Science-based regulations and challenges associated with animal biotechnologies:
Using science to inform risk assessment and regulation

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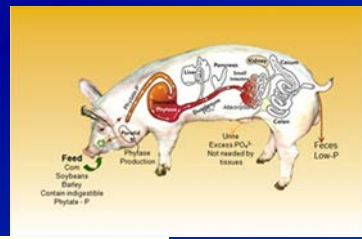
Applications of animal biotechnology…

- Goats expressing human antithrombin III in milk
- Pigs expressing phytase → better utilization and lower excretion of phosphorus
- Goats expressing lysozyme, reducing bacterial loads in milk
- Cattle producing b-lactoglobulin-free milk
- Pigs expressing a-lactalbumin to increase pre-weaning growth
- Cattle lacking prion protein, cannot transmit BSE
- Chickens that will not transmit avian influenza
- …Who could *argue* with the utility of such applications?



What are the issues pertinent to regulation of animal biotechnology?

Science issues:

- Food safety
- Environmental safety
- *Can* be addressed through application of science

Non-science, values issues:

- Animal welfare
- "Right to know"
- Rejectionism
- Anti-corporatism
- Can*not* be so addressed

Let's consider the science-based issues in the context of a case study...

Food safety

Three risk pathways:

Bioactivity of transgene product:

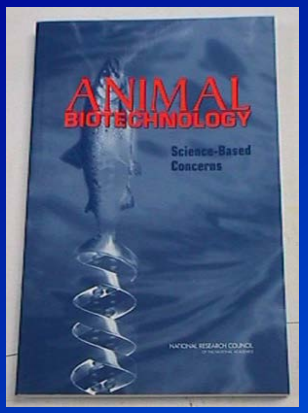
- Salmon GH, its breakdown products, and hormones secreted in response are not bioactive in humans

Allergenicity of transgene product:

- Can be assessed for transgene products derived from foods traditionally part of our food supply
- Can be *difficult* to assess for transgene products from sources *not* traditionally part of our food supply
- Those allergic to fish would not buy product!

Toxicity:

- Not at issue



National Research Council (2002)

Food safety

Food safety can be assessed using well-established methods.

- The intent is to assess *biological* as opposed to *statistical* significance

- For example, in our case study, the food safety assessment of the AA salmon was criticized by some NGOs because sample sizes were too small to attach statistical significance to small changes in composition.
- FDA's VMAC found that an "overall appropriate and a large number of test results established similarities and equivalence between AquAdvantage Salmon and Atlantic salmon".
- That is, if the difference in composition is too small to be statistically significant in a sample of reasonable size, then it is not *biologically* significant.

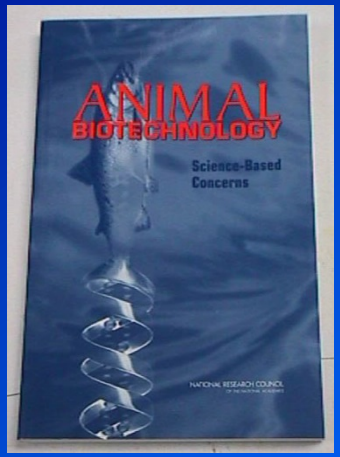
Environmental safety

Risk assessment framework:

