National Institute of Environmental Health Sciences

The Ethics of Gain-of-Function Studies: Considering Risks and Benefits in the Context of Uncertainty

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Basic Ethical Questions

- Should gain-of-function (GOF) research be conducted? Funded? Classified? Published in full? In redacted form?
- How should we make these decisions when the benefits and risks are uncertain?

Expected Utility Theory

- Choose the option whose outcomes have the greatest net expected utility.
- Expected utility = probability x utility.
- Utility can be positive (benefit) or negative (harm).
- A quantitative approach to risk management is used in regulatory decisions, economic cost-benefit analysis, and utilitarian ethical theory.

Expected Utility Theory

Should the FDA approve a new drug?*

Actions	**Outcomes**	**Expected utility**
Approve drug X	P = 0.5 to save 1000 lives	
	P = 0.5 to kill 100	
	(0.5 x 1000) + (0.5 x -100) =	**450**
Don't approve	P = 0.0 to save 100	
	P = 0.0 to kill 50	
	(0.0 x 1000) + (0.0 x -100) =	0

*This is a highly simplified example. A real example would consider outcomes other than mortality, such as morbidity and quality of life.

Expected Utility Theory

Should we publish a gain of function study on H5N1?

Actions	**Outcomes**	**Expected Utility**
Publish	p = 0.25 to save 4,000 by preventing disease	
	p = 0.25 to kill 8 by accidental contamination	
	p = 0.0001 to kill 10,000 through misuse	
	(0.25 x 4,000) + (0.25 x -8) + (0.001 x -10,000) = **988**	
Don't publish		
	(0.0 x 4,000) + (0.0 x -8) + (0.0 x -10,000) = 0	
Redacted publication		
	(0.10 x 4,000) + (0.125 x -8) + (0.0001 x -10,000) = 398	

Expected Utility Theory

- Expected utility theory assumes that we can assign probabilities to the different outcomes.
- Do we have enough evidence to make objective probability estimates?
- Benefits may be speculative.
- The most significant risk—terrorism—is a low-probability/high-impact event. This probability can't be estimated objectively without more data.
- We could use a subjective (best guess) approach to estimate this probability. We could develop models to estimate the probability of terrorism.
- Problem: All models make assumptions that could be mistaken. We could be orders of magnitude off (P = 0.0001, 0.001, 0.01, 0.1), which could significantly affect our expected utility estimates.

Maximin

- Maximin is a frequently discussed strategy for making decisions when we don't know the probabilities of different outcomes.
- Choose the action that avoids the worst possible outcome.
- Better safe than sorry.

*Other strategies from decision theory that I won't discuss here include maximax, and minimax regret.

Maximin

Example: Should I play Russian roulette when I don't know if there is a bullet in the gun?

Actions	**Outcomes**
Play Russian Roulette	Win $1,000 or Die
Don't play	Win $0 or Don't die

Maximin would tell you not to play to avoid the worst possible outcome (death).

Maximin

Example: Should I fly on a commercial airplane to DC to give a talk?

Actions	**Outcomes**
Fly	Crash and die, don't crash and give a successful talk, don't crash and give a lousy talk
Don't fly	Don't crash, don't give a successful talk

Maximin would tell me not to fly to avoid the worst outcome (crash and die).

Maximin

- Maximin is a very risk-aversive, conservative decision-making strategy.
- You end up forgoing important benefits to avoid risks.
- It would probably instruct us not to do any GOF experiments to avoid the worst possible outcome (e.g., misuse of knowledge for terrorism).

Precaution

- GOF experiments have important potential benefits (e.g., promoting public health, advancing science) that we might want to pursue.
- How can we make a reasonable choice to maximize benefits while minimizing risks?
- The Precautionary Principle (PP) is a way of making decisions in uncertainty when expected utility theory and maximin either don't apply or are undesirable.
- It first appeared in public discourse in the 1980s as a way of dealing with environmental risks.
- It has been endorsed by the United Nations and the European Commission for making some types of decisions.

Precaution

- The PP has been criticized as unscientific, vague, subject to political manipulation, and excessively risk-aversive.
- There are many version of the PP. I think mine answers these objections.
- My version: Take reasonable measures to prevent, minimize, or mitigate risks that are plausible and serious…A precautionary measure is reasonable if it (1) is proportional to the severity of the risk, (2) carefully balances the competing values, and (3) is effective.

Resnik DB. H5N1 Avian flu research and the ethics of knowledge. Hastings Center Report 2013; 43(2): 22-33.

Precaution

- There must be some evidence that the risk could occur (not dealing with crazy nightmare scenarios).
- Reasonableness involves balancing the different values at stake (e.g., public health, environment, economy, industry, human rights) in light of the information and options.
- Balancing involves making a value judgment (i.e., setting priorities).
- A qualitative, not quantitative, approach to risk.
- Depending on how one balances these different values, the most reasonable measure may be prevention, minimization, or mitigation of the risk.

Precaution and GOF Experiments

- Risks: accidental contamination, misuse of research for terrorism
- Values in balance: harm avoidance, promoting public health, scientific freedom and openness
- Options: conduct GOF research, don't conduct, fund, don't fund, classify, full publication, redacted publication

Precaution and GOF Experiments

Example: Should we publish research that shows how to genetically engineer a virus with a 50% fatality rate so that it can be transmissible by air?

Precautionary Measures	**Values in Balance**
Don't publish	Avoids causing harm but forgoes public health benefits and interferes with scientific openness/freedom
Publish in full	Promotes public health and science but may lead to serious harm
Publish in redacted form	Tries to reach a compromise between science, public health, and harm avoidance but may have practical problems.*

*E.g., one needs to establish a system for giving scientists access to redacted information, and research may still be available through Freedom of Information Act requests.