
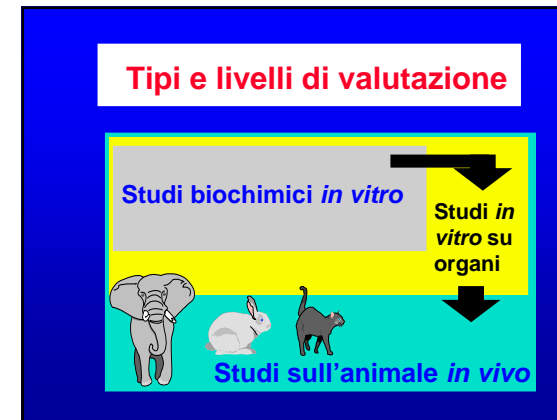


Scoperta e Sviluppo dei Farmaci
11 novembre 2004
Prof. Stefano Govoni – Università di Pavia



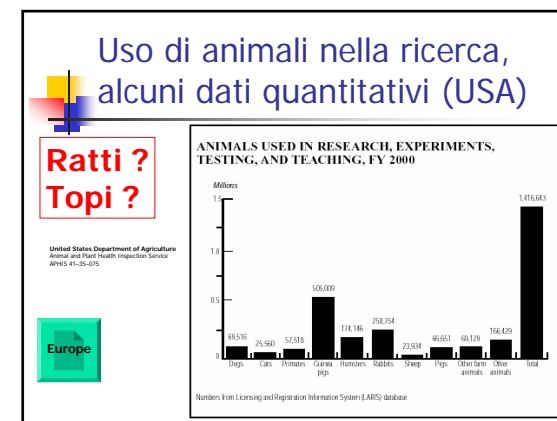
Uso degli animali nella ricerca scientifica: problema scientifico e problema etico.



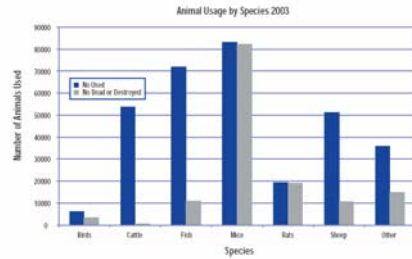
■ Quale è la vostra opinione personale?

Uso di animali nella ricerca, alcuni dati quantitativi

Ratti, topi ed altri roditori	85/90%
Cani e Gatti	< 1%
Primati non umani	< 0,3%



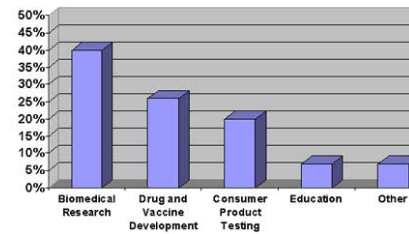
Uso di animali nella ricerca, alcuni dati quantitativi (NZ)



National Animal Ethics Advisory Committee
 C/O Ministry of Agriculture and Forestry
 P O Box 2526
 Wellington
 New Zealand

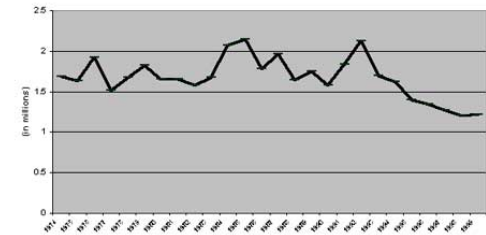
Uso di animali nella ricerca, alcuni dati quantitativi

Uses of Animals in US Laboratories
 (Including rats, mice and birds)



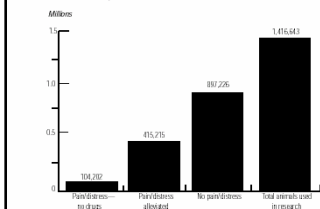
Uso di animali nella ricerca, alcuni dati quantitativi

Number of Animals Used in US Laboratories--1973 to 1990
 (excluding mice, rats, and birds)



