

**Q&A on the Commission 2019 report on the Statistics on the Number of Animals used for Scientific Purposes in the Member States of the European Union
February 2020**

REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL 2019 - COM(2020)16/1 and COM(2020)16/2

Report on the statistics on the use of animals for scientific purposes in the Member States of the European Union in 2015-2017 and the accompanying Staff Working Document

What is the objective of the report?

The Objective of the report is to present statistical information on the **use** of animals in procedures in the European Union in accordance with Directive 2010/63/EU of 22 September 2010 regarding the protection of animals used for scientific purposes.

What is the basis of the data provided in the report?

The report summarises the data provided by all 28 Member States between 2015 – 2017 in accordance with article 54(2) of Directive 2010/63/EU which requires member states to collect annually statistical information on the use of animals in procedures (including actual severity of the procedures and on the origin and species of non-human primates used in procedures). This information has been submitted to the Commission since 2015 and every year thereafter. The report is accompanied by the Commission Staff Working Document which provides the detailed information provided by each member state. The data were collected in member states according to the Commission implementing decision 2012/707/EU of 14 November 2012 establishing a format for the submission of the information pursuant to Directive 2010/63/EU of the European Parliament and the Council on the protection of animals used for scientific purposes

Article 57 of the Directive previously required that the Commission submit a report on the implementation of the Directive and on the statistical information on the use of animals in procedures, by 10 November 2019. This article has since been deleted by Regulation 2019/1010. However, the Commission has gone ahead and published the reports for transparency.

Is this report comparable to previous Commission reports?

The new report brings new and more comprehensive information and improves the way of reporting.

The new data are not comparable with the previous (2011 and before) reports under the previous Directive 86/609/EEC. The introduction of new 'use' categories as well as new species (cephalopods, foetal forms of mammals) significantly changed the scope of the reporting obligations. The previous reports only gave detailed information on the first use of an animal, whereas now all subsequent uses must be reported – from the first use of an animal to any subsequent uses, in line with the 3R principles. Furthermore, there is reporting now on genetically altered animals (creation of any line, maintenance of lines with severe impairments) and additional information on NHPs, including generation of breeding. In addition, the actual severity experienced by animals being used is reported.

Comparison table

Reporting	Former Directive (86/609/EEC)	Current Directive (2010/63/EU)
Scope - Species	Only vertebrate species	Vertebrate species, cephalopods and foetal forms of mammals as from the last third of their normal development.

Scope - purpose	No reporting of breeding of genetically altered animals	Maintenance (breeding) of genetically altered (GA) animals with intended harmful phenotype (characteristic/trait) and which have experienced suffering
First use and reuse (Animals versus use of animals)	Number of new animals, and only the number of reuses of the species covered by the Annex I of Directive 86/609/EEC with no related details of the reuse	Number of new animals, and in addition all reuses. All uses reported with full data sets
Source of NHPs	Information on European origins but not from other geographical regions	More detailed information on where NHPs have been obtained, in particular outside Europe
Generation of NHP breeding	Not reported	Information on progress from wild caught (F0), to first generation purpose bred (F1), second generation purpose-bred animals (F2), to self-sustaining colonies.
Genetic status	Not reported	<ul style="list-style-type: none"> • No genetic alteration (GA) • GA with a non-harmful phenotype • GA with a harmful phenotype
Purposes	Broad headings	More detailed information of previously reported categories with further sub-categorisation, such as for ecotoxicity, routine production and GA maintenance
Creation of a new genetically altered line	Not reported	Creation of a new GA line together with the intended purpose
Actual severity	Not reported	Actual severity reported under four categories <ul style="list-style-type: none"> • Non-recovery • Mild • Moderate • Severe

How accurate is the information provided?

The Commission have based the report on uses for 2017 as the highest accuracy came through this year as it took time for users and authorities to adapt to the new reporting requirements. Introduction of new reporting criteria brought with it a number of challenges, with expectations of new requirements, terms used and data categorization. At national level, the requirements could be interpreted differently and also lead to different data quality or classifications.

How do we (user community) overcome this?

- Development, dissemination and take up of guidance at a national level + trainings
- Workshops organised by stakeholders have taken place across Europe to address severity classification and reporting

Ultimately, the responsibility is within Member States which should develop harmonized guidance.

