



Balancing Public Interests, Benefits, and Risks in Animal Research

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OLAW Online Webinar
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First questions:

Why is harm: benefit analysis, or analysis of potential benefit vs potential risk, **required**?

What is the **goal**?

What does **success** look like?

In the US, the use of nonhuman animals depends on a social contract with the American public.



In the US, formal ethical justification is required for almost all nonhuman **animal research**.



The public, via law and regulatory agencies, requires that animal research and testing only be conducted when:

- there are **no alternatives** to achieve **purpose**
- potential **benefit** likely to outweigh potential **risks/harm**

Animal welfare standards to ensure humane treatment and every effort to reduce unnecessary harm.



National Institutes of Health
Office of Laboratory Animal Welfare

Research
Institutions'
IACUCs

Public Interests:

1. Animals are in laboratories for **a reason** – one that is **morally justifiable** – science that benefits individuals, society, other species, the environment.
2. **When** animals are in laboratories, they receive excellent and humane care.

How does the public know whether or not these two conditions are met?



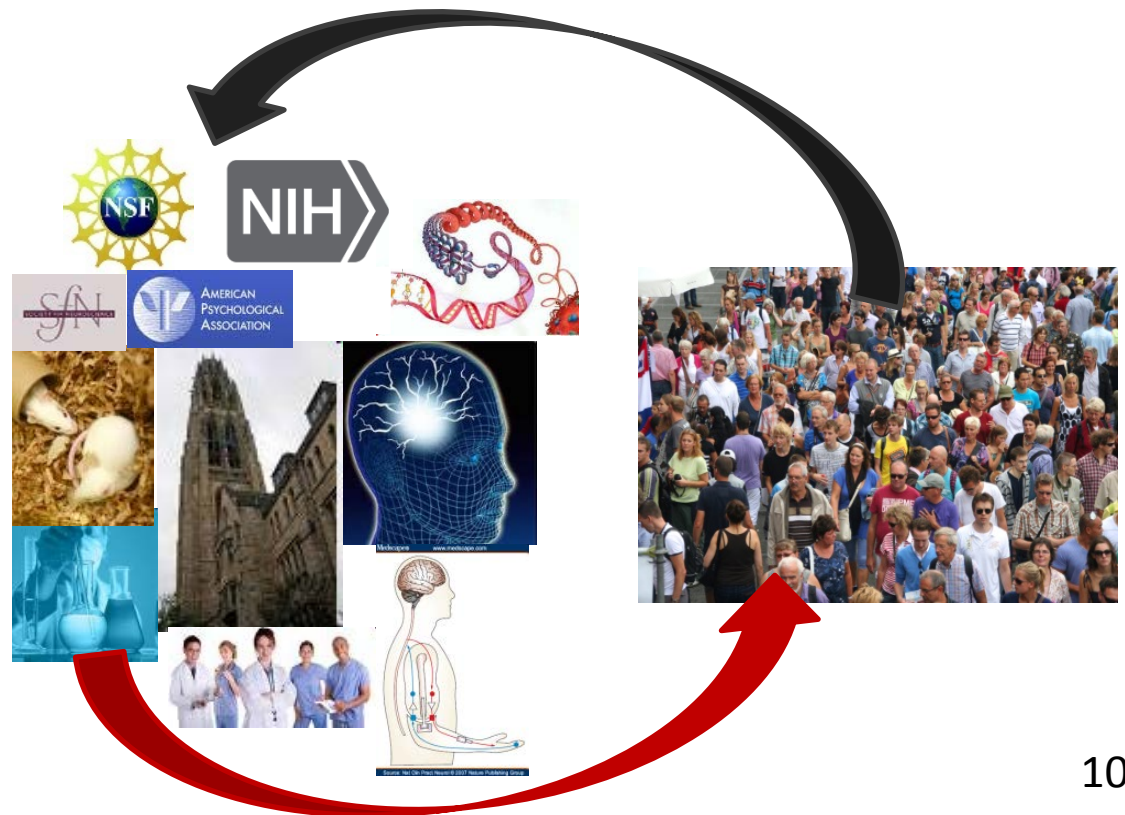
Responsibility to the public is to conduct analysis *and* to communicate:

1. Analysis of potential benefit, risk, alternatives
2. How analysis is conducted at different levels
3. Goals of analysis, along with inherent limitations



The Goal:

Ensure that scientific goals – new knowledge and discoveries – are met and are **balanced** with compassion and commitment to our moral obligation for humane care and treatment of research animals.