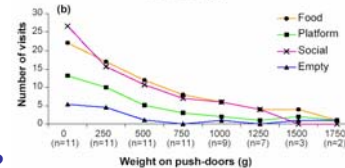
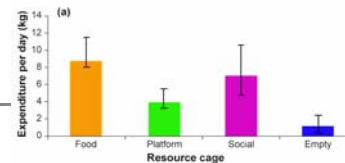
Uso di animali nella ricerca, alcuni dati quantitativi

ANIMALS EXPERIENCING PAIN/DISTRESS, PAIN/DISTRESS RELIEF, OR NO PAIN/DISTRESS DURING EXPERIMENTS, FY 2000



Numbers from Licensing and Registration Information System (LRIS) database

Che cosa significa benessere per un animale da laboratorio?



(a) Median total expenditure (kg lifted) per day for different resources, showing that rabbits rank food and social contact as being of almost equal importance.
 (b) Mean number of visits to each resource cage when push-doors were unweighted and weighted up to 1750 g.

L'esempio di una storia personale

- Attività didattica ed attività scientifica di S.Govoni (> 230 pubblicazioni censite dalla National Library of Medicine) e del Dipartimento di Farmacologia Sperimentale ed Applicata (Facoltà di Farmacia)

L'esempio di una storia personale

- Pubblicazioni 1980-1985
- 44/51 (86%)
- Pubblicazioni 1999-2004
- 13/43 (30%)
- Rinuncia all'uso di animali nella didattica

Fatti e miti sull'uso degli animali nella ricerca scientifica

- Foundation for Biomedical Research (<http://www.fbresearch.org/>)
- FactMyth.pdf



Fatti e miti sull'uso degli animali nella ricerca scientifica

Physicians and scientists overwhelmingly agree that animal systems provide invaluable and irreplaceable insights into human systems because there are striking similarities between the genetic and physiological systems of animals and humans.

MYTH: Computer models and cell cultures can replace animal testing.

While medical and scientific advances achieved through animal research are frequently supplemented by knowledge obtained through non-animal methods—such as computer models, *in vitro* research, clinical observation, epidemiology, genetic research and post marketing drug surveillance—these alternative methods serve only as adjuncts to basic animal research.

Mito: I modelli computerizzati e le colture cellulari possono rimpiazzare l'uso degli animali

<http://www.nih.gov/news/arc2.html#GENERAL>

Fatti e miti sull'uso degli animali nella ricerca scientifica

Practically *all* research animals are rodents—mice and rats—bred for this purpose. Dogs, cats and non-human primates *together* account for **less than one percent** of the total and their number has been declining for over 20

MYTH: Dogs, cats and monkeys are used more than any other animal in medical research.

years. Since 1979, the number of dogs needed in animal research has declined by 66 percent and the number of cats needed has declined by 69 percent. Primate use, representing 0.3 percent, has remained relatively constant—in the 50,000 range—for the past decade.

Mito: I cani, i gatti e le scimmie sono la specie animale più usata in laboratorio

Fatti e miti sull'uso degli animali nella ricerca scientifica

MYTH: Lost and stolen pets are sold to laboratories.

In fact, scientists neither *need nor want* to do research on pets.

According to United States Department of Agriculture (USDA), one of several government agencies overseeing the use of animals in medical research, 70,541 dogs and 23,238 cats were involved in biomedical research in 1999. The vast majority of these animals were bred specifically for research. The remainder was acquired directly from the "death row" of animal pounds or purchased from one of about 35 USDA-licensed and regulated dealers. In 1999, in quarterly "trace back" audits of these dealers, the USDA found **no evidence of theft.**

Mito: I cani ed i gatti persi o rubati sono venduti ai laboratori di ricerca

Fatti e miti sull'uso degli animali nella ricerca scientifica

Federal regulations governing the care and use of animals in biomedical research are more extensive than those covering human research subjects. The Animal Welfare Act sets high standards of care for research animals with regard to their housing, feeding, cleanliness, ventilation and medical needs. It also requires the use of anesthesia or analgesic drugs for potentially painful procedures and during post-operative care. Most importantly, research institutions are required—by

MYTH: There are no laws or government regulations to protect research animals.

law—to establish an Institutional Animal Care and Use Committee (IACUC) to oversee their work with animals. And IACUCs require researchers to justify their need for animals, select the most appropriate species and use the fewest number of animals possible to answer a specific question.

