Ethical Aspects of (Animal) Research

Introduction to the concepts of Necessity, Appropriateness and Proportionality

Dr. Dr. Matthias Eggel

Laboratory Mouse

Education

Caltech, Oxford, Stanford, Harvard, MIT, Princeton, Cambridge, Imperial, Berkeley, Chicago, Yale, ETH Zurich, Columbia, UPenn, John Hopkins, UCL, Cornell, Northwestern, UMichigan, Toronto, Carniege Mellon, Duke, UWashington, UTexas at Austin, GA Tech, Tokyo, Melbourne, Singapore, UBC, Wisconsin-Madison, Edinburgh, McGill, Hong Kong, Santa Barbara, Karolinska Institute, UMinnesota, Manchester ... and just about every other major university, medical school & research institution in the world.

Nobel Prizes

1905 - Transmission and treatment of TB
1906 - Structure of Nervous System
1907 - Role of protozoa in disease
1908 - Immunity to infectious diseases
1928 - Investigations on typhus
1929 - Importance of dietary vitamins
1939 - Discovery of antibacterial agent, Prontosil
1945 - Discovery of penicillin
1951 - Yellow fever vaccine
1952 - Discovery of streptomycin
1954 - Culture of the polio virus
1960 - Understanding of immunity
1970 - Understanding of neurotransmitters
1974 - Structural & functional organisation of cells
1975 - Tumour-viruses and genetics of cells
1977 - Hypothalamic hormones
1984 - Techniques of monoclonal antibody formation
1986 - Nerve growth factor and epidermal growth factor
1990 - Organ transplantation techniques
1992 - Regulatory mechanisms in cells
1996 - Immune-system detection of virus-infected cells
1997 - Discovery and characterisations of prions
1999 - Discovery of signal peptides
2000 - Signal transduction in the nervous system
2004 – Odour receptors and organisation of olfactory systems
2008 - Role of HPV and HIV in causing disease
2010 - Development of in vitro fertilization
2011 - Discoveries around innate and adaptive immunity
2012 - Reprogramming mature cells to pluripotent ones

Overview

- Involved in around 75% of research
- Short life-span and fast reproductive rate means mice are suitable for studying disease across whole life cycle
- 98% of genes have comparable genes in humans
- Similar reproductive and nervous systems and suffer many of the same diseases as humans including cancer diabetes and anxiety
- Can be genetically modified to include human genes in enhance biological relevance
- Can act as an avatar for a human cancer to allow drug therapies to be trialled safely

Research Areas

Alzheimer's disease, anaesthetics, AIDS & HIV, anticoagulants, antidepressants, asthma, blindness, bone and joint disease, brain injury, breast cancer, cardiac arrest, cystic fibrosis, deafness/hearing loss, Down's sndrome, drugs for high blood pressure, transplant rejection, Hepatitis B, C & E, Huntington's disease, influenza, leukaemia, malaria, motor neurone disease, multiple sclerosis, muscular dystrophy, Parkinson's disease, prostate cancer, schistomiasis, spinal cord injury, stroke, testicular cancer, tuberculosis,

Contact

www.understandinganimalresearch.org.uk
www.animalresearch.info
www.amprogress.org
www.speakingofresearch.com

CV of a Lifesaver


STOP
ANIMAL
TESTING


Buzzle.com
ANIMAL-TESTED DRUGS
FAIL ON HUMANS 90% OF
THE TIME.

Animal Research requires Authorization

DIRECTIVES

DIRECTIVE 2010/63/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 22 September 2010

on the protection of animals used for scientific purposes

(Text with EEA relevance)

Animal Welfare Act
(AniWA)

of 16 December 2005 (Status as of 1 May 2017)

The Federal Assembly of the Swiss Confederation,
based on Articles 80, paragraphs 1 and 2, and 120, paragraph 2 of the Federal Constitution[1],
after consideration of a Federal Council Dispatch dated 9 December 2002[2],
decrees:

Animal Protection Ordinance
(AniPO)

of 23 April 2008 (status as at 1 March 2018)

The Swiss Federal Council,
based on the Animal Protection Act of 16 December 2005[1]

(AniPA),
and on Article 19, paragraph 1 of the Gene Technology Act of 21 March 2003[2,3]
decrees:

Which animals are protected?

- all sentient animals

(CH):

Art. 1

This Ordinance regulates the handling, housing, use of, and interventions on vertebrates, cephalopods *(Cephalopoda)* and decapods *(Reptantia)*.

Article 112 Scope

The provisions set forth in this chapter apply to:

a. vertebrates;

b. decapods and cephalopods;

c. mammals, birds and reptiles in the last third of the gestation period prior to birth or hatching;

d. larval stages of fish and amphibians that take in food freely.

EU Directive:

3. This Directive shall apply to the following animals:

(a) live non-human vertebrate animals, including:

(i) independently feeding larval forms; and

(ii) foetal forms of mammals as from the last third of their normal development;

(b) live cephalopods.

Why is animal research so strictly regulated?

widely agreed assumption, that

sentient animals possess a moral status or have an inherent worth.

=> interests of the animals not to suffer or to fulfill certain species-specific needs are morally relevant – they have to be considered for the animal's sake.

„Moral Community“

Who is part of the Moral Community?