How do we judge the merits and the balance?

The public expects judgments based largely in facts and expert knowledge to identify most likely outcomes.



Levels of Benefit and Risk Analysis for Animal Research

Researchers' selection of questions, methods, and experimental design

Funding agencies, expert scientific review, scientific organizations, scientific journals

Institutional Animal Care and Use Committees

External public agencies USDA, Public Health Service
Office of Laboratory Animal Welfare

External private agencies including AAALAC

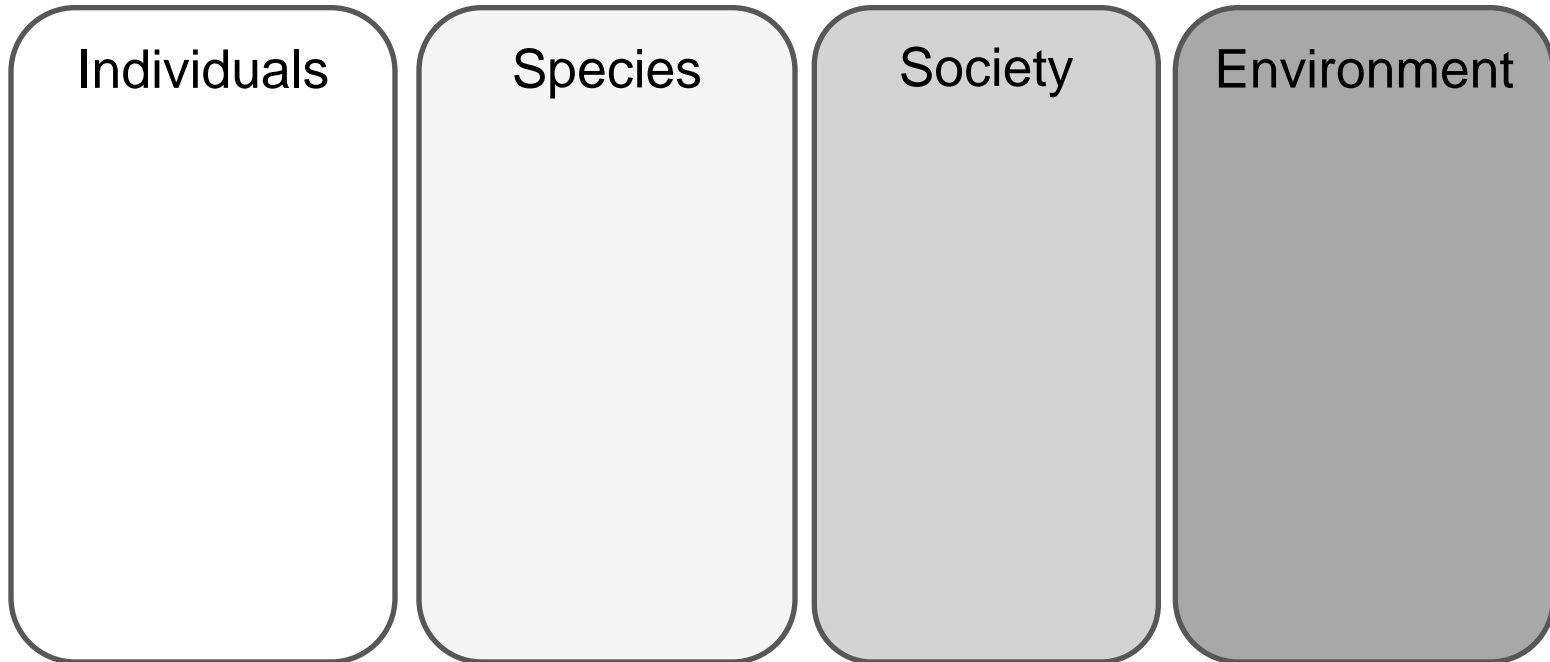
Factors in Play in Benefit: Risk Analysis

- Interest holders
- Potential benefit
- Importance of null results in science
- Potential risks, harm
- Harm of inaction
- Timescales
- Range of impact