Mito: non ci sono leggi né regolamenti che tutelino gli animali usati per la ricerca

Fatti e miti sull'uso degli animali nella ricerca scientifica

For humane, compassionate and scientific reasons, researchers are deeply concerned about the condition of the animals they study. This is not a controversial position—there is no constituency for inhumane or irresponsible treatment. Poor care results in unreliable research data. For results to be valid, animal subjects must be in good condition and appropriately healthy.

Also, pain and distress are thought to have a negative impact on the immune system so researchers are careful to protect their animals from undue stress.

MYTH: Researchers are indifferent to the well being of animals.

Mito: i ricercatori sono indifferenti al benessere degli animali

Fatti e miti sull'uso degli animali nella ricerca scientifica

The 1999 USDA Annual Report reveals that 55 percent of all research procedures with animals involved no more than slight or momentary pain or distress (i.e.: an injection). Thirty-six percent of the research procedures employed anesthesia and, postoperative painkillers.

MYTH: Research animals are kept in pain.

Mito: gli animali usati in ricerca sono costantemente sofferenti

Fatti e miti sull'uso degli animali nella ricerca scientifica

Manufacturers of food, drugs, household goods, cosmetic products, pesticides and other chemicals have an ethical and legal obligation to protect consumers from hazardous consumer products. They are able to meet that obligation through animal testing, for which there is no completely valid alternative.

Some companies promote their products by claiming they do not test on animals. This can mislead consumers into believing that animal testing is not necessary when in fact, such products—or their ingredients—were previously tested on animals, probably by another company and found to be safe. Once an ingredient or formula has been tested and proven safe, it rarely has to be tested a second time.

MYTH: There is no need to test consumer products on animals—some companies claim.

Mito: non c'è bisogno di saggiare i prodotti destinati al consumatore sugli animali ed alcuni produttori non lo fanno

La sperimentazione animale è/è stata utile alla ricerca scientifica? (I)

Possono essere a riguardo ricordate alcune pietre miliari dei rapporti tra sperimentazione animale in endocrinologia e impiego nell'uomo dei suoi risultati (Preziosi, 1990):

- 1889** Minkowski e Von Mering ablatano chirurgicamente il pancreas nel cane, provocando nell'animale i segni caratteristici del diabete mellito.
- 1921** Banting e Best scoprono che un estratto alcolico di pancreas cura il diabete del cane spiancreato e che nell'estratto è contenuta insulina che, ottenuta dal pancreas di bue e di maiale, serve per la cura dei diabetici per oltre 50 anni, oggi solo in parte sostituita dall'insulina umana ottenuta in via ricombinante.
- 1925** Callipri riesce ad incrementare il calcio presente nel siero di animali paratiroideomizzati con estratto di paratiroide, ponendo le basi della patogenesi e della cura della tetania paratiroidea.
- 1929** Koch *et al.* fanno ricrescere la cresta a galli castrati utilizzando testicoli di toro.
- 1953** Pincus *et al.* descrivono gli effetti inibitori di steroidi di sintesi sulla funzione gonadotropica ipofisaria (ovulazione) nel coniglio.
- 1956** Sulla base di tali risultati sperimentali, Rock, Garcia e Pincus dimostrano la inibizione della ovulazione della donna con steroidi.

(dal Documento del comitato Nazionale di bioetica – vedi successiva)

La sperimentazione animale è/è stata utile alla ricerca scientifica? (II)

Here is a short list of important medical advances achieved through animal research and the animals to which we give credit.

