HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Annual statistical report for animals used in Ireland under scientific animal protection legislation - 2018

19 JUNE 2019

Table of Contents

1 INTRODUCTION

The Health Products Regulatory Authority (HPRA) is the state agency with responsibility for regulating human and veterinary medicines, medical devices and other health products. From 1 January 2013, an EU Directive[1] to protect animals used for scientific purposes came into effect in Ireland. In January 2013, the HPRA became the competent authority responsible for the Directive's implementation, and thus has been publishing statistical data on animals used from 2013 onwards.

The Directive is among the world's most advanced pieces of legislation concerning animal welfare. The restrictions and standards set by the Directive aim to enhance animal welfare and ensure that animals are used in studies only when their use is strongly justified and following independent assessment. The Directive firmly anchors in EU Legislation the 3Rs, i.e. Replacement, Reduction and Refinement:

- **Replacement** involves the acceleration of the development and use of models and tools, based on the latest science and technologies, to address important scientific questions without the use of animals. Examples of alternative methods would include *in vitro* tests such as the use of cell lines, computer simulation and modelling, video material, or the use of invertebrates such as fruit flies or worms.

- **Reduction** refers to methods that minimise the number of animals used per project or study consistent with the scientific aims. It is essential for reduction that studies with animals are appropriately designed and analysed to ensure robust and reproducible findings. Reduction also includes methods which allow the information gathered per animal in a study to be maximised in order to reduce the use of additional animals. Examples of this include the use of some imaging modalities which allow repeated measurements in the same animal to be taken over time (rather than, for example, imaging different animals at each time point) or microsampling of blood, where limiting the amount of blood taken each time to small volumes enables repeat sampling in the same animal.

- **Refinement** refers to methods that minimise the pain, suffering, distress or lasting harm that may be experienced by the animals, and which improve their welfare. Refinement means that animals are provided with the best possible care and this applies to all aspects of animal use, from the animals' housing and husbandry to the scientific procedures performed on them. Examples of refinement include ensuring the animals are provided with housing that allows the expression of species-specific behaviours, using appropriate anaesthesia and analgesia to minimise pain, and training animals to cooperate with procedures to minimise any distress.

[1] 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

Although complete replacement of animal studies is the ultimate goal of the Directive, this is not currently possible. Where biological processes are not sufficiently understood or are very complex, non-animal research or test methods are often not available. After generating as much information as possible using non-animal alternatives, animal studies can be necessary to fill knowledge gaps in order to safeguard human, animal and environmental health. However, the Directive is a significant tool to protect those animals that are still required.

The HPRA regulates the sector by means of authorisation at three levels:

1. **Breeder/supplier/user establishments:** Breeders and suppliers of animals, as well as establishments where procedures are performed, must be authorised and are subject to HPRA inspections, including unannounced inspections. In 2018, the HPRA performed 22 inspections, of which 36% were unannounced. The HPRA was satisfied with overall levels of compliance nationally.
2. **Projects:** Scientific procedures involving animals can only take place following a detailed submission of the planned study and subsequent approval by the HPRA on the basis of a favourable harm/benefit analysis.
3. **Individuals:** Any person wishing to carry out scientific procedures involving animals, as well as project managers and those conducting euthanasia in an authorised establishment, must be adequately trained to do so and hold a HPRA individual authorisation.

The HPRA aims to improve the welfare of animals used for scientific purposes and to promote the principles of the 3Rs. Every application received for a project involving animals is subject to a detailed evaluation process based on the 3Rs and requires scientific justification for the research techniques being applied. The likely impact on the animals must be minimised as far as possible by applying refinements and any harms experienced by the animals must be outweighed by the expected benefits of the work. The HPRA considers whether alternative (non-animal) methods are available or appropriate, as alternatives to the use of live animals must be used where possible. In fulfilment of the HPRA's mandate to promote the 3Rs, in 2018 the HPRA continued its efforts to enhance awareness and utilisation of non-animal alternatives as well as refinements in the conduct of scientific studies in animals through its work, including the regular dissemination of pertinent information to the regulated sector.

The objective of this report is to present statistical data on the number of uses of animals for scientific purposes in Ireland during 2018 in accordance with Article 54(2) of the Directive. This is the sixth report to be prepared by the HPRA since it became the competent authority for the protection of animals used for scientific purposes. The Department of Health published all reports in this area prior to 2013.