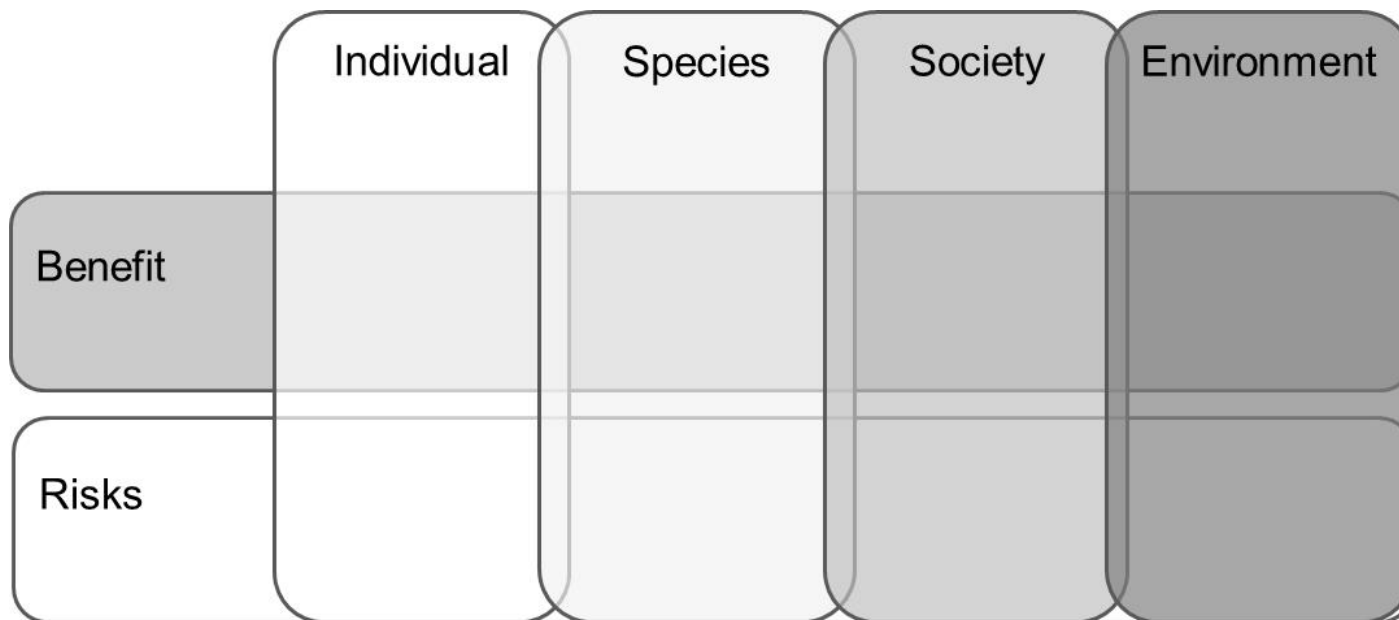
Interest Holders

Who and what are potentially affected by the decision – either the action or the choice of inaction?



Interest Holders: who and what are potentially affected by the decision – either the action or the choice of inaction?