- | | | |
|---|--|---|
| 1751 First Measurement of Blood Pressure (Dog) | 1790 Vaccine for Smallpox Developed (Cow) | 1964 Regulation of Cholesterol Discovered (Rat) |
| 1880 Vaccine for Anthrax Developed (Sheep) | 1908 Vaccine for Rabies Developed (Dog, Rabbit) | 1968 Rabella Vaccine Developed (Monkey) |
| 1902 Malaria Link Cured (Unconscious Piglet) | 1905 Polio Vaccine of Tobacco Root Discovered (Guinea Pig?) | 1970 Lithium Approved (Rat, Guinea Pig) |
| 1919 Mechanisms of Immunity Discovered (Guinea Pig, Horse, Rabbit?) | 1912 Vaccine for Typhoid Discovered (Guinea Pig, Rat, Mouse?) | 1973 Animal Social and Behavior Patterns Discovered (Rat, Fish, Bird) |
| 1923 Insulin Discovered (Dog, Pig) | 1929 Vaccine Suppresses Nervous Growth Discovered (Rabbit?) | 1982 Treatment for Leprosy Developed (Armadillo) |
| 1928 Polio Vaccine of Tissue Discovered (Guinea Pig, Rat, Mouse?) | 1932 Insulin Discovered (Cat, Dog?) | 1984 Monoclonal Antibodies Developed (Mouse) |
| 1929 Vaccine Suppresses Nervous Growth Discovered (Rabbit?) | 1933 Vaccine for Tetanus Developed (Horse) | 1989 Organ Transplantation Advances Developed (Dog, Sheep, Cow, Pig) |
| 1932 Insulin Discovered (Cat, Dog?) | 1939 Antipsychotics Developed (Cat) | 1992 Laproscopic Surgical Techniques Developed (Pig) |
| 1933 Vaccine for Tetanus Developed (Horse) | 1942 The Rh Factor Discovered (Monkey) | 1995 Gene Transfer for Cystic Fibrosis Developed (Mouse, Non-Human Primate) |
| 1939 Antipsychotics Developed (Cat) | 1943 Vaccine for Cholera Discovered (Rat, Dog, Chick, Mouse?) | 2000 Brain Signal Transduction Discovered (Mouse, Rat, Non-Slag?) |
| 1942 The Rh Factor Discovered (Monkey) | 1945 Penicillin Tested (Horse?) | 2001 Promising Drug for Prevention of AIDS Developed (Monkey) |
| 1943 Vaccine for Cholera Discovered (Rat, Dog, Chick, Mouse?) | 1954 Rabies Vaccine Developed (Horse, Monkey) | |
| 1945 Penicillin Tested (Horse?) | 1956 Upright Knee Surgery and Cardiac Pacemakers Developed (Dog) | |

...ma non tutti sono d'accordo

Scientific American Article Animal Research is Wasteful and Misleading February 1997.htm

<http://www.sciam.com/0297issue/index.htm>

...ma non tutti sono d'accordo

■ Better Methods

- Researchers have better methods at their disposal. These techniques include epidemiological studies, clinical intervention trials, astute clinical observation aided by laboratory testing, human tissue and cell cultures, autopsy studies, endoscopic examination and biopsy, as well as new imaging methods. And the emerging science of **molecular epidemiology**, which relates genetic, metabolic and biochemical factors with epidemiological data on disease incidence, offers significant promise for identifying the causes of human disease.

<http://pub.nlm.nih.gov/animat/au02.htm#GENERAL>

■ Esistono delle regole?

■ Chi fa le regole?

- Importanza dell'autoregolamentazione delle Società Scientifiche
- Importanza della conoscenza delle leggi esistenti

■ In Italia esistono posizioni o documenti ufficiali?

