



The case of the AquAdvantage salmon

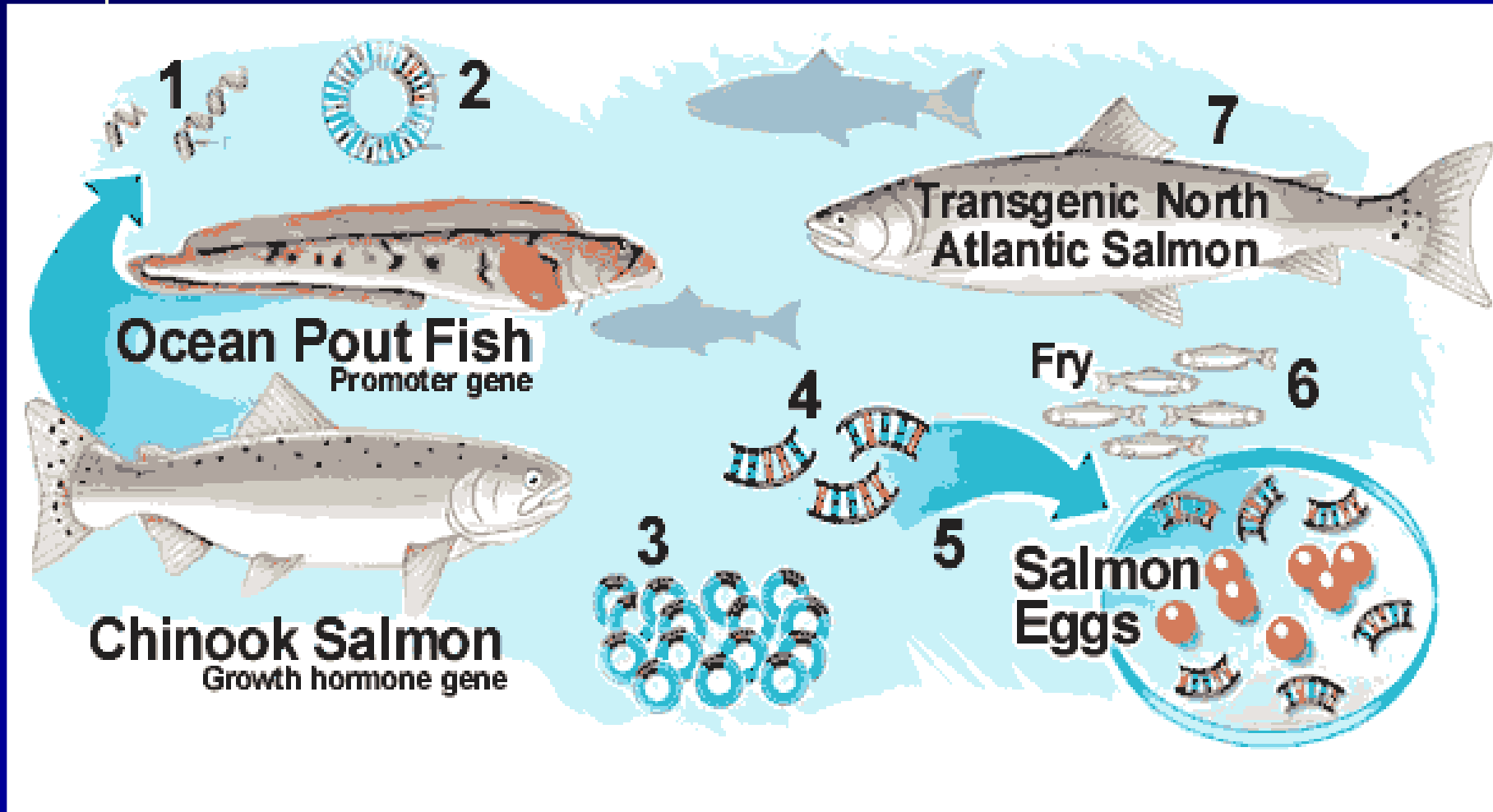
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<http://animalscience.ucdavis.edu/animalbiotech/>



What is the AquAdvantage salmon?