General Q&A

Why are animals used for research?

Research involving the use of animals can provide much information – for instance they can help to advance scientific knowledge, understand the basis of diseases, and to investigate and develop new medicines. Non-animal alternative methods are used to gain this information whenever possible. Applying improved biological knowledge, technological advances, computer simulations and test tube methods will allow significant reduction of the number of animals actually used, however, these methods are not yet able to fully replicate the complexity and reactions of a living organism especially for systemic and chronic conditions.

What is animal research exactly?

Studies performed on animals help advance scientific research and medicines development. Animal research takes several forms.

Basic or fundamental research helps advance scientific knowledge about how animals and humans behave, develop and function biologically. In the EU, basic research accounts for the majority of all animals used for research purposes and tends to be publicly funded with some private funding from industry and medical research charities.

Targeted or applied research helps scientific understanding of diseases leading to and including the development of new medicines and vaccines. This type of research is both publicly and privately funded and may also use findings obtained from basic research. Applied research is the second largest area where animals are used. In the EU this accounts for approximately a fifth of animals used for research purposes.

On average around 10 % of animals are used in toxicological or other product safety evaluation, which are performed to assess the potential risks of harm to animals, humans or the environment. Such research is required by European legislation and international legislation. Of these, just over half of the animals are used for evaluating human (incl. dentistry) and veterinary medicines. The remainder are used to obtain quality and safety data from household and industrial chemicals, herbicides, fertilizers, and food additives. Quality and safety studies are usually funded by private organizations. The use of animals to assess safety of cosmetic ingredients and products is banned in the EU, this includes a marketing ban (i.e. the prohibition to market cosmetics in the EU if tested on animals outside the EU).

The remaining majority of animals are used for the purposes of production and quality control required by authorities, diagnosis of diseases, education and training or other purposes.

Animal research – views from different stakeholders?

Research view

The pharmaceutical and scientific community focus on developing new medicines to ensure world-leading, innovative and responsible medical research in Europe.

The pharmaceutical industry is required to demonstrate that potential new medicines are effective and safe in humans, and that potential side effects are identified before they get a licence to produce and go to market. This process involves in vitro and in silico models in the earlier stages, with animals being used in the later phase of preclinical development.

The scientific community maintains that even though animal research, (as any other models in vitro or human), doesn't always deliver perfect results for human relevance, it's still – in combination with relevant non-animal methods - the primary way to do research to understand living systems and to provide the best possible assurance of the effects of new medicines prior to the first clinical trials in humans. Clinical trials are not able to give results with 100% accuracy due to the large variability of the human population. The medicines development process involving in silico, in vitro, pre-clinical (animals) and clinical (human) phases decreases the risk for the Human population as a whole.

- Europe must remain a world leader in medical research and innovation to address the unmet medical needs of its citizens and to preserve its capacity to shape its health strategies as well as the unmet medical needs of world regions that do not have the resources or expertise to address their healthcare issues, e.g. addressing Malaria, Ebola;
- All healthcare products must comply with safety, quality and efficacy requirements set in national and European legislation. Those conducting biomedical research should have access to the most appropriate tools to achieve this imperative objective;
- While it is desirable to replace the use of animals in R&D, research involving animals continues to be necessary to:
 - o Protect human, animal, and environmental health;
 - o Respond to regulatory requirements, and;
 - o Understand the causes of diseases and functioning of complex biological systems in the body.

Legislative view

In the Lisbon treaty, animals have been given rights as sentient beings, and it's now a legal requirement not to use animals where there's an effective alternative.

European, national and global legislation requires that all medicines are evaluated using a combination of non-animal and animal methods before they can be evaluated in humans.

Some medicines and vaccines must be evaluated on animals for every batch to ensure that they are of appropriate quality. This is a legislative requirement. These tend to be medicines that are made of, or derived from a live product – such as polio vaccine etc.

Directive 2010/63, on the protection of animals took effect in member states on 1st January 2013. The Directive has enhanced animal welfare standards and mandated the application of Replacement, Reduction and Refinement ('3Rs') across the EU.