As in previous years, the data provided are based on self-declarations by the establishments concerned. The methodology and legal basis for the requirements for data collection were substantially changed with the introduction of the Directive in 2013. For example:

- Previous data (i.e. prior to 2013) reported only on the first use of each animal, whereas this report includes any subsequent uses of the same animals (reuse).
- Each use of an animal must now be assigned to a specific project purpose outlined by the legislation, e.g. basic research, translational research, regulatory use etc.
- The breeding of genetically altered animal lines was not required to be included in previous reporting years and this is now a requirement of the legislation.
- The actual severity experienced by the animals must now be reported under four categories: non-recovery, mild, moderate or severe.

This format meets the requirements for a European database which has been developed by the European Commission. The data for 2018 has been presented in a similar manner to the 2017 and 2016 reports but in a slightly different manner to the previous reports published by the HPRA, following clarification as to the precise formatting requirements.

Please refer to the Appendix for definitions relating to some of the terminology used in this report.

2 SUMMARY

In 2018, there were a total of 199,800 uses of animals for procedures, with reuse representing <1% of this number. Mice were the most commonly used species at 75% of the total animal use.

Of the total number of uses of animals in procedures (199,800), some (72%) were used for regulatory purposes, which refers to legal requirements to test the safety, quality and potency of medicines (e.g. biological medicines such as vaccines).

Of the total number of uses of animals in procedures (199,800), 9,814 involved genetically altered animals, which represents 5% of all animal use.

The most common reported actual severity experienced by the animals during their uses in procedures was ‘mild’, at 55%, followed by ‘moderate’, at 27%.

3 RESULTS

3.1 Species and numbers of uses of animals in procedures

Table 1 shows the number of uses of animals in procedures. It shows both the first, and all the subsequent uses of the animals that were completed in the year 2018. A single use of an animal extends from the time when the first technique is applied to the animal until the completion of data collection, or when the animal is removed from the project. It should be noted that this does not represent the total number of animals used because some animals are reused (see section 3.2).

Mice (75% of the total uses of animals) were by far the most commonly used species. The next most common species used were rats and fish. The category 'other fish' (9%) primarily represents wild fish being studied for conservation projects. For example, European eels are a critically endangered species and Irish salmon stocks are critically low, so monitoring projects are required to improve the survival of these species. Likewise, the category 'other birds' (<1%) represents wild bird species being studied in monitoring and conservation projects. It should be noted that the following species have been excluded from this table as they were not used in Ireland in 2018: Mongolian gerbils, hamsters, other rodents, dogs, cats, other carnivores, reptiles, rana, other amphibians, cephalopods and non-human primates.

Table 1: Numbers of uses of animals by species

Animal species	Number of uses	Percentage
Mice	149966	75%
Rats	21635	11%
Guinea pigs	589	<1%
Rabbits	171	<1%
Ferrets	288	<1%
Horses, donkeys & cross-breeds	54	<1%
Pigs	1662	<1%
Goats	19	<1%
Sheep	644	<1%
Cattle	3137	2%
Other mammals	1	<1%
Domestic fowl	30	<1%
Other birds	654	<1%
Xenopus	42	<1%
Zebrafish	3054	2%

Animal species	Number of uses	Percentage
Other fish	17854	9%
Total uses	**199800**	**100%**

3.2 Reuse of animals

Table 2 shows the proportion of reuse (see Appendix for definition), which represents 0.1% of animal use. Animals are only permitted to be reused on second or subsequent projects if the severity they have experienced to date is 'mild' or 'moderate' (see Appendix for definition of severity categories). It should be noted that the true number of animals that are reused cannot be deduced from this data due to the fact that some animals may be reused more than once (i.e. the figure 180 represents *uses of animals,* not actual numbers of animals reused). Cattle were the only species to be reused during 2018. In Ireland, cattle are used only for agricultural research studies (for the benefit of the species, the environment or the agricultural sector). The overwhelming majority of projects of this nature are of overall 'mild' severity, with only a tiny minority reaching 'moderate' severity. Since the severity cattle experience on these projects is limited, and they return to full general health between projects, it is acceptable that they are reused in further projects.