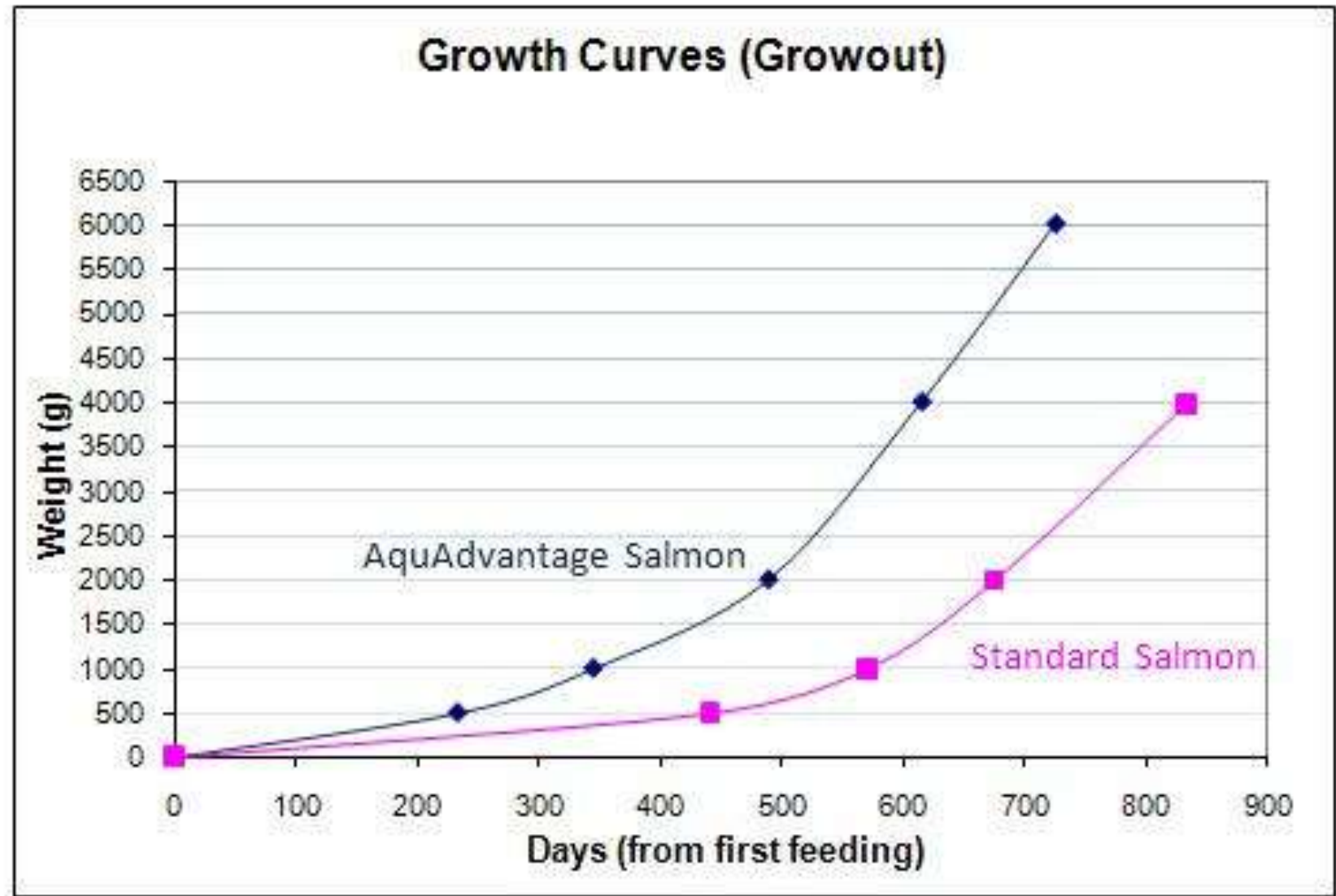


Same-age siblings – one carrying a hemizygous copy of the transgene



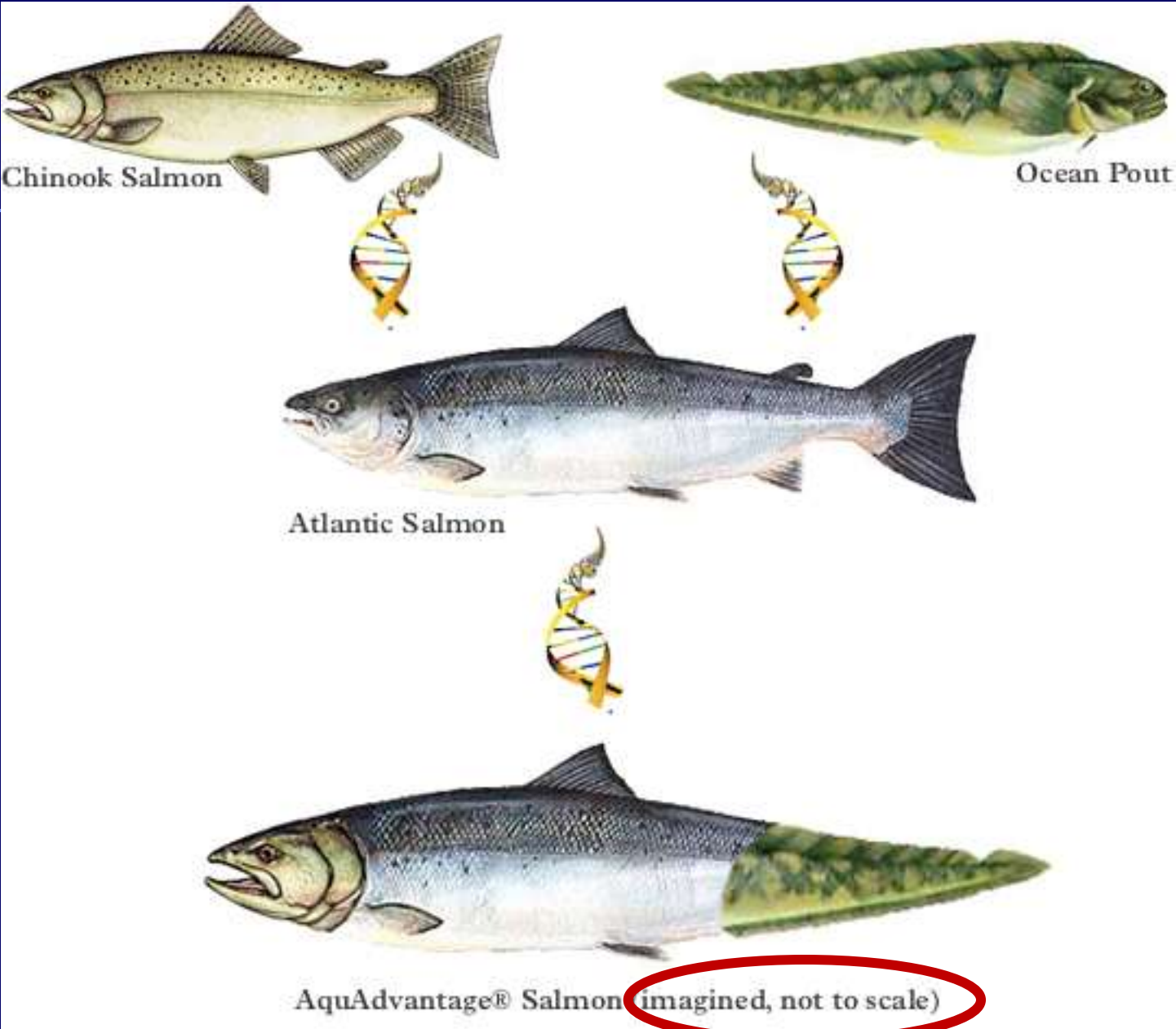


Fish reach adult size in 16 to 18 months instead of 30 months





Retrieved from "AquAdvantage" image search on web





Retrieved from "AquAdvantage" image search on web Frankenfish





Retrieved from "AquAdvantage" image search on web



GENETIC ENGINEERING

A Perfect Day for Bananafish

101 MotivatedPhotos.com





What are the regulatory options for GE animals?

1. "Substantial Equivalence" approach
2. "Food Additive" approach
3. "New Animal Drug" approach





"Substantial Equivalence" approach

- Similar to approach taken with crops
- FDA could encourage developers to voluntarily consult with agency but no formal regulatory proceeding required
- If materially different (i.e. has toxin or allergen) then FDA can require additional approvals and labeling
- Developer accepts legal responsibility
- NO PUBLIC INPUT





"Food Additive" approach

- "any substance ..in food ... that is not generally recognized as safe (GRAS)"
- If GRAS then FDA has to show otherwise through an enforcement proceeding
- The FDA determines the safety (reasonable certainty of no harm) of a food additive) with public comment
- Once safe then any food manufacturer can use it for the approved purpose





"New Animal Drug" approach

- "Drugs are ...articles...intended to affect the structure or function of the body of man or other animals"
- The expression product of the new construct (e.g. growth hormone) is also considered to be the new animal drug
- Application process requires that the developer demonstrate that no harm comes to individuals who use the drug under prescribed conditions





ENVIRONMENTAL SAFETY:

Potential authorities

Could regulate transgenic fish:

1. under existing federal laws that apply to conventional aquaculture (numerous including clean water act, rivers and harbors act, Lacey act, endangered species act, and many more)
2. as a "new chemical substance" under the Toxics Substances Control Act (TSCA)
3. "new animal drug" under the FFDCA