→ **„Do not harm!“**
„Do not kill!“
…

Members of the moral community have moral status

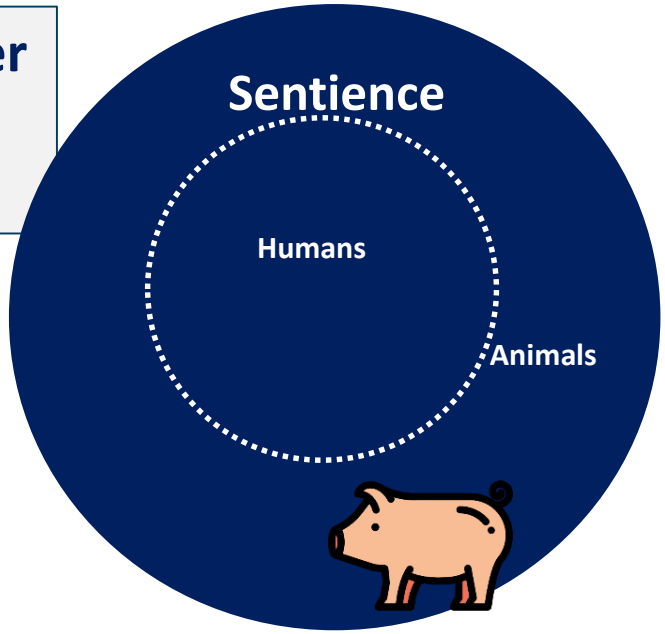
=

They deserve moral consideration for their own sake, i.e. they have an inherent value

≠

Not because they are of use to someone (i.e. instrumental value)

The ability to feel pain and suffer as morally decisive criterion



If we consider the ability to suffer as significant for interpersonal morality, then all non-human living beings who exhibit this ability should also be included in the circle of those who are morally worthy of protection.

Most famous footnote in animal ethics

„[...]Is it the faculty of reason, or perhaps the faculty of discourse? But a full-grown horse or dog is beyond comparison a more rational, as well as a more conversable animal, than an infant of a day or a week or even a month old. But suppose they were otherwise, what would it avail? The question is not, Can they reason? nor Can they talk? but, Can they suffer?”

Jeremy Bentham (1748 - 1832)

Peter Singer:

- All animals are equal; Singer 1975)
- Arguments against speciesism (equal interests should be considered equally)

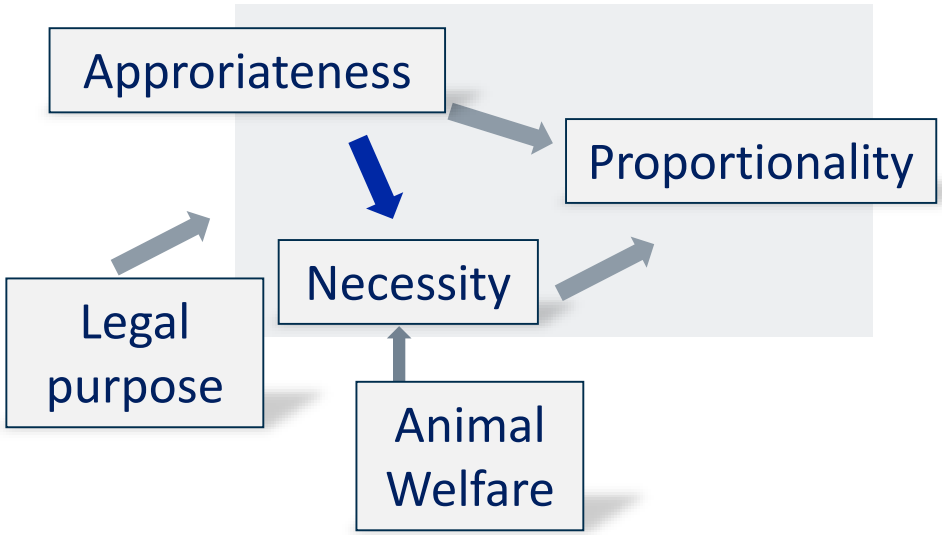
"When a being suffers, there can be no moral justification for refusing to consider that suffering. The nature of the being does not matter - the principle of equality requires that its suffering count as the same suffering - as far as an approximate comparison can be drawn - of any other being. If a being is incapable of suffering or incapable of experiencing joy or happiness, then there is nothing to consider.

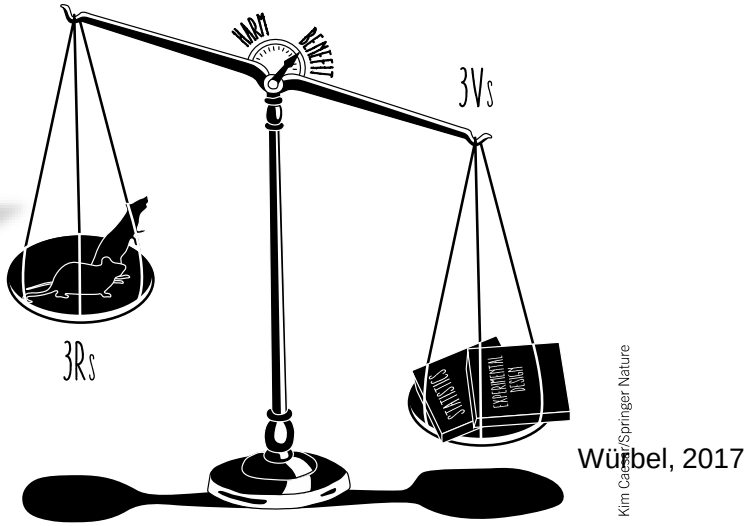
Singer 1994 [1979], 85

- **Suffering morally counts**, be it human or animal sufferin
- **Overcoming Speciesism** (Ryder 1972, 81)
- Extension of the moral community

Pillars of ethically permissible animal research

If an animal has a moral status, inherent worth or dignity, it follows, that harming such a creature has to be justified. Because of this, animal research is only authorized when the following legal requirements are met: Necessity (3R), Appropriateness (Quality), Proportionality (HBA)





Würbel, 2017

Legal purposes according to Directive

Article 5, Purposes of procedures
Procedures may be carried out for the following purposes only:
(a) basic research;
(b) translational or applied research [...]
(c) for any of the aims in point (b) in the development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feed-stuffs and other substances or products;
(d) protection of the natural environment in the interests of the health or welfare of human beings or animals;
(e) research aimed at preservation of the species;
(f) higher education, or training for the acquisition, maintenance or improvement of vocational skills;
(g) forensic inquiries.