Table 2: Reuse

Reuse	Number of uses	Percentage
No	199620	>99%
Yes	180	<1%
Total uses	**199800**	**100%**

3.3 Origin of animals at the first use

Table 3 shows the number of animals according to their place of birth, but only includes animals used for the first time as the place of birth is not recorded for animals on their second (or subsequent) use(s). The majority (93%) of animals were born in the EU at a registered breeder, which means that they were born at breeding establishments authorised under the Directive. Animals born in the EU but not at a registered breeder (3%) include wild animals and farm animals. Animals born in the rest of Europe and the rest of the world includes animals that have been obtained from breeding establishments outside the EU (e.g. specific strains of mice not available in the EU) as well as wild animals that have travelled into Ireland from other regions (e.g. migratory birds).

Table 3: Origin of animals

Place of Birth	Number of uses	Percentage
Animals born in the EU at a registered breeder	185932	93%
Animals born in the EU not at a registered breeder	4908	3%
Animals born in rest of Europe	7680	4%
Animals born in rest of world	1100	<1%
Total uses	**199620**	**100%**

3.4 Project purposes

Table 4 shows the primary purposes for which animals were used. The most common primary purpose at 72% was 'Regulatory use and routine production'. This is defined as the "use of animals in procedures with a view to satisfying legal requirements for producing, placing and maintaining products/substances on the market, including safety and risk assessment for food and feed".

The primary purposes are further sub-divided in Tables 5-11. It should be noted that the following primary purposes were excluded from this table as no uses were reported under these purposes in 2018: 'Preservation of species' and 'Forensic enquiries'.

Table 4: Primary purpose for which animals are used

Primary purpose	Number of uses	Percentage
Basic research	7887	4%
Translational and applied research	38477	19%
Regulatory use and routine production	143895	72%
Protection of the natural environment in the interests of the health or welfare of human beings or animals	8741	4%
Higher education or training for the acquisition, maintenance or improvement of vocational skills	343	<1%
Maintenance of colonies of established genetically altered animals, not used in other procedures	457	<1%
Total uses	**199800**	**100%**

Table 5 shows the number of uses of animals in more specific categories of 'Basic research'. 'Basic research' refers to studies of a fundamental nature, which are designed to add knowledge about the structure, functioning or behaviour of organisms. The most common sub-field of 'Basic research' at 38% was research into the nervous system. Nervous system research involves studies that look at particular cells and disorders related to diseases of the brain and spinal cord, e.g. Alzheimer's, Parkinson's, and multiple sclerosis. These types of studies most commonly use mice and rats. The next most common purpose was research into ethology, animal behaviour and animal biology (27%). In Ireland, this is mainly accounted for by agricultural research (e.g. nutrition and reproduction studies in farm animals) or research into the behaviour of wild animals (e.g. fish or bird tracking studies).

Table 5: Uses of animals for basic research

Basic Research	Number of uses	Percentage
Oncology	30	<1%
Cardiovascular, blood and lymphatic system	59	<1%
Nervous system	2968	38%
Respiratory system	82	1%
Gastrointestinal system including liver	602	8%
Musculoskeletal system	46	<1%
Immune system	1729	22%
Urogenital/reproductive system	28	<1%
Sensory organs (skin, eyes and ears)	24	<1%
Endocrine system/metabolism	6	<1%
Multisystemic	147	2%
Ethology / animal behaviour /animal biology	2166	27%
Total uses	**7887**	**100%**

Table 6 shows the number of uses of animals in more specific categories of 'Translational and applied research', which refers to studies which aim to prevent, diagnose, detect or treat disease in animals or humans as well as studies which aim to improve animal welfare. The most common purpose at 25% was research into human nervous and mental disorders, which includes research into treatments for diseases such as epilepsy, autism, and depression, using mice and rats. The next most common purpose, at 24%, was research into animal welfare, which is mainly accounted for by research into the wellbeing, housing standards and health of farmed animals such as pigs and cattle.

Table 6: Uses of animals for translational and applied research

Translational and applied research	Number of uses	Percentage
Human cancer	1202	3%
Human infectious disorders	768	2%
Human cardiovascular disorders	1004	3%
Human nervous and mental disorders	9436	25%
Human respiratory disorders	227	<1%
Human gastrointestinal disorders including liver	1063	3%
Human musculoskeletal disorders	828	2%
Human immune disorders	5838	15%
Human urogenital/reproductive disorders	122	<1%
Human sensory organ disorders (skin, eyes and ears)	4110	11%
Human endocrine/metabolism disorders	1347	4%
Animal diseases and disorders	3425	9%
Animal welfare	9095	24%
Diagnosis of diseases	12	<1%
Total uses	**38477**	**100%**

Table 7 shows the breakdown of animal uses for 'Regulatory use and routine production'. Regulatory testing refers to procedures carried out with a view to satisfying legal requirements for producing, placing and maintaining products/substances on the market. The majority of reported uses (>99%) can be attributed to quality control testing.