"Conventional aquaculture" approach



- Conventional aquaculture raises some environmental concerns (pollution etc) but NO CLEAR FEDERAL AUTHORITY IN CHARGE
- One regulatory option would be to review the environmental impacts of transgenic fish in the same way that the environmental impacts of aquaculture are considered – done by ARMY CORPS OF ENGINEERS – but can't act on the basis of assessment
- This would mean limited federal review of environmental impacts prior to commercialization



"Toxic substances control" approach

- TSCA gives the EPA the authority to review "new chemical substances" which may present an "unreasonable" risk of injury to human health or environment.
- TSCA exempts food and drugs so would have to regulate by claiming jurisdiction over the genetic construct used to modify the fish
- Requires a weighing of benefits and risks in determining what is an "unreasonable" risk





"New Animal Drug" approach

- Because of the requirements set forth in the National Environmental Protection Act (NEPA) and FDA environmental impact regulations in 21 CFR 25, the agency typically must prepare an environmental assessment (EA) for each New Animal Drug Application (NADA)
- FDA has to consider the possible effects on the human environment and possible risk mitigation strategies that may arise from the specific conditions of use that are the subject of the NADA.
- There will be a 60 day comment period following the release of the FDA's Environmental Assessment
- In the event that the EA results in a finding that a significant environmental impact may result, an Environmental Impact Statement (EIS) may need to be prepared.
- Does the FDA have a appropriate expertise ??





Regulations conclusion

"while the FDA's use of the new animal drug approval authority for regulating transgenic fish addresses food safety and provides some opportunity to consider environmental risks ...it does not reflect a unified federal strategy to address the potential risks of genetically modified fish in a transparent manner that provides public confidence that these risks will be adequately considered and addressed.





That was then...this is now

- In January 2009, the Food and Drug Administration issued a final guidance for industry on the regulation of genetically engineered (GE) animals (had 28,000 comments on draft!!)
- FDA plans to regulate GE animals under the new animal drug provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA), and FDA's regulations for new animal drugs.
- The guidance was intended to help industry understand the statutory and regulatory requirements as they apply to these animals, including those of the National Environmental Policy Act (NEPA), to inform the public about the process FDA is using to regulate GE animals, and to gather input from the public and the regulated industry.

Source: <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM113903.pdf>





FDA NEWS RELEASE

FOR IMMEDIATE RELEASE

January 15, 2009

Media Inquiries:

Michael Herndon, (301) 796-4673

Consumer Inquiries:

888-INFO-FDA

FDA Issues Final Guidance on Regulating Genetically Engineered Animals

En Español

The U.S. Food and Drug Administration today issued a final guidance for industry on the regulation of genetically engineered (GE) animals under the new animal drug provisions of the Federal Food, Drug and Cosmetic Act (FFDCA). The guidance, titled "The Regulation of Genetically Engineered Animals Containing Heritable rDNA Constructs," clarifies the FDA's statutory and regulatory authority, and provides recommendations to producers of GE animals to help them meet their obligations and responsibilities under the law.

Genetic engineering generally refers to the use of recombinant DNA (rDNA) techniques to introduce new characteristics or traits into an organism. When scientists splice together pieces of DNA and introduce a spliced DNA segment into an organism to give the organism new properties, it is called rDNA technology. The spliced piece of DNA is called the rDNA construct. A GE animal is one that contains an rDNA construct intended to give the animal new characteristics or traits.

"Genetic engineering is a cutting edge technology that holds substantial promise for improving the health and well being of people as well as animals. In this document, the agency has articulated a scientifically robust interpretation of statutory requirements," said Randall Lutter, Ph.D., deputy commissioner for policy. "This guidance will help the FDA efficiently review applications for products from GE animals to ensure their safety and efficacy."

The FDA released the draft guidance in September 2008 with a 60-day public comment period, and received about 28,000 comments. The agency has summarized and responded to these comments on the Web site listed below.

The FDA's Center for Veterinary Medicine (CVM) has been working with developers of GE animals on both early stage and more mature applications.

"At this time, it is our intent to hold public scientific advisory committee meetings prior to making decisions on GE animal-related applications" said Bernadette Dunham, D.V.M., Ph.D., director of CVM.

The FFDCA defines "articles (other than food) intended to affect the structure or any function of the body of man or other animals" as drugs. An rDNA construct that is in a GE animal and is intended to affect the animal's structure or function meets the definition of an animal drug, whether the animal is intended for food, or used to produce another substance. Developers of these animals must demonstrate that the construct and any new products expressed from the inserted construct are safe for the health of the GE animal and, if they are food animals, for food consumption.

