatible species
Dispersion under control
No invasive potential (for OX513A)
Not important in the wild life food chain

Agri-environments/ rivers

Some kind of lethality (OX513A) or male or female sterility, i.a.

For OX%!#A, perhaps…

What uses have the <u>many</u> hazards derived from the multiple stakeholders perceptions in the risk assessment?

Logic answer: NONE (false answer)

Real world answer: assess all of them

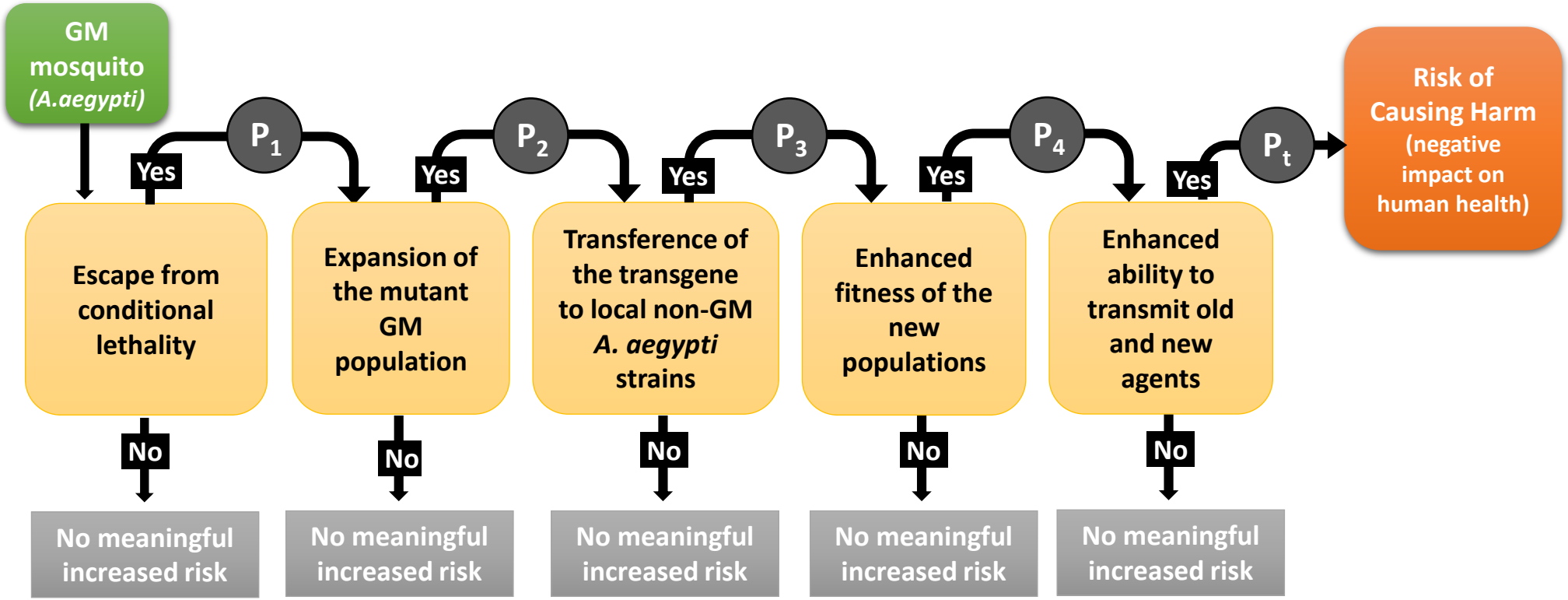
Disregards public opinion, is offensive and politically unsustainable

What about costs and time?

Solution: to build plausible *pathways to harm* and to discard every hazard that does not fit in some pathway (Step 3 Risk characterization of ERA)

A hypothetical pathway to harm (there may be many)

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



Logical reasoning, usually no need for experiments or large costs

The first hypothesis is the failure of the transgene to kill the released insects and their progeny, what may happen both by the presence of tetracycline in the environment or by mutations in the promoter of the lethal gene or by some other obscure mechanism. The likelihood (P1) is very small as 1- Oxitec has followed thousands of generations of these mosquitoes and never observed any change in conditional lethality and 2- environmental tetracycline is rare and usually well below the threshold to ensure survival of a significant fraction of the mosquitoes.

If, by some unanticipated mechanism, the GM mosquitoes survive, they must reproduce at least as fast as the regular mosquitoes in order to have a chance to increase their population (supposing that the original mutant population will be necessarily very small). Because of competitiveness with the wild population, P2 (the likelihood of such an expansion) is also small (*this could be disputed…*).
By freely crossing with the local (or wild) *A. aegypti* population, the **mutant*** GM mosquitoes will be able to transfer their non-lethal gene to the wild population. P3 is 100%. (* - here I suppose that the phenotypic change is due to a change in one or more DNA sequences)

The new mutant transgene, however, does not add any advantage to the mosquito, because it is a non functional gene and represents just a burden in replication and maybe also in metabolism. Therefore, it is highly unlikely that if will enhance the fitness of the new populations. P4 is, therefore, very small.