Instrumentel Essentiality: Necessity

The necessity of the experiment depends on whether the requirements of the 3R principle (**replacement, reduction, refinement**) have been fully complied with.

- research goal cannot be achieved using alternative (non-animal)

methods, or with phylogenetically lower species (Replacement)

- Smalles, ‚adequate' number of animals (Reduction)
- and/or less harmful interventions (Refinement)

Instrumentel Essentiality: Appropriateness/Suitability

Is the proposed project suitable to achieve a specific study goal?

Suitability depends on:

- Meaningfulness (i.e. Reproducibility and generalizability
- Can study question/hypothesis be answered?

- Choice of animal model

- **Operationalization** (i.e. How is the question to be answered? E.g. what variables/parameters/read-outs are measured?

- Suitable experimental design

- Criteria of good scientific practice, e.g. randomization, blinding, sample size calculation, statistical analysis

The concept of Proportionality

An experiment which is considered Necessary and Appropriate is not per se ethically justified

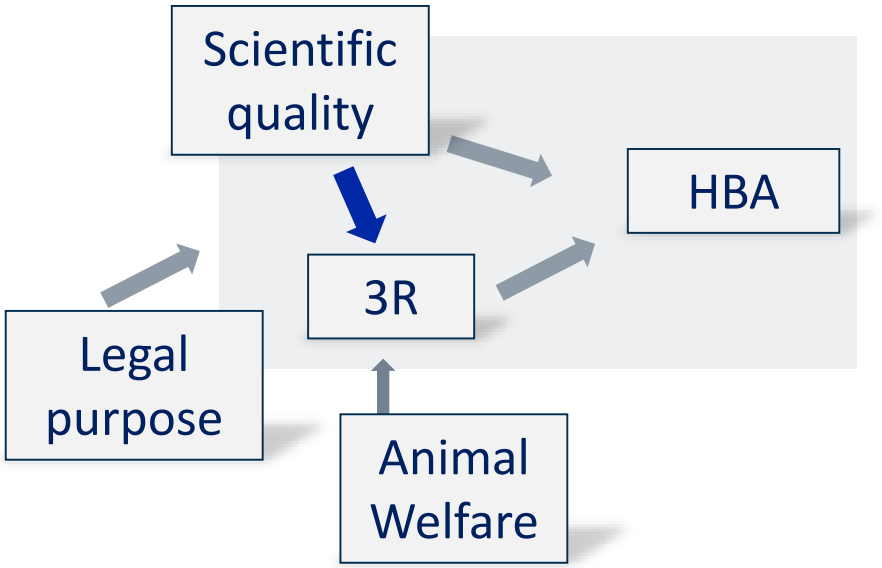
Assessment of goal-related essentiality

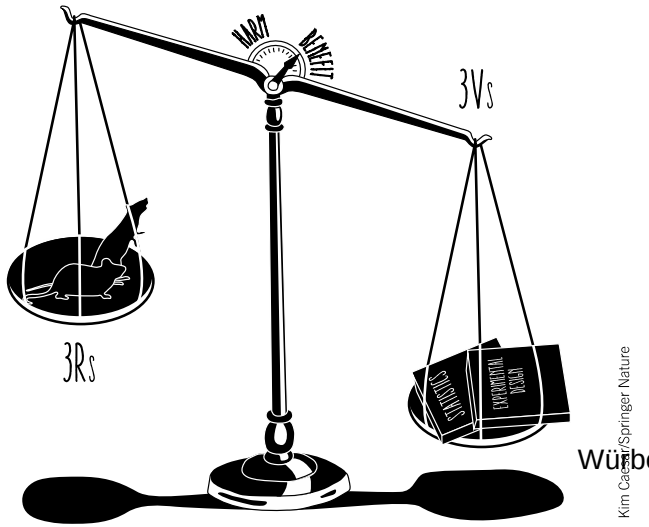
Benefits may be disproportionate compared to the harms inflicted on animals

proportional only when the expected gain in knowledge or benefit is deemed sufficiently important to outweigh the harm inflicted on animals.