It supports research involving animals only when there are no alternative methods, where the potential benefits are compelling, when it is scientifically, legally and ethically justified, and welfare standards are met. The testing requirements outside Europe often require animal use. Therefore some tests not performed for the European market will be required in other markets.

Animal rights view

Animal rights groups, on the whole, object to all animal research and may advocate that the results of the research are unreliable, and that all experiments could be replaced with non-animal (or animal derived products such as plasma) testing methods.

Many argue that scientists automatically opt to use animals rather than seeking out non-animal alternatives, and that this mindset needs to change.

They campaign to modernise parts of the legislation governing animal research arguing that it is out dated. They claim that animal research is not validated while there is a scientific and legal demand to prove that alternatives are effective.

Animal rights groups want to see animals being regarded as sentient beings with rights. There is also concern about the rise in use of animals in genetic manipulation and cloning.

Are there any non-animal alternatives?

Yes, there are many non-animal methods approved and used today. Animals are replaced, either by methods that don't involve animals at all or by those that use only the cells or tissues of animals. Many replacement alternatives involve these in-vitro ("in glass") techniques, where the studies are done with cells or tissues in culture. Other alternatives include in-silico methods replicating animals' reactions through a computer program.

These methods are very useful for studies on particular types of tissue and help considerably to limit the number of animals used. However, they are still not able to simulate an entire organism with all its cells, tissues and systems interacting with each other. There has been more success in finding alternatives for acute and local rather than systemic and chronic effects.

Bans - Impact on number of animals used in research

A deadline and ban on using animals in research in the EU would not have a large impact on the number of animals used by the pharmaceutical industry globally. The pharmaceutical industry operates globally, and under the OECD Mutual Acceptance of Data scheme, duplication of regulatory studies for OECD countries is already minimised. Since regulators in other developed countries, such as the FDA and PDMA, will continue to require animal studies, a ban in the EU would not cause a significant decrease in the number of animals used globally.

Bans - Economic impact

The pharmaceutical industry employs 765 000 people in the EU, with 115,000 of them in research and development, and invests over €36bn a year in R&D in the EU¹. As highlighted above, a deadline would likely result in significant levels of research moving outside of the EU, accompanied by a significant exodus of highly skilled medical and scientific jobs. This would cause a significant negative impact on employment and the competitiveness of EU industry.

¹ The Pharmaceutical Industry in Figures 2019, EFPIA, 2019.

<https://www.efpia.eu/media/413006/the-pharmaceutical-industry-in-figures.pdf>

Beyond the pharmaceutical industry, a ban would significantly damage the EU science base, access to research funding in the EU (including from the pharmaceutical industry which collaborates significantly with public researchers in the EU), and ultimately the EU's competitiveness in the global scientific community. Decreased funding would have significant long-term impact on the EU's innovation, productivity, and ultimately on human health within the EU. Furthermore, other medical and health areas will be affected, including those in robotic surgery, behaviour, learning, psychiatry, microbiotic impact, etc....

As Directive 2010/63/EU is the strictest welfare regulations in the world, the negative implications for animal welfare are obvious if it were to move outside of Europe. Equally, creating a future ban on animal science in the EU or prohibiting marketing of drugs developed elsewhere through animal science will impact European citizen's access to needed medicines.

Enforcement of Directive 2010/63/EU on the protection of animals used for scientific purposes

The Directive sets the most stringent protection framework worldwide for animals. National Competent Authorities are required to have effective inspection and investigation measures in place and any identified case of breach of the Directive must be investigated and the necessary actions taken rapidly. EFPIA and its Members are committed to high animal welfare standards and to the development of alternatives to the use of animals in research. Anytime animals are required for the assessment of the safety and efficacy of potential new treatments, this must be done with the utmost ethical consideration.

Genetically altered animals

This is the first time through EU statistics that there is reporting on genetically altered animals (creation, maintenance). Animals used for the creation are reported in the annual statistics under the basic/applied research purpose for which the line is being created for. The exception is wild type offspring is not reported in the annual statistics.

Refer to [Commission poster](#) outlining the information requirements on reporting GA animals.

Why are Genetically Altered (GA) animals required

The vast majority of GA animals used in research are mice. Advances in technology (eg CRISPR, "humanisation" of models used to increase predictivity of models for efficiency and safety) have enabled modifications of animals to allow them to serve as appropriate models for disease research, making research outcomes more beneficial for patients, and hence makes animal use more acceptable.

Funding alternatives

The Commission have made significant contributions to funding alternatives under their [Framework programmes](#), with around 30 million provided per year under Frame Work Programme 6, and 45 million a year for both Framework Programme 7 and Horizon 2020.

Many [Member States](#) are also investing considerably in Alternatives. Their individual contributions are voluntarily loaded onto the Commission website.

The [Innovative Medicines Initiative \(IMI\)](#) is a public-private partnership between the European Union and EFPIA. With a budget of over 5 billion, IMI is pursuing the goal of developing the next generation of medicines, vaccines and treatments by improving research practice; getting new healthcare

solutions to patients faster; and improving health outcomes thanks to new tools, methodologies, research infrastructure and big data. Established in 2009, and further expanded in 2014, the IMI consortia (involving industry, academia, SMEs, patients, regulators, etc.) are contributing enormously to animal welfare:

- IMI helps to drive animal welfare and 3Rs – Presently numerous IMI consortia impact on the use of animals and IMI projects contribute to the 3Rs.
- IMI successes have addressed and brought results in 3Rs or new research paradigms or more predictive testing tools that do not require – or require fewer – animals
- IMI projects are contributing to a better understanding of the challenges faced in using animal models and are impacting on the use of laboratory animals in research and development.

Animals bred but not used

REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT AND THE COUNCIL on the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes in the Member States of the European Union and Staff Working Document (COM(2020)15/1 and COM(2020)15/2) provide information for the first time on animals bred but not used.

Research laboratories keep records of animals that are not used in ‘regulated’ procedures and the EU has introduced a requirement to publish these numbers every 5 years. These additional animal statistics provides a record of all animals in the EU which are killed in a research setting whether or not they have undergone a regulated procedure. This is the first time we have access to those data.

Are these animals’ lives wasted?

Many animals killed without undergoing a procedure still play a key part in the scientific process; For example, sentinel animals are used to monitor for potential diseases within a laboratory, whereby safeguarding the welfare of other animals and supporting quality research. Some animals are killed outside of the procedure framework as enforced by the Directive 2010/63 and are used for collecting tissue for in vitro studies, allowing researchers an alternative method of studying cells and organs in a controlled setting that may not be possible with living animals, this may in some instances lead to the replacement of live animals.

Examples of reason for why some animals are killed without use

EFPIA encourages all users to ensure active management of colonies to limit breeding and to deliver on time the animals needed, while cryopreserving lines of non desired genotypes and to re-start the breeding if needed.

List of examples

The published figures do not provide an accurate break down of the reasons for animals being killed without a use. However, some examples of why animals are bred and not used in a regulated procedure include:

- Animals that were bred for research but could not be used. Reasons include:
 - o The number bred was over and above the numbers needed for the research programme (Litter sizes are unpredictable).
 - o User demand: Trying to meet research needs by breeding animals to supply requirements over a wide range of ages. From a scientific point animal studies will require the use of animals of differing age ranges depending on the research area, body organ and/or the

hypothesis being researched. For example, some areas of research may require the use of very young animals where others may require the use of older animals.

- Sex bias: Requirement by users for an unequal number of male and female animals (This may be driven by the research area e.g.: basic research firstly evaluated in one sex and if good results, confirmation in the other sex (3Rs application also to avoid to apply procedure on both sexes))
 - Inconsistent and unpredictable demands: Research programs are considered at a high level in advance and require authorization through licences or ethical permits. Individual studies are planned in advance. However, as research progresses the results may indicate the hypothesis being investigated is not valid (hence the research stops) or the results may lead to different hypotheses requiring investigation. This results in variable demands and can lead inadvertently to considerable surplus because breeding programs cannot effectively be switched on and off. This is especially a challenge for breeding of large animal species due to a relative long gestation period.
 - Unwanted phenotypes: Animals that does not meet the requirements of the desired phenotype (i.e. were born as wild types).
 - Genetically altered animals: Animals that do not meet the genotype of a given genetically modified strain and cannot be included in study.
- Retired animals used as breeders (old animals, animals with poor breeding performance, breeders with health issues),
 - animals used for collection of tissues (euthanized before the sampling, therefore not considered as a regulated procedure)
 - Animals used to sustain inbred colonies (this includes breeding stock and neonatal losses)
 - 'Sentinel animals' used for health screening of other animals in the laboratory

Current approaches to reduce the numbers of animals bred but not used

The effective management of breeding colonies to reduce surplus is one critical area of focus. The Animal Welfare Body has a role in overseeing and providing a framework for regular assessment of this within an establishment. Examples here would include ensuring there are good internal communication processes that allow for accurate forecasts of animal requirements, and to ensure that consideration is given to flexibility in ages & phenotype where possible and without a significant impact on the science.

What is the life experience of the animals which are bred but not used?

These animals live within a laboratory environment from birth; they have access to food, water, species specific environmental enrichment and veterinary care and are, in nearly all situations, socially housed. However, they can also experience the ordinary stressors associated with life in a laboratory, such as frequent handling and more limited space than their natural habitats as with any other laboratory animals that is used in a study.

If animals cannot be rehomed, they are then humanely killed by trained and competent staff using an approved method.

Severity Classification

Through Directive 2010/63/EU, severity experienced by animals is reported under 4 categories: Non-recovery, mild, moderate and severe. This is the first time this type of data has been collected and published in EU and has led to more transparency on animal use.

The understanding of animal behaviour and welfare and how to assess severity is an area where there still remains limited evidence. More focused research into this is required to better understand severity. This means there remains discrepancies and differences in the severity assessment (both prospective and actual) between member states, establishments and users. Industry acknowledges there are challenges where companies are either operating across member states or globally and the severity assessment is not standardized. With clear guidance and implementation, plus regular training, these processes will improve. Furthermore, with continued knowledge sharing within and between member states, this will improve consistency in severity assessment.

There are several efforts ongoing to reduce the type and duration of severe suffering, e.g. by applying early Humane Endpoints, relevant (need-to-know) scientific endpoints, use of clinical assessment, score sheets, improving housing conditions and daily care/handling as well as training/habituation to the experimental procedures. Furthermore, industry participates in and supports numerous activities to inform on and decrease severe suffering of animals. Workshops to train and understand the severity classification categories are organized jointly by the user community and regulators. They have taken place over the past few years in many of the member states and in conjunction with relevant important conferences, to ensure outreach and training to a vast number of the user community and other stakeholders. In addition, industry participates in and supports the RSPCA activities and workshops focusing on reducing severe suffering

The use of animals in scientific procedures is regulated through Directive 2010/63/EU. Authorisation from a National Authority is required, including assessment of the severity classification. A Harm Benefit Assessment (HBA) is prepared where the benefits from the work must overcome the harms caused to the animals. The HBA often has independent input e.g. from ethicist, lay people, animal welfare groups.

Non-Human Primates (NHPs)

EU legislation has the strictest requirements for the care and use of laboratory animals – and it has special and justified emphasis on the care and use of e.g. dogs, cats, pigs and NHPs. Continuing studies with these animal species within the EU places EFPIA members in a unique position to go beyond minimal legal requirements and lead by example by having an open communication on improving the conditions for all species used, but in particular for dogs, pigs and NHPs.

On the 2nd June 2017, the Scientific Committee on Health and Environment Risks (SCHEER) published its final report on the need for non-human primates in biomedical research, production and testing of products and devices. Following EFPIA's evaluation of the report and its recommendations, it is considered that it is an accurate reflection of today's status quo in relation to the use of NHPs. It is well-balanced, showing support overall for the appropriate use of NHPs in research, and considers current trends in relation to science, 3Rs and animal welfare.

Why are non-human primates used and what are the benefits from their use?

NHP are used for exploring the safety and efficacy of a new drug before it can be tested in humans/patients.

To allow the development of new medicines, authorities require the selection of potential new molecules with various assays including in silico and in vitro assays. Data on drug safety needs to be submitted to regulatory authorities around the world before they approve clinical trials, this data includes evaluating the possible adverse effects in animals. The species used for safety evaluation are chosen on a scientific basis (e.g. required pharmacological target, relevant metabolism and pharmacokinetics). Rat and dog are often the chosen species for this evaluation. However, NHPs must be used if the drug is specific for humans (biologically relevant species) where the drug does not have a pharmacological effect in rat and dog. This is the case for many biotechnology-derived drugs such as therapeutic antibodies, oligonucleotides or gene therapies, especially in oncology or autoimmune pathology domain. NHPs are also used in the earlier phases of drug discovery, e.g. when a specific receptor - like the one in humans - for a new potential drug, only is present in the NHP.

It is important to note that it is difficult to separate USA/other countries and Europe as the file required for market authorization of pharmaceuticals is similar in most of countries, with similar requirements for animal studies. Therefore, it is not possible to simply change the European requirements for animal use without also changing global requirements. If not, the studies no longer permitted in Europe shall be performed for regulatory purposes outside of Europe.

What are the reasons for numbers increasing in Europe?

- there are more biotechnology-derived drugs being developed, i.e. drugs that are only able to be evaluated in NHPs. For instance, out of 29 drugs that were approved by the US FDA in 2019, 5 drugs (17%) were biotechnology-derived products and all of those used NHP to evaluate toxicity. The same trend occurs in Europe.

- Many of the new biotechnology-derived pharmaceuticals target neurodegenerative pathologies, immune-inflammatory pathologies, or tumors. Those diseases still represent a high medical need for improved therapies.
- While there is an overall increase in the number of NHP used in procedures, the number of NHP per drug development project seems to decrease, as scientists continue to learn about new classes of pharmaceuticals and how their side effects can be assessed and due to the emergence of new technologies (e.g. in vivo imaging).

Are NHP still caught from the wild? Why?

All NHPs used in experiments that are conducted in EU need to derive from F2 generations (by 2022). These do not include Great Apes as they are banned under Directive 2010/63/EU. Already now, most (on average 85 %) NHPs are derived from colonies outside of the EU that were closed many years ago, hence both parents were raised in captivity. The grandparents could still be wild caught until all breeders have achieved full F2 compliance by 2022.

Are the techniques used on NHP invasive and do the animals suffer?

In the context of safety evaluation of potential new medicines, the drug needs to be administered by the same route as it is administered in patients. In case of drugs that are administered under the skin, into a muscle or directly into the vein, this means an invasive procedure. These administrations are typically conducted in manually restrained animals or even in un-restrained animals that have been trained to partake in the procedure voluntarily. For some specific techniques (e.g. intrathecal), as necessary, anesthesia/analgesia are used in accordance to the 3Rs. Harm, i.e. the level of pain and distress is kept at a minimum where it is typically graded as mild for the single procedure. The accumulated harm of all procedures is most often classified as 'moderate'. Effects of the drug may cause a moderate level of pain and distress; this is regularly monitored and where necessary the dose may be lowered or the drug administration may be stopped. Any animal that is at risk to experience severe pain or distress will be euthanized.

Many procedures are in place and many new initiatives are developed by the pharmaceutical industry in Europe to reduce the accumulated harm experienced by the NHPs. These include socializing to the caretakers, the use of species-specific enrichment and housing conditions, group-housing, training and habituation to procedures.

Why can't there be an immediate ban on the use of NHPs?

In terms of safety evaluation for medicines in development, NHPs are still required, since for some very specific molecules, safety cannot be evaluated in alternative animal species such as rat or dog. Until today, in vitro methods including micro physiological systems such as organs-on-a-chip are not able to fully replace those experiments, since they do not allow to accommodate for the complexity of an intact organism.

If studies in NHP were banned in the EU, those studies would have to be conducted outside of the EU, since they are required by regulatory authorities around the world to safeguard patients who participate in clinical trials. New animal models such as humanized transgenic rodents or pigs may have the potential to replace the use of NHPs in the future, but they have not been established so far. For fundamental research, where NHP is the only species showing physiology/pathology like human e.g. in many areas of neuroscience, progress would be stopped in Europe.

Along those lines, the SCHEER opinion on the need for NHPs in biomedical research, production and testing of products and devices states that the development of a timetable for phasing-out the use of NHPs is currently impractical, as there are often no other available species that can help answer key questions specific to human health, and in vitro assays remain far from replacing animals in research.