The guidance also describes the manufacturer's responsibility in meeting the requirements for environmental review under the National Environmental Policy Act.

For more information:

- [Genetically Engineered Animals](#)



Product Definition for the AquAdvantage Salmon

Product Identity

Triploid hemizygous, all-female Atlantic salmon (*Salmo salar*) bearing a single copy of the α -form of the opAFP-GHc2 rDNA construct at the α -locus in the EO-1a lineage.

Claim

Significantly more of these Atlantic salmon grow to at least 100 g within 2700 deg C days than their comparators.

Limitations for Use

These Atlantic salmon are produced as eyed-eggs for grow-out only in the FDA-approved physically-contained fresh water culture facility.





FDA public Veterinary Medicine Advisory Committee (VMAC) Meeting was held September 19-20th, 2010

Labeling meeting was held September 21st, 2010





Elliot Entis, Founder of AquaBounty at the Public Hearing on the Labeling of Food Made from AquAdvantage Salmon, September 21st, 2010



Frankenfood, Coming Soon to a Store Near You?

Published September 20, 2010 | FoxNews.com

Print Email Share Comments (0) Recommend 799 Text Size



Reuters/Barrett & McKay Photo/AquaBounty Technologies

A genetically engineered AquAdvantage Salmon (background) is compared to an Atlantic salmon of the same age (foreground). The U.S. Food and Drug Administration will hold a two-day meeting starting September 19 to discuss whether to approve the altered fish for U.S. consumers to eat.

WASHINGTON – Watch for a new section between "frozen foods" and "organic" in your supermarket: genetically engineered. That is, if the government approves the so-called "frankenfoods" for sale.

The [Food and Drug Administration](#) Monday began a two-day look at the issue Monday, focusing on genetically modified salmon, which would be the first such food approved for human consumption.

The agency has already said the salmon, which grow twice as fast as conventional ones, are safe to eat. But salmon act as a genetic gatekeeper in this case: Approve them and open the door for a variety of other genetically engineered animals, including an environmentally friendly pig that is being developed in Canada or cattle that are resistant to mad cow disease.

"For future applications out there the sky's the limit," said [David Edwards](#) of the [Biotechnology Industry Association](#). "If you can imagine it, scientists can try to do it."

CAST 10/6/2010

Industry Fights Altered Salmon

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By ALICIA MUNDY And BILL TOMSON

The fishing industry and politicians from commercial-fishing states are mobilizing against a possible Food and Drug Administration approval of genetically modified salmon for the American dinner table.

"Putting unlabeled, genetically altered salmon in the marketplace is simply irresponsible, and the FDA needs to strongly consider what impacts this will have before they approve this Frankenfish," Sen. Lisa Murkowski, a Republican from Alaska, said Thursday.



View Full Image

Associated Press

Icy Bay crewmen remove sockeye salmon from their net in July. Commercial fisheries are fighting the introduction of genetically altered salmon.

They cited concerns about "human health and environmental risks" from the AquAdvantage salmon.

The resistance could raise difficulties for the FDA, whose scientists have said the AquAdvantage Atlantic salmon developed by AquaBounty Technologies Inc. is safe for human consumption. AquAdvantage contains a growth-hormone gene from another salmon that helps it grow twice as fast as conventional farmed fish.

A coalition that includes Pacific Coast trollers, Atlantic fishing companies and organic-yogurt maker Stonyfield Farm says the genetically altered salmon might threaten their livelihoods by spreading unease about salmon and other foods.

"This stuff is not healthy for people, and it's not like our fresh fish," said Angela Sanfilippo, president of the Gloucester Fishermen's Wives Association of Massachusetts.

Ms. Sanfilippo's group and others have joined with 39 lawmakers who wrote to the FDA this week asking the agency to stop its approval process for the genetically modified salmon.

Alison Van Eenennaam, Ph.D., UC Davis



Environmental Safety: What is the likelihood that AquAdvantage Salmon will escape the conditions of confinement?

Where will the AquAdvantage Salmon be raised?

If approved, the AquAdvantage Salmon will be raised **in inland tanks**. They will not be raised in ocean net pens. Any change would require a new application and approval.

There are multiple and redundant physical and mechanical barriers in place in the water systems at the PEI egg production and Panama grow-out facilities to prevent the accidental release of eggs and/or fish to nearby aquatic environments. These barriers have been designed specifically to prevent the escape of different life stages of AquAdvantage Salmon. Both facilities have a minimum of three to five mechanical barriers in place for all internal flow streams which release water to the environment. Standards and has been verified by an FDA inspection or site visit. Therefore, the likelihood is considered very low that AquAdvantage Salmon will escape from confinement at these sites.