=> The «legitimate interests of society» are weighed against the interests of animals in a so-called „Harm-Benefit-Analysis“ (HBA)

Pillars of ethically permissible animal research

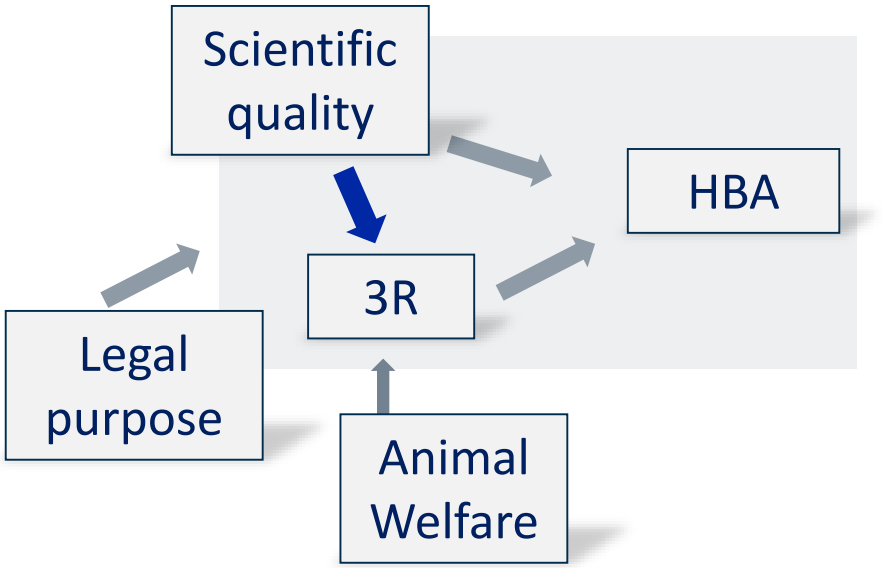


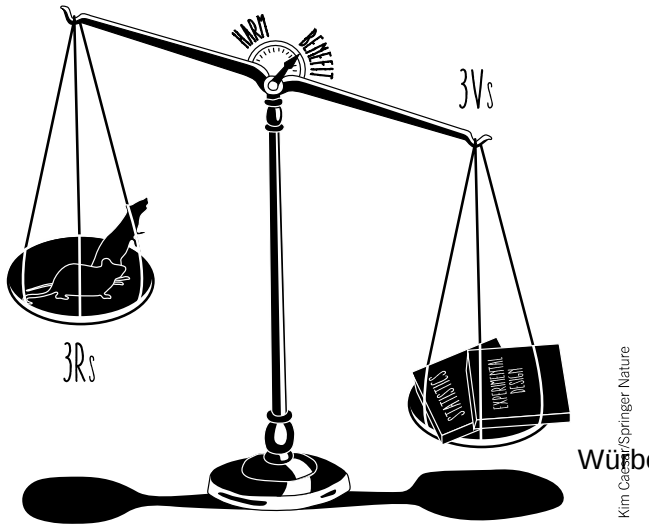


Würbel, 2017

Kim Caesar/Springer Nature

Pillars of ethically permissible animal research





Würbel, 2017

Kim Caesar/Springer Nature

So what about in silico, in vitro („organoids“) and chimera research?

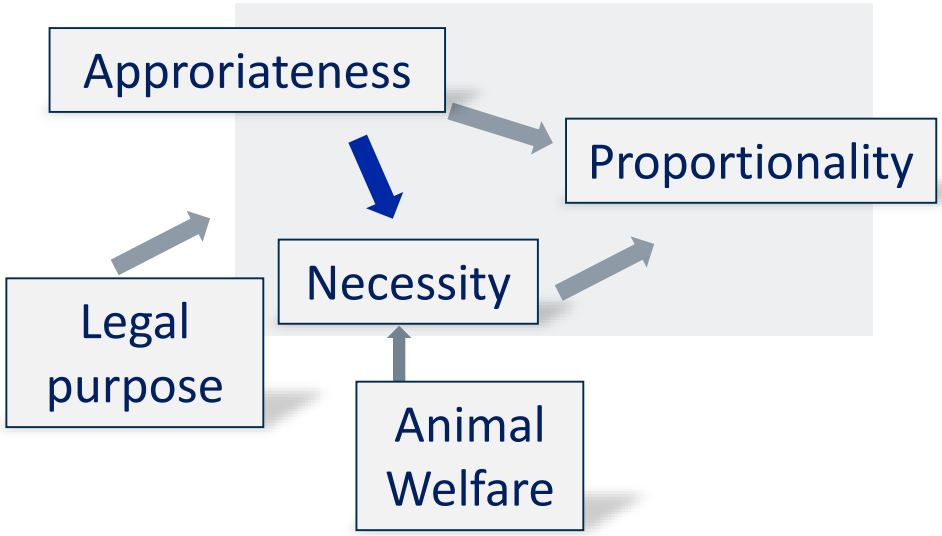
Ethical aspects of in silico and in vitro („organoids“) research?

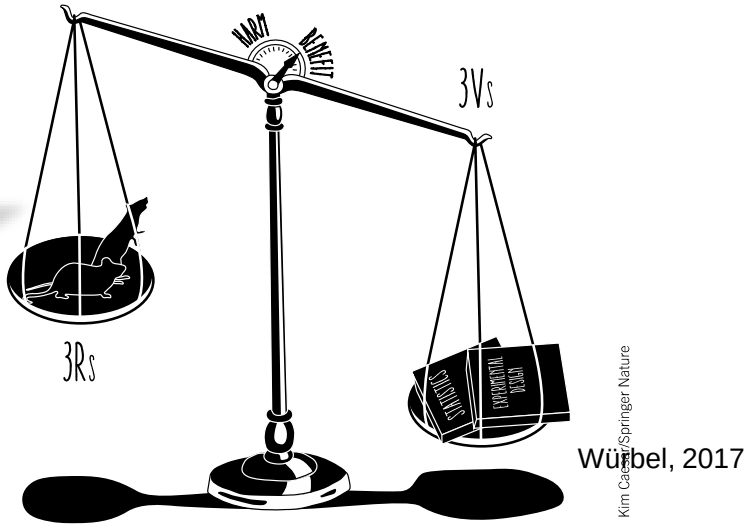
They do **not** need to be authorized

No animals required

Is scientific quality sufficient? i.e. reproducibility, generalizability?