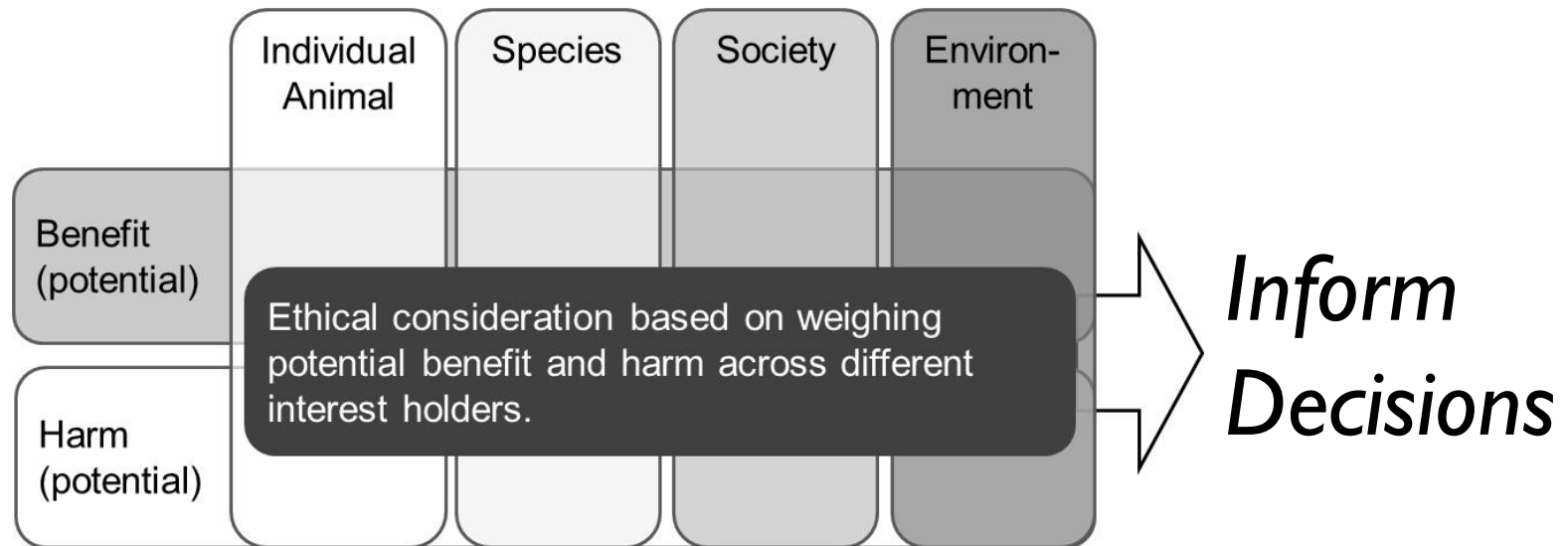
Benefit and Risk: how are interest holders affected?



Broad and Inclusive Ethical Consideration

Interest Holders: **who and what** are potentially affected by the decision – either by the action or by the choice of inaction?

Benefit and Risk: **how** are interest holders affected?



What is morally justifiable?

In part, scientific objectives are balanced with animal welfare.

However, the “weighing” must occur in advance of conducting the work.

Thus, evaluation is of **potential** vs **actual** consequences.

Potential



Prior

ACTION

Actual consequence



Subsequent

Possible outcomes, potential consequences, what we don't know, and what we consider:

- Likelihood that the study will succeed (*though note - null results and “failures” are a critical positive feature of science*).
- Likelihood that the study will produce useful knowledge.
- How much benefit? What kind? To whom?
- How much harm? What kind? To whom?
- **Actions** have risks, **inaction** (doing nothing) also has risks.
What is the potential harm of choosing to do nothing?
Who bears that harm?

Moral dilemmas and societal challenges: what can we learn from history?

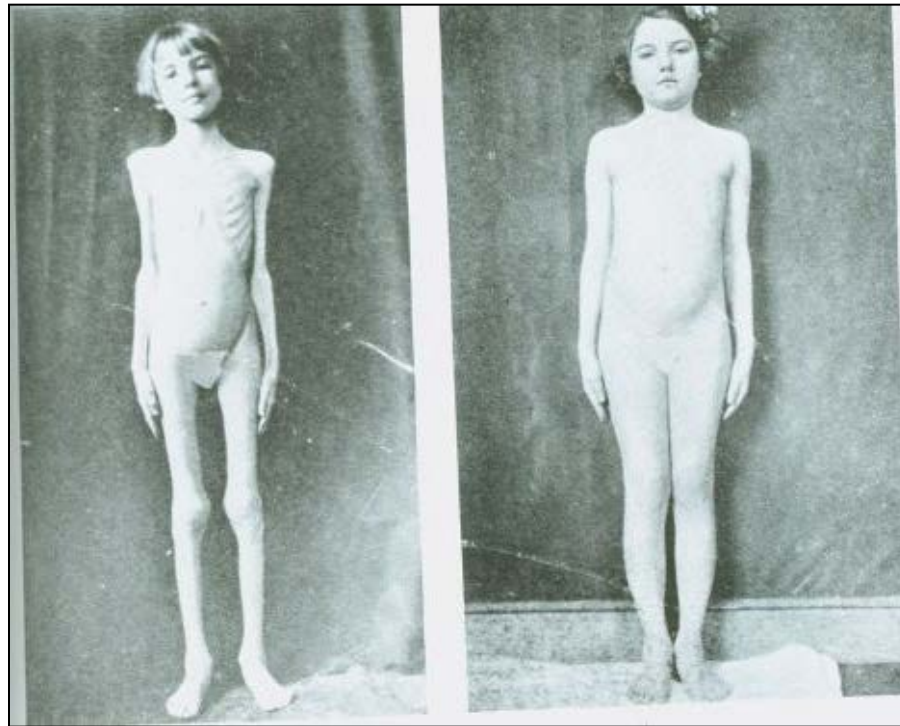
What can we learn from post-hoc analysis?