Finally, even if it is established among the vector population, it will be just able o transmit the same diseases as their non-GM parental. There is no mechanism by which the transgene could confer enhanced ability to transmit new disease or to be a better vector of the original diseases transmitted by A. aegypti. Therefore, P5 is also very low.

Hence, the likelihood for the whole pathway to be accomplished is very low. Moreover, since the mechanism supporting such behavioral changes is very imaginative and the changes were generally not been observed, the harm will be restricted to a few populations and could be reverted by the use of insecticides and other control measures already available for vector control.

OX513A
A. aegypti

GM mosquito mates with beneficial insect

Progeny is fertile

Transgenes are expressed in the new host

Transgene spreads in the population

Large populations of beneficial insects are driven to extinction

What are the relevant questions if we don´t have a protection goal that could be plausibly affected?

Animal	Trait	Protection goal	Question (after R.A.)
Cow	Hornless	None	None
Goat	Virus-resistant	None	None
Tilapia	Fast growth	Other river dwelling organisms	Some (in case of escapes)
Snail	Female sterility	None	Transboundary movement Regulated by the Cartagena Protocol
GM Ae. aegypti	Conditional lethal	Very broad (human health)	None

What are the relevant questions if we don´t have a *protection goal* that could be plausibly affected? None

Impasse…

How to proceed with the regulatory process if we do not have questions?

How to fulfill public´s expectation on rigor and precaution?

The worst solution: Create an imaginary risk assessment by adding irrelevant questions only to suppress or reduce public outrage

Some of the irrelevant questions can be social-economical issues, including coexistence

The best solution: find relevant protection goals and work on them or otherwise be transparent to all stakeholders, but don’t create imaginary risk assessments

If there are relevant questions, how should the developer/applicant produce the answers?

Literature

It makes no sense to repeat experiments, either in the lab or in the fields, ***if the needed information is available*** and can be transported

Lab experiments

It makes no sense to do expensive, ill controlled field labs, ***if you can get the right answer in the lab***

Field releases

Although much used for GM plants, they seldom produce relevant answers for the environmental risk assessment. They will possibly be of very limited use for GM animals risk assessment. Methodologies are also very different for containment of plants and animals (sometimes plainly impossible)

In spite of the robust Brazilian regulatory framework…

Challenges were big:

- The GM Aedes aegypti was the first GM animal assess by the National Biosafety Commission (CTNBio)
- The specific details of a mosquito biology were a challenge to the regulators
- The first field trials were by far the biggest regulatory challenge
- On the other hand, risk communication was very well planned and results were good

Moreover

- No clear protection goals could be devised
- No clear risks, even small ones, could be identified
- However, opposition grew rapidly, fueled by local anti-biotech and anti corporative organizations

After 4 years (2010-2014) all steps from the initial assessment to the commercial release were done

Risk communication was essential:

- To reduce opposition among many stakeholders
- To produce a positive feedback in the media

Moreover

- The technology advantages were clearly in favor of the Brazilian society (and not restricted to a small group)
- No obvious risks and a long history of successful use of biotechnology in Brazil (and elsewhere) helped a lot
- Opposition faded out rapidly. Oxitec Brasil took very positive measures to ensure a good benefit/risk communication

Approaches to do an environmental release of mosquitoes developed via biotech (or by any other regulated methodology)

1) Scrutinize your regulatory framework and see if you can get rid of pitfalls or at least circumvent them …
- Lack of clear guidelines for animals
- List of useless questions
- Obligatory use of certain data
- Obligatory use of field releases prior to a commercial release
- Etc

2) Start doing your hypothetical risk assessments ***much before*** having your product and discuss the results with the regulators

3) Once a consensus is achieved, start your broad ***benefit/risk communication***, engaging a skilled staff to help you coming to a happy end

4) Then proceed with your experiments, and good luck!

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.

Am. J. Trop. Med. Hyg., 96(3), 2017, pp. 530–533
doi:10.4269/ajtmh.16-0726

Perspective Piece

Results from the Workshop "Problem Formulation for the Use of Gene Drive in Mosquitoes"

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Abstract. Reducing the incidence of malaria has been a public health priority for nearly a century. New technologies and associated vector control strategies play an important role in the prospect of sustained reductions. The development of the CRISPR/Cas9 gene editing system has generated new possibilities for the use of gene-drive constructs to reduce or alter vector populations to reduce malaria incidence. However, before these technologies can be developed and exploited, it will be necessary to understand and assess the likelihood of any potential harms to humans or the environment. To begin this process, the Foundation for the National Institutes of Health and the International Life Sciences Institute Research Foundation organized an expert workshop to consider the potential risks related to the use of gene drives in *Anopheles gambiae* for malaria control in Africa. The resulting discussion yielded a series of consensus points that are reported here.

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