Food/Feed Safety: Does food or feed from the GE animal pose any risk to humans or animals consuming edible products from GE animals compared with the appropriate non-transgenic comparators?

Conclusion of food/feed safety evaluations:

*"We therefore conclude the food from AquAdvantage Salmon (the **triploid** ABT salmon) that is the subject of this application is as safe as food from conventional Atlantic salmon, and that there is a reasonably certainty of no harm from the consumption of food from this animal. No animal feed consumption concerns were identified".*

Page 62, AquAdvantage Briefing packet. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM224762.pdf>



Direct effects

- Isoelectric focusing and 2-dimensional gels of protein extracts revealed no differences in patterns between the AquAdvantage salmon and control Atlantic salmon
- Analysis of 10 farmed control, 33 sponsor control and 30 genetically engineered salmon revealed no statistically significant difference in the muscle/skin levels of growth hormone, insulin growth factor 1 (IGF1), estradiol, testosterone, triiodothyronine (T3), thyroxine (T4), or 11-keto testosterone
- Mean IGF1 levels (ng IGF1/g): **9.263 diploid GE (n=6) versus 8.892 control (n=7)**. Not significantly different, $P=0.93$, two-tailed t-test assuming unequal variances

Pages 62-75, <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM224762.pdf>



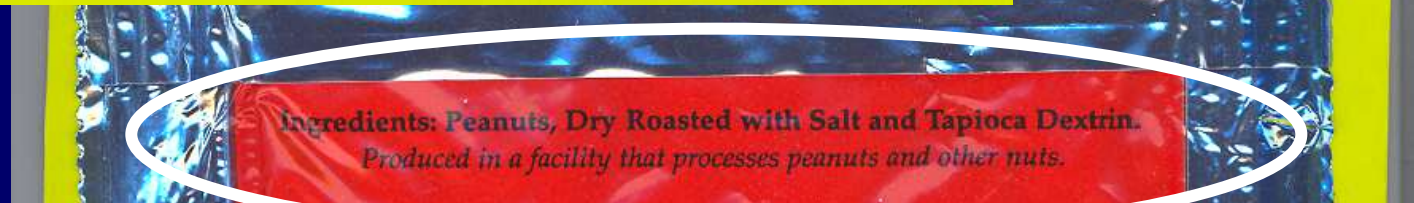
Table 18. IGF1 levels in Various Foods

Species	Source (tissue)	units	Range	Mean
Chinook salmon ¹	Plasma	ng/ml	5-35	-
Coho salmon ²	Plasma	ng/ml	7-13	-
Coho salmon ³	Plasma	ng/ml	10-15	-
Gilthead Bream ⁴	Plasma	µg/L	36-100 ⁵	-
Bovine ⁶	Raw milk	ng/ml	Intentionally Blank	5.6 ± 0.56
Bovine ⁶	Pasteurized milk	ng/ml	Intentionally Blank	8.2 ± 0.35
Bovine ⁶	Raw bulk milk	ng/ml	1.27-8.10	4.32 ± 1.09
Homo sapiens ⁶	Milk	ng/ml	1 d post partum 17.6 2 d 12.8 3 d 6.8 6-8 wk 13-40	19
Chum salmon ⁷	Plasma	ng/ml	Depends on maturity/sex/month: varies between 16.5 and 100	-
Rainbow trout (O.kiss) ⁸	Plasma	ng/ml	Function of temperature/time Lowest value 11.2 Highest 33.6	-
Japanese beef cattle ⁹	Plasma	ng/ml	Intentionally Blank	Prewaning 11.7± 3.6 Postweaning 50.5 ± 2.1

Mean IGF1 levels (ng IGF1/g) reported in briefing packet were 9.263 diploid GE (n=6) versus 8.892 sponsor control (n=7).

Page 69 & 71, AquAdvantage Briefing packet. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/VeterinaryMedicineAdvisoryCommittee/UCM224762.pdf>

Endogenous allergenicity – some foods are allergenic (e.g. nuts)





Natural variation exists in the allergenicity of available food crops due to differences in the genetics of commercial varieties, and interactions with the environment (Goodman et al., 2008)

In plants there is wide variation in IgE binding to different varieties of the same species¹

Apart from differences between varieties, natural variability in allergenicity can also occur due to harvest timing and storage conditions^{2,3}

Even between individual apples from a single cultivar and harvest, up to tenfold differences in allergenicity have been reported⁴.