Opportunity costs?





Würbel, 2017

Kim Caesar/Springer Nature

Ethical Aspects of Chimera research

according to Greek mythology, was a **monstrous fire-breathing hybrid creature** composed of the parts of more than one animal. It is usually depicted as a lion, with the head of a goat protruding from its back, and a tail that might end with a snake's head (wikipedia)

A chimeric mouse with its offspring, which carry the agouti coat color gene; note pink eye

What is a “chimera“?

“The term chimera […] indicates **organisms** comprised **of cells from two or more individuals of the same or different species**.

Behringer (2007): “A chimera is an individual composed of somatic and, in certain cases, germ line tissues derived from more than one zygote. […]

Göran Hermerén, Ethical considerations in chimera research, Development (2015) 142, 3-5 doi:10.1242/dev.119024

Applications of Chimeras

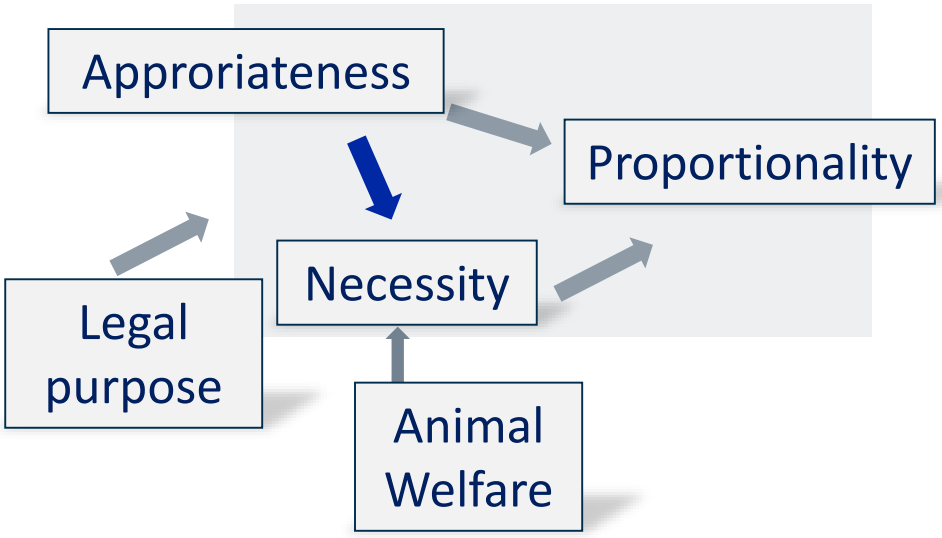
- As “better” models for human pathology, e.g. humanized mice, human cancer models
- As “incubators” for growing human organs to “fight” organ shortage

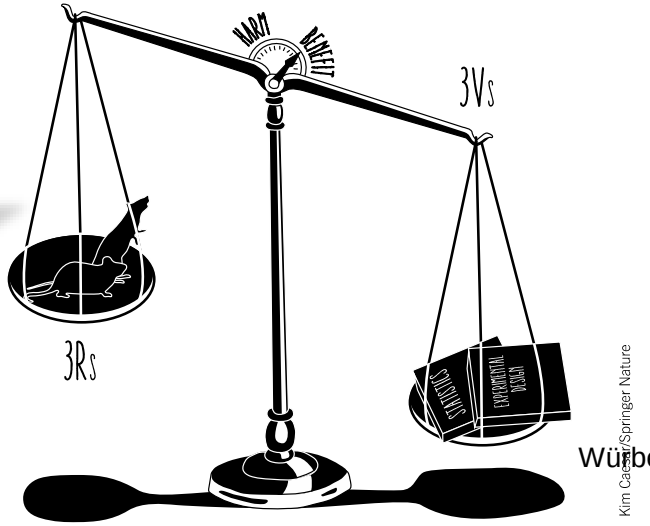
Ethical aspects of chimera research?

needs to be authorized -> justification for the use of animals

Is scientific quality sufficient? i.e. reproducibility, generalizability?

Moral status of chimera? Ethical concerns?



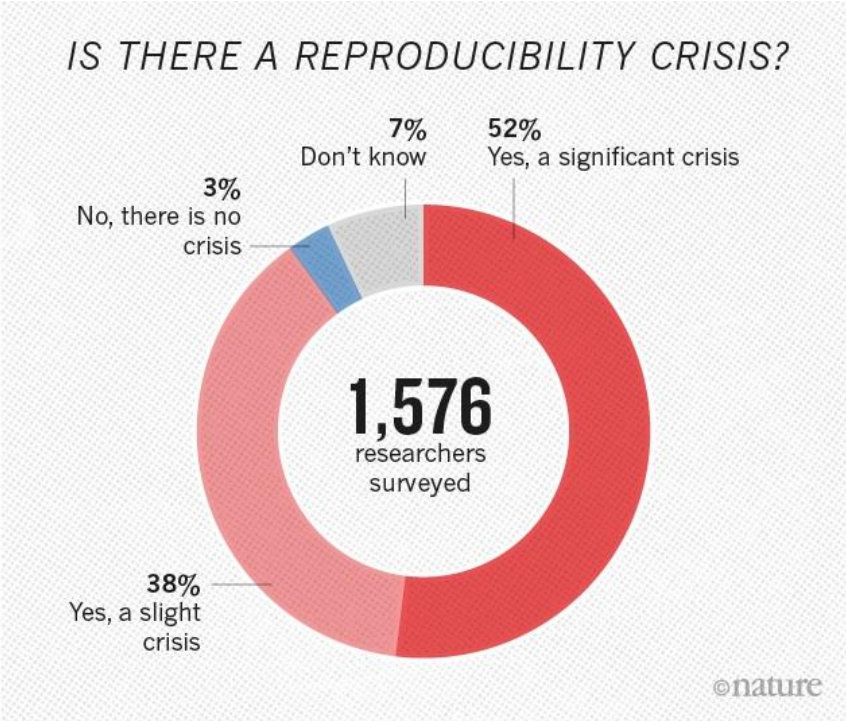


Würbel, 2017

Kim Caesar/Springer Nature

Quality of Science

Reproducibility crisis?