- Timescales: what time window should be used to measure benefit?
- How long between discovery and impact on interest holders?
- How can we estimate range of impact, unanticipated results, and number of beneficiaries?

Examples for consideration of *a priori* (potential) vs *post hoc* (actual) analysis



Diabetes: Benefit Clear?



An early patient: before and after four months of treatment with insulin.

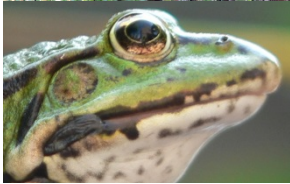
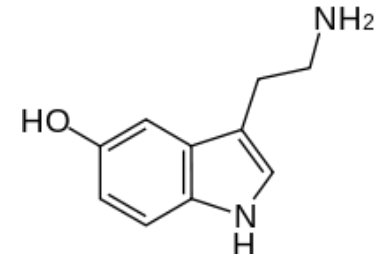
Diabetes



Timescale ~ 40 years

- 1879 – discovery that pancreas produces insulin. Remove pancreas, dog develops symptoms of diabetes.
- 1921 – insulin from healthy dogs injected into diabetic dogs, they are restored normal state.
- Refined extraction of insulin from pancreas of cattle.
- Tested dose, purity, and safety of insulin in rabbits.
- 1922 – first human patient receives insulin.

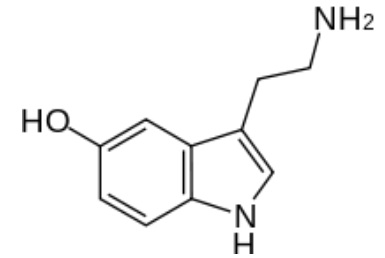
The Discovery of Serotonin



Timescale 35 years

- **1935** – Enteramine discovered by Erspamer. Caused smooth muscle contraction.
- **1948** – Serotonin discovered. Page, Rapport, Green working on vasoconstrictors.
- **1949** – Structure determined.
- **1951** – Synthetic serotonin for research.
- **1954** – Discovered in mammalian brain by Twarog.
- **1963** – D.W. Woolley
“The Biochemical Bases of Psychoses or the Serotonin Hypothesis About Mental Illness.”
- **1970s** – First antidepressant selective serotonin reuptake inhibitors.

The Discovery of Serotonin



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Note - Timescale for realized benefit extends into future.

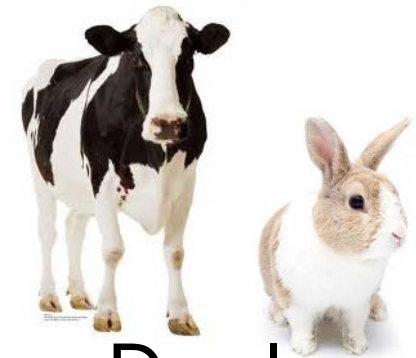


Timescale for realized benefit extends into future.
Number and range of interest holders may also increase.