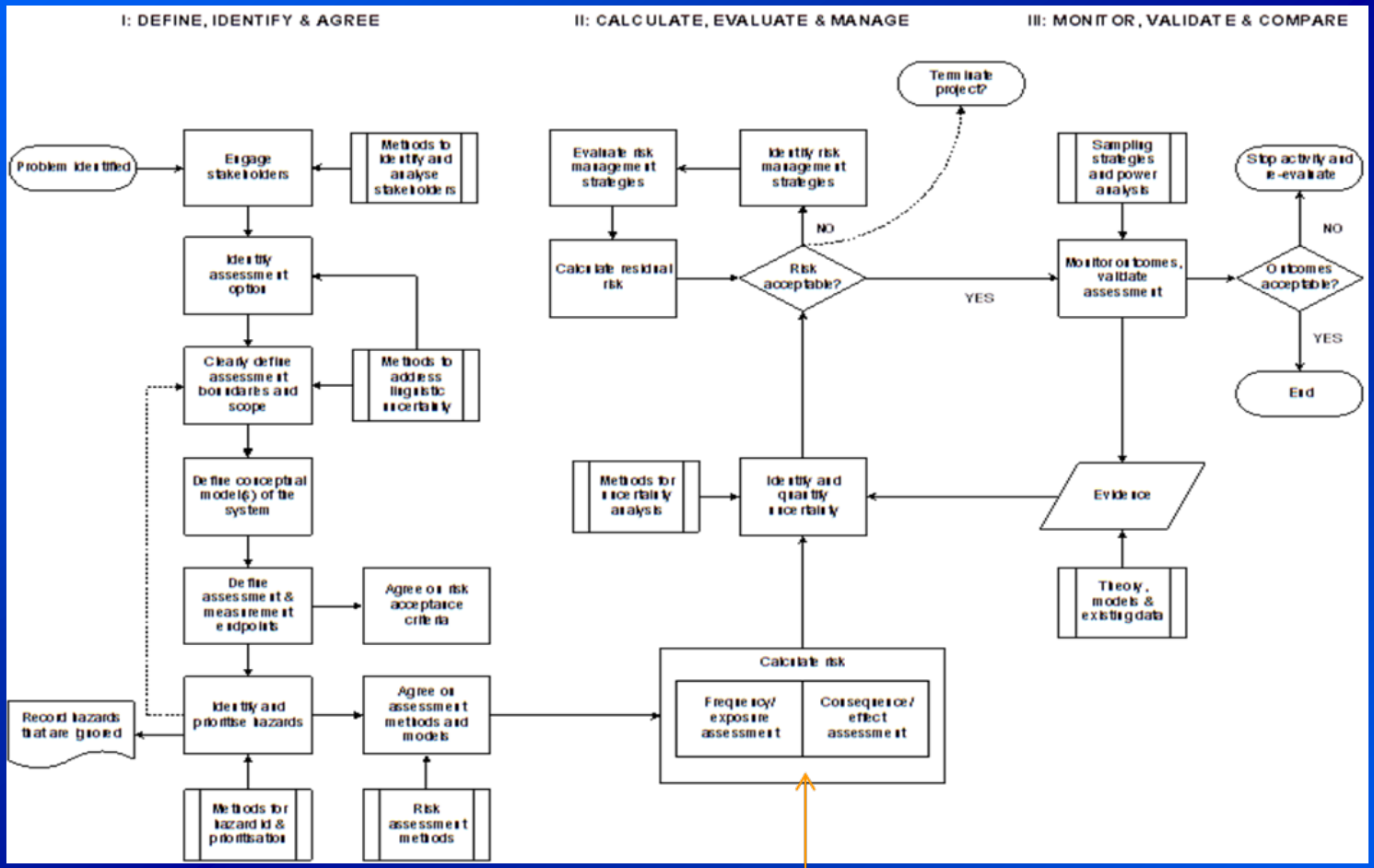
- Identify potential *harms* - outcomes
- Identify *hazard* that might lead to harms – the transgenic stock
- Assess *probability of exposure* – likelihood of escape and persistence of transgenics in receiving ecosystem
- Assess *probability of harm given exposure*
- $R = P(E) \times P(H|E)$

Ecological risk assessment for transgenic organisms

- Considered on a case-by-case basis:
- Host species
- Introduced genetic construct
- Integration event
- Receiving ecosystem