Generalizablity/Translatability?

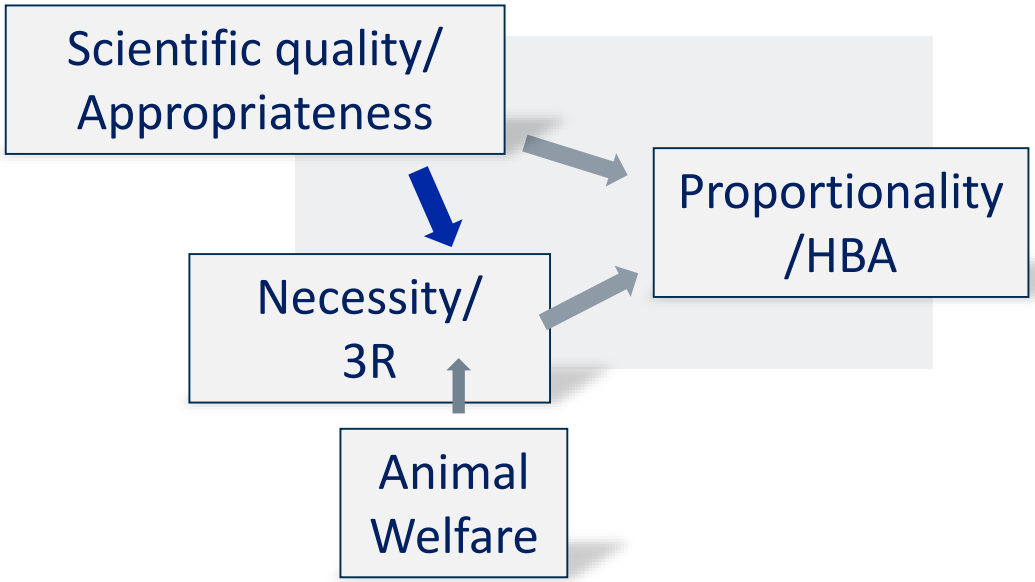
High attrition rates of drugs

Are always the best available models used?

Do we need better models?

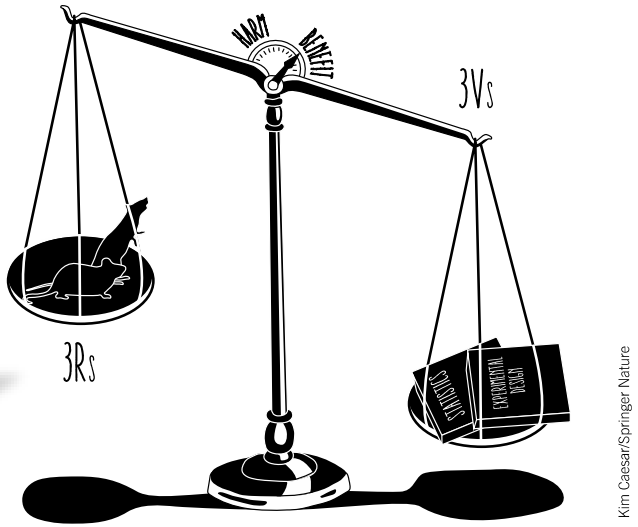
Suitability:

Low translatability of research findings into the human clinic
High attrition rate
Low reproducibility



Necessity:

If no other alternatives exist?