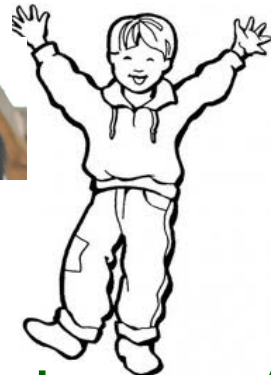
Insulin for Treatment of Diabetes



Basic
Research



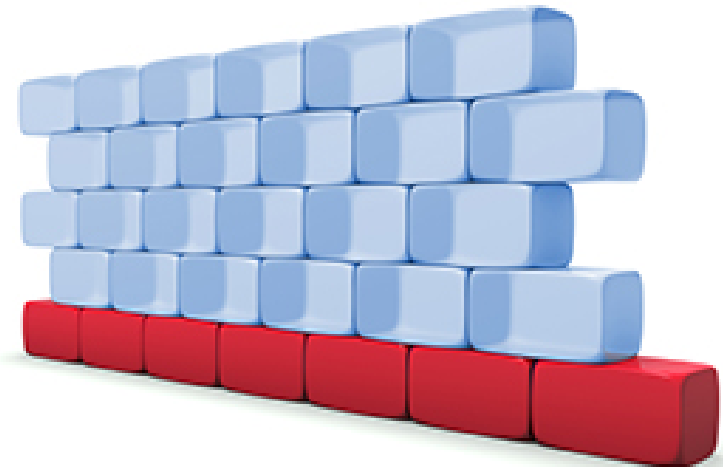
Drug Development
and Testing

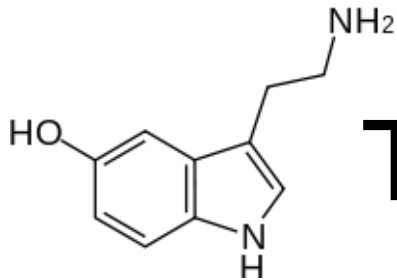


Improved Human and Nonhuman Animal Health

Evaluating potential consequences:
what can **post hoc** analysis tell us about
evaluating breadth of potential benefit and risks?

Range of impact (and unanticipated impact):
what effect does the discovery have and
how broadly does it extend?