Table 7: Uses of animals for regulatory testing

Regulatory use	Number of uses	Percentage
Quality control (including batch safety and potency testing)	143578	>99%
Toxicity and other safety testing including pharmacology	300	<1%
Routine production	17	<1%
Total uses	143895	100%

Table 8 shows a further breakdown of animal use for 'Quality control' tests. Quality control refers to animals used in the testing of purity, stability, efficacy, and potency parameters of a final medicinal product, in order to satisfy regulatory requirements. The majority of quality control tests were for batch potency (97%), and of these tests, 90% were performed on mice. Batch potency testing is mainly carried out for biological products, which are products made

in a living system such as a microorganism, or plant or animal cells, as opposed to being manufactured through chemical synthesis. The nature of biological products is that they can be inherently variable, and therefore it is necessary to perform batch potency testing to ensure that each manufactured batch of product is of a consistent strength, and therefore both safe and effective for patients. In relation to pyrogenicity testing (<1%), non-animal alternatives have been developed to replace this type of testing for certain medicines which has resulted in a 76% reduction in this type of testing since 2014. However, there are still some limited circumstances in which it is not possible to use a non-animal alternative to pyrogenicity testing, and therefore it is necessary to continue to employ animal-based tests in some instances. It should be noted that 'other quality controls' were excluded from this table as no uses were reported under this purpose in 2018.

Table 8: Uses of animals for regulatory testing - quality control

Quality control	Number of uses	Percentage
Batch safety testing	4587	3%
Pyrogenicity testing	145	<1%
Batch potency testing	138846	97%
Total uses	**143578**	**100%**

Table 9 shows a further breakdown of animal use for 'Toxicity and other safety testing'. All of these tests were for ecotoxicity testing.

Table 9: Uses of animals for regulatory testing - toxicity and other safety testing including pharmacology

Toxicity and other safety testing	Number of uses	Percentage
Acute and sub-acute testing	0*	0%
Repeated dose toxicity	0**	0%
Ecotoxicity	300	100%
Total uses	**300**	**100%**

*No uses were reported for 'Acute and sub-acute testing', therefore no additional 'Acute and sub-acute toxicity testing methods' table provided in this report.
**No uses were reported for 'Repeated dose toxicity', therefore no additional 'Repeated dose toxicity' table provided in this report.

Table 10 shows that the animals used for 'Routine production' were all for the production of blood based products. This refers to the collection of animal blood for use in other regulatory tests required under legislation for human medicinal products (the other categories were excluded from this table as no uses were reported).

Table 10: Uses of animals for routine production

Regulatory use	Number of uses	Percentage
Blood based products	17	100%
Total uses	**17**	**100%**

Table 11 shows that animals used for ecotoxicity testing were all reported as being used in acute toxicity tests (the other categories were excluded from this table as no uses were reported). All of the ecotoxicity tests were conducted on fish.

Table 11: Uses of animals for regulatory testing - ecotoxicity

Ecotoxicity	Number of uses	Percentage
Acute toxicity	300	100%
Total uses	**300**	**100%**

3.5 Use of animals to meet legislative requirements

Table 12 shows which type of legislation is being satisfied in the performance of the regulatory tests for which animals were used. The vast majority (>99%) were performed on medicinal products manufactured for use in humans. The category 'other legislation' is accounted for by ecotoxicity testing performed under pollution control legislation. **Table 13** shows the geographical origin of the legal requirement. All tests were performed to satisfy EU legislative requirements.

Table 12: Regulatory testing by type of legislation

Testing by Legislation	Number of uses	Percentage
Legislation on medicinal products for human use	143573	>99%
Legislation on veterinary medicinal products	22	<1%
Other legislation	300	<1%
Total uses	**143895**	**100%**

Table 13: Origin of legislative requirement

Legislative Requirement	Number of uses	Percentage
Legislation satisfying EU requirements	143895	100%
Legislation satisfying national requirements only [within EU]	0	0%
Legislation satisfying non-EU requirements only	0	0%
Total uses	143895	100%

3.6 Use by genetic status

Table 14 shows the number of uses of animals with a genetic alteration, broken down by whether the animal exhibited a harmful phenotype at the time of the study or not. The majority of animals were not genetically altered, with 2% of all uses involving animals with harmful phenotypes (see Appendix for definitions).