Sperimentazione sugli animali e salute dei viventi, Comitato Nazionale per la Bioetica 1997

http://www.palazzochiigi.it/Presidenza/comitat_commissioni.htm

- [sperimentazione_animali.pdf](#)
 - [sperimentazione_animale1.pdf](#)
 - [sperimentazione_animale2.pdf](#)
 - [sperimentazione_animale3.pdf](#)
- (vedi tab 8, 9, e considerazioni sulla normativa)
- [sperimentazione_animale4.pdf](#)

- E' relativamente poco noto che l'attività di ricerca sull'animale è regolamentata da una legge, una delle più restrittive in Europa:

- la legge del 19/2/1992
- [CIRCOLARE 14 maggio 2001, n. 6.htm](#)

http://www.comune.jesi.an.it/MV/gazzette_ufficiali/2001/144/gazzetta144.htm

Termine della vita dell'animale da esperimento

ANIMAL BEHAVIORAL CONSIDERATIONS

The need to minimize animal distress, including fear, anxiety, and apprehension, must be considered in determining the method of euthanasia. Gentle restraint (preferably in a familiar and safe environment), careful handling, and talking during euthanasia often have a calming effect on animals that are used to being handled. Sedation and/or anesthesia may assist in achieving the best conditions for euthanasia. It must be recognized that any sedatives or anesthetics given at this stage that change circulation may delay the onset of the euthanasia agent.

Termine della vita dell'animale da esperimento

- In evaluating methods of euthanasia, the panel used the following criteria: (1) ability to induce loss of consciousness and death without causing pain, distress, anxiety, or apprehension; (2) time required to induce loss of consciousness; (3) reliability; (4) safety of personnel; (5) irreversibility; (6) compatibility with requirement and purpose; (7) emotional effect on observers or operators; (8) compatibility with subsequent evaluation, examination, or use of tissue; (9) drug availability and human abuse potential; (10) compatibility with species, age, and health status; (11) ability to maintain equipment in proper working order; and (12) safety for predators/scavengers should the carcass be consumed.
- The panel discussed the definition of euthanasia

- Possibili evoluzioni dettate da ragioni....politiche?
- legge Regione sper. animale

- Il comitato etico per la sperimentazione animale dell'ateneo Pavese



<http://www.unipv.it/safety/welcome.html>

- Che cosa succedeva noi e in altri paesi: navigando un po'....analizzando le diverse posizioni...

Siti di Bioetica, compresi quelli relativi all'uso di animali nella sperimentazione scientifica

- [Laboratory Animal Care and Use - Bioethics Resources on the Web -](#)
- [The Guide](#)
<http://www.nap.edu/catalog/5140.html>

In ogni caso, da un punto di vista generale, le regole di base all'estero sono simili

- Assicurare che tutti gli animali usati per la ricerca ricevano cure adeguate ed un trattamento umano.
- Usare modelli animali quando non sono disponibili alternative.
- Usare il minimo numero possibile di animali.
- Disegnare gli studi in modo che producano risultati validi e affidabili.

Siti delle associazioni dei ricercatori

- [EBRA \(European Biomedical Research Association, Home Page.htm\)](http://www.ebra.org/aboutebra/index.html)
- [EBRA \(European Biomedical Research Association, European Statistics.htm\)](http://www.ebra.org/aboutebra/index.html)

<http://www.ebra.org/aboutebra/index.html>

Siti Preoccupati della difesa della sperimentazione

- [National Association for Biomedical Research.htm](http://www.nabr.org/about.html)

<http://www.nabr.org/about.html>

Siti delle associazioni contro la sperimentazione animale

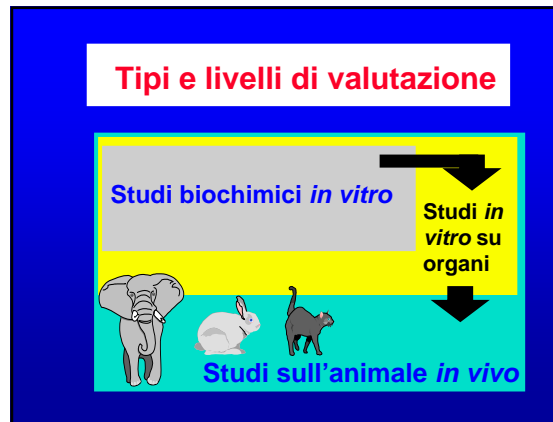
- [Recenti sondaggi](http://www.novivisezione.org/index.htm)
<http://www.novivisezione.org/index.htm>