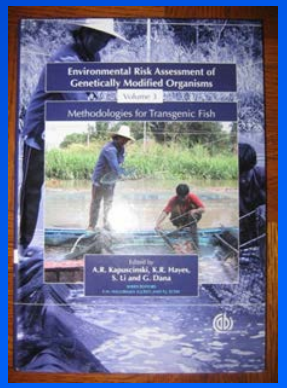


Ecological risk assessment for transgenic organisms



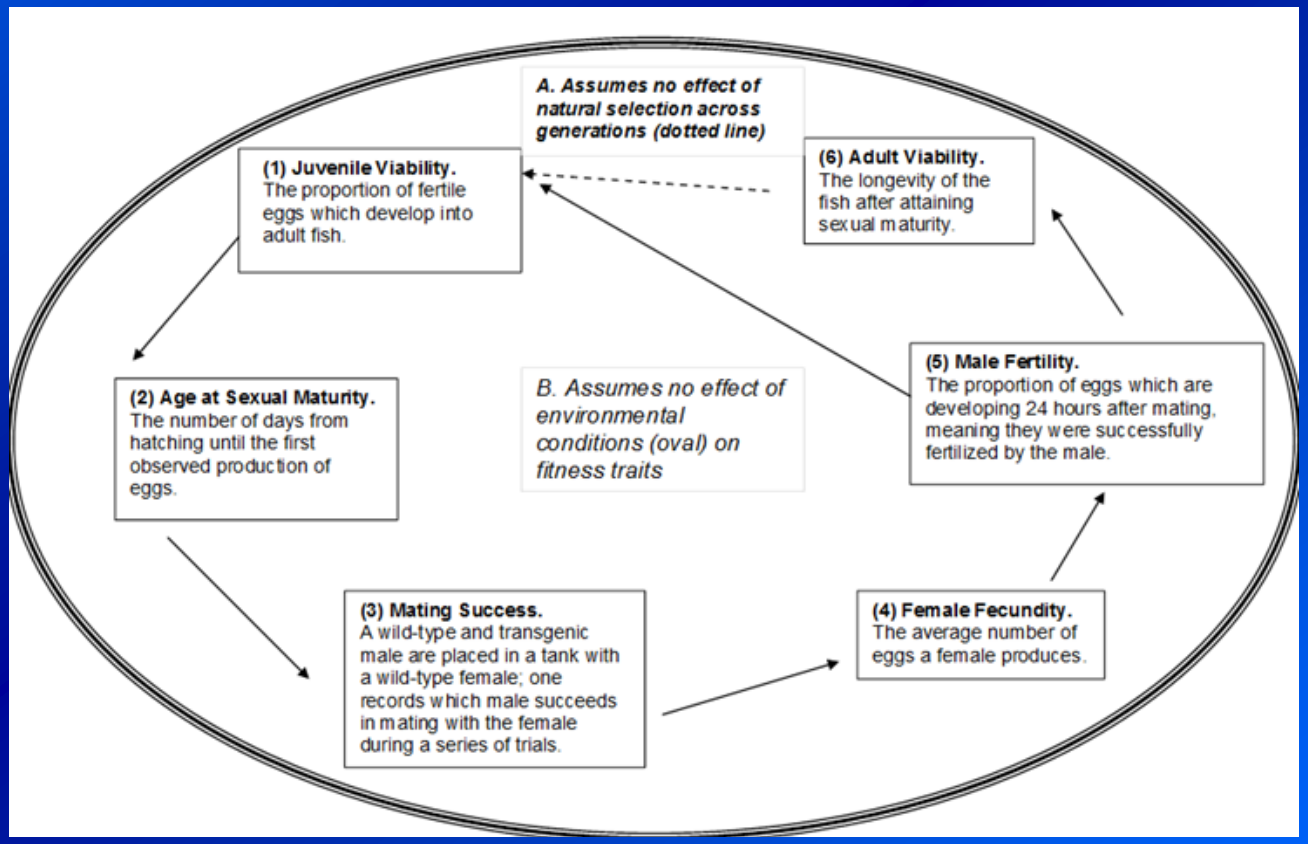
(Hayes et al. 2007)

Focus on estimating risk associated with genetic and ecological processes



Case study: Assessment of fitness of growth hormone-transgenic Atlantic salmon

- Consider effect of transgene expression on *net fitness* of individuals…



Survival component of fitness

- Oxygen metabolism: transgenics had higher critical oxygen level, 6 mg/l vs. 4 mg/l (Stevens et al. 1998)
- Energy metabolism: under starvation, transgenics depleted body protein, dry matter, lipids and energy more quickly than controls, and had lower initial energy reserves (Cook et al. 2000a,b,c)
- Feeding behavior: transgenics' consume 5x controls, fed in presence of predators (Abrahams and Sutterlin 1999)
- Smoltification: transgenics reached smolt size (16cm) sooner, transition not inhibited by high temperature (19C) or constant light (Saunders et al. 1998)
- Cardiorespiratory function: 18% lower metabolic scope, 9% lower critical swimming speed (Deitch et al. 2006)