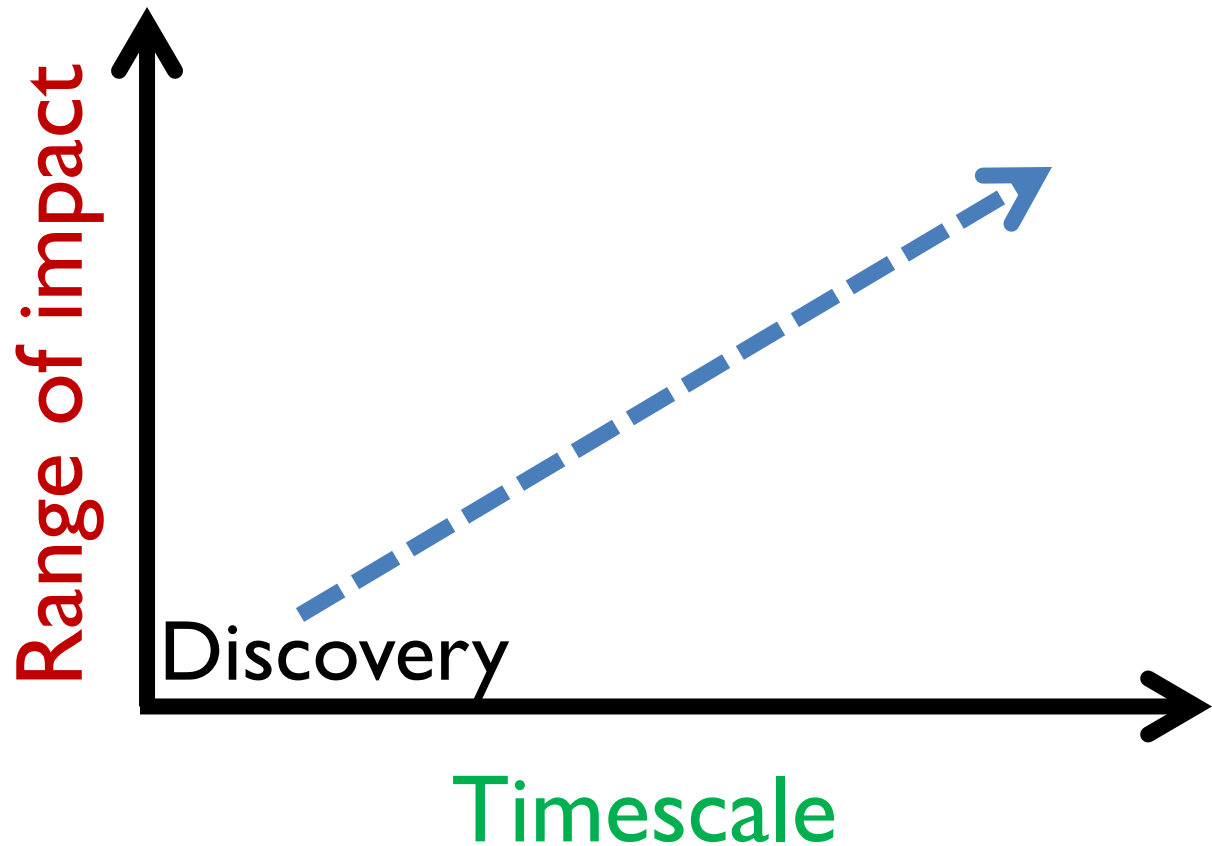
The Discovery of Serotonin

All subsequent discoveries and applications that depend on knowledge gained from discovery of serotonin and identification of its roles.

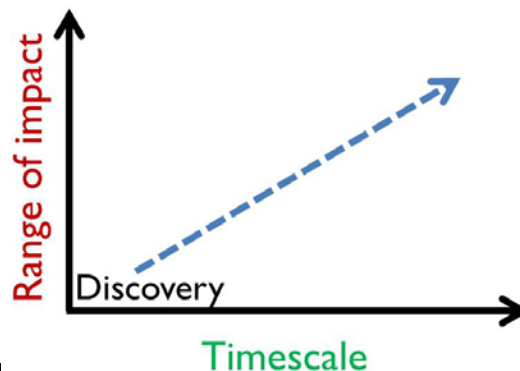


Range of impact

Post hoc analysis underscores importance of timescales and range of impact for realistic expectations about realized benefit



Performing a reasonable analysis to estimate potential benefit and risk requires knowledge and understanding of the science.



Such analysis occurs at multiple levels, with content area scientific expertise.

Researchers' selection of questions, methods, and experimental design

Funding agencies, expert scientific review, scientific organizations, scientific journals



F | GB USA MEX

**ONE SIZE
DOES NOT
FIT ALL**



Von links bügeln / Iron inside out /
repasser sur l'avers / 只熨反面

1) **Purpose and necessity:**

- What is the potential benefit vs potential risks?
- Are there alternatives?

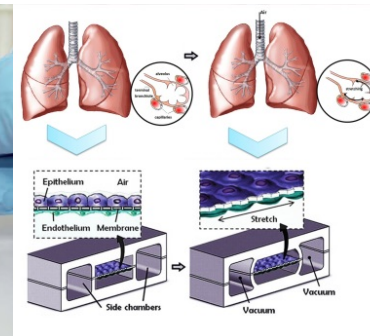
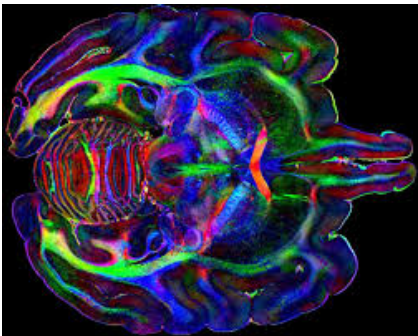
2) *If* it is justified, *then*:

- How is animal welfare protected in balance with research aims?
- Minimizing discomfort and harm.
- Fewest number of animals that are needed without compromising the science.

Animal Testing \neq Animal Research

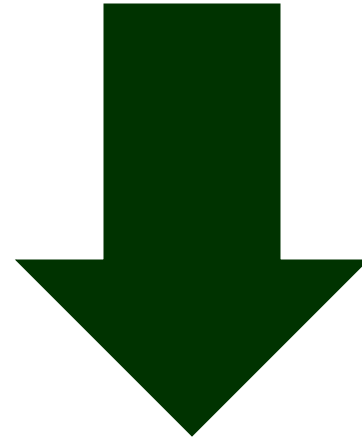
Why is the difference relevant to ethical consideration and decisions?

Estimation of benefits and risks (including harm of inaction) differ in critical ways – especially alternatives, timescales, and range of impact.