1. Sten, E. *et al.* A comparative study of the allergenic potency of wild-type and glyphosate-tolerant gene-modified soybean cultivars. *APMIS* **112**, 21–28 (2004).
2. Sancho, A.I. *et al.* Maturity and storage influence on the apple (*Malus domestica*) allergen Mal d 3, a nonspecific lipid transfer protein. *J. Agric. Food Chem.* **54**, 5098–5104 (2006).
3. Sancho, A.I. *et al.* Effect of postharvest storage on the expression of the apple allergen Mal d 1. *J. Agric. Food Chem.* **54**, 5917–5923 (2006).
4. Marzban, G. *et al.* Localization and distribution of the major allergens in apple fruits. *Plant Sci.* **169**, 387–394 (2005).



Endogenous allergens in fish

- The major allergens responsible for cross-reactivity among distinct species of fish and amphibians are parvalbumins. These proteins control calcium flow in the muscular sarcoplasm of the white meat and have a molecular weight of approximately 12 kD¹.
- Parvalbumins are resistant to thermal and enzymatic degradation.
- Parvalbumin (Sal s I) is the major allergen in the white muscle of Atlantic salmon²
- The Chinook salmon GH protein has no structural similarity to known allergens

1. Wild LG, and S.B Lehrer. 2005. Fish and shellfish allergy. *Current allergy and asthma reports*. 5:74-49.
2. Lindstrom CD, van Do T, Hordvik I, *et al.* 1996. Cloning of two distinct cDNAs encoding parvalbumin, the major allergen of Atlantic salmon (*Salmo salar*). *Scand J Immunol* 44:335–344.



Important Variations in Parvalbumin Content in Common Fish Species: A Factor Possibly Contributing to Variable Allergenicity A. Kuehn, T. Scheuermann, C. Hilger, F. Hentges· 2010. *Int Arch Allergy Immunol* 2010;153:359-366 (DOI: 10.1159/000316346)

Table 1. Parvalbumin contents in raw fish, and commercially processed and cooked fish samples by quantitative ELISA

	Fish sample	Fish n	Extracts n	Parvalbumin mg/g	Parvalbumin % ¹
Herring	raw	2	12	3.8–5.7	3.3
	pickled	2	6	1.2–2.8	5.6
	cooked	2	12	3.0–4.4	16
Carp	raw	2	12	2.5–5.0	3.0
	cooked	2	12	2.1–4.0	15
Redfish	raw	3	18	2.0–3.0	2.2
	cooked	2	12	1.7–2.3	14
Trout	raw	6	36	2.0–2.5	1.3
	smoked	2	6	0.9–1.1	9.2
	cooked	2	12	1.7–2.0	11
Salmon	raw	2	12	1.9–2.5	1.2
	smoked	2	6	0.7–1.0	8.9
	cooked	2	12	1.5–1.9	9.5
Cod	raw	4	24	1.5–2.5	1.7
	cured	2	6	1.0–1.3	1.3
	cooked	2	12	1.3–1.9	7.2
Mackerel	raw	3	18	0.3–0.7	0.1
	smoked	2	6	0.08–0.15	2.3
	cooked	2	12	0.2–0.5	5.3
Tuna, white	raw	6	36	0.01–0.05	0.03
	cooked	2	12	0.01–0.03	0.2
Tuna, dark	raw	2	12	ND	–
Tuna	canned	2	6	ND	–

Two tissue samples were taken from each raw fish at different longitudinal body positions. ND = Not detected.

¹ Percentage per total soluble protein.

“The parvalbumin content of most commonly consumed fish species varies considerably. Differences range from several fold to one hundredfold. In raw fish, parvalbumin levels decreased significantly in the following order: herring > carp > redfish > salmon/trout > cod > mackerel > tuna. Differences in herring and tuna Parvalbumin levels were found to vary by a factor of 100”.



“What level of change in endogenous allergens would be (un)acceptable?”

“There is no consensus in the scientific and medical communities regarding the magnitude of the increase in endogenous allergens in an allergenic food that would present an additional risk to public health (Goodman et al., 2008), especially given that individuals that are allergic to a particular food would likely avoid that food”



United States Senate

WASHINGTON, DC 20510

September 28, 2010

Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Dear Commissioner Hamburg:

We the undersigned members of the United States Senate request you halt all proceedings related to the U.S. Food and Drug Administration (FDA) approval of the first genetically engineered (GE) animal for human consumption – a hybrid salmon produced by AquaBounty Technologies. There are a number of serious concerns with the current approval process and many potential human health and environmental risks that are associated with producing GE fish have not been fully or openly reviewed. Critical information has been kept from the public and consequently, only FDA and AquaBounty know important details about the approval process for this GE salmon, or the product itself. Accordingly, we urge you to discontinue the FDA's approval process of the GE salmon at this time to protect consumers, fishing and coastal communities, and the environment.