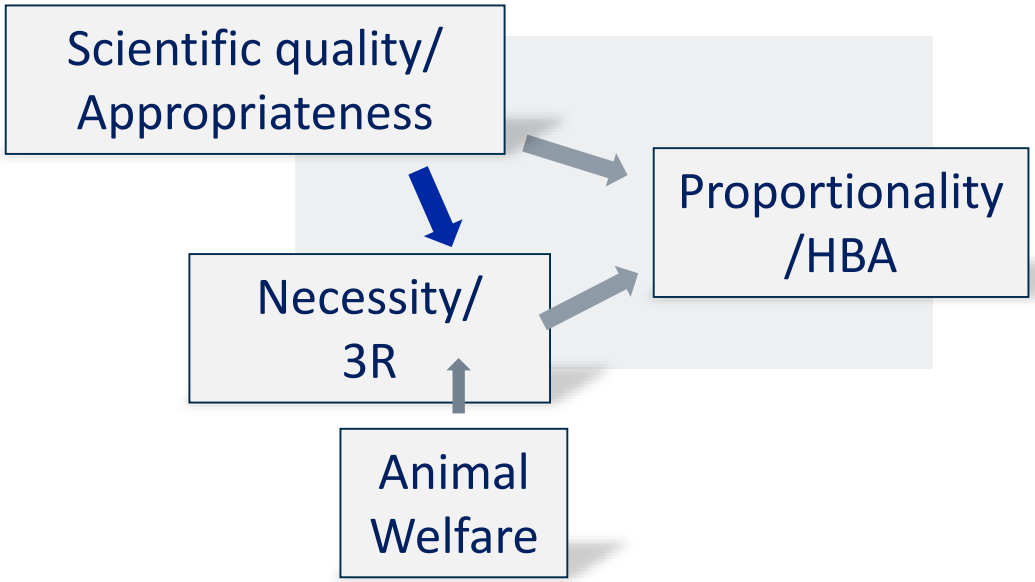


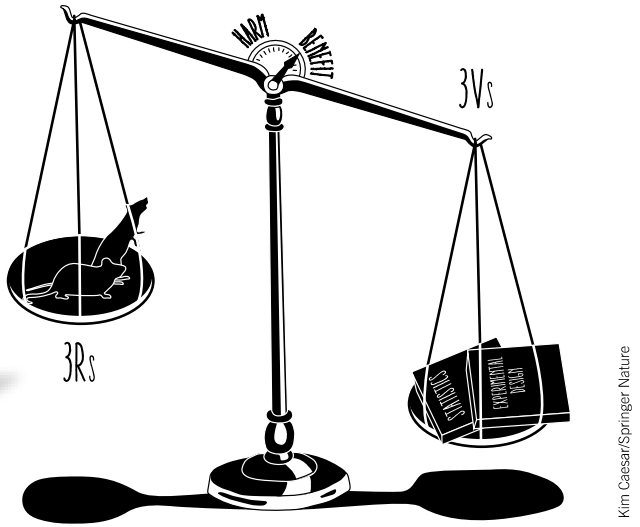
Kim Caesar/Springer Nature

Würbel, 2017

Proportionality: Do the expected benefits outweigh the harm?

Moral status of chimera?
Violation of dignity
Risks?





Würbel, 2017

Human dignity

International Bill of Rights (IBR) recognizes: “the inherent dignity and …

equal and inalienable rights of all members of the human family

[as] the foundation of freedom, justice and peace in the world” [29–31]. The rights contained in these documents “derive from the inherent dignity of the human person” Under this conception,

human beings possess intrinsic worth and consequently bear dignity, which in turn grounds human rights.

Dignity is shorthand for the moral rights that humans are entitled to because of their inherent worth.

Dignity of animals

Article 3, Swiss Animal Welfare Act

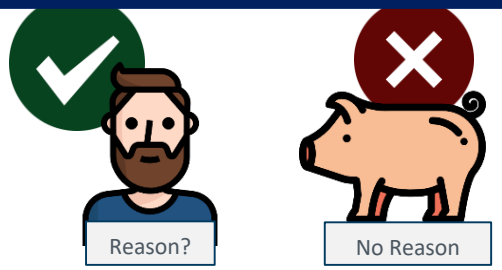
dignity means the **inherent worth of the animal** that must be respected when dealing with it. If any strain imposed on the animal cannot be **justified by overriding interests**, this constitutes a disregard for the animal's dignity. Strain is deemed to be present in particular if pain, suffering or harm is inflicted on the animal, if it is exposed to **anxiety or humiliation, if there is major interference with its appearance or its abilities or if it is excessively instrumentalised**;

Humans: have moral status, dignity and inalienable rights

Animals: also have moral status (dignity?) but alienable rights/interests

H and A treated differently, different ethical and legal status:
animals are not legal entities and do not have rights in the way that humans do.

A fundamental difference (an "anthropological difference") is assumed between humans and animals.(*Human= Animal plus X**)



The defined difference allows, so the argument goes, different moral behavior

Potential Ethical Concerns

”Humanized” Animals: non-human animals with human central nervous system (CNS)

establishment of mice in which the forebrain glial cells are completely replaced by human glia (Han et al., 2013).

The fact that these “humanised” mice displayed apparently enhanced cognitive capacity raises ethical questions

Potential Ethical Concerns

moral status? Of humans? Or of animals?

major interference with its appearance or its abilities?

Excessive instrumentalization?

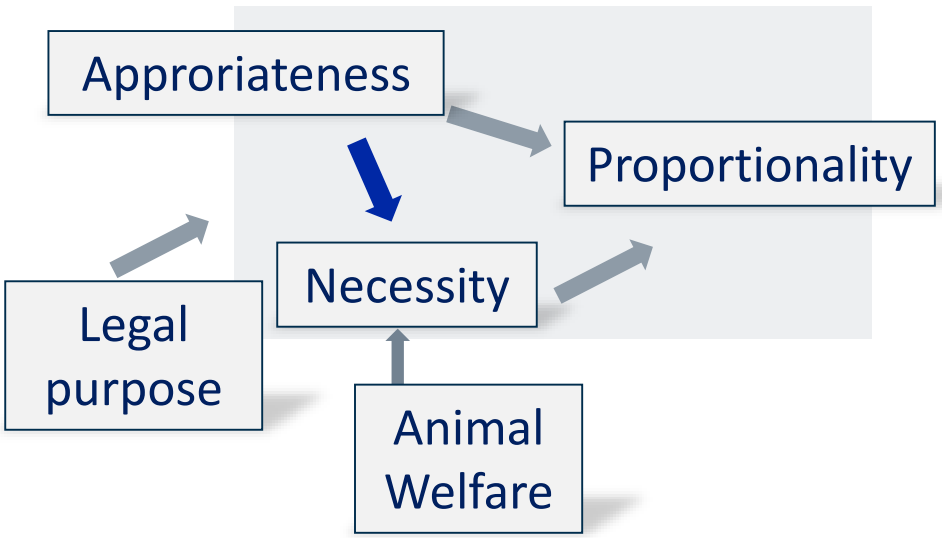
dignity means the **inherent worth of the animal** that must be respected when dealing with it. If any strain imposed on the animal cannot be **justified by overriding interests**, this constitutes a disregard for the animal's dignity. Strain is deemed to be present in particular if pain, suffering or harm is inflicted on the animal, if it is exposed to **anxiety or humiliation, if there is major interference with its appearance or its abilities or if it is excessively instrumentalised**;