Research – Basic Discovery Science

- Basic knowledge to understand normal function and disease
- Long timescales
- Delivers necessary building blocks
- Progress halts without basic research



Testing

- Safety and efficacy
- FDA Rule
- Focus of alternatives development because **some** testing can be done *in vitro* and **some** does not require novel discovery

Key differences between animal research and animal testing

Research is how we learn new things about the world.
Ending research closes a major path to discovery and understanding.

Is ending research a positive goal?



Basic Principles for Ethical Evaluation, Conduct, and Regulation of US Nonhuman Animal Research

1) **Purpose and necessity:**

- What is the potential benefit vs potential risks?
- Are there alternatives?

3 Rs are mainly here

2) ***If*** it is justified, ***then***:

- How is animal welfare protected in balance with research aims?
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- Fewest number of animals that are needed without compromising the science.

Replacement, Reduction, Refinement

Risks and Harms: How Do We Evaluate These?

- Diminished quality of life
 - Pain, suffering
 - Loss of potential
- } type
extent
degree
time experienced
- Death } Amount of pain, suffering

Individual's experience. Also others who are affected by the individual's experience – suffering, diminished quality of life, death – that result in others experiencing pain and suffering.

What do we need to know to evaluate harms (quality of life, pain, suffering, loss of potential)?

- Physiological systems and subjective experiences.
- Are these the same for all species?
- In what ways do differences matter?

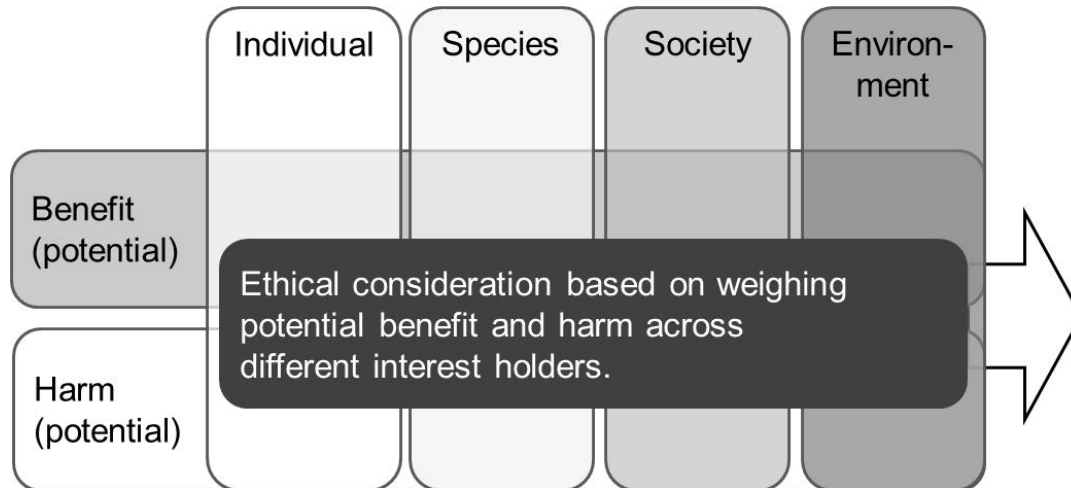


Summary.

Complex analysis and questions.

However, analysis occurs at multiple levels and by people with different types of expert knowledge.

Acknowledging multiple levels of review and interplay between them is critical to providing an accurate representation of the analysis that informs decisions.



Questions?

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During live webinar broadcast: submit questions to the **Questions** pane on your webinar control panel.

After the webinar: email OLAWDPE@mail.nih.gov



Question 1

How do you conduct risk benefit analysis with animals at the University of Wisconsin?

Question 2

Risk benefit analysis is a complicated process, with a lot of unknowns.

Has anyone tried to develop a way to conduct an analysis using a scoring system or other mathematical approach?

Question 3

Do IACUC members at the University of Wisconsin-Madison engage in public outreach?

Question 4

What is OLAW's expectation for risk benefit analysis by IACUCs?

Question 5

What is the position of the Guide for the Care and Use of Laboratory Animals on scientific merit review?

Upcoming OLAW Online Seminars

September 8, 2016: **Implementing VVC**

speakers Elaine Kim, CPIA and Lon Kendall, DVM

December 15, 2016: **Self-Evaluation and Reporting:
Always Let the Guide be Your Conscience**

speaker George Babcock, PhD