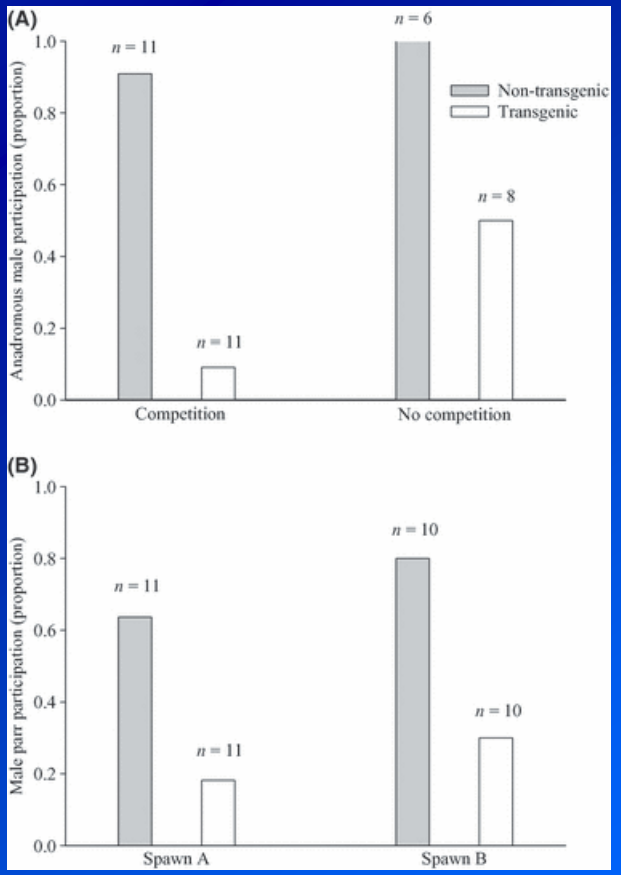
Survival component of fitness

No difference between transgenics and controls (Moreau et al. 2011a) regarding:

- Oxygen consumption rate
- Developmental rate
- Survival until emergence from gravel
- Fry behavior (classic intruder-resident relationships)
- Growth and survival in artificial stream

Reproductive component of fitness

- Transgenic *anadromous males* were outcompeted in terms of nest fidelity, quivering frequency, and spawn participation (A)
- Transgenic *parr* were inferior competitors relative to wild-type parr in terms of nest fidelity, spawn participation (B), and fertilization success
- Transgenic males exhibiting either reproductive strategy exhibited *low*, but *non-zero* reproductive fitness



(Moreau et al. 2011b)

Net fitness of GH-transgenic Atlantic salmon and transgene fate in near-natural ecosystems

Summarizing this case study…

- Survival fitness *equal to* or *less than* wild type.
- Reproductive fitness *decreased* relative to wild type.
- Net fitness is *reduced* → transgene will be purged from population following a *single* episode of introduction.
- *But what if introductions are recurring?*
- *Because of GxE interactions, we can never know and quantify risks for all potential receiving ecosystems.*

Risk management → Risk assessment

- Recognizing that $R = P(E) \times P(H|E)$, R may be minimized by minimizing $P(E)$.
- *Risk management is an* inherent *part of risk assessment and regulation*

Application within the context of our case study:

- Ecological risk may be minimized by culturing transgenic fish under strict confinement.
- Upon seeing the data, AquaBounty determined that it would seek to produce its fish only under strict confinement.

Risk communication

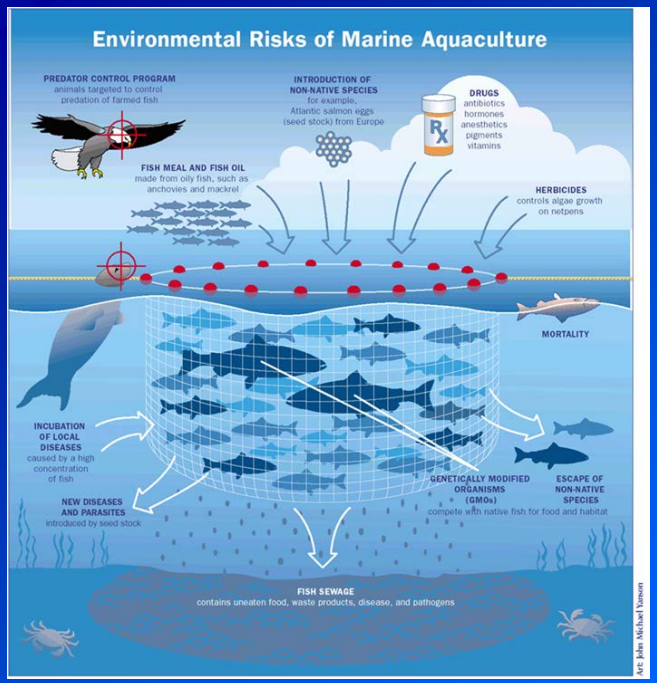
- Should be inherent part of regulatory regime.
- Covered in another session of our workshop.

- Was practiced in our case study: In September 2010, USFDA held a public meeting of its Veterinary Medicine Advisory Committee (VMAC) on the AA salmon

Choice of relevant baseline

- The regulatory process in most countries focuses on potential *risks* associated with GE animals
- Often, there is little consideration of *benefits* of GE animals
- *Risks and benefits should be considered relative to relevant baseline alternatives*

- In the case study, benefits and risks of confined production of sterile transgenic AA salmon should be compared to those of producing fertile, selectively bred Atlantic salmon in floating netpens



Key points

- Animal biotechnology may pose economic, animal welfare, and food safety benefits, but may present environmental risks
- Science-based risk assessment and risk management protocols must be applied to regulatory oversight
- Benefit and risk must be considered with regard to appropriate comparators

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