AquaBounty's GE product is a transgenic Atlantic salmon egg, in which genes from an ocean pout have been inserted into the genes of Chinook salmon, and then inserted into an Atlantic salmon. The egg is meant to produce a fish that grows to full size twice as fast as a normal Atlantic salmon. The eggs are intended for sale to aquaculture companies which will grow them to market-sized fish to be sold for human consumption.

One of the most serious concerns regarding AquaBounty's application is the FDA has no adequate process to review a GE animal intended as a human food product. FDA is considering this GE fish through its process for reviewing a new drug to be used by animals, not for creation of a new animal, especially one intended for human consumption. Clearly, this is inappropriate. Creation of a new genetically engineered species should not be treated as an animal drug issue but undergo formal evaluation by FDA's Center for Food Safety and Applied Nutrition to review the product's potential health effects on humans.

Such a limited review of the first GE animal for human consumption is wholly inadequate to review potential public safety concerns associated and recklessly and needlessly endangers consumer health. A recent *New York Times* article reported, "the engineered salmon have slightly higher levels of insulinlike growth factor," and "some

This letter
was signed by
11 Senators,
and a similar
one was
signed by 29
members of
Congress

Higher levels
of insulinlike
growth factor!



Alison Van Eenennaam, Ph.D., UC Davis



My reflections on the process

The VMAC participated in a candid, transparent discussion of the data. While such scientific discussions are rarely entertaining enough to make the nightly news, I consider that there was a sincere attempt to fairly and impartially evaluate the data presented

Unfortunately others used this important occasion to unfairly misrepresent the data. There is little benefit to society if attempts to increase public participation and transparency in the regulatory process provide an unfettered opportunity to demonize technology and undermine the science-based regulatory review process.

In my opinion, this process seriously jeopardized the future of genetically-engineered animals in the United States, both for food and pharmaceutical applications, with global implications.



Voluntary labeling is allowed if it is not false or misleading





Fish case at my local supermarket





SALMON COHO FILLET COLOR ADDED FRESH

FARM-RAISED PRODUCT OF CANADA

269310 91510

SAFE HANDLING INSTRUCTIONS
THIS PRODUCT WAS PREPARED FROM INSPECTED AND PASSED MEAT AND/OR POULTRY. SOME FOOD PRODUCTS MAY CONTAIN BACTERIA THAT COULD CAUSE ILLNESS IF THE PRODUCT IS MISHANDLED OR COOKED IMPROPERLY. FOR YOUR PROTECTION, FOLLOW THESE SAFE HANDLING INSTRUCTIONS:
KEEP REFRIGERATED OR FROZEN. THAW IN REFRIGERATOR OR MICROWAVE.
KEEP RAW MEAT AND POULTRY SEPARATE FROM OTHER FOODS.
WASH WORKING SURFACES (INCLUDING CUTTING BOARDS), UTENSILS, AND HANDS AFTER TOUCHING RAW MEAT OR POULTRY.
COOK THOROUGHLY.
KEEP HOT FOODS HOT. REFRIGERATE LEFT-OVERS IMMEDIATELY OR DISCARD.



Tare	Store No.	Sell By
0.06 lb	1205	Sep 19, 10
Net Wt/Ct	Unit Price	
1.01 lb	\$9.99/lb	
P 12: Safeway Inc. Pleasanton, CA 94588		

SAFeway.
Total Price
\$10.09

CLUB PRICE	YOU SAVE	WITH CARD YOU PAY
\$7.99/lb	\$2.02	\$8.07

SEAFOOD for BAKING



Country of Origin Labeling (COOL) is a labeling law that requires retailers to notify their customers with information regarding the source of certain foods – including fish and shellfish.

SALMON COHO FILLET COLOR ADDED
FRESH
FARM-RAISED PRODUCT OF CANADA

COD TRUE FILLET FRESH
WILD PRODUCT OF USA

SHRIMP RAW 21-25 CT SHELL ON
W/SALT FROZEN / DEFROSTED
FARM-RAISED PRODUCT OF THAILAND

CATFISH FILLET PREVIOUSLY FROZEN
FARM-RAISED PRODUCT OF USA



**ATLANTIC SALMON FILLET
FRESH
FARM-RAISED PRODUCT OF CANADA AND PANAMA**