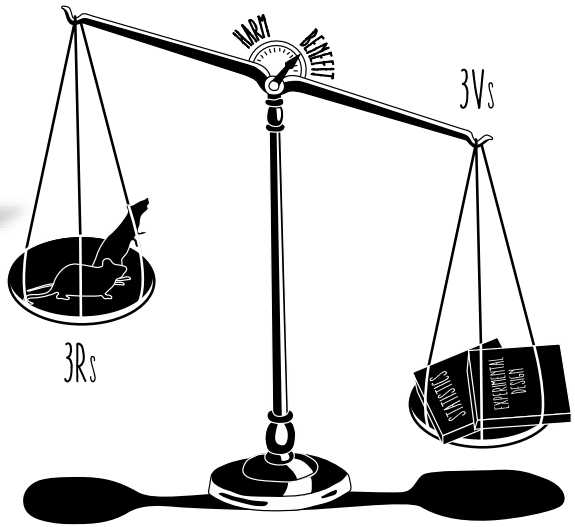
Applications of Chimeras

- As “incubators” for growing human organs
- Many people die because there is a shortage in donor organs

major interference with its appearance or its abilities?

„Major interference with its appearance or its abilities“ and „Excessive instrumentalization“ count as significant harms which need to be justified by the expected benefit





Würbel, 2017

Kim Caesar/Springer Nature

Precautionary principle or proportionality?

„When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically"

Raffensperger C, Tickner J, eds. Protecting Public Healthand the Environment: Implementing the PrecautionaryPrinciple. Washington, DC:Island Press, 1999

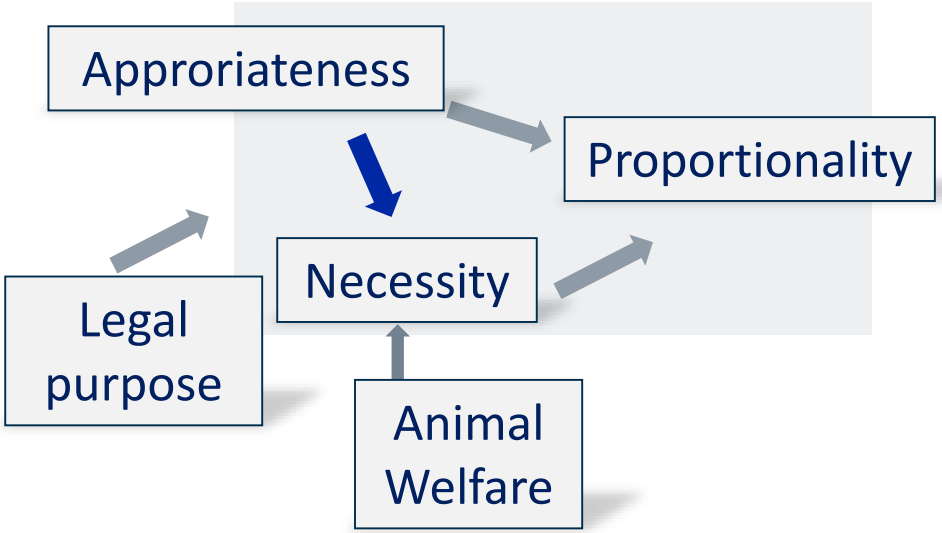
Precautionary principle or proportionality?

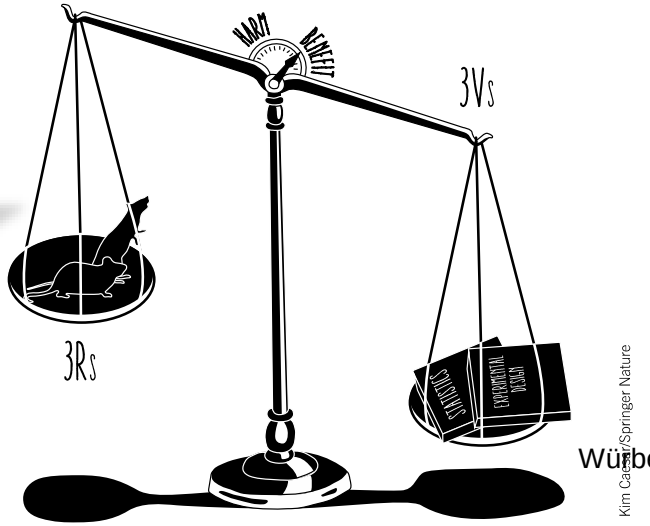
if there is a risk, you should do nothing?

Inaction may also be risky and can lead to harm: medical research will be stifled and progress will be impossible.

risk-benefit analysis:
Is the research objective important? Are the methods to achieve them feasible and are the facilities adequate? Are there no less risky or controversial methods available? Do the relevant personnel have the training required to deal with the research equipment and the animals? Porsdam Mann et al. BMC Medical Ethics (2019) 20:10

Thank you very much for your attention





Würbel, 2017

Kim Card/Springer Nature

e-mail: matthias.eggel@ibme.uzh.ch