Siti Preoccupati della difesa dei diritti degli animali



<http://www.labanimalwelfare.org/>

■ Alla fine...una possibile posizione




- ### Modelli animali
- Preditivi di efficacia e tossicità?
 - Costosi, lunghi, variabili, pongono problemi etici, richiedono personale molto esperto.
 - Sottoposti a controlli di legge.
 - Autorizzazione del personale e delle strutture
 - Autorizzazione della specifica sperimentazione
 - **NECESSITA' DI ARRIVARE IN TEMPI BREVI ALLA SPERIMENTAZIONE UMANA.**

- ### Riduzione dell'uso degli animali
- Circa 2.6m animali/anno usati in UK (11.6m in Europa)
 - Questo numero potrebbe aumentare per l'incremento delle ricerche in ambito biomedico.
- ## •3Rs -- 3Rs -- 3Rs
- RIMPIAZZARE: uso di testo che non impieghino animali (meno costosi, meno problematici, meno variabili, ma non sempre possibili).
 - RIDURRE: utilizzare un disegno statistico appropriato, non replicare lavoro inutile, non produrre capi in eccesso).
 - RAFFINARE: le tecniche riducendo sofferenza ed invasività delle procedure

- ### USO DI ALTERNATIVE AI TEST NELL'ANIMALE
- [About IIVS - Alternatives to Animal Testing.htm](http://www.iivs.org/about.html)
<http://www.iivs.org/about.html>

USO DI ALTERNATIVE AI TEST NELL'ANIMALE – LA POSIZIONE DELL'FDA

The FDA states, "many procedures intended to replace animal tests are still in various stages of development...While the best means may begin with valuable adjunct tests, ultimately testing must progress to a whole intact, living system – an animal." Not using animal tests when necessary would subject humans and other animals to unreasonable risks.




Prendere una posizione che salvaguardi i diritti dell'uomo ed il benessere degli animali

Manufacturers of food, drugs, household goods, cosmetic products, pesticides and other chemicals have both ethical and legal obligations to protect the safety of consumers. Federal statutes including the Food, Drug, and Cosmetic Act; Toxic Substances Control Act; Federal Insecticide, Fungicide, and Rodenticide Act; Clean Air and Water Acts and the Consumer Product Safety Act mandate that the federal government be involved in assuring product safety and in protecting public health.

Federal agencies such as the Food and Drug Administration, the Environmental Protection Agency, the Consumer Product Safety Commission and the Occupational Safety and Health Administration play a significant role in monitoring product safety.

Federal agencies and professional groups agree that alternative methods are not available at this time to completely replace the use of animals in product safety testing. Nevertheless, in a formalized interagency effort, the federal government is actively working to establish the validity of new nonanimal tests that may be accepted for regulatory purposes and further reduce animal use.


The vast majority of test animals are rodents (primarily mice and rats).



Prendere una posizione che salvaguardi i diritti dell'uomo ed il benessere degli animali

The "classic" LD-50 test has been replaced, in almost all cases, by modified tests that require fewer animals. However, there are still rare instances when statistically precise acute-dose toxicity data are needed.

The Draize test, developed in 1944, has changed considerably over the years to reduce or eliminate any pain test animals may experience. It is the FDA's position that "the Draize test is currently the most meaningful and reliable method for evaluating the hazard or safety of a substance introduced into or around the eyes." Companies that claim their products are not tested on animals — and, therefore, are "cruelty free" — mislead consumers since almost all products, or the chemical compounds that comprise them, were previously tested on animals. Such testing need not be repeated.



■ Alla fine...una possibile posizione