Table 14: Genetic status

Genetic Status	Number of uses	Percentage
Not genetically altered	189986	95%
Genetically altered without a harmful phenotype	6177	3%
Genetically altered with a harmful phenotype	3637	2%
Total uses	**199800**	**100%**

3.7 Use in creation of a new genetic line

Table 15 shows the numbers of animals used in the creation of a new genetically altered line. This represents less than 1% of overall animal use.

Table 15: Creation of a new genetically altered line

Creation of new genetic line	Number of uses	Percentage
No	199507	>99%
Yes	293	<1%
Total uses	**199800**	**100%**

3.8 Actual severity of uses

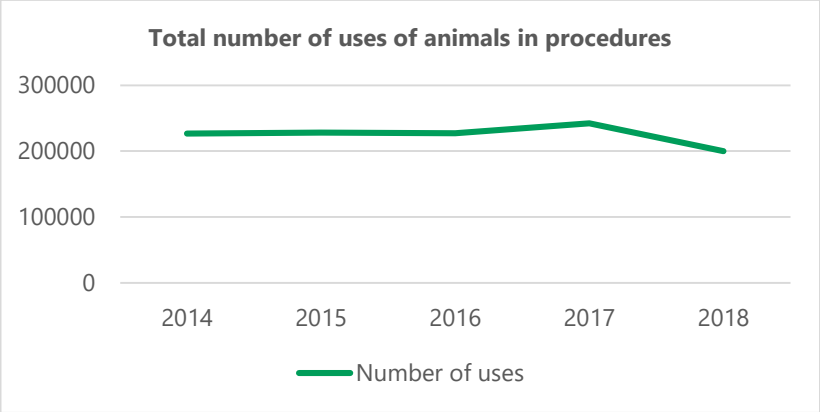
Table 16 shows the reported actual severity experienced by the animals during their uses in procedures. Overall, 0.5% of uses were classified as non-recovery, 55% were classified as mild, 27% were moderate and 17% were severe (see Appendix for definitions). Of the animals that were involved in severe procedures in 2018, 99% were mice. It should be noted that the severe classification was not exceeded, nor did the HPRA grant any exemptions for the severe classification to be exceeded.

Table 16: Classification of actual severity

Severity	Number of uses	Percentage
Non-recovery	1065	<1%
Mild [up to and including]	110202	55%
Moderate	54787	27%
Severe	33746	17%
Total uses	**199800**	**100%**

4 TRENDS

a) In 2018, there were a total of 199,800 uses of animals in procedures, which represents an 18% decrease on the number of uses reported for 2017 (242,302). This is the first year the total animal use has dropped below 200,000; however, as it follows an increase between 2016 and 2017, it should not be taken as an established trend. The below graph illustrates the total number of uses of animals over the past five years.



b) The project purpose 'Regulatory use and routine production' accounted for most animal use in 2018 (143,895 uses), which is a 26% decrease in regulatory use from 2017 (194,896 uses). Regulatory use has consistently accounted for the biggest use of animals over the last five years. Although non-animal alternative tests have replaced the need to use animals for regulatory testing for a number of human and veterinary medicinal products, these non-animal alternatives are not yet available/approved for all medicinal products which require regulatory testing. Consequently, there remains in some instances a requirement to perform regulatory testing of medicinal products using animals. In addition, non-animal tests can occasionally fail or malfunction, thereby resulting in unreliable results and necessitating replacement by an animal test. In relation to the other project purposes, 'Translational and applied research' has remained largely consistent and the number of uses of animals for 'Basic research' purposes has decreased over the past two years. This shift may be due to a greater emphasis being put on ensuring animal research is translatable, but may also be related to users becoming more familiar with the reporting requirements.

c) As in previous years, in 2018 mice were still the most commonly used species representing 75% of overall animal use. No dogs were used in 2018 and other significant changes in the uses of particular species over the last five years were a marked reduction in the use of rabbits, and a marked increase in the use of 'other fish'. The main contributory factor to the decrease in the use of dogs relates to the closure of one animal facility in Ireland. The decrease in rabbits relates primarily to a reduction in regulatory testing on rabbits due to the transition to non-animal

alternative tests. The increased use of 'other fish' represents a greater research focus on the behaviour and conservation of wild fish (e.g. European eel and Atlantic salmon), such as research into the effects of climate change on their life cycle and survival.

d) Of the 199,800 procedures completed in 2018, 180 involved reuse of animals. This represents a 73% decrease on reuse reported in 2017 (675 uses) and a 93% decrease since 2014 (2,435 uses). Reuse has been decreasing consistently over the past 5 years, and this is likely due to a reduction in the use of species (other than cattle) that are more traditionally reused, e.g. rabbits, dogs and cats.

e) In terms of actual severity of procedures, the majority of procedures are still reported as mild (55%), which has been the trend since 2015. The proportion of non-recovery and moderate procedures have been largely consistent over the past four years, and the proportion of severe procedures was at its lowest in 2018 (17%). The reduction in the proportion of procedures reported as severe is attributed to the reduction in regulatory use of animals, as well as efforts made by the HPRA, animal welfare bodies, and animal users to reduce the severity of procedures by the implementation of refinements and earlier humane endpoints.

5 CONCLUSION

In the year 2018, there were 199,800 reported uses of animals in procedures in Ireland. This is an 18% decrease on the number of uses reported for 2017, and follows a 7% increase between 2016 and 2017. Aside from the 26% decrease seen in regulatory testing, the number of other uses appears to be quite consistent over the last five years. The proportion of animals that experienced a severe severity in 2018 is lower than previous years, and as with previous years, the most commonly reported actual severity remains at mild.

The HPRA's focus will continue to be the reduction of severe suffering, for example, with the continued application of early humane endpoints, as well as ensuring that the 3Rs are applied to all authorised projects. In addition, the HPRA will ensure that procedures are only performed where there is no alternative (non-animal) technique available and where the expected benefits outweigh any possible harms.

6 APPENDIX: DEFINITIONS

Procedures

The Directive defines a procedure as: "any use of an animal for scientific or educational purposes, which may cause the animal a level of pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice". This includes the creation and maintenance of any genetically altered animal lines that may result in pain or distress as per the above definition. Each procedure may consist of several stages or techniques for a single scientific purpose, which is then counted as *one* procedure and reported in the year it was completed.

Reuse

Reuse means that having fully recovered from a completed procedure, and having been certified by a veterinarian as having returned to full health, that animal can then be enrolled on another project.

Genetically altered animals

Genetically altered animals are those that have been genetically modified, for example, by the introduction (into an animal) of genetic material from another animal, or by 'knocking out' or disrupting an existing gene. Statistics are only collected on genetically altered animals that have an impairment to their well-being from the genetic alteration (a harmful phenotype), or when a new genetic line of animals is being created and the effect on the animals is not yet known.

Actual severity

At the end of the use of an animal on a procedure, the impact of the procedure must be determined and reported as 'actual severity'. This means that the *highest severity* that an animal may have experienced throughout the course of their time on procedure (rather than the severity at the end or the average severity throughout) must be recorded. Therefore, it is based on the real impact of the procedure, rather than any predicted impact. The legislation defines four categories of actual severity, in order of least to most harmful, as: non-recovery, mild, moderate and severe.

Non-recovery: This means the entire procedure is carried out under general anaesthesia and at the end the animal is humanely euthanised rather than being allowed to wake up.

Mild: Any pain or suffering experienced by the animal is only slight, minor or temporary so the animal recovers in a short period of time. This would include an injection, a short period of social isolation, or non-invasive imaging under sedation or anaesthesia (e.g. MRI scanning).

Moderate: Any suffering experienced by the animal is short-term moderate pain, suffering or distress, or long-lasting mild pain, suffering or distress, or involves a moderate impairment to their well-being. This would include surgery performed under general anaesthesia, repeated injections or blood tests and the induction of tumours that cause moderate impairment to well-being.

Severe: Severe procedures indicate a major departure from the animal's usual state of health or well-being, and cause long-lasting moderate pain, suffering or distress, or short term severe pain. This might include toxicity testing under legislation where fatalities may occur, surgical procedures that cause severe post-operative pain and the breeding of animals with serious genetic disorders.

It should also be noted that procedures that involve severe pain, suffering or distress that are *long-lasting* are prohibited